AN AUSTRALIAN POPULATION-BASED STUDY OF THE INCIDENCE AND OUTCOMES OF HEPATOCELLULAR CARCINOMA: THE HEPATOMAS OF MELBOURNE EPIDEMIOLOGICAL RESEARCH (HOMER) STUDY

Thai Phuoc Hong
MBBS Honours, BMedSci, FRACP
ORCID ID: https://orcid.org/0000-0002-7399-4531

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Department of Gastroenterology and Medicine
St Vincent’s Hospital
University of Melbourne

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Abstract

Liver cancer, the world’s second highest cause of cancer death, is reportedly increasing in incidence in developed countries including Australia. Hepatocellular carcinoma (HCC), the predominant type of liver cancer, has a complex epidemiology involving the interplay of many dynamic risk factors including chronic viral hepatitis B and C, alcohol-related liver disease and non-alcoholic fatty liver disease. Recent trends in these risk factors, changes in Melbourne’s population demographics, together with advances in HCC diagnostics are thought to be increasing HCC incidence, although this may be currently underreported by the cancer registry. Accurate local epidemiology is required to inform healthcare policy for the appropriate allocation of resources for treatment, prevention and research that will improve clinical and economic outcomes.

The major study of this thesis, to my knowledge, is the first in the world to determine the population incidence of HCC using clinical case capture independent of the cancer registry. In doing so, it is also the first study to validate the completeness and accuracy of a cancer registry in reporting HCC, which is critical given that the HCC epidemiology literature has been mostly dependent on local registry data.

Over 12 months (July 2012 to June 2013), there were 272 new cases of HCC identified from multiple primary sources including multidisciplinary meeting reviews, hospital inpatient, outpatient and emergency attendance at any of Melbourne’s seven tertiary hospital networks, pathology, radiology and pharmacy databases. After cross-referencing with the Victorian Cancer Registry cases for the same period, the HCC incidence determined by this study was found to be twice as high as that reported by the registry.

The recruited population-based prospective cohort of HCC patients then provided the opportunity to examine clinical outcomes across the breadth of presentation, demographics and institutional expertise. This allowed for the determination of factors associated with improved survival, in particular, the influence of HCC surveillance participation. The commonest risk factors for HCC were chronic hepatitis C (41%) and alcohol-related liver disease (39%) followed by chronic hepatitis B (22%). While participation rates were low (40%), surveillance was associated with
earlier tumour stage at diagnosis, being offered curative therapies, and improved survival probability.

In the era of advanced diagnostic imaging and therapeutics for HCC, only some of which is publicly funded, the economic cost of the HCC disease burden is an important consideration in cost-effectiveness analyses. This HCC incidence cohort provides the basis for the first direct costings study of HCC management in Australia, with associated clinical factors that determine high cost.

The highest costs occurred at both of ends of the disease spectrum, with early stage disease curable by liver transplantation or surgical resection, as well as in the sickest patients with advanced disease and only palliative options available. Thus, investment of healthcare expenditure towards disease prevention and early detection would likely be most cost-effective with improved survival and reduced morbidity achieved.

This world-first research, using a novel methodology for clinical case capture, determined the population-based incidence of HCC in Melbourne, confirmed the underreporting of incidence by the cancer registry and contributed to the correction of registry classification practices. For cancers with rapidly changing epidemiology such as HCC, accurate and contemporary local data is important in disease prevention and management and in guiding healthcare policy and research.
Declaration

I certify that this thesis entitled

“Hepatocellular carcinoma epidemiology and outcomes in Melbourne”

comprises my original work towards the degree of

Doctor of Philosophy

The work has not been previously submitted for an award at this or any other higher education institution. To the best of my knowledge and belief, the thesis contains no material previously published or written by another person except where due reference is made. The thesis has fewer than 100,000 words in length, exclusive of tables, maps, bibliographies and appendices.

Signature: ____________________________________________

Date: 5 February 2019
Preface

While this was a multi-centre study involving collaborators from all of Melbourne’s seven tertiary hospital networks, I was the primary researcher and first author of the three research papers contained in this thesis. I had a leading role in the research design, with the conceptual elements partly formed by members of the Melbourne Liver Group. The data collection, analysis and writing of the thesis and papers were my original work, with support from my supervisors and feedback from other collaborators.

My principal supervisor A/Prof Sally Bell, and two co-supervisors, Prof Alex Thompson and A/Prof Paul Desmond provided ongoing support with advice and review assistance of methodology, analyses of the studies and review of the thesis and research papers. All collaborating co-authors reviewed and advised in the editorial process for submission of the research papers. A/Prof Vijaya Sundararajan provided formal statistical advice and analysis assistance. Helen Farrugia and Vicky Thursfield from the Victorian Cancer Registry collaborated for the first incidence study to provide cross-referencing and validation of cases.

Publications arising from this work are:


The paper entitled “Direct Costs of Hepatocellular Carcinoma Management in Australia” is in the process of being submitted to *Journal of Gastroenterology and Hepatology*. 
An Australian population-based study of the incidence and outcomes of hepatocellular carcinoma: the Hepatomas of Melbourne Epidemiological Research (HoMER) study
Acknowledgments

I would like to offer my sincere thanks and appreciation to my principal supervisor A/Prof Sally Bell, and two co-supervisors, Prof Alex Thompson and A/Prof Paul Desmond for their tremendous support, encouragement and patience in guiding me through this very long period. A heartfelt (and amazed) gratitude to Sally who was reviewing this thesis while recovering from an ‘adventure’ holiday. Best wishes with your next adventure that is Monash, Sally.

I would like to thank my collaborating co-authors for the warm welcome and assistance they provided to enable access to their respective hospitals and outpatient clinics, as well as their feedback and encouragement throughout.

Thank you to my colleagues, Dr Catherine Croagh, Dr Lucy Lim and Dr Jacinta Holmes for helping to cover my clinical work while I finished writing this thesis.

I am grateful for the financial support provided by the Australian Postgraduate Award through the University of Melbourne and Department of Gastroenterology at St Vincent’s Hospital.

Thank you to my parents and my sister Thanh who have provided the comfort and security that only family can, to allow me to complete this research.

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Finally, I am thankful to God for all His blessings in the opportunities, the people, the patients and the path He has planned for me.
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Chapter 1: Introduction

This introductory chapter will outline this research, beginning with the background of the problem of hepatocellular carcinoma, its epidemiology and outcomes (Section 1.1). Following this, the context and purpose of each study will be discussed (Section 1.2). Section 1.3 then describes the scope of this research and its significance. Finally, an outline of the thesis will be presented in Section 1.4.
1.1 BACKGROUND

Liver cancer consists of primary and secondary forms, the former arising from liver cells whereas the latter, more common form, occurs as metastases from another primary cancer source. This thesis deals with primary liver cancer, and the term “liver cancer” hereafter will refer only to primary liver cancer.

Liver cancer is the fifth most common cancer and the second highest cause of cancer mortality worldwide. Despite the global significance of the problem, liver cancer is only starting to be recognised as a major disease burden in developed countries such as Australia where historical incidence has been low.

Hepatocellular carcinoma (HCC), the dominant liver cancer subtype and focus of this study, is a complex disease in its aetiology, diagnosis, treatment and prognosis. HCC occurs mostly in cirrhosis, which is the end stage of many chronic liver diseases including chronic hepatitis B virus (HBV) infection, chronic hepatitis C virus (HCV) infection, alcohol-related liver disease, non-alcoholic fatty liver disease (NAFLD), autoimmune hepatitis, genetic haemochromatosis and others. HCC can also develop without cirrhosis, mainly in HBV infected patients, many of whom are migrants with undiagnosed or poorly managed infection.

In the West, it is thought that there is an increasing incidence of HCC due to a number of phenomena, of which three are most important: the culmination of the cirrhosis burden from chronic HCV infections decades earlier, the migration of chronic HBV infected patients from areas of high HBV prevalence, and the emerging obesity and metabolic syndrome epidemic in Western societies. With so many interacting risk factors whose distributions vary with period, geography and populations, local epidemiology is needed to accurately predict trends in HCC incidence.

While cancer registries record population incidence and have been the primary source for most reports of HCC epidemiology worldwide, the changing practice of HCC diagnosis may impair registry completeness and validity. The main study of this thesis was established to determine HCC incidence through primary capture sources independent of the cancer registry.

The second study of the thesis further describes the local epidemiology of HCC and evaluates outcomes of the incidence cohort, with particular emphasis on the influence of surveillance participation on survival outcomes.
HCC can present in several ways: 1) with clinical symptoms of either chronic liver disease and its decompensation (commonly) or tumour-related (less common) or 2) without symptoms, by incidental diagnosis or direct surveillance of high-risk patients. Surveillance is associated with earlier stage diagnoses, allowing these patients access to curative treatment that may improve survival. However, surveillance rates are low due to poor adherence, undiagnosed chronic liver disease and other barriers (language and cultural barriers to seeking medical care, poor health literacy, substance abuse and lack of organised surveillance programs outside major tertiary hospitals).

An increasing number of treatments are available for HCC ranging from curative therapies such as surgical resection, ablation and liver transplantation to loco-regional treatments such as transarterial chemoembolization for disease control. Advanced HCC may be offered palliative treatments such as multi-kinase inhibitors, check-point inhibitors and other small molecules that are moving from clinical trials into routine practice.

While survival outcomes associated with particular stages of disease and treatment regimens have been described in the literature, there is little Australian data at the population level. Understanding the determinants of survival including the influence of different aetiologies of liver disease and the influence of surveillance participation rates, will help inform local policy.

The third study of the thesis examines the cost of HCC management in the Australian healthcare context. The direct cost of HCC management, inclusive of the diagnostic processes, inpatient hospital admissions, outpatient follow-up, and use of therapeutics, is a considerable burden to the healthcare system, especially in countries with universal healthcare like Australia. Consequently, policymakers need to develop strategies to reduce disease burden such as reduction of risk factors or screening for early disease. Local costings data will be useful for instituting cost-effective programs to reduce disease burden.
1.2 CONTEXT

Members of the Melbourne Liver Group, a group of liver disease specialists from all of Melbourne's tertiary hospitals, believed that HCC incidence was rising in Melbourne from their own practice experience. Further, as HCC diagnosis is now based on clinical and radiological criteria, it was suggested that the Victorian Cancer Registry which traditionally uses histological basis of diagnosis may be underreporting incidence.

A population-based study was designed to capture new HCC diagnoses across Melbourne and determine the annual incidence rate, independent of cancer registry data. To the best of my knowledge, this major study of the thesis (Chapter 4) is the first study in the world to establish HCC incidence using multiple primary sources with clinical verification. In contrast, all previous reports of HCC population incidence around the world have been extracted from the corresponding population cancer registry (see Section 0). This study is also the first to validate cancer registry cases of HCC against a population-based capture method, whereas others have only validated with a select clinical trial or institution-based cohort.

To establish population incidence, the completeness of case capture is paramount. A complex and relatively uncommon cancer such as HCC, whose management in developed health care systems is referred to expert tertiary centres, is an ideal subject to help achieve this end. There are limited experts treating HCC and of these, referral for discussion at a multidisciplinary centre is part of their routine private practice. This was confirmed through a preliminary survey conducted prior to commencing this study.

Once established, the incidence cohort provided a prime opportunity to describe HCC epidemiology and outcomes in the Australian setting. While population epidemiology exists through the cancer registry data, and institution- or study-based clinical cohorts of HCC have been described, a population-based clinical cohort of HCC patients has never been studied in Australia. This cohort allows the study of disease across the spectrum of presentations, demographics and institutional expertise. In particular, full characterisation of the cohort allowed for the analysis of factors that might impact survival outcomes including surveillance participation.
The advent of the first-generation direct acting antiviral (DAA) drugs used in combination with pegylated interferon and ribavirin for HCV treatment coincided with the beginning of this research. Subsequently, the second generation of all oral DAA drugs became available on the Australian Pharmaceutical Benefits Scheme. It was anticipated that these highly expensive treatments will be cost-effective by reducing the burden of HCV infection, which includes cirrhosis and HCC development.

While these types of funding decisions undoubtedly accounted for the economic costs of the HCC burden, there has yet been any direct costings data on HCC management in the Australian context. This incidence cohort again provided a well characterised population-based cohort from which to assess cost determinants over time. However, given the limited time frame available for completion of this thesis, analysis was only performed on the available data from half of the cohort.
1.3 PURPOSE

Therefore, the purposes of the studies contained in this thesis are:

1. To determine the incidence of HCC in Melbourne using population based clinical capture from multiple primary sources, independent of cancer registry data

2. To compare with the HCC incidence reported by the Victorian Cancer Registry and assess the validity of case capture and classification of HCC at the registry

3. To characterise HCC disease in Melbourne at the population level in terms of presentation, treatment and outcomes

4. To determine overall survival in HCC in a longitudinal population-based clinical cohort and the factors influencing survival

5. To describe the direct costs of HCC management in Australia and the factors associated with higher costs
1.4 SIGNIFICANCE AND SCOPE

This is the first study worldwide to determine the population incidence of HCC with clinicoradiological basis of diagnosis using primary sources independent of cancer registry data. In the context of changes in reported incidences and diagnostic criteria, as well as literature dominated by dependence on cancer registry data, this novel methodology highlights the need for regular reassessment of local epidemiology.

Particular gaps in the literature that this research attempts to address include:

• There are no studies of population incidence of HCC captured from primary sources using clinical criteria

• There are no validation studies of cancer registry reported HCC incidence at the population level

• There are no studies describing an Australian clinical cohort of HCC patients encompassing the spectrum of disease presentations in the population

• There are no Australian studies of HCC surveillance participation and survival outcomes at a population level

• There are no studies of HCC costs in the Australian context

The scope of this research is limited to the population of Melbourne, Australia’s second largest city. Results may be applicable to other metropolitan cities in Australia and other countries with a similar demographic profile to Melbourne. However, as HCC has many interacting risk factors that vary by geography, generalisation needs to be done with caution.

The longitudinal cohort study is limited to a short follow-up period of 24 months due to the time limitations of this thesis. Similarly, the costings data is limited to a sample of half the cohort which is representative of the population, and for which costs data was available.
1.5 THESIS OUTLINE

The thesis begins with background chapter (Chapter 2) to provide the reader sufficient context to understand the significance and scope of the research. The chapter itself contains four sections. The first of these (Section 2.1) is an overview of hepatocellular carcinoma, from its pathology and diagnosis, to current treatment and prognosis. This is intended to provide a general medical audience a synopsis of the current management of HCC to understand the subsequent sections, rather than a thorough literature review of each topic in itself, which is beyond the scope of this thesis. The other three sections (Section 2.2, 2.3 and 2.4) are literature reviews for each of the three studies in this thesis.

Chapter 3 is a description of the methodology used over the three studies. As each study is a publication with its own methodology section, this chapter will focus mainly on aspects of the methodology not fully covered in the publications.

Chapter 4 contains the primary publication arising from this research, which is the determination of the incidence of HCC in the Melbourne population.

Chapter 5 contains the publication of the survival outcomes of the longitudinal clinical cohort captured in the incidence study. In particular, the influence of surveillance participation on survival is explored.

Chapter 6 contains the study of the costs of HCC treatment in Australia, which has been submitted in its entirety for peer-review.

Chapter 7 is a general discussion of the entire research in the context of recent literature and the impact that this research has made since publication of the first two studies.

Chapter 8 is a final concluding chapter that draws together the key messages of the research. It also provides some conceptual directions for future research and offers suggestions to improve HCC management in Australia.
2 Background and Literature Review

2.1 HEPATOCELLULAR CARCINOMA – AN OVERVIEW

This section will provide an overview of hepatocellular carcinoma, its pathological basis, diagnostic methods, staging, treatment options and prognosis. This aims to provide a background for understanding the subsequent literature review. Sections 2.2, 2.3 and 2.5 more specifically presents a literature review of the three major studies in this thesis.

2.1.1 Pathology

Primary liver cancer is a tumour arising from one of many cell types of the liver: hepatocytes (hepatocellular carcinoma), biliary epithelial cells (cholangiocarcinoma), endothelial cells (angiosarcoma, or other mesenchymal cells (e.g. hepatoblastoma). Secondary liver tumours resulting from metastases of other primary (non-liver) tumours are far more common (30 times more in one study). Hepatocellular carcinoma (HCC) is the predominant liver cancer in most of the world and is the subject of this thesis. The other subtypes are mentioned only briefly below to serve as a background.

Hepatocarcinogenesis is a multifactorial process with the contributions of environmental, infections, nutritional and metabolic factors in association with genetic predispositions. These factors are further discussed in Section 2.2.1. Cirrhosis, which is the end stage of most types of chronic liver disease, provides a tumour macroenvironment that promotes malignant transformation. Here, like with other cancers, cycles of inflammation, injury and regeneration with increased cell turnover provide the milieu for gene mutations, leading to dysplastic cell formation and failed tumour suppression, eventually becoming neoplasia.

Dysplastic nodules, a preneoplastic lesion, can arise through this process with nodules generally smaller than 1cm, with either low- or high-grade dysplastic histology. They may not have fully induced the arterial supply and stromal invasion
that is present in early carcinoma, and hence may show atypical imaging characteristics.

Once formed, HCCs can occur as a single large nodule with or without adjacent microsatellite nodules, or as multifocal disease that is within one lobe or as diffuse disease throughout the liver. In multinodular disease, it can either present as multiple primary tumours occurring independently, or as intrahepatic metastases from a primary tumour. Multifocal HCC can occur in half of patients with compensated cirrhosis undergoing surveillance, and is more common in patients with multiple risk factors for liver disease.

Despite this, HCC tends to be clinically indolent in its early stages which contributes to patient and physician complacency and subsequent late symptomatic diagnoses. The rate of its natural progression can be highly variable, although the median doubling time for tumours less than 4.5cm in diameter is about 6 months. Prognosis is better with smaller volume of disease: single tumour less than 5cm, or up to three tumours, each less than 3cm – which forms the basis for the Milan Criteria for liver transplantation for HCC. Conversely, prognosis is poorer with the presence of satellite nodules, large tumour size (>6cm), poorly differentiated histology, lack of fibrous capsule and early vascular invasion.

HCCs can progress towards vascular invasion and develop metastases even in the asymptomatic patient. A Swedish autopsy series found 56% of 490 cases of HCC had evidence of vascular invasion. Even smaller tumours less than 2cm may have microscopic venous invasion in 40% of cases. In a study of primary liver cancer from the Surveillance, Epidemiology and End Results (SEER) database, metastases were present at baseline in 18% of 7681 HCC cases, and in 36% of 986 ICC cases. The most common sites for HCC metastases are lung (44%), portal vein (35%), portal lymph nodes (27%), bone and adrenal gland.
2.1.1.1 Other subtypes of primary liver cancer

**Intrahepatic cholangiocarcinoma**

Cholangiocarcinoma arise from the biliary epithelium, anywhere along the biliary tree, and can be divided into extrahepatic (75-80%) and intrahepatic cholangiocarcinoma (ICCs) (20-25%).\(^\text{11}\) Apart from differences in anatomical location, the two types have different risk factors, clinical presentation, treatment and prognosis. Only ICCs are considered a primary liver tumour by definition based on anatomical location, and will thus be the topic for discussion here.

ICCs represent the second most common primary liver cancer subtype in most regions of the world, accounting for about 10-15%.\(^\text{12}\) However, in some areas they form the major subtype at greater than 50%.\(^\text{13}\) Hence it is important to not underestimate the contribution of ICCs, which is further discussed in Section 2.2.3.1.

Incidence varies globally with rates of less than 1.0 per 100,000 in the Western countries and up to 2.0 per 100,000 in most other countries.\(^\text{14}\) Thailand has the highest rates at about 4.0 per 100,000 (age-standardised rates by World Standard Population)\(^\text{15}\) overall although some areas report incidence as high as 62.0 per 100,000 males and 25.6 per 100,000 females (age-standardised rates, Standard population unclear).\(^\text{13}\)

Incidence rates have also been rising in many countries; in the US, it has increased from 0.32 per 100,000 in 1975-79 to 0.85 per 100,000 in 1995-99.\(^\text{16}\) After increasing incidence trends were noted England and Wales,\(^\text{17}\) there was postulation that results were due to misclassification of Klaskin tumours as intrahepatic rather than extrahepatic cholangiocarcinoma. However, after reclassification, the increased trend was still apparent.\(^\text{18}\)

A number of risk factors are associated with the development of ICCs without any specific risk factor being predominant.\(^\text{12}\) While chronic liver disease (cirrhosis and viral hepatitis) are well-recognised risk factors for ICCs, particularly in the context of this thesis, other significant risk factors include primary sclerosing cholangitis, fibropolycystic liver disease (choledochal cysts), chronic intrahepatic stone disease (recurrent pyogenic cholangitis), parasitic infections (liver flukes) and genetic conditions such as Lynch syndrome and biliary papillomatosis.
Patients with ICCs may present with indolent dull right upper quadrant pain, weight loss or elevated alkaline phosphatase. They are less likely to be jaundiced compared with extrahepatic cholangiocarcinoma that often present with biliary obstruction. ICC patients may also be asymptomatic, with diagnosis detected incidentally after workup for abnormal liver function tests or via surveillance for HCC if they have cirrhosis or viral hepatitis.\(^\text{11}\)

The diagnostic work-up for ICCs include serum markers, biopsy and radiology tests. Ca 19-9 is a widely used serum marker with sensitivities 50-90% and specificity 54-98%.\(^\text{19}\) Radiological features on contrast enhanced CT or MRI (hypodense lesion, biliary dilatation, poorly defined arterial peripheral enhancement) are usually distinct from HCC, with less propensity for arterial enhancement and washout (diagnostic criteria for HCC) except in the case of mixed HCC-ICC tumours.\(^\text{20}\)

Despite advancements in some adjuvant therapies, surgical resection remains the primary curative treatment option for ICCs. Suitable patients for resection must have sufficient residual liver reserve post-resection, making severely cirrhotic patients poor candidates. Five year survival rates after resection range from 17 to 44%.\(^\text{11}\) A limited number of centres offer liver transplantation in unresectable disease, especially in the presence of advanced cirrhosis, with mixed results. Disease-free survival rates have been as low as 40% at 1 year,\(^\text{21}\) with high recurrence rates (51-80%),\(^\text{22}\) and overall survival at 1 year and 5 year, 74% and 38% respectively.\(^\text{23}\) Non-surgical therapy have a limited role with small survival benefits in the palliative context for cisplatin/gemcitabine chemotherapy (about 3 months survival benefit)\(^\text{24}\) and transarterial chemoembolization.\(^\text{25}\)

**Fibrolamellar carcinoma**

Generally presenting as a solitary, firm, large and well-circumscribed tumour, fibrolamellar carcinoma is distinct from HCC in clinical, histological and molecular features. Specifically with regards to clinical features, it tends to affect younger ages (5 to 35 years), without male predominance and is not associated with cirrhosis or chronic viral hepatitis.\(^\text{26}\) Patients present with pain or abdominal mass, and normal alpha-fetoprotein in most cases. Prognosis is generally better than with HCC.
**Hepatoblastoma**

Hepatoblastoma arise from primitive cells of various cell lines including foetal or embryonic stage hepatocytes. As the most common primary liver cancer in early childhood, hepatoblastoma occur before the age of two in most cases, and rarely in children after five years. AFP levels are markedly elevated and features of sexual precocity may be present as a result of ectopic gonadotropin synthesis. The tumour growth can be rapid, leading to rupture, haemorrhage and death.

**Mesenchymal tumours**

The two main mesenchymal liver tumours are epithelioid haemangioendothelioma and angiosarcoma, which are low- and high-grade malignant vascular neoplasms, respectively. Both are associated with high rates of regional and distant metastases. Angiosarcomas in particular commonly lead to liver failure and liver rupture and intraabdominal haemorrhage.
2.1.1.2 Diagnostic coding of primary liver cancer

WHO International Classification of Diseases

The World Health Organization International Classification of Diseases (ICD) is the international standard that is used to code for primary liver cancer and its subtypes. The versions are updated with developments in scientific understanding and diagnostic practices. While these are common standards used internationally, it is important to be aware that cancer registries, hospital informatics departments and government agencies may be coding using different ICD versions. Updated versions may also take time to be applied by each organisation. The relevant diagnostic codes for this study are listed below.

Of particular importance is the change from ICD-9 to ICD-10. ICD-10 was endorsed for use in 1990 but may be applied by different registries at a later date. In ICD-9, primary liver cancer is simply divided into three groups: primary liver, intrahepatic bile ducts and unspecified. In ICD-10, the subtypes are given different codes.

**ICD 9**

- 155.0 Malignant neoplasm of liver, primary
- 155.1 Malignant neoplasm of intrahepatic bile ducts
- 155.2 Malignant neoplasm of liver, not specified as primary or secondary

**ICD 10**

- C22.0 Liver cell carcinoma
- C22.1 Intrahepatic bile duct carcinoma
- C22.2 Hepatoblastoma
- C22.3 Angiosarcoma
- C22.4 Other sarcomas of liver
- C22.7 Other specified carcinomas of liver
- C22.8 Malignant neoplasm of liver, primary, unspecified as to type
- C22.9 Malignant neoplasm of liver, not specified as primary or secondary.
International Classification of Diseases for Oncology

This was developed to provide greater detail for the classification of neoplasms and is used by cancer registries in addition to the ICD coding. ICD-O is currently in its third edition (since 2001) called ICD-O-3.

There are two axes of coding to describe a tumour:

• Topographical code, which describes the anatomical site of origin
• Morphological code, which describes the cell type (histology) and behaviour (malignant or benign)

For primary liver cancer, the relevant ICD-O-3 codes are:

Topographical code

C22.0 Liver
C22.1 Intrahepatic bile duct

Morphological code

<table>
<thead>
<tr>
<th>Benign</th>
<th>8170/0 Liver cell adenoma</th>
</tr>
</thead>
<tbody>
<tr>
<td>Malignant</td>
<td>8170/3 Hepatocellular carcinoma, NOS</td>
</tr>
<tr>
<td></td>
<td>8171/3 Hepatocellular carcinoma, fibrolamellar</td>
</tr>
<tr>
<td></td>
<td>8970/3 Hepatoblastoma</td>
</tr>
<tr>
<td></td>
<td>8020/3 Carcinoma, undifferentiated, NOS</td>
</tr>
</tbody>
</table>
2.1.1.3 Clinical features

Patients with HCC can present either symptomatically or asymptotically, each of which can occur in a number of contexts.

Symptomatic presentations can range from the indolent symptoms associated with the tumour (fatigue, loss of weight, vague abdominal discomfort or pain, palpable abdominal mass) to the life-threatening complications such as variceal bleeding or intra-abdominal bleeding from HCC tumour rupture. More often than not, patients present with symptoms of their underlying cirrhosis and decompensation (ascites, encephalopathy, variceal bleeding, spontaneous bacterial peritonitis etc.) rather than that directly attributable to HCC. Other times, the HCC may precipitate decompensation in patients who have undiagnosed cirrhosis, leading to diagnosis of cirrhosis and its underlying cause, such as untreated (and undiagnosed) viral hepatitis.

An increasing number of patients are presenting asymptotically, with HCC diagnosed incidentally by imaging, via HCC surveillance programs or general screening as part of initial workup in patients recently diagnosed with viral hepatitis. A comparison of two cohorts of HCC patients presenting to an Australian tertiary hospital showed that symptomatic presentations had dropped from 100% in the 1975-1983 cohort to 58% in the 1995-2002 cohort.\(^\text{27}\)
2.1.2 Diagnosis

2.1.2.1 Serum tumour markers

Alpha fetoprotein (AFP) is the most widely used biomarker for HCC. It is normally produced by the yolk sac and foetal liver in gestation at high levels but declines after birth. In adults, AFP can become elevated in HCC and gonadal tumours. Used as a diagnostic test in chronic liver disease, it has a sensitivity of 60% and specificity of 80% at the cut-off level of 20 ng/mL.\textsuperscript{28} A higher cut-off level of 400ng/mL brings the specificity beyond 95% with loss of sensitivity (15%)\textsuperscript{29,30} but in patients at high-risk for HCC, this was considered specific enough to be diagnostic.\textsuperscript{29} While it has now been removed as a diagnostic test from some guidelines, a high degree of elevation remains a useful adjunct to imaging that may be suggestive but not quite diagnostic of HCC. AFP level has also been used to exclude patients from liver transplantation prioritisation, with levels greater 1000ng/mL associated with higher risk of recurrence.\textsuperscript{31,32}

False positive elevations of AFP (for diagnosing HCC) can occur with acute or chronic viral hepatitis, especially when there is a high degree of transaminitis.\textsuperscript{33} It can also be elevated in pregnancy, with gonadal tumours\textsuperscript{34} and with some cancers, including gastric cancer.\textsuperscript{35} Conversely, false negatives are even more common as many HCCs do not secrete AFP; serum AFP levels are normal in up to 40% of small HCC.\textsuperscript{36}

Despite its development as a diagnostic test, AFP is now mainly used in surveillance of HCC with some contention. This is discussed further in Section 0.

Other serum markers found to be elevated in HCC include microRNA expression, des-gamma-carboxy prothrombin, lens culinaris agglutinin-reactive AFP and glypican-3 but additional data is required before they can be recommended for use in HCC diagnosis.
2.1.2.2 Ultrasound

Ultrasound is a convenient, readily available, non-invasive test often used in the first line work-up for HCC. Clinicians request liver ultrasounds in a number of contexts including: investigation of abnormal liver function tests, symptomatic presentation with abdominal pain, anorexia and jaundice, and of course, in the surveillance for HCC in high risk patients.

On ultrasound with B-mode imaging, HCC may be seen as a hypodense lesion which of itself is non-specific. Features such as irregularity, the presence of a feeding vessel, distortion of the surround liver architecture, size and number of lesions and evidence of cirrhosis and/or portal hypertension increase the likelihood of HCC although these are also not diagnostic. It may also be useful in providing other information for known HCC, such as patency of hepatic blood supply, vascular invasion or used intraoperatively to assess for small satellite lesions.

Ultrasound is operator-dependent and hence accuracy may vary between different centres based on experience and volume. Optimal views may be difficult to achieve with lesions under the diaphragm, excessive overlying bowel gas or in obese patients. A systematic review of 14 ultrasound studies found a pooled sensitivity of 60% (95% CI 44-76) and specificity of 97% (95% CI 95-98) for the detection of HCC compared to histology from biopsy or resection specimen. However, it should be noted that most of the studies analysed used ultrasound in the surveillance rather than diagnostic setting.

The use of ultrasound in HCC surveillance is discussed in Section 0. Ultrasound used in diagnosis with contrast enhancement is discussed in Section 2.1.2.5.

2.1.2.3 Computed tomography (CT)

CT imaging has become the first-choice diagnostic test for HCC in most centres. It is usually employed following the finding of a non-specific lesion on ultrasound or screening CT (often non-contrast, or portal-venous contrast without arterial phase).

Like other contrast-enhanced dynamic imaging modalities discussed below, CT imaging of the liver is reliant on the typical pathological feature of HCC angiogenesis. Tumours induce angiogenesis to facilitate their growth, such that HCC are preferentially supplied by branches of the hepatic artery, unlike the normal liver which
is supplied by the portal vein. Consequently, in the arterial phase of a contrast-enhanced CT, intravenous contrast will first reach the liver via the hepatic artery. This causes enhancement of the tumour, which is hyperdense compared to the normal liver. In the portovenous phase, contrast reaches the liver via the portal vein, by which time the arterial contrast has cleared the tumour. Now, the normal liver is hyperdense compared to the unenhanced tumour, creating an effect called ‘washout’. Depending on the degree of tumour differentiation (and angiogenesis), this washout may not occur until shortly after the portovenous phase, called the delayed phase.

This imaging characteristic of arterial enhancement and portovenous/delayed washout is diagnostic for HCC in the context of a high-risk patient (cirrhosis or chronic hepatitis B), according to international guidelines. Poorly differentiated HCC or advanced diffuse tumours that have distorted the surrounding anatomical structures may not exhibit this characteristic enhancement. In these cases, a second dynamic imaging modality or biopsy may be required for diagnosis.

Optimal diagnostic accuracy will require a number of factors: correct timing of intravenous contrast injection, an appropriately sensitive modern CT with sufficient multidetector and power, and high-resolution acquisition with thin <5mm sections for reconstruction. This can produce a single lesion sensitivity of 65% and specificity 96%. For smaller lesions less than 2cm, sensitivity is reduced to 40%. In lesions larger than 2cm, the positive predictive value was 92% in a study of cirrhotic patients having work-up for liver transplantation.

For this reason, it has been recommended that diagnostic CTs for HCCs be performed at experienced centres with adequate protocols. Patients with poorer quality CT scans performed in the community may require repeat imaging.

Contraindications for CT include an allergy to iodine-based contrast (that can range from hives to anaphylaxis in severity), and relative contraindications in chronic kidney disease (eGFR < 30ml/min). Irradiation has been a concern with the use of CT, which in modern CT scanners, is about 15mSv to assess a liver lesion. This is equivalent to approximately five years of natural background radiation. While a concern for younger patients in other diseases, the risk of radiation-induced oncogenesis is unlikely to be clinically significant in older patients who are already expose to mortality risks from cirrhosis and HCC.
2.1.2.4 Magnetic resonance imaging (MRI)

Contrast-enhanced MRI is increasingly being used in HCC diagnosis due to its high sensitivity and specificity without ionizing radiation and nephrotoxic contrast agents, although issues of availability and funding are barriers to it being the preferred choice.

For the diagnosis of HCC, the sensitivity of MRI is 72% and specificity 87% overall, with reduction of sensitivity to 47% for lesions smaller than 2cm. In cirrhotic patients being evaluated for liver transplantation, the positive predictive value for detecting an HCC greater than 2cm is 93%. A meta-analysis found a pooled sensitivity of 86% (95% CI 79-91 percent) and specificity 89% (95% CI 83-93 percent) compared with histopathologic findings.

To achieve its diagnostic accuracy, MRI also requires dedicated liver images taken with correctly timed contrast administration and appropriate section thickness. Moreover, MRI requires greater experience in interpretation and thus should be performed at higher volume centres that also manage HCC. Currently, the Australian Medical Benefits Schedule does not reimburse diagnostic MRI imaging for liver lesions, which limits access due to high cost to the patient or hospital funding the test.

Gadolinium is the main contrast agent used in MRI imaging, and the basis for its HCC specificity is related to the preferential blood supply of HCC, as previously discussed for iodine-based contrast CT. Gadolinium-enhanced MRI has the benefit of being well tolerated with lower risk of contrast allergy (and no cross-reactivity with iodine-base contrast).

However, as gadolinium is almost exclusively renally cleared, its use in chronic kidney disease (eGFR <30ml/min) may still be a concern. While not directly nephrotoxic, deposition of accumulated gadolinium may cause nephrogenic systemic fibrosis in 2.4% to 2.9% of those with end-stage renal failure.

Claustrophobia may also be an issue as patients are required to lie still in the scanner for 30-40mins, in addition to holding their breath for 20-25 seconds; otherwise poor image quality may reduce sensitivity. Like with all MRI imaging, patients with permanent pacemakers or other metal devices are contraindicated.

Gadoxetate is an alternative MRI contrast that is taken up by hepatocytes and excreted through the biliary system (rather than renal excretion by gadolinium which
remains in the extracellular space). An additional hepatobiliary delayed phase image is taken to capture this contrast take up. Normal hepatocytes show enhancement whereas malignant cells are hypointense, having loss this capability. However, in patients with impaired biliary excretion (elevated bilirubin), non-malignant cells may also be affected, reducing test accuracy.

The addition of a gadoxetate-enhanced MRI to evaluate patients with HCC diagnosed by CT has been show to pick up additional nodules in 16% of patients. This retrospective study of 700 patients with single nodular HCC detected on CT, of which half had additional gadoxetate-enhanced MRI, found that the MRI group also had significantly lower rate of recurrence (HR 0.72, 95%CI:0.54-0.96) and overall mortality (HR 0.65, 95%CI: 0.44-0.96).

### 2.1.2.5 Contrast enhanced ultrasound

Contrast-enhanced ultrasound (CEUS) is another dynamic imaging modality that may have a role in the diagnostic algorithm. The intravenous contrast is observed in real-time to preferentially enhance the tumour compared to the surrounding tissue, with a subsequent wash-out in the portovenous phase, in a similar way to contrast enhanced CT or MRI. It may be particularly useful for patients who have contraindications to CT (renal failure, contrast allergy) or MRI (pacemakers, claustrophobia, agitation) or where such other modalities are unavailable due to cost or geography. However, the technique is even more highly operator dependent than B-mode ultrasound with experience required for adequate diagnostic performance. Further, as the contrast injection and tumour effect occur in real-time, only a single lesion can be assessed via the correct ultrasound view before the contrast has passed through. Thus, its role is to add diagnosis for a known lesion, but it cannot exclude the presence of other lesions in the liver. Nevertheless, for the characterisation of a previously seen lesion on non-contrast ultrasound, CEUS is very accurate in diagnosing HCC with sensitivity 90% and specificity 97% with a positive predictive value of 97% in chronic liver disease. In lesions less than 2cm, the sensitivity is reduced to 70%.44,45
2.1.2.6 Biopsy

The liver biopsy has traditionally been the gold standard for diagnosis of HCC in the same way that histological diagnosis is required for most solid organ tumours. In addition to confirming the diagnosis, histology provides information on degree of differentiation, microvascular invasion and possibly the nature and severity of underlying liver disease if adequate non-tumour tissue is also sampled.

However, beyond the risks of invasive procedures such as bleeding, other iatrogenic injury (1.5–2.6% in cirrhosis)\(^46\) or even death (9 per 100,000 procedures)\(^47\), liver biopsy in HCC can also rarely cause tumour seeding beyond the primary site along the tract of the biopsy needle. A systematic review showed that this risk was about 2.7% (95% CI 1.8 – 4.0%).\(^48\) The other less recognised risk with liver biopsy is that of false negative, which can occur with smaller lesions less than 2cm, with resulting diagnostic yield of only 70%\(^49\).

The advent of increasingly accurate imaging technology has enabled the use of clinical and radiological features as sufficient basis for HCC diagnosis without the need for biopsy (Section 2.1.2.7). Less than 5% of HCCs are now diagnosed by liver biopsy.\(^50\) Within this new diagnostic algorithm, biopsy is indicated where there remains diagnostic uncertainty following dynamic imaging with CT and/or MRI. This may be in patients without high risk for HCC (e.g. non-cirrhotic) or with suspicion for ICC (e.g. atypical imaging, elevated CA 19-9) or metastatic disease.

2.1.2.7 Diagnostic algorithm

The diagnostic algorithm for HCC begins with the identification of a non-specific liver lesion by ultrasound or other imaging modality. This may occur on initial work-up for a clinical presentation with symptoms or abnormal bloods tests, by incidental finding during investigations for an unrelated condition or by surveillance of patients at high risk for HCC. This latter context (surveillance) is discussed in detail in Section 2.2.3.10.

Current diagnostic guidelines from the international liver societies\(^31,51,52\) recommend that liver lesions greater than 1cm in patients with cirrhosis be investigated further with a dynamic cross-sectional imaging such as with a contrast-enhanced multiphase CT or MRI. If the lesion does not show the typical arterial enhancement
and washout which is diagnostic of HCC, then a second dynamic imaging test should be performed. If the imaging characteristic remains atypical, then a biopsy of the lesion is recommended. With relatively small lesions between 1cm and 2cm, the biopsy yield is lower and so observation and repeat imaging in 3 months is an alternative.

For lesions less than 1cm at initial detection, diagnostic accuracy of imaging and biopsy is lower. Hence, short interval observation with 3 monthly ultrasounds to assess for growth is suggested for up to 2 years. If there are no changes over this period, the patient may return to routine 6 monthly surveillance if they fulfilled initial surveillance criteria for high HCC risk. Conversely, any changes such as growth of the original lesion, further lesions identified or rising AFP should be investigated with CT or MRI.

This diagnostic algorithm is widely used by physicians and multidisciplinary teams in the management of HCC. It tends to be applied to all patients at high risk of HCC, especially patients with indication for HCC surveillance, including non-cirrhotic patients with chronic HBV infection. It should be noted that this diagnostic algorithm, has not been validated in groups without cirrhosis. Nevertheless, the high risk associated with non-cirrhotic HBV patients translates to a sufficient pre-test probability to extend the algorithm to these groups.\textsuperscript{38}
2.1.3 Staging

Staging of cancer helps to guide assessment of outcomes, direct therapeutics and provide a means of comparison for clinical trial design and analysis. Where staging for most cancers is focused on tumour burden (histology, appearance and anatomical spread of the tumour), staging in HCC is also dependent upon the severity of liver disease and the functional reserve of the liver.

Liver dysfunction

The functional capacity of the liver in chronic liver disease may be classed according to Child-Pugh scores, MELD scores or simply as compensated or decompensated. Regardless of the classification system, the severity of liver dysfunction affects prognosis even without HCC. For example, patients with Child-Pugh C cirrhosis (without HCC) have a survival rate of less 45% at 1 year\(^5\) with medical management. As such, liver failure becomes a competing cause of mortality when HCC is also present.

Surgical risk is also influenced by liver dysfunction; Child Pugh C cirrhotic patients have a mortality rate of 82% with abdominal surgery.\(^5\) Similarly, the patients ability to tolerate a proposed HCC treatment is determined significantly by the degree of liver dysfunction.

Disease extent

Unlike with many solid organ cancers, assessing for disease extent (extrahepatic spread) is not routine for HCC. Instead, the decision is individualised, dependent upon the treatment offered and patient and tumour features. For patients planned for liver transplantation, extrahepatic disease exclusion is mandatory. For example, the Organ Procurement and Transplantation Network in the US requires contrast-enhanced CT abdomen and chest, and a bone scan if there are skeletal symptoms\(^5\) to exclude spread to these three most common areas (lung, abdominal lymph nodes and bone). This is based on a Korean study of 381 patients newly diagnosed with HCC who underwent a chest X-ray, CT chest and bone. Metastatic disease detected on bone scan was also
seen on chest X-ray or CT in most cases. Overall, only 3 patients had a shift of their BCLC stage from BCLC-B (localised disease) to BCLC-C (extrahepatic disease).\textsuperscript{56}

For patients having surgical resections, the decision for further staging investigations may be based on tumour number, size and location, the extent of intended resection and other patient factors. Risk of extrahepatic disease is higher in patients with larger tumours (>5cm), subdiaphragmatic tumour location or with vascular invasion; these patients warrant additional staging imaging. Routine assessment for extrahepatic spread occurs less commonly with ablative procedures and is uncommon with palliative therapies such as TACE or systemic therapy.

**Staging systems**

Several staging systems have been proposed in HCC management that takes into account tumour burden and severity of liver dysfunction to define prognosis and guide treatment options. Each has been developed in different patient populations, and then validated extensively by other studies. However, there is no agreed consensus on the use of any specific system. The variables used in each system can be broadly divided into four categories:

- Tumour factors (tumour size, number, AFP level, portal vein invasion, nodal or metastatic spread)
- Global health of the patient (performance status)
- Underlying liver function (bilirubin, albumin, Child-Pugh score, portal hypertension)
- Specific intervention recommended for each stage

**TNM (Tumour, Node, Metastasis) staging system**

Developed by the American Joint Committee on Cancer and the Union Internationale Contre le Cancer, the TNM system is widely used in many solid cancer staging. In HCC, in addition to the standard variables included in descriptors of tumour and anatomical spread, a two-tier fibrosis score has been added – F0 for early fibrosis, and F1 for advanced fibrosis/cirrhosis. The TMN system has been validated in large
surgical cohorts in resection and post-transplantation with five year survivals: T1/F0 64%, T1/F1 49%, T2/F0 46%, T2/F1 30%, T3/F0 17%, and T3/F1 9%. However, while useful in patients offered surgical resection, an important limitation of the TNM system is that it does not account for liver dysfunction which is likely to impact survival outcomes. The surgical cohorts used in its validation are also biased as patients with severe liver dysfunction would have been excluded from surgery.

**Okuda staging system**

Developed in 1985 by a Japanese group Okuda et al, this was the first system to include variables measuring liver function; its parameters are based on tumour size, presence of ascites, serum bilirubin and albumin. However, each parameter is only two-tiered, splitting patients into very advanced disease, and intermediate disease (e.g. tumour variable is either less than or greater than 50% involvement of the liver), such that it has poor discriminatory value for earlier stages. In Stage I patients, with all four parameters at their lower tier, median survival was only 8.3 months without treatment. The Okuda system has not been prospectively validated but compared with other system, it has lower predictive capacity.

**Cancer of the Liver Italian Program (CLIP) scoring system**

This is a prognostic index derived from a retrospective analysis of 435 patients with HCC treated at 16 Italian centres from 1990 to 1992 to assess factors associated with overall survival. The multivariate Cox model found four independent predictive factors of survival: Child-Pugh stage, tumour morphology, AFP and portal vein thrombosis. CLIP scores of 0, 1, 2, 3 and 4-6 were associated with 2-year survival rates of 65%, 45%, 17%, 12% and 0%, respectively, after external validation and found to be superior to the Okuda and TNM systems, especially for non-surgical treatments. Conversely, it lacks discriminatory ability in the smaller CLIP scores (1-3) which would apply to patients undergoing curative therapies such as surgical resection or liver transplantation. Some groups have attempted to modify the CLIP score with MELD score instead of Child-Pugh score which may improve its ability to predict outcomes for patients treated with loco-regional therapy.
Japanese Integrated System (JIS)

A number of retrospective studies developed a scoring system based on TNM staging, with the addition of Child-Pugh score, MELD score or other marker of liver disease severity, resulting in good prediction of prognosis. However, these studies were conducted on Japanese patients, whereas other studies using Western patients did not reach the same conclusion.

Barcelona Clinic Liver Cancer (BCLC) Staging System

The BCLC staging system is the most widely referenced of the various HCC prognostic staging systems, with endorsement by the American and European liver societies. It was introduced by Llovet et al in 1999 with the model containing four components: Tumour size/number/spread, Child-Pugh score, presence of portal hypertension and the Eastern Cooperative Oncology Group (ECOG) performance status, which is commonly used in oncology. External validation by large comparison studies have shown it offers the best discrimination for HCC prognosis, especially in early and intermediate stage HCC. It has been used to stratify patients for choice of treatment in major prospective clinical trials.

Based on the four components mentioned, patients are assigned to one of five stages with the following characteristics:

- Stage 0 – very early stage, single HCC <2cm, well compensated liver disease without portal hypertension
- Stage A – early stage, single HCC <5cm or 3 lesions each <4cm, Child-Pugh A or B
- Stage B – intermediate stage, single large HCC >5cm, multifocal (> 3 lesions), Child-Pugh A or B
- Stage C – advanced stage, symptomatic (ECOG 1 or more), vascular or extrahepatic spread
- Stage D – terminal stage, Child-Pugh C, ECOG >2
The BCLC staging system is unique to other systems in its linkage of each stage with a suggested treatment option and estimated survival rate based on published studies. However, there are still gaps that are not addressed, namely, liver transplantation for patients who have small HCC with Child-Pugh C class, or for expanded liver transplant criteria for larger tumours.\textsuperscript{70}
2.1.4 Treatment

2.1.4.1 Multidisciplinary care

HCC disease is complex and management involves many specialties from diagnosis to treatment and subsequent follow-up. The gastroenterologist/hepatologist and radiologist are mostly present throughout the process with contributions from surgeons, medical oncologist, radiation oncologist and palliative care physicians at various stages appropriate to the treatment offered. Multidisciplinary care allows for peer input so that recommendations are less biased by one provider’s expertise and decisions are made for optimal therapy of the patient.

As HCC occurs mostly in cirrhosis, patients are at risk of developing complications either as a result of ongoing chronic liver disease or following HCC treatment. Patients may also require antiviral therapy for HBV or HCV infection and endoscopic screening for oesophageal varices. Hence, the wholistic team approach provides comprehensive care to manage the underlying liver disease simultaneously with treatment of HCC.

A recent study of 3988 patients with HCC treated by the US Veterans Administration health network found that patients reviewed by a multidisciplinary tumour board had reduced mortality (HR 0.83, 95%CI 0.77 – 0.90).\textsuperscript{71}

Similarly, a study comparing outcomes at one US institution prior to and after the establishment of a multidisciplinary HCC clinic found that patients treated in the latter period received earlier treatment and had better overall survival (HR 2.5, 95% CI 2 – 3).\textsuperscript{72} After adjusting for BCLC stage and treatment given, multidisciplinary care remained an independent predictor of better survival with median survival 13.2 months compared with 4.8 months (p=0.005).

However, comparisons between HCC patients treated before and after the establishment of a multidisciplinary HCC need to be interpreted cautiously given the improvements in treatments and outcomes in the recent era. This is despite adjustments for stage and treatment, since advances within treatment modalities and other aspects of liver disease management have also contributed to improved survival over time.

An Australian single institution study addressed this issue in a study of patients with HCC treated at the Royal Darwin Hospital. Parker et al\textsuperscript{73} found no significant survival difference between patients presenting after the establishment of the
multidisciplinary service (2006-2011), compared to those before (2000-2005). However, less than half of the patients in the second period were actually managed through the service. Comparing between those managed and not managed by the service in the second period, on multivariate analysis, management by the multidisciplinary service was the only significant predictor of survival, adjusted hazard ratio 0.35 (95%CI: 0.16–0.81).

### 2.1.4.2 Treatment overview

The treatments for HCC can broadly be divided into two main groups based on either curative or palliative intent. Curative treatments, which include surgical resection, ablation therapies and liver transplantation, are aimed at cure, although recurrence is common and long-term survival is dependent upon many factors, discussed in Sections 2.1.4.3-5. In contrast, treatments traditionally grouped as palliative (Sections 2.1.4.6-9) are aimed at disease control, recognising that prolonging survival is the objective rather than seeking cure which is no longer possible at that stage.

However, this latter palliative-intent category of therapies is quite heterogenous, with treatments varying from transarterial chemoembolisation with reasonable survival gains to the other extreme where only best supportive care can be offered.

Further, downstaging can occur whereby disease regression induced by a palliatively intended therapy then allows curative intent treatments to be attempted. This somewhat blurs the border between these traditional intent-named categories. This is discussed further in each therapy section.
2.1.4.3 Surgical resection

Surgical resection is an HCC treatment option with high curative potential, with 5-year survival rates up to 90% in highly selected patients. It is the optimal therapy for patients with low tumour burden, absence of vascular invasion and portal hypertension and adequate functional liver reserve. However, as HCC occurs mostly in cirrhosis, which increases surgical mortality risks proportional to the degree of liver dysfunction, and also presents more commonly in late tumour stage, the operative window to achieve this benefit is small. Only 15-30% of patients have potentially resectable disease in low-incidence regions, and this is even lower in high-incidence regions (10-15%). The implementation of HCC surveillance in high risk patients improves earlier stage detection, thus providing opportunity for curative resection. See Section 2.2.3.10.

The decision for surgical resection is dependent on two major issues: 1) the anatomical extent of HCC, i.e. the exclusion of extrahepatic spread, and 2) the risk of operative morbidity and mortality based on the lesion size and location, considering the patient’s underlying liver disease and function.

Thorough assessment of disease extent is important as many patients initially referred for surgery do not have resectable disease. Dynamic contrast-enhanced cross-sectional imaging with CT and MRI provides both diagnosis of HCC (Section 0) as well as tumour characterisation and liver anatomy for surgical planning. Laparoscopic examination and ultrasonography can help define disease extent and avoid a laparotomy for more than half of patients with eventual unresectable disease.

While there is no general rule regarding tumour size and resectability, most surgeons prefer to restrict resection to tumours less than 5cm in size. Studies regarding tumour size have found that lesions less than 5cm had better 5 year survival (47% versus 28% in lesions more than 5cm, p<0.0001) whereas lesions larger than 10cm had a lower 5 year survival of 27%.

Equally important is the assessment of hepatic reserve as few (5-15%) patients have enough hepatic reserve for resection at the time of first presentation with HCC. Surgical mortality is twice as high in cirrhotics compared to non-cirrhotics (10% vs 5%), especially with decompensated (Child-Pugh B or C stage) cirrhosis. In general, patient who have decompensated with complications of cirrhosis (ascites, bleeding, or
marked portal hypertension) are deemed to have insufficient hepatic reserve for resection. Even Child-Pugh A patients who are generally considered compensated patients can decompensate following resection, as one study found, where 38% developed liver failure that was still unresolved three months after HCC resection.\textsuperscript{80}

In cirrhotic patients being considered for resection, functional reserve can be estimated using hepatic volumetry to determine the post-resection volume. Some units, especially in Asia, use the elimination of indocyanine green to select for residual synthetic function. Other groups have used hepatic vein wedge pressure to assess for portal hypertension.\textsuperscript{80}

If the volume is considered insufficient for resection, portal vein embolisation (PVE) may be used to cause hypertrophy of the unaffected liver lobe (future remnant), prior to resection of the affected segment/s. This technique is used for surgical resection for other liver malignancies, including ICC and liver metastases. A meta-analysis of 37 studies of 1088 patients (265 HCC) undergoing PVE prior to resection found that PVE increased the liver volume by 10-12\% four weeks after the procedure, allowing 85\% to proceed to laparotomy for major hepatectomy. Post-resection complications included transient liver failure in 2.5 \% and death from acute liver failure in 0.8\%.\textsuperscript{81} A single institution retrospective study reported outcomes for 21 patients having PVE compared to 33 who did not.\textsuperscript{82} The PVE group had better outcomes than those who did not with fewer major complications, no 90-day mortality, and better overall survival at three years (82\% with PVE, 63\% without PVE), although this was not statistically significant, possibly owing to small study numbers.

Several types of resections are performed depending on the location of the lesion(s) and the severity of cirrhosis. The traditional anatomical resections are performed along anatomical planes to remove whole liver segments. This is thought to provide more complete removal to reduce recurrence risk and improve survival. Non-anatomical resections aim to remove the least amount of tissue to preserve liver function which is critical in cirrhosis. A large retrospective study of 658 propensity matched HCC patients who either had anatomical or non-anatomical resections found no difference in HCC recurrence or survival at two years.\textsuperscript{83}

For centrally located tumours in segments IV, V and VIII, the traditional approach was an extended right or left hemi-hepatectomy. This is associated with high morbidity and mortality due to the volume of liver removed, and the complexity of the
procedure because of the location of important central structures. The central hepatectomy (mesohepatectomy) was developed to only resect the central segments, leaving the lateral areas intact. These two approaches were compared in a retrospective study which showed similar short term morbidity and mortality, although the risk of long-term biliary stricture was apparent.\textsuperscript{84}

Laparoscopic hepatic resection is a newer development that aims to reduce the invasiveness of surgery, although it is technically challenging. A systematic review and meta-analysis of 1238 patients from 15 studies found that laparoscopy was associated with reduced postoperative morbidity and blood loss. There was a trend towards more positive surgical margins with laparoscopy but no difference in overall survival and recurrence-free survival at one, three and five year outcomes.\textsuperscript{85}

Postoperative mortality rates, ranging from 4 to 7\% at 30 days,\textsuperscript{86,87} are dependent on the extent of the resection and the underlying liver disease. However, most deaths result from liver failure rather than operative complications.\textsuperscript{88} As many patient deaths occur after 30 days, a growing consensus suggests that 90 day mortality rates would be more informative.\textsuperscript{87}

Similarly, long-term outcomes are related to resection extent (tumour features) and residual liver function. The best outcomes have been in patients with solitary lesions without vascular invasion and clear surgical margins of >1cm, with five year overall survival rates as high as 75\%,\textsuperscript{89} and 93\% in small lesions (<2cm) with early stage histology.\textsuperscript{90} Five year overall survival rates have improved even after major hepatectomy from 30\% in 1981-1989 to 51\% in 2000-2008.\textsuperscript{87} In contrast, long term survival rates remain poor for patients with decompensated liver disease and larger tumours with 5 year survival at 27\%.\textsuperscript{77} Non-cirrhotic patients do very well with four year overall survival rates of 81\% compared to 35\% in cirrhotic patients, in one series of 295 Japanese patients.\textsuperscript{91} The reasons for this may be related to both better liver function (hence fewer competing causes for mortality) and the fact that HCC is more commonly multi-centric in cirrhosis.
2.1.4.4 Liver transplantation

Liver transplantation is a curative option for patients who have unresectable disease. In most cases, surgical resection is contraindicated because of surgical mortality risk associated with severe liver dysfunction. In some cases, for larger tumour volume, resection is contraindicated due to lack of post-operative functional liver reserve.

However, liver transplantation itself is limited by extent of tumour burden to reduce the risk of post-operative recurrence. The Milan criteria, developed by Mazzaferro et al\textsuperscript{5} and now applied at most liver transplant centres, defines this upper limit of tumour burden to be:

- A single HCC less than 5cm, or
- Three or fewer lesions, each less than 3cm
- Absence of gross vascular invasion, regional nodal or distal metastases

This seminal study was relatively small, with only 48 patients studied of whom 35 patients were transplanted within this pre-determined criteria, and 13 patients had tumour burden beyond these limits. The four year overall survival rates were 85\% and 50\%, respectively (\(P=0.01\)).\textsuperscript{5}

However, some believe that the Milan criteria was too limiting, excluding patients who could benefit. A group from the University of California, San Francisco (UCSF) expanded the criteria to include:\textsuperscript{70}

1. A single HCC less than 6.5cm, or
2. Three or fewer lesions, the largest being less than 4.5cm, and the cumulative tumour size (sum of lesion diameters) being less than 8cm.

Patients receiving transplantation using this UCSF criteria had outcomes comparable to those from the Milan study, with 1 and 5 year survival rates, 90\% and 75.2\%, respectively, although this study similarly had low patient numbers (\(n=70\)).\textsuperscript{70}
Patients who had tumour burden beyond even this expanded criteria were found to have significantly lower 1 year survival rate at 50% (P=0.0005).

Other studies, including Mazzaferro from the original Milan study, agreed that treatment criteria may be expanded. In a retrospective analysis of 1556 patients who underwent transplantation for HCC, Mazzaferro et al\(^9\) found that 283 patients transplanted outside Milan criteria but without microvascular invasion and with a cumulative tumour size of up to 7cm had similar 5 year overall survival (71.2%, 95%CI: 64.3-77.0) compared to 444 patients transplanted within Milan criteria (73.3%, 95%CI: 68.2-77.7). In contrast, 454 patients transplanted outside Milan criteria with microvascular invasion had lower 5-year overall survival (53.6%, 95%CI:50.1-57.0).

French authors present another expansion criterion called the 5/5 criteria for transplantation in HCC patients with no more than 5 tumours, with the largest tumour no greater than 5cm. In a retrospective study of 110 patients who underwent liver transplantation from 1990-2005, they found that 5 year survival rates were comparable between Milan, UCSF and 5/5 criteria, at 77%, 68% and 77%, respectively.\(^9\)

Another large study\(^9\) of expanded criteria of 467 patients transplanted at UCLA medical centre concluded that UCSF criteria was not significantly different in survival outcomes compared to Milan criteria, with 5 year survival rates 61% and 79% (P=0.061), respectively, using pre-operative imaging definitions of extent/size and 71% and 86% (P=0.057, respectively, using explant pathology definitions. However, the trend is readily apparent and could suggest that larger patient numbers may have altered this towards significance.

Indeed, other authors report that expanded criteria beyond Milan is associated with poorer outcomes. In their study of 4482 patients with HCC who were waitlisted for liver transplantation, they performed an intention-to-treat survival analysis for all patients listed, and not just those transplanted. The overall 5-year survival for patients within Milan criteria at listing was 61%, compared to 32% in those exceeding Milan criteria (P<0.0001). An explanation for this discrepancy is that the previously reported favourable results with expanded transplant criteria were retrospective analyses of patients who had already undergone transplantation, thereby excluding those who had been taken off due to tumour progression or death.
The current status is that the Milan criteria remains the benchmark, as recommended by the 2010 International Consensus Conference on liver transplantation for HCC, with some consideration allowed for individual cases within the dynamics of the local waiting list. In Australia and New Zealand, all liver transplant centres have adopted UCSF criteria for HCC.

Due to the finite supply of organs in most populations, transplant waiting list prioritization must be both equitable and clinically appropriate. Liver transplant allocation is based mainly on MELD score which predict survival probabilities with degree of liver dysfunction. However, HCC patients often have minimal liver dysfunction until late in their disease course when their tumour burden has likely progressed beyond transplant criteria. Hence, to rectify this, some transplant centres apply priority MELD points for HCC patients, based on their waiting time, tumour size and number, such as suggested by the US Organ Procurement and Transplantation Network.

In addition to the peri-operative morbidity and mortality risks, and the possible side effects and risks of life-long immunosuppression, HCC patients on the liver transplantation waiting list are at risk of tumour progression. During this process, loco-regional treatment is offered as “bridging therapy” to maintain patients within transplant criteria.

Downstaging is a recent development in which patients who initially exceed the Milan are treated with loco-regional therapy with the aim of offering liver transplantation if their tumour burden recedes within transplant criteria. Most of the data on downstaging has been with the use of TACE or TARE. A systematic review of 13 studies (950 patients) found that downstaging was 48% successful in reducing tumour burden to within Milan criteria, with no difference between TACE or TARE. Post-transplant recurrence after downstaging is low at 16% with good survival, 75% at 2 years.

With these processes in place and with carefully selected patients, liver transplantation for HCC can produce long-term survival rates similar to or only slightly worse than non-HCC transplant indications – at up to 74% overall survival at 5 years, with an 83% recurrence-free rate.
2.1.4.5 Ablative therapies

Ablative therapies may be considered in patients with localised disease and smaller tumours who are not candidates for surgical resection or liver transplantation. These therapies include:

1. Radiofrequency ablation (RFA) in which high-frequency thermal currents are applied via electrodes inserted into the lesion, percutaneously, laparoscopically or by open laparotomy. Outcomes are better for smaller lesions and some clinicians restrict RFA to lesions <4cm in Child-Pugh A or B patients only. Anatomical structures and access may also restrict application of RFA; lesions beneath the diaphragmatic dome, gallbladder injury needs avoidance and large blood vessels may reduce efficacy due to a heat sink effect.

2. Microwave ablation (MWA) is similar to RFA in approach, except that microwave is used, with the advantage of multiple simultaneous ablations possible. MWA has been used in Asian countries for some time and in the West, some centres (including St Vincent’s Hospital, Melbourne) have replaced RFA with MWA.

3. Percutaneous Ethanol Injection (PEI) is an option with small tumours and poor liver function and was the most widely used local treatment for HCC prior to RFA. However, a meta-analysis of prospective randomised trials have shown that thermal ablation has better mortality outcomes than PEI (HR 1.49, 95%CI 1.12-2.79). However, it may still have a role if access to RFA is limited.

4. Irreversible Electroporation (IRE) is a newer non-thermal ablation technique which uses high-voltage/intensity electrical pulses to induce tumour cell apoptosis. However, the little data available comes from studies that include all liver tumours including ICC and liver metastases and have only short-term follow-up.

RFA/MWA can also be used as ‘bridging therapy’ to control progression of HCC in patients awaiting liver transplantation or in ‘downstaging’ of HCC disease initially beyond transplant criteria. It is also used in treatment of recurrent HCC following partial heptectomy.
Compared with RFA, a Cochrane review\textsuperscript{101} of four randomized clinical trials found resection had a non-significant all-cause mortality reduction (HR 0.80, 95\%CI 0.6-1.08) but was better for cancer-specific mortality (HR 0.35, 94\%CI 0.19-0.65). Surgery also had higher adverse events (23\% compared to 1.7\%). However, most clinicians still prefer resection over RFA/MWA for HCC disease within Milan criteria in Child-Pugh A cirrhosis.\textsuperscript{104}

In patients within Milan criteria for liver transplantation, RFA offers five year survival rates of 40 to 77\%, lower in cirrhotic patients excluded from surgery.\textsuperscript{105} Long-term results for MWA are similar with five year survival at 52\%, and significantly better in patients with smaller tumours <4cm.\textsuperscript{106}
2.1.4.6 Transarterial chemoembolisation

In the same way contrast-enhanced diagnostic imaging utilise the specificity of the HCC tumour’s hepatic artery blood supply, transarterial chemoembolisation (TACE) allows the direct delivery of cytotoxic chemotherapy. Using a technique similar to cardiac catheterisation, the tumour is approached via the hepatic artery (usually from a common femoral artery entry). The chemotherapy agent is retained within the tumour with the assistance of lipiodol (a lipophilic contrast agent – conventional TACE) or drug-eluting polyvinyl alcohol microspheres (also called “beads” or drug-eluting beads – DEB-TACE). Both the occlusion of the hepatic arterial supply to the tumour (embolisation) as well as the chemotherapy agent (usually doxorubicin and cisplatin or other combinations) are thought to contribute to the anti-tumour effect. Bland chemoembolisation is also performed where no chemotherapy is used, with reliance entirely on the occlusive effect.

TACE is indicated in patients with large or numerous unresectable HCC confined to the liver, and who are not immediate transplant candidates. If patients are within transplant criteria or waitlisted, TACE is commonly used as ‘bridging therapy’ to keep disease control. For patients beyond transplant criteria, TACE may also downstage lesions to within criteria if the tumour responds. However, in most cases, TACE is a palliative measure to improve survival duration.

Contraindications to TACE mainly relate to the risk of liver failure with further chemotherapy induced liver toxicity, and include decompensated cirrhosis, portal vein thrombosis (high risk of liver failure if both hepatic artery and portal vein supply are impaired), encephalopathy and biliary obstruction.

Consequently, the complications of TACE include common adverse effects such as postembolisation syndrome in 60-80% of patients. This occurs over 3-4 days post-TACE with self-limiting symptoms including fever, nausea, right upper quadrant pain and transient liver function abnormalities, which are thought due to tumour necrosis or ischaemic damage of normal liver tissue. Other complications such as nausea, vomiting and bone marrow suppression may be due to escape of chemotherapeutic agents beyond retention in the liver. More serious complications may include liver failure in 7.5%, though in most cases the hepatic decompensation is reversible.
Efficacy in TACE can be discussed in terms of tumour response as well as survival benefit. Using a greater than 25% reduction in tumour size to define successful response, about 35-40% of patients achieve this. However, since tumour necrosis can be hard to define on imaging, using other surrogate markers such as failure of contrast enhancement or drop in AFP to define successful response brings the rate up to 60% of TACE procedures.

Survival benefit of TACE was dramatic enough to terminate a trial early, with TACE achieving a survival benefit compared to placebo (HR 0.47, 95%CI 0.25-0.91) in a randomised control trial from the Barcelona Liver group in 2002. This result was confirmed by a 2003 systematic review of 14 randomised trials which showed that arterial chemoembolisation showed a significant survival benefit at 2 years (OR 0.53, 95%CI: 0.32-0.89) but bland embolisation did not (OR 0.59, 95%CI: 0.29-1.20).

However, more recent studies have not been as certain regarding the survival benefits of TACE. A 2012 Cochrane meta-analysis of nine randomised trials (645 patients) did not show any significant survival benefit of TACE or bland embolisation over placebo (HR 0.81, 95%CI 0.64-1.02). Four of these trials also included patients with localised disease having resections. Sub-analysis of three trials of advanced HCC patients only showed a better trend towards survival benefit, although still not significant (HR 0.65, 95%CI: 0.40-1.05).

These differing results may be explained by the heterogenous nature of TACE, in its technical application as well as the target population. Clinicians use different techniques of delivery, cytotoxic agents, embolisation agent and degree of vascular selectivity. Patient selection is also very different from transplant candidates on bridging therapy or potential transplant candidates being downstaged, to palliative disease control with varying degrees of liver function.

Despite this, some comparisons have been attempted. In comparing conventional TACE with DEB-TACE, a meta-analysis of 693 in five prospective randomised trials and two retrospective studies found no significant difference in disease control (OR 1.37, 95%CI: 0.95-1.98).
2.1.4.7 Transarterial radioembolisation (TARE)

Transarterial Radioembolisation (TARE), also known as Selective Internal Radiation Therapy (SIRT), is administered via the hepatic artery like TACE. However, the active ingredient is yttrium-90, a radioactive isotope, attached to microspheres which causes tumour necrosis. It is delivered more proximally compared to TACE and thus affects a larger area of the liver at the segment or lobar level. As the microspheres are not embolic in nature, portal vein thrombosis is not a contraindication. Although generally well tolerated, liver-related toxicities can occur in 20% and treatment-related death in 3%. Unlike TACE, it is generally offered as a once-off treatment.

Cohort studies have shown some response in patients with intermediate or advanced HCC with 40% tumour response and median survival of 15 months overall, and 10 months in those with portal vein invasion.

Currently, there are no studies that demonstrate a survival benefit for TARE, and there is no consensus recommendation among the expert groups. The AASLD and EASL have not made any recommendations for TARE, with guidelines acknowledging emerging data that remains inadequate for recommendation. In contrast, APASL and the American Hepato-Pancreato-Biliary Association have recommended that TARE might be considered in patients with bulky tumours, portal vein thrombosis or as downstaging/bridge to curative therapy.

In Australia, TARE is not funded by Medicare and hence access is limited to privately funded patients due to its substantial cost (approximately $10,000).
2.1.4.8 Radiotherapy

The use of radiotherapy in HCC treatment is evolving with development of more precise techniques such as stereotactic body radiotherapy (SBRT) for targeting lesions. Both HCC tumours and the normal liver tissue are radiosensitive, hence there is risk of injury to surrounding liver, which these newer techniques can reduce. Radiotherapy has been used for local control of unresectable HCC in compensated cirrhotic patients; patients with Child-Pugh score of 8 or more have higher risk of liver toxicity. Patients with portal vein thrombosis are ideal candidates if other loco-regional therapies such as TACE are contraindicated. It may also be used for symptomatic bone metastases.

In the largest SBRT study to date, 93 Korean patients with HCC treated with SBRT were analysed with a three year overall survival rate of 53.8%. However, most of the deaths were due to disease recurrence outside of the treated area. Local recurrence-free survival was very high at 92.1% at 3 years, suggesting that SBRT was a good option for local control.

However, due to the lack of good quality evidence for overall survival, the major liver societies have no specific recommendations for the use of radiotherapy in HCC management at this stage.
2.1.4.9 Systemic therapies

Systemic therapies are indicated for patients with advanced HCC which includes vascular invasion, nodal and systemic metastases.

**Sorafenib** is an orally administered small molecule that inhibits RAF kinase and the VEGFR intracellular kinase pathway to inhibit cell growth, induce apoptosis and disrupt tumour microvasculature through anti-angiogenic effects.

The SHARP randomised controlled trial,\(^6^9\) published in 2008, was a phase 3 European (mainly) multicentre trial to assess the efficacy of sorafenib compared to placebo in 602 patients with advanced HCC. The trial was stopped early when interim results showed a survival benefit for sorafenib, with median overall survival 10.7 months compared to 7.9 months in the placebo group (HR 0.69, 95%CI: 0.55-0.87). Time to radiologic progression was also better in the sorafenib group, but there was no difference in time to symptomatic progression. There was also no difference in tumour response, including an absence of complete response in any treated patient. Nevertheless, it was the first agent to show a significant survival benefit, and would remain so for some time as other agents continued to fail.

A follow-up randomised placebo-controlled phase III trial of sorafenib in 226 Asian patients with Child-Pugh A cirrhosis also found a significant survival benefit for sorafenib (median overall survival 6.5 months vs 4.2 months).\(^6^8\) However, while there was a significant difference between the two arms, the magnitude of survival in both was less than in the SHARP trial; in fact, the treatment arm of the Asian study did worse than the placebo arm of the SHARP study. One explanation for this was that the Asian patients had more advanced disease at enrolment and worse performance status. Another explanation might be the differences in the underlying aetiology of liver disease. Sub-group analysis of the SHARP trial and a meta-analysis of three other phase III trials found that median overall survival was better in both sorafenib and placebo arms in patients with HCV (14 months vs 7.4 months, difference 6.6 months) than HBV (9.7 vs 6.1, difference 3.6) and alcohol-related liver disease (10.3 vs 8, difference 2.3); the sorafenib survival benefit within each group was also better with HCV.\(^1^2^2,1^2^3\)

In the clinical trial setting, the treatment was well tolerated with severe grade ¾ adverse events of diarrhoea and hand-foot skin reaction occurring in only 8% of
patients, compared to 1-2% in the placebo group. Overall, the commonest adverse effects were diarrhoea, weight loss, hand-foot skin reactions and hypophosphataemia.

However, the situation appears different in clinical practice. A recent Australian retrospective cohort study assessed the real world outcomes of sorafenib treatment in 320 patients with advanced HCC. The study found that adverse reactions occurred in the majority of patients (77%), requiring dose reduction in 31%. One explanation for this discrepancy is related to the differing level of liver dysfunction between the clinical trial and routine practice settings. Patients in the trial were mostly Child-Pugh A class (95%), with few Child-Pugh B class (5%) and no Child-Pugh C class, whereas in the Australian study, the distribution was 69%, 26% and 4%, respectively. Unsurprisingly, the median survival in this study was low at 5.4 months (IQR 2.8-9.7).

With sorafenib monotherapy recommended by the major liver societies as first-line treatment for advanced HCC, there was interest in sorafenib combination therapy to improve survival. Several randomised controlled trials compared TACE with sorafenib compared to TACE alone in patients with unresectable HCC, Child-Pugh A cirrhosis. There were trends towards survival benefit without statistical significance, although sorafenib was used at sub-optimal doses due to toxicity. Sorafenib has also been used following TACE and liver transplantation (in conjunction with mTOR inhibitors) with some data supporting efficacy albeit with associated toxicity.

**Lenvatinib**, an inhibitor of VEGFR-1/2/3 and other targets, is an alternative first-line treatment for advanced HCC which was shown to be non-inferior to sorafenib in a randomised trial. Lenvatinib had lower rates of hand-foot skin reaction (3% vs 11%) but higher rates of hypertension (23% vs 14%).

**Regorafenib**, similar in structure and mechanism of action to sorafenib, is approved as a second-line agent for patients who have progressed on sorafenib. It was shown to prolong median overall survival compared to placebo (10.6 months vs 7.8 months) in a randomised trial of 573 sorafenib-progressed patients who retained good performance status and compensated liver function.

**Nivolumab** is among the first of the immunotherapy drugs to be approved for second-line therapy in advanced HCC. It is a human monoclonal antibody, which functions as an immune checkpoint inhibitor to restore anti-tumour T cell immune
activity. In a Phase II study of patients with advanced HCC who had progressed on sorafenib or who were intolerant, nivolumab achieved a tumour response in 15-20% of patients and median overall survival was 15 months. It was well tolerated, with the most toxic adverse being abnormal liver biochemistry in 10% with immune-mediated hepatitis requiring corticosteroid treatment in 5%.130
2.1.5 Prognosis and natural history

The prognosis of HCC has been very poor until recent times. Only a few decades ago, most patients died within 1 year of diagnosis\textsuperscript{58} as patients presented late and there were fewer therapeutic options available. The implementation of surveillance of high-risk groups has led to the diagnosis of earlier stage tumours in 30-40% of patients in developed countries.\textsuperscript{131} Curative therapies can be utilised at these earlier tumour stages and has improved survival rates, which depend upon patient and treatment factors as discussed above.

However, for one reason or another, some patients remain untreated. For some, this might be due to advance disease with decompensated cirrhosis such that all treatments are contraindicated. For others, it might be that while options are available, patients choose quality of life rather than prolongation with therapies associated with toxicities.

Khalaf et al\textsuperscript{132} identified 518 patients with untreated HCC in the US Veteran Affairs system and found the median overall survival was 3.6 months. Grouped by BCLC stages, the survival times were 13.4, 9.5, 3.4, and 1.6 months for patients of Barcelona Clinic Liver Cancer stages 0/A, B, C, and D, respectively.

The cause of death in pooled data of 1,673 patients is most commonly liver failure (34%), followed by bleeding (30%), and advanced cancer (24%).\textsuperscript{10} While metastases are often the contraindication to loco-regional therapy, death directly due to metastases is low at 7.6%, in a study of 342 patients with metastatic HCC either at initial presentation or following treatment for local disease.\textsuperscript{133} The authors concluded that control of the local disease and performance status were better prognostic factors than the presence of metastases.
2.2 EPIDEMIOLOGY OF HEPATOCELLULAR CARCINOMA

2.2.1 Pathogenesis and Risk Factors for Hepatocellular Carcinoma

Hepatocellular carcinoma is the predominantly form of primary liver cancer, accounting for 70-90% of total numbers. It arises from the hepatocyte, the parenchymal cell type of the liver. Intrahepatic cholangiocarcinoma makes up the minority 10-20% with other rarer subtypes forming the remainder.

The pathogenesis of HCC is multifactorial, involving a host of environmental, infectious, metabolic, nutritional, genetic and other factors that make it a complex and heterogeneous disease. The majority of HCC occurs in the setting of chronic liver disease, with cirrhosis being a necessary precursor to HCC development. In some types of chronic liver disease, particularly that due to HBV, HCC can also occur in the absence of cirrhosis. This distinction between cirrhotic and non-cirrhotic HCC becomes important in its diagnosis, treatment and prevention.

The relative contribution of particular risk factors to the HCC burden varies according to the incidence of HCC in different regions. In the high HCC incidence regions of Asia and Africa, the predominant risk factors are chronic HBV infection and aflatoxin exposure. Conversely, in low risk regions such as in most developed countries, the major risk factors are chronic HCV infection, alcoholic liver disease and fatty liver disease associated with diabetes and obesity.

Globally, it is estimated that viral hepatitis accounts for approximately 80% of HCC and of these, HBV contributes two-thirds and HCV one-third. This is according to a pooled study of over 250 study populations worldwide of patients with cirrhosis or HCC, with prevalence of serologic markers of HBV or HCV analysed. The authors also found that cirrhosis itself was due to viral hepatitis in 57% of cases (HBV 30%, HCV 27%).

However, some issues exist in attributing the cause of HCC to particular risk factors as many cases have more than one risk factor. In Western countries, chronic hepatitis C is prevalent in the injecting drug use community, where alcoholism is also common. Similarly, fatty liver disease is becoming increasing prevalent in some Asian countries where HBV is also common.
It can also be difficult to distinguish the primary driver from the background risk factor, if such a distinction exists. For example, in a cirrhotic patient with previous heavy alcohol use, current fatty liver disease associated with diabetes as well as HCV, all these factors contribute to HCC risk.

### 2.2.1.1 Cirrhosis

Chronic liver disease has a variety of aetiologies that, individually or in combination, can cause inflammation, fibrosis and architectural distortions leading to cirrhosis, the final common pathway to most cases of HCC. The specific aetiological risk factors of chronic liver disease have different natural histories in their rate and risk of progression to cirrhosis.

Once cirrhosis is established, about one-third of patients will develop HCC in their lifetime, with an annual incidence of 1-8%. The underlying aetiology of cirrhosis also influences the risk of HCC development. In cirrhosis secondary to HBV, the annual HCC risk is 2% whereas in HCV-infected patients the risk is 3-8%.

The severity of cirrhosis, defined by the liver function (such as Child-Pugh score, MELD score), or by the presence of portal hypertension (thrombocytopenia, oesophageal varices) is associated with increased risk of HCC. Portal hypertension was an independent predictor of HCC development with patients having a hepatic venous pressure gradient greater than 10mmHg having a 6-fold increase in HCC risk. The degree of liver stiffness measured using transient elastography was found to be significantly associated with HCC risk (RR 1.11: 95% CI, 1.05–1.18) in a recent meta-analysis.

Conversely, the regression of cirrhosis, is associated with reducing risk. Cirrhosis was previously thought to be an irreversible pathological process but recent studies have shown that treatment of the underlying aetiology of chronic liver disease may lead to fibrosis regression. Long-term viral suppression in CHB with nucleos/tide analogues has been shown to be associated with biopsy-proven reversal of cirrhosis, and fibrosis regression. In HCV-related cirrhosis, following sustained virological response with interferon-based therapy, long term follow-up has shown reduction of HCC risk.
2.2.1.1 Chronic hepatitis B virus infection

Chronic hepatitis B virus (HBV) infection affects about 3.5% of the world’s population (about 257 million people), according to World Health Organisation estimates for 2015.\textsuperscript{143} A recent systematic review and pooled analysis for studies up to 2013 showed a similar worldwide prevalence (3.6%).\textsuperscript{144} The African and Western Pacific regions accounted for 68% of those infected. The regions with highest prevalence are Asia and sub-Saharan African where HBV seroprevalence is between 8-12%, compared to lower prevalence of 0.3-1.5% in Western countries.\textsuperscript{145}

Most infections in high prevalence countries are transmitted perinatally or horizontally in early childhood, whereas in lower prevalence countries transmission by other blood contact such as injecting drug use, sexual contact, tattoos and iatrogenic causes are more common.\textsuperscript{146} The risk of chronicity is higher with early infection (90% in infants, 25-30% in children aged between 1 and 5 years) compared to adult infection which mostly results in acute hepatitis and viral clearance (chronicity in only 5%).\textsuperscript{147}

The evidence for a causal association between CHB infection and HCC is substantial. There is a high correlation between areas with high incidence and mortality from HCC and those with high HBV prevalence.\textsuperscript{148} Conversely, countries with HBV prevalence of greater than 2% have increased incidence and mortality rates of HCC.\textsuperscript{149} Case-control studies have shown that CHB is much more common in HCC cases than controls, with odds ratio between 5:1 and 65:1.\textsuperscript{51} One of the earliest evidence came from the seminal large prospective study of 22,707 men in Taiwan\textsuperscript{150} which found that those with HBV sAg had a liver cancer incidence of 1,158 per 100,000 compared to 5 per 100,000 in non-carriers, with a relative risk of 223. Liver cancer and cirrhosis accounted for more than half the deaths in those with HBV, compared to just 1.5% of deaths in the non-carriers. Similarly, a more recent Chinese study of 90,000 people followed for eight years found the cumulative risks of HCC mortality was 8% in HBV sAg positive men compared to 0.5% in non-carriers.\textsuperscript{151}

Chronic HBV accounts for more than 50% of total HCC cases worldwide and nearly all cases in children.\textsuperscript{135} HBV seroprevalence in HCC varies considerably however, from as high as 70% in Korea, 55% in Greece, to medium levels of 19% in Italy, 10-15% in the United States, to as low as 3% in Sweden.\textsuperscript{148}

The lifetime risk of HCC in those with chronic HBV varies from 10 to 25% depending on a number of factors. The natural history of CHB infection and its activity
state influences HCC risks. Most cases of HBV-related HCC (70-90%) occur in patients with cirrhosis,\textsuperscript{152} with the rest occurring in inactive carriers without liver inflammation, or those with chronic hepatitis without cirrhosis. A systematic review and meta-analysis of 66 studies including nearly 350,000 untreated CHB infected patients found that a compensated cirrhotic state had the highest risk with annual incidence of 2.97%, compared to chronic hepatitis at 0.42% and inactive carrier state at only 0.05%. In Asian subjects however, the annual incidence rates are higher at 3.7%, 0.6% and 0.2%, respectively.\textsuperscript{153}

The higher lifetime risks of Asian and African HBV patients are partly related to longer duration of infection, with most having acquired HBV in early life. This long exposure allows DNA integration of the HBV genome into the liver tissue to activate oncogenes and inactivate tumour suppressor genes. Even after seroconversion and seroclearance (surface antigen negative, with antibodies to surface antigen or core antigen), HBV DNA can still be detected in 10-20% of tumours.\textsuperscript{38} Hence, guidelines recommend the ongoing surveillance for HCC in these patients.

Other viral factors predicting development of HCC include HBV e antigen positivity, HBV viral load and HBV genotype. Cumulative HCC risk in those with e antigen positivity up to age 70 is estimated at 87% compared to 12% in those who are e antigen negative.\textsuperscript{154} However, most patients with high HBV viral load have positive e antigen, and so the greater effect is likely related to the viral load. This was shown in REVEAL-HBV, a Taiwanese prospective cohort study of mostly eAg negative HBV patients (85% were eAg negative) that found a cumulative HCC incidence of 14.9% over a mean follow-up of 11 years for patients with HBV DNA levels greater than 1 million copies/mL compared to 1.3% for DNA levels less than 300 copies/mL. This difference was retained among the e antigen seronegative patients with normal ALT and no cirrhosis, with cumulative incidence 13.5% and 0.7%, respectively.

HBV genotype is also predictive, with genotype C associated with higher HCC risk than the other genotypes due the spontaneous mutations including YMDD mutations, preS deletions, and enhancer/basal core promoter mutations. Genotype C patients are predisposed to higher viral loads, persistent eAg positivity and more aggressive development of cirrhosis.\textsuperscript{155,156} In North America and Western Europe, of the more prevalent genotypes A and D, genotype D is associated with higher HCC
risk.\textsuperscript{148} Other aspects of the HBV viral genome such as the presence of mutations (basal core promoter, precore region) are also independent predictors of HCC risk.\textsuperscript{157}

Treatment of CHB is associated with reduction in HCC risk, from 6.4\% in untreated to 2.8\% in treated patients, in a systematic review of 21 studies including 3881 treated and 534 untreated patients.\textsuperscript{158} In a study of later generation antivirals (entecavir and tenofovir) at 10 European centres, cirrhotic patients treated with a nucleos/tide analogue for five years had annual HCC incidence reduced significantly from 3.22\% to 1.57\% (p=0.039) although this did not change in non-cirrhotics (0.49\% to 0.47\%).\textsuperscript{159} In contrast, a US study of tenofovir treatment for CHB involving Asian Americans together with a Taiwanese cohort did find a risk reduction in both cirrhotics (77\%) and non-cirrhotics (73\%).\textsuperscript{160} Available treatments for HBV include pegylated interferon alfa, lamivudine, adefovir, telbivudine, entecavir and tenofovir, which should be used according to guidelines from the international liver societies.

Prevention of HBV infection through vaccination can effectively reduce the risk of HCC. The World Health Organization recommends vaccination against hepatitis B for all newborns and high-risk groups (e.g. health workers, travellers to endemic regions, injecting drug users, people with multiple sex partners).

Most of the burden of disease from HBV occurs from infection acquired in the first five years of life, which generally leads to chronicity.\textsuperscript{150} Infants born to HBV-infected mothers with HBeAg-positivity are at high risk of perinatal transmission (70-100\% in Asia, 40\% in Africa), while those who are HBeAg-negative have lower risk (5-30\% in Asia, 5\% in Africa).\textsuperscript{161,162} Perinatal vaccination can reduce this risk to near 0\% in HBeAg negative mothers,\textsuperscript{163} but despite this, transmission from HBeAg positive mothers still occurs in up to 20\% of cases.\textsuperscript{164} Treatment of women in the third trimester with antiviral therapy is a recent intervention that can significantly reduce mother-to-child transmission rates by over 70\% with reduction of viral load to under 6 log copies/mL by delivery.\textsuperscript{165}

Although the HBV vaccine may be ineffective in 5-10\% of individuals (less effective at older ages), widespread neonatal vaccination programs starting from the mid-1980s has reduced seroprevalence of HBV in children under 5 years, to 1.3\% worldwide from 4.7\% in the pre-vaccination era.\textsuperscript{143} In Taiwan, 20 years after commencing newborn vaccinations, the seroprevalence rate in people younger than 20 years has fallen from 10-17\% to 0.7-1.7\%, with an associated decrease of 70\% in HCC
incidence in those vaccinated.\textsuperscript{166} While most countries (92\%) have introduced newborn HBV vaccination, and 70\% receive the full 3 dose course,\textsuperscript{143} some high-risk countries, especially those in sub-Saharan Africa, still have trouble implementing effective vaccination. Addressing aflatoxin contamination, which is synergistic with HBV for HCC risk, is an important adjunct to vaccination in these countries.

\subsection{2.2.1.1.2 Chronic hepatitis C virus infection}

Chronic hepatitis C virus (HCV) affects about 1\% of the world’s population, about 71 million people, with the highest prevalence in Eastern Mediterranean (2.3\%) and European (1.5\%) regions; prevalence is between 0.5\% and 1\% in all other regions.\textsuperscript{167} Within these regions, prevalence rates are heterogeneous within countries and between communities. The world’s highest rates are in northern Africa, especially Egypt, where the rate is about 13\%, whereas the rest of Africa has varying prevalence from intermediate (2-5\%) to moderately high (5-10\%).\textsuperscript{168} In Asia, Mongolia has the highest prevalence (10\%) but the rest of Asia has intermediate prevalence. Developed countries such as Australia, UK and Canada have prevalence rates approximately 1\% although it is slightly higher in the United States at 1.8\%.\textsuperscript{168} The estimated annual incidence globally is 23.7 per 100,000 (1.75 million new cases) in 2015, according to WHO.

HCV infection is transmitted through blood contact via a number of means that differ by geography, time period and social practices. Virological studies describe the chronology of HCV as having existed for hundreds of years at low-level endemic rates, with worldwide spread beginning after 1900,\textsuperscript{169} especially in Japan (1920s), southern Europe (1940s) and North America(1960s-70s). The first documented epidemic affected Japan in the 1920s when large numbers of young adults were given intravenous anti-Schistosoma therapy.\textsuperscript{170} This continued into 1950 when this was included in the Japanese national program before it was ceased in the 1970s. Similarly, mass publicly funded vaccination programs against Schistosoma in Egypt in the 1950-80s was the cause for the epidemic there.\textsuperscript{171} In the United States, the HCV epidemic was spread via contaminated needles and injecting drug use in the 1960s, followed by spread via contaminated bloods supplies until 1989 when the virus was identified.\textsuperscript{148}

Globally, about 25\% of HCC can be attributed to HCV,\textsuperscript{135} which is a more dominant risk factor for HCC in regions where HCC incidence is in the low to medium
range, in contrast to high HCC incidence regions where HBV is the predominant risk factor. The highest contribution of HCV to HCC incidence is in Japan where 70-90% of HCC are HCV-related, followed by Italy (44-66%) and the United States (30-50%).

However, as the HCV epidemic started and ended in Japan earlier than the rest of the world, so too has HCC incidence which has peaked and is now on the decline. Likewise, the HCV-related proportion of HCCs in Japan has reduced to 67.7% in 2005. The advent of direct acting antiviral therapy for HCV is expected to reduce the HCV contribution to HCC in other countries, including the United States where alcoholic liver disease has replaced HCV as the leading indication for liver transplantation.

Prospective studies show that acute hepatitis C progresses to chronic infection in 80% of cases, of which 10-20% will develop cirrhosis within two to three decades, and 1-5% will develop liver cancer.

The risk of HCC is highest in cirrhosis, with annual incidence rates of 1-4%, and up to 8% in Japan. Other risk factors that increase HCC risks in HCV patients include male sex, co-infection with HIV or HBV, older age, diabetes, obesity and chronic alcohol consumption. HCV genotype 1b has a 2-fold greater risk of developing HCC than other genotypes, although the mechanism by which this occurs is not entirely certain. It may be that genotype 1b contains a specific nucleotide that causes direct pathogenesis or triggers a stronger immune response, or the difference sequence may allow it to better evade adaptive immunity.

While HCV viral load titres have not been shown to affect HCC risk, the elimination of viraemia, i.e. treatment that eliminates the virus, has been shown to decrease HCC risk. Randomised controlled trials and non-randomised studies have shown a HCC risk reduction of 57% to 75% in HCV-infected patients who achieve a sustained virological response following treatment with interferon-based regimens. However, despite HCV cure, the risk of HCC remains at 0.33% per year and thus patients who have been cured with advanced fibrosis warrant ongoing HCC surveillance.
2.2.1.1.3 Alcohol-related liver disease

According to the Australian Bureau of Statistics, about two thirds of alcohol-induced deaths in Australia in 2017 were due to alcoholic liver disease.\textsuperscript{184} Globally, this figure is approximately one quarter.\textsuperscript{185} In the western hemisphere, alcoholic liver disease is now a leading cause of HCC\textsuperscript{186} and the top indication for liver transplantation.\textsuperscript{176}

Per capita consumption of alcohol is highest in Europe (21.3g/day) and lowest in the Middle East and Northern Africa (1.2g/day), compared to a world average of 15.1g/day. However, among drinkers, the spread is not as great, being highest instead in the Middle East (46.1g/day), lowest in South-East Asia (12.1g/day), with Europe at 37.4g/day and the world average at 32.8g/day. Since 1960, consumption has declined in Europe, North America and Africa but increased in South East Asia and the Western Pacific region.\textsuperscript{185}

Alcoholic liver disease as a HCC risk factor is more prominent in regions with low HCC incidence, such as in Europe and North America, where it is present in 32\% (United States)\textsuperscript{187} to 45\% (Italy)\textsuperscript{188} of HCCs. In contrast, in high HCC incidence regions where HBV is more prevalent, alcohol is less commonly present at 10\% of HCCs.\textsuperscript{66}

Alcoholic liver diseases encompass a spectrum of pathology including alcoholic hepatitis, steatosis, steatohepatitis, progressive fibrosis and cirrhosis, leading to HCC. In those who drink more than 60g of alcohol per day, many (60\%) would develop steatosis, but only a minority progress to steatohepatitis and 10-20\% eventually develop cirrhosis.\textsuperscript{189,190} The mechanism of injury is not completely understood but involves the formation of acetaldehyde and free radicals, cytochrome P4502E1 induction, oxidative injury to hepatocellular structures and progressive fibrosis with regenerative nodules.\textsuperscript{190}

Alcohol was first determined to have a causal relationship with liver cancer by the International Agency for Research on Cancer in 1988.\textsuperscript{191} More recently, a meta-analysis of 19 prospective studies found that consumers of three or more drinks of alcohol per day had a 16\% increased risk of liver cancer, and those drinking six or more had a 22\% increase.\textsuperscript{192} Even lower doses of alcohol (two drinks, or 25g per day) were associated with higher risks in another meta-analysis.\textsuperscript{193} Heavy drinking of more
than 80g per day for at least 10 years was associated with a five-fold risk of liver cancer,\textsuperscript{194} with a number of studies showing a dose-response.\textsuperscript{195,196}

The HCC risk attributable directly to alcoholic cirrhosis has been difficult to estimate due to the co-presence of other known risk factors for HCC such as viral hepatitis B and C, especially with studies prior to the identification of HCV in 1990. However, recent studies have shown an independent role of alcohol in both development of cirrhosis and HCC, with the 5-year HCC cumulative incidence at 8% for alcohol without viral hepatitis.\textsuperscript{197} Two European prospective study of patients with alcoholic cirrhosis (without viral hepatitis) undergoing HCC surveillance found the annual HCC incidence to be 2.6%\textsuperscript{198} and 5.6%.\textsuperscript{199} The latter study had patients with slightly older ages and with more diabetes, both of which are additional HCC risk factors. Studies from other regions with high HBV prevalence and low alcohol use (a South African case-control study,\textsuperscript{200} and a Taiwanese prospective cohort study\textsuperscript{201}) have found approximately 2 to 4-fold increase risk of HCC, after excluding viral hepatitis comorbidities.

These studies mentioned above were based on liver clinic cohorts, and differ considerably to HCC risks found in population-based studies.\textsuperscript{202,203} A Danish nationwide cohort of 8482 patients with alcoholic cirrhosis of whom 169 patients had HCC, retrieved from cancer registry data, concluded that the annual HCC incidence was 0.2%.\textsuperscript{203} Such population-based studies may be limited by lack of diagnostic rigour in both cirrhosis and HCC diagnoses, and failure to capture alcoholism diagnoses. Documentation of alcohol history can be very heterogeneous in studies, ranging from yes/no variables, to “drinks per day” (which can vary according to alcoholic content of the beverage) and the more accurate quantification of grams of ethanol per day. Population-based studies would have particular difficulty with this, as the diagnosis may be missed from hospitalisation records, which may lead to underestimation of alcohol-related HCC incidence.

Many studies have found that alcohol acts synergistically with other HCC risk factors including HCV, HBV, fatty liver disease, obesity and smoking. In HCC patients with HCV, the additional history of alcohol use caused a two-fold increase in HCC risks compared to HCV alone, based on case control studies from Italy,\textsuperscript{194} the United States,\textsuperscript{187} Japan\textsuperscript{204} and Taiwan.\textsuperscript{205} A large longitudinal study of 795 Japanese
patients with HCV or alcohol-related cirrhosis also found alcohol intake to be an independent risk factor for HCC on multivariate analysis.\textsuperscript{206}

Alcohol may also negatively influence outcomes of HCV-related HCC with early age of presentation (younger than 50 years),\textsuperscript{207} more poorly differentiated tumours,\textsuperscript{208} and shortened disease-free and overall survival.\textsuperscript{209}

Studies of the interaction between alcohol and HBV in HCC risk were conducted prior to HCV testing became available, making results difficult to interpret. Nevertheless, findings suggest a 3- to 5-fold effect of alcohol on the HCC risks of patients with HBV.\textsuperscript{210,211} Alcohol may be associated with earlier age of presentation in HBV-related HCC patients, by approximately 10 years.\textsuperscript{212,213}

More recent data from the REVEAL-HBV study cohort, in an analysis of 2260 Taiwanese men with HBV, alcohol increased HCC risks synergistically with being overweight (HR 2.4), obese (HR 2.0) and extremely obese (HR 2.9).\textsuperscript{214}

Patients with cleared HBV infection (sAg negative, anti-Hbc positive) and alcoholic cirrhosis were found to have higher cumulative risk of HCC than patients who did not have previous HBV, at 10 years this was 40.4\% compared 22.1\%, respectively.\textsuperscript{215}

Diabetes was also synergistic with alcohol as an HCC risk factor. Hasan et al,\textsuperscript{187} in a hospital based case control study of 115 HCC patients and 230 non-liver cancer controls, found that diabetes and alcohol each had a 2.5 fold increase in HCC risk, but together presented an odds ratio of 9.9. This study also found synergism between alcohol and viral hepatitis B or C.

Once cirrhosis has developed, discontinuation and abstinence from alcohol does not appear to improve HCC risks for at least 10 years. Donato et al\textsuperscript{194} found that compared with current drinkers, discontinuation of alcohol use within the previous 5 years and between 6-10 years were still associated with elevated risk of HCC (odds ratio 5.0 and 4.0, respectively). Only after 10 years of abstinence did the HCC risk became level with current drinkers. While this finding appears somewhat counter-intuitive, there are a number of possible explanations. Patients may have recently stopped drinking due to symptoms of decompensated cirrhosis, a state that has higher HCC risks than with current drinkers who likely have compensated or even non-cirrhosis. Conversely, current drinkers have higher risk of non-HCC liver mortality.
such as alcoholic hepatitis, and die before HCC can develop. Finally, the hepatic regeneration that occurs with alcohol cessation may also increase the immediate risk of HCC. With prolonged abstinence however, there is evidence that fibrosis regression can occur, hence explaining the reduction in HCC risks 10 years after discontinuation.

2.2.1.1.4 Non-alcoholic fatty liver disease

Non-alcoholic fatty liver disease (NAFLD) is defined as the condition of hepatic steatosis (based on imaging or histology) without a secondary cause of hepatic fat accumulation such as significant alcohol use, medications or hereditary disorders. Global prevalence of NAFLD is estimated at 25% from a recent meta-analysis of 86 studies with a total of 8.5 million patients from 22 countries by Younossi et al.\textsuperscript{216} The highest rates are reported in the Middle East (32%) and South America (31%), followed by Asia (27%), the USA (24%) and Europe (23%), with the lowest rates in Africa (14%). However, even within regions, there is a clear urban-rural divide with urban rates twice that of rural rates in China (20.3% vs 11.1%)\textsuperscript{217} and varying widely from 9% to 35% in India.\textsuperscript{218}

NAFLD is highly associated with metabolic risk factors such as obesity, diabetes and dyslipidaemia, and is much more prevalent in these patient groups at up to 90%, 69% and 50%, respectively.\textsuperscript{219} As the prevalence of these risk factors rise, NAFLD is expected to become even more prevalent.

NAFLD can also occur in non-obese patients with a prevalence of 10-20%; these patients tend to be younger, less likely to have metabolic syndrome compared to obese NAFLD patients, and have higher insulin-resistance and triglyceride levels than those without NALFD.\textsuperscript{220}

Non-alcoholic steatohepatitis (NASH) is the progression of NAFLD towards inflammation with hepatocyte injury (ballooning) and collagen deposition, diagnosed on histology. It can occur in up to 44% of NAFLD cases, even in the absence of baseline inflammation.\textsuperscript{221} The estimated prevalence of NASH among NAFLD patients is 59% among those who are biopsied.\textsuperscript{216} However, as liver biopsy is invasive, less severe cases of NALFD may not undergo this procedure. The estimated NASH prevalence among NAFLD patients without biopsy is much lower, at 7% in Asia and 30% in North America.\textsuperscript{216} NASH itself progresses towards advanced fibrosis and
cirrhosis, of which 30-40% and 10-15%, respectively, are already present at initial diagnosis.\textsuperscript{222} This progression of NASH towards cirrhosis occurs in about 23-41% of cases over the next 10-15 years.\textsuperscript{216,222}

Many, if not most, cases of cryptogenic cirrhosis have subsequently been found to be secondary to NASH. A study of liver explants that had been diagnosed pre-transplant as cryptogenic cirrhosis reclassified 63\% as NASH-related cirrhosis after histological examination.\textsuperscript{223} Cryptogenic cirrhosis also accounted for 5.4\% of HCCs in a Korean study, finding that this group had higher BMIs, triglyceride levels, diabetes and hypertension than those with well-defined aetiology.\textsuperscript{224}

The risk of HCC development in NAFLD/NASH depends upon the stage of underlying NAFLD, the degree of fibrosis and the associated comorbidities and their severity. Notwithstanding this, the estimated annual incidence of HCC in NAFLD is 0.044\%, and in NASH it is higher at 0.53\%.\textsuperscript{216} In NASH cirrhosis, it is higher at 2.3\% to 4.0\% per year.\textsuperscript{225,226}

While the absolute HCC risks are lower in NAFLD compared to other risk factors for HCC such as viral hepatitis and alcoholic liver disease, the impact is potentially much greater due to enormity of the global population affected NAFLD, and the alarming trends of increasing obesity, diabetes and metabolic syndrome prevalence. NAFLD is already the second leading indication for liver transplantation in the US\textsuperscript{227} and is expected to become the leading cause of liver failure in the near future.\textsuperscript{228}

\textbf{2.2.1.1.5 Other causes of cirrhosis}

Patients with other causes of cirrhosis are also at risk of HCC. In hereditary haemochromatosis (HH), HCC almost always occurs with cirrhosis – for example, in a prospective study following 152 patients with homozygous HH, 28 of the 97 patients with cirrhosis developed HCC whereas none of those without cirrhosis did.\textsuperscript{229}

Similarly, in primary biliary cholangitis (PBC), a meta-analysis of 17 studies found PBC was associated with a higher relative risk of HCC compared to the general population (RR 19, 95\%CI: 11-27). Multivariable analysis of the risk factors of HCC in PBC found that the only independent risk factor was advanced histologic stage.\textsuperscript{230}
2.2.1.2 HCC without cirrhosis

In a significant minority of patients, HCC can develop without cirrhosis. This phenomenon has been well characterised in the case of chronic HBV infection. Emerging data suggests that HCC may be present in non-cirrhotic chronic liver disease due to other risk factors as well, as discussed in this section.

2.2.1.2.1 HBV

HBV infection can be directly carcinogenic through integration of viral genome causing host DNA mutations that lead to the development of HCC independent of cirrhosis. Studies estimate that about 10-20% of HBV-related HCC occur in non-cirrhotic livers.

The significance of HBV-related HCC in non-cirrhotic patients has been well recognised with international guidelines recommending HCC surveillance for this risk group. The annual HCC incidence in Asian male carriers was 0.5% in a Taiwanese prospective cohort and 0.4% in a Japanese study. In North American patients, Sherman also found a similar annual incidence of 0.46% although most of this Toronto study population were Asian. The risk was lower in Alaskan patients at 0.26% per year. More recently, the annual HCC incidence in non-cirrhotic CHB patients was found to be 0.4% overall, increasing from 0.2% from age 45 for men to 1.3% after 65, and for women 0.3% from age 55, in an Asian American cohort.

European carriers of HBV without cirrhosis have not been found to have significant risk and hence were not included in earlier HCC surveillance guidelines. However, the recent European guidelines have now recommended non-cirrhotic Caucasian HBV carriers for surveillance based on risk-scores that combine multiple risk factors.

A recent Korean study suggest the role of previous HBV exposure and occult HBV infection in non-cirrhotic HCC. The authors examined 710 HCC cases from resection or liver transplantation and found a non-cirrhosis rate of 25%, of which the majority (59%) were related to HBV infection, with 7% HCV, 12% alcoholic and 21% cryptogenic disease. Interestingly, looking at the prevalence of non-cirrhosis among each of the risk factors, there were 19.2% of HBV-related HCCs with non-cirrhosis compared to significantly greater rates in HCV (32.5%), alcoholic (50%) and...
cryptogenic (48.7%) liver disease. Seemingly, this would appear counter to current understanding of HBV being the most common risk factor in non-cirrhotic HCCs. The authors went on to assess for evidence of previous HBV exposure (HBeAb positivity) and occult HBV infection (DNA PCR positivity in liver tissue) and found that among the non-HBV cases, 80.2% were HBeAb positive and 38.5% had occult HBV infection. In the non-cirrhotic HCC cases who had alcoholic liver disease, 95.5% had HBeAb positivity and 40.4% had occult infection, whereas of the non-cirrhotic cryptogenic cases, 78.9% had HBeAb positivity and 47.4% had occult infection. Thus, in HBV endemic areas, HBV is an important contributor to non-cirrhotic HCC disease, especially among non-viral hepatitis related HCC.

2.2.1.2.2 HCV

Unlike with CHB, there is limited data of HCC in HCV-infected patients without cirrhosis. A Mayo Clinic cohort of 118 HCV-related HCC patients were found to have a non-cirrhotic rate of 7%\(^{152}\) while another European study found a similar rate of 6%\(^{239}\).

In the much larger prospective HCV HALT-C cohort which followed 1005 HCV-infected patients who had failed therapy found that 17% of HCV-related HCC only have fibrosis on biopsy. The annual incidence of HCC in patients with bridging fibrosis was 0.8%, and 1.4% in those with cirrhosis.\(^{137}\) After 7 years, the cumulative incidence of HCC was about 8% in patients with fibrosis.\(^{240}\) These findings have contributed to the recent addition of HCV patients with advanced fibrosis being added to HCC surveillance guidelines by the European Association for the Study of the Liver,\(^{52}\) whereas this group remains absent from other guidelines.\(^{51,104}\)

2.2.1.2.3 Alcohol-related liver disease

There is little direct evidence of alcohol causing HCC development in the absence of cirrhosis, and yet there are limited reports of HCC in non-cirrhotic patients with alcoholic liver disease. A US study of 804 biopsy proven HCC with non-neoplastic liver available found that there were 155 cases of “alcoholism” (based on clinical history but not otherwise defined) associated HCCs, of which 25 (16%) were non-cirrhotic.\(^{241}\) Note however that these cases were from the pre-HCV diagnosis era,
and so HCV may have contributed to this rate. Additionally, the study was unusual in that 42.6% of total HCC cases were non-cirrhotic, that is, the cirrhosis prevalence was 57.4%, which is significantly less than the 80-90% found in the majority of later HCC studies. In another study from the post-HCV diagnosis era, an Italian study found a non-cirrhosis rate of 13% in 163 patients with HCCs from all aetiology, and 14% non-cirrhosis among those HCC secondary to alcohol only. 242

2.2.1.2.4 Non-alcoholic steatohepatitis

There is emerging data of NAFLD-related HCC occurring in the absence of cirrhosis. A retrospective study of 54 patients from an Australian liver transplant centre with NAFLD associated HCC found 15% to be non-cirrhotic, with significantly larger tumour size than cirrhotic patients. 243 A French study of HCC in 31 patients with metabolic syndrome found 65% had only minimal (F0-F2) fibrosis. 244 In the largest study to date of this phenomenon, 87 Japanese patients with biopsy proven NASH and HCC were examined to find that half did not have cirrhosis with fibrosis stage 1 (11%), stage 2 (17%), stage 3 (21%), stage 4 cirrhosis (51%). 245

2.2.1.3 Other risk factors

A number of risk factors have minimal contribution to the global burden of HCC compared to the risk factors discussed previously but have an additive effect when they are also present.

2.2.1.3.1 Aflatoxin and other environmental toxins

Aflatoxin is produced by Aspergillus species and is often a contaminate found in grains, corn, soybeans and peanuts. It may be associated with mutations of the p53 tumour suppressor gene with chronic exposure. 246 Regions with high aflatoxin contamination such as parts of sub-Saharan Africa and East Asia have high incidence of HCC, although these same regions also have high HBV prevalence.

The hepatocarcinogenesis effects of aflatoxin are synergistic with chronic HBV infection, increasing the risk of HCC in HBV patients with aflatoxin exposure compared to those without, in both cirrhotic and non-cirrhotic HBV-related HCC (OR 5.5, 95%CI: 2.2-13.6 and OR 5.4, 95%CI: 1.1-26.2). 247 This was found in a large
Taiwanese community case-control study which also showed that aflatoxin exposure was associated with shorter time to both cirrhosis and/or HCC development.

Drinking contaminated water containing Microcystin, a toxin of blue-green algae found in ponds, has been associated with increased risk of HCC. A study from rural China found that the risk in people drinking pond water was more than 5 times the risk of those drinking water from other sources.\textsuperscript{248}

There are also reports that Betel nut chewing (a common practice in parts of Asia) is associated with increased risk of cirrhosis and HCC, as well as oesophageal cancer.\textsuperscript{249}

2.2.1.3.2 Diabetes mellitus

The association between diabetes mellitus and HCC has been noted by multiple studies including several meta-analyses and systematic reviews. This increased risk was consistent across types of studies: the pooled risk from 17 case-control studies was OR 2.40, 95\%CI:1.85-3.11,\textsuperscript{250} that from 25 cohort studies was RR 2.23, 95\%CI: 1.68-2.96,\textsuperscript{250} while for 14 prospective epidemiological studies, the relative risk was 1.9; 95\% CI 1.2-2.3\textsuperscript{251} and a large population-based cohort of 19,349 diabetics and 77,396 non-diabetics found a high incidence of HCC in diabetes who had 1.7 times the risk of non-diabetics (95\%CI: 1.5-2.0).

However, some important confounding factors need to be considered, although it can be difficult to resolve this with observational studies. Firstly, there are overlapping risk factors also associated with diabetes such as obesity and metabolic syndrome, all of which are individual risk factors for NAFLD, a well-recognised cause of cirrhosis and HCC. Secondly, some patients in these observational studies who report new diagnosed diabetes may in fact have undiagnosed cirrhosis which has precipitated the glucose intolerance. Hence, diabetes here is the consequence of cirrhosis which is the greater risk for HCC, rather than diabetes itself.

These studies also reveal an association between metformin use and a risk reduction for HCC. In a meta-analysis of 10 studies with 334,307 diabetic patients, metformin use had a lower odds ratio of developing HCC – OR 0.50 over 8 studies.\textsuperscript{252} Conversely, there was increased risk with sulfonylurea (OR 1.62) and insulin (OR 2.61). Again, these results based on observational studies may be confounded as
subsequent post-hoc analysis of the randomised trials (from this same meta-analysis) did not find an association between diabetic medications and risk of HCC.

2.2.1.3.3 Obesity

Obesity at the highest BMI category confers a HCC relative risk of 1.8 (95%CI: 1.6-2.1) compared to those with normal BMI, according to an analysis of observational studies by the International Agency for Research on Cancer.\textsuperscript{253}

2.2.1.3.4 Tobacco

Tobacco smoking is associated with a 1.5 fold increase in HCC risk in current smokers compared to those who had never smoked, according to a meta-analysis of 38 cohort studies and 58 case-control studies.\textsuperscript{254} However, the interaction of smoking with other co-factors such as viral hepatitis and alcohol is difficult to elucidate.

2.2.1.3.5 Family history

Many initial reports of family history as a risk factor for HCC were from Asia where HBV is prevalent, making it difficult to differentiate whether clustering was in fact due to vertical transmission of infection. A study by Yu et al tried to address this by only comparing patients with HBV: 553 patients with HCC and 4,684 controls. They found that patients with HBV and a family history were 2.4 times more likely to develop HCC (OR 2.4, 95%CI: 1.5-3.9).\textsuperscript{255}

In the West, first-degree family history of liver cancer was associated with HCC development independent of HBV or HCV infection in American and European populations.\textsuperscript{256} In this case-control study of 287 HCC patients and 450 controls, the odds ratio for family history of HCC was OR 2.4 (95%CI: 1.2-4.7) overall; it was still significant after excluding other risk factors (HBV, HCV, alcohol) – OR 2.0 (95%CI: 0.6-6.9). Patients with a family history of liver cancer had a synergistic increase in risk with the other risk factors being present.
2.2.1.3.6 Diet

Coffee has been associated with reduced HCC risk in a dose-response relationship. A meta-analysis of coffee drinkers in Europe and Japan showed reduced risk, RR 0.70 (95% CI 0.57-0.85), in light drinkers (1-2 cups per day), and even lower risk, RR 0.45 (95% CI 0.38-0.53) in heavier drinkers (≥ 3 cups per day) as compared to non-drinkers.\textsuperscript{257}

While some initial studies suggested an association between red meat intake and HCC risk, a meta-analysis of 17 studies with 1,670,930 patients did not find an association – RR 1.10 (95%CI: 0.86-1.42) between the highest and lowest intake groups.\textsuperscript{258}


2.2.2 Incidence and Mortality

Liver cancer was the fifth most common cancer in men and ninth most common cancer in women, according to the International Agency for Research on Cancer\textsuperscript{259} and GLOBOCAN,\textsuperscript{260} with an estimated 782,451 new cases worldwide in 2012 when this research study commenced. It accounted for 7.5% and 3.4% of all incident cancer cases in men and women, respectively.\textsuperscript{259}

2.2.2.1 Regional variance

The majority of incident liver cancer (83%) occurred in less developed regions, and half (50%) in China alone.\textsuperscript{259} This represents a huge disparity in liver cancer incidence worldwide, with rates varying by more than nine-fold between the highest and lowest regions.\textsuperscript{261} Among men, age-standardised incidence rates (per 100,000) in 2012 were highest in Eastern Asia (ASR 31.9), South-Eastern Asia (22.2), Northern Africa (18.0) and Western Africa (16.4), and the lowest were reported in South-Central Asia (3.7), Eastern Africa (4.9) and Western Asia (5.0). Among women, the highest were found in Eastern Asia (ASR 10.2 per 100,000), Western Africa (8.1), Melanesia (7.6) and South-Eastern Asia (7.2), and the lowest were reported in Micronesia/Polynesia (1.4), Northern Europe (1.8), Central and Eastern Europe (2.0) and South-Eastern Asia (2.1).\textsuperscript{261}

A three-tier rating of incidence is also useful in grouping countries with high incidence at greater than 20, intermediate between 10-20 and low as less than 10 per 100,000. By this measure, high incidence regions are countries of East Asia, South-East Asia and sub-Saharan Africa, with intermediate incidences in West Africa, Southern Europe (Italy, Greece, Spain) and low incidences in North America, South America, Northern Europe and Australasia.\textsuperscript{148,262}

The geographic distribution of HCC incidence appears to correlate with the distribution of chronic HBV infection.\textsuperscript{148} In regions where HBV is endemic, HCC incidence rates are among the highest. In China where the incidence is 40 per 100,000 in men and 15 per 100,000 in women, and HBV is present in 63.9% of liver cancer,\textsuperscript{51} the prevalence of HBV is 12%. South East Asia and sub-Saharan Africa also have high HBV prevalence between 8 and 12%, with HBV the dominant risk factor in HCC in more than 50% of cases.\textsuperscript{148}
Outside of these endemic regions, in southern and eastern Europe, South America and the Indian subcontinent, where hepatitis B prevalence is in the intermediate range, HCC incidence rates also drop accordingly. In regions of low hepatitis B prevalence including western Europe, North America and Australia, HCC incidence rates are the lowest\textsuperscript{148} although immigrants from endemic countries have contributed to the rising incidence in these areas.\textsuperscript{66}

Franceschi and Raza\textsuperscript{263} in their meta-analysis of 27,881 HCC cases from 90 studies worldwide found a predominance of HBsAg positive cases in most Asian, African and Latin American countries. In contrast, hepatitis C was the predominant cause of HCC in Europe, North America, Japan, Pakistan, Mongolia and Egypt.

The other major risk factors for HCC, chronic hepatitis C, alcoholic liver disease and non-alcoholic fatty liver disease, are more prevalent in regions with low-moderate HCC incidence. These regions tend to encompass more developed countries, including those from Europe, North America and Australasia. The distribution of these risk factors are further discussed in section 2.2.1.
Table 2-1. Global incidence and mortality of liver cancer in 2012.

ASR = Age-standardised rate per 100,000 (World Standard Population)

Source: GLOBOCAN 2012. Adapted from Wong et al.

<table>
<thead>
<tr>
<th>World regions</th>
<th>Population size (million)</th>
<th>Incidence (ASR)</th>
<th>Mortality (ASR)</th>
<th>Incidence: mortality ratio</th>
</tr>
</thead>
<tbody>
<tr>
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<td>Female</td>
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<td>Female</td>
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</tr>
</tbody>
</table>
2.2.2.2 Age

The incidence of HCC progressively increases with increasing age; in Australia, the liver cancer age-specific incidence rates are highest in men at ages 75-79 (at 67.5 per 100,000) whereas in women, this occurs slightly later at 80 years and beyond (24 per 100,000). There is often an earlier smaller peak at ages 55-59, with rates of 42 per 100,000 men and 8.2 per 100,000 women, likely secondary to the non-cirrhotic causes of HCC which tends to occur earlier.

Patients from Asian and African populations are notably younger at presentation with HCC, likely due to higher rates of HBV-associated HCC in these patients. Chronic HBV is acquired at birth or in early childhood in these regions, and thus the early exposure contributes to younger age of HCC development. Guidelines recommend commencement of HCC surveillance at an earlier age in HBV-infected patients from Asian and African background, compared to other risk groups.

In contrast, in low HCC incidence areas, HCV infection and other risk factors are acquired later in life, and HCC development occurs at older ages. For example, Japanese HCC patients have the highest age-specific incidence in men aged 70-79.

2.2.2.3 Sex

HCC risk is higher among men at two- to four-fold higher rates than females in most regions, with typically higher male:female ratio in areas of high HCC incidence. East and South East Asian countries have ratios greater than 4 (South/North Korea 4.1, Vietnam 4.1, Indonesia 4.3) whereas Europe and the Americas have lower ratios (UK 1.9, USA 2.8, Argentina 1.8). Some notable exceptions to this include some regional European registries (Italy 4.4, Switzerland 5.6, France 6.0) with the greatest gender disparity, whereas others report relatively equal incidence rates (Mexico, Columbia, Costa Rica).

The reason for these differences between the sexes can be hard to determine due to confounding environmental risk factors that are more prevalent in males. Men have higher rates of chronic HBV or HCV infection, consume more alcohol and cigarettes, have higher rates of obesity and have increased iron stores. There are also reports of significantly greater levels of aflatoxin markers in men than women 42.5% vs 21.6%, OR 2.6 (1.4-5.0).
Nevertheless, it is postulated that hormonal factors may be involved. Oestrogen may be protective for women, reducing liver injury and compensatory regeneration via suppression of interleukin-6 mediated inflammation.\textsuperscript{268} Testosterone may increase risk by promoting liver cell proliferation via increased androgen receptor signalling.\textsuperscript{269}

### 2.2.2.4 Race / Ethnicity

The variance in incidence between countries and regions can also be seen within major Western cities between ethnic sub-populations. A large US study of 48,048 cases of HCC from cancer registries that cover 83\% of the US population found that compared to whites, the HCC incidence rate was 4 times higher in Asians/Pacific Islanders and 1.7 times higher in blacks.\textsuperscript{270}

Even between Asian subgroups, incidence rates vary significantly. A study of 41,929 HCC cases diagnosed in California during 1988-2012 found that Southeast Asians (Vietnamese, Cambodians and Laotians: age-standardised rates of 47.3, 42.8 and 45.6 per 100,000 males, respectively) had incidence rates 8- to 9- times higher than non-Hispanic whites, but also much higher than Japanese (8.1 per 100,000 males). Differences in HCC risks among Asian subgroups were attributed to HBV prevalence in the foreign-born Asians, with prevalence rates ranging from 0.6\% among Japanese to 12.5\% in Vietnamese and 13.6\% in Laotians.\textsuperscript{271}

The study also highlighted an important point about the effects of migration on HCC risks. While some ethnicities such as the South East Asians have incidence in the US similar to those in their native countries, Japanese in the US have much lower incidence than those in Japan (8.1 vs 23.5 per 100,000).\textsuperscript{15} It is worth noting that these South East Asians were almost entirely (97\%) foreign born compared to only 63\% of Japanese being foreign born.\textsuperscript{271} Similarly, Chinese populations living in the US have lower incidence of HCC than those living in China or Singapore.\textsuperscript{149} This suggests that differences in HCC risks between ethnic populations are related to the prevalence of risk factors in each group.

These findings suggest the importance of recognising differences between ethnic sub-populations in cancer research in Western settings.
2.2.2.5 Socio-economic status

The distribution of liver cancer burden worldwide correlates with measures of socioeconomic development. Wong et al.\textsuperscript{261} analysed the incidence and mortality rates of liver cancer retrieved from the GLOBOCAN database for 184 countries in 2012 for correlations to indices of socioeconomic development - the Gross Domestic Product (GDP) and the Human Development Index (HDI) which consists of life expectancy, education, and income. Global incidence of liver cancer varied nine-fold and were negatively correlated with HDI (men: \( r = -0.232, p = 0.003 \); women: \( r = -0.369, p < 0.001 \)) and GDP per capita (men: \( r = -0.164, p = 0.036 \); women: \( r = -0.212, p = 0.007 \)). Mortality showed similar correlations.

2.2.2.6 Trends in incidence

Trends in incidence and mortality rates of liver cancer appear to take a direction of incline or decline, seemingly split according to the recently prevailing incidence.

Countries with low or moderate liver cancer incidence, from Australasia to Europe, North America to South America, are widely reported to experience increasing trends. Over the last 30 years, liver cancer incidence have tripled - from 1.6 to 4.9 per 100,000 between 1975 and 2005 in the USA\textsuperscript{272} and from 1.38 to 4.96 per 100,000 between 1982 and 2014 in Australia.\textsuperscript{273}

A number of reasons are thought to contribute to this phenomenon. These countries have a higher proportion of HCV-related HCC compared to countries with high HCC incidence. They were also exposed to high prevalence of HCV transmission due to injecting drug abuse in the 1960s and 70s. The development of HCV-related cirrhosis and HCC in the current era would fit this natural history. In addition, these more affluent societies are experiencing an epidemic of obesity and metabolic syndrome, with associated non-alcoholic steatohepatitis and consequent cirrhosis that is fast becoming a major indication for liver transplantation.\textsuperscript{274} Finally, these same countries are often the destination for migrants from countries in Asia and Africa with high HBV prevalence, bringing with them the risk factors for HCC.
In contrast, countries with previously higher incidence have incidence and mortality rates that are plateauing or declining. In China, the average annual percentage change between 2002-2012 was -2.6% in HCC incidence in men and -2.2% in women. 261 Similarly, the Global Burden of Disease Study 2015 found that between 1990 and 2015, incidence rates in China, and some countries in sub-Saharan Africa have decreased by over 20%. 275 The effects of HBV immunisation and reduced exposure to aflatoxins are thought to be major contributors to this reduction. 262

In Japan between 1990 and 2003, peak HCC incidence have markedly declined with average annual change of -7.9, -22.3, and -12.4 per 100,000 men in the age groups 50-59, 60-69 and 70-9 years, respectively. 173 The majority of HCC in Japan is attributed to HCV infection beginning in the 1920s through to after World War II, earlier than in Western countries which was mostly post-war. In addition, HCV transmission terminated earlier in Japan in the 1990s. 173 Hence, this decline in HCC incidence is thought related to the similar downward trends in HCV transmission occurring decades earlier.

Thus, trends in incidence rates may reflect changes in migration of populations at risk, implementation of public health measures such as hepatitis B vaccination, or treatment and eradication of risk factors.

### 2.2.2.7 Mortality

Liver cancer is second leading cause of mortality from cancer worldwide, with an estimated 746,000 deaths in 2012 (9.1% of all cancer deaths that year). 259 Many countries, including Australia, 276 the United States 277 and the UK, 278 report liver cancer as the fastest rising cause of any cancer death. Compared to most cancers with decreasing mortality in recent years, liver cancer mortality rates are disturbingly increasing. In Australia, it has the highest rate of change over all cancer types in the last 30 decades, with age-standardised mortality rates increasing by 161%. 279

Liver cancer has generally poor prognosis, with low survival rates even in developed countries where multiple treatment options are available. In North America, one year survival is approximately 50%, and 5 year survival is about 10%. 272,280 and European studies show similarly poor survival. 281,282
As a consequence of this poor prognosis, mortality rates often parallel incidence rates in most regions of the world. It can be expressed as a ratio of incidence to mortality; the ratio is higher in countries where survival is more favourable (see Table 2-1). Across the world, the ratio is just 1.07, indicating that most incident cases result in death. In more developed countries in North America, Southern and Western Europe, the ratio is 1.23 to 1.39 with an average of 1.21 whereas less developed countries have an average ratio of 1.05. Some areas record higher mortality rates than incidence rates, which likely reflects the inclusion of secondary liver cancers in rates of primary liver cancer due to inaccuracies in the diagnostic process.

### 2.2.2.8 The burden of disease in Australia

Liver cancer is the 16th most commonly diagnosed cancer in Australia (ranking 11th in males, and 20th in females) in 2014, according to the Australian Institute of Health and Welfare. The incidence rate in Australia in 2014 was 7.4 cases per 100,000 persons (12 in males, 3.6 in females), with peak incidences in the 55-59 and 75-79 age groups.

In terms of mortality, liver cancer was the 7th leading cause of cancer mortality in Australians in 2016 (6th in males, 9th in females). The lifetime risk of dying from liver cancer by age 85 in Australia is estimated at 1 in 102. Survival rates for liver cancer diagnosed in 2010-2014 was 18% at 5 years, which is much improved compared to 6% in 1985-1989.

Incidence rates vary between Australian states and territories, with highest rates in the Northern Territory (11.8 and 3.1 cases per 100,000 males and females, respectively), followed by Victoria (7.7 and 2.4, respectively) and New South Wales (7.0 and 2.3, respectively) and lowest in Tasmania (4.8 and 1.4, respectively). The presence of sub-populations such as Indigenous Australians and migrants with higher prevalence of risk (e.g. chronic HBV infection) are major contributors to this difference between the reported incidence rates in these regions.

The trends in incidence and mortality rates of liver cancer in Australia are alarming. Incidence rates between 1982 and 2014 rose from an age-standardised incidence rate of 1.8 cases per 100,000 persons (2.9 for males and 0.9 for females) in 1982 to 7.4 cases per 100,000 in 2014. It should be noted that these rates refer to all primary liver cancer subtypes. A recent study calculated rates for HCC specifically...
over the same period across Australia and found incidence was 1.38 cases per 100,000 in 1982 and 4.96 per 100,000 in 2014.\textsuperscript{73} This discrepancy between HCC-specific and liver cancer incidence rates is discussed in detail in section 0.

In contrast, another study specific to incidence rates in the Northern Territory showed no significant change in annual age-standardised incidence between 1991 and 2010.\textsuperscript{73} Data was derived from the Northern Territory cancer registry, where possible barriers such as remoteness and accessibility may have influenced HCC diagnosis and completeness of cancer registration, thus leading to this absence of trend.
2.2.3 Issues with current hepatocellular carcinoma epidemiology

There are a number of important issues worth considering when discussing the epidemiology of hepatocellular carcinoma. Some issues are relevant globally whereas others are particularly important for local epidemiology and for comparisons with global trends. This section provides a background to understand the aim of this research to directly address some of these epidemiological challenges.

2.2.3.1 Distinguishing hepatocellular carcinoma-specific data

HCC incidence described in much of the literature is based on assumption and extrapolation from total liver cancer rates. Referencing the relevant population-based cancer registry, these incidence papers often begin by quoting total incidence, mortality and other epidemiological statistics relating to total liver cancer rather than HCC-specific data. Subsequent to this, a statement is made regarding the fact that HCC accounts for the majority of liver cancer.\textsuperscript{149} With this implicit (or at times explicit) disclaimer, the rest of the paper refers to HCC, its incidence, risk factors and so forth, without further distinction from non-HCC liver cancer. Despite reference to HCC in the text, graphs and tables in the same paper are often sourced from undifferentiated liver cancer data. Sometimes, captioning correctly refers to liver cancer rates\textsuperscript{52} while other times incorrectly as HCC rates\textsuperscript{286} when the original registry data refers to liver cancer.

The use of liver cancer rates as a surrogate for HCC rates is problematic for two reasons. Firstly, while HCC is the predominant subtype of primary liver cancer in most populations, its contribution varies from 50% to 90% and in certain areas, it instead is the minor contributor with ICC being the major subtype.\textsuperscript{13,15} For example, in northeast Thailand, ICC are the major liver cancer subtype comprising 58% of primary liver cancer rates compared to HCC at 42%.\textsuperscript{13} Cancer registries in England and Wales have also reported that ICC represents the commonest cause for liver cancer mortality, compared to trends for HCC which were unremarkable.\textsuperscript{17} While misclassification of some forms of ICC that were extrahepatic may have contributed to these initial ICC
rates, the marked increases of ICC remained following correction in subsequent analyses.\textsuperscript{18}

Distinguishing the two subtypes at the local level becomes especially important in interpreting trends in incidence and mortality to avoid erroneous assumptions based on generalised relative proportions. For example, in countries such as Thailand, Italy and Japan, cancer registries report recent trends of plateaux in liver cancer incidence, yet closer analysis reveals that HCC rates are decreasing while ICC rates are increasing.\textsuperscript{14}

Secondly, the distinction of pathological types of liver cancer is important because management is vastly different, from prevention and diagnosis to treatment and survival outcomes. While sharing some risk factors with HCC, the differences in the epidemiology of intrahepatic cholangiocarcinoma can have significant implications. In the same example of Thailand, the high incidence of ICC was related to liver flukes causing chronic biliary tract infections which is a major risk factor for ICC development.\textsuperscript{270} Thus public health intervention necessary here would be quite different from that directed towards HCC risk factors.

However, not all studies of HCC incidence lack clarity in distinguishing HCC from other liver cancer subtypes. These studies\textsuperscript{288-291} have methodologies that clearly describe their extraction of HCC-specific data from cancer registries using ICD coding to properly select HCC and exclude other subtypes. While still subject to the inherent flaws of cancer registration (e.g. accurate coding and complete capture), these studies give greater assurance that the findings can be applied to HCC without the unknown contribution of ICC.
2.2.3.2 Dependence on cancer registries

Cancer registries provide population-based data that has been important in identifying the rising incidence of HCC. The population defined by individual cancer registries differ greatly, ranging from metropolitan regions to states and entire countries. Certain countries in Scandinavia have robust, long-standing registries that are remarkably complete as a result of their geography and health care system, whereas other countries such as Australia have legislation that mandates cancer registration, thus improving completeness. However, the majority of the world’s population, especially those in developing countries, are not included in registry data. The International Association of Cancer Registries (IACR) which has approximately 450 member registries, estimates that it represents only 21% of the world’s population.\(^{292}\)

An extensive literature search has found that most previous studies reporting HCC incidence have extracted data from the relevant population-based cancer registry covering the geographical region under study. This may be at a state, national, regional or global level as in some of the examples below.

State level

In Australia, each state or territory has a cancer registry which covers the defined geographical boundaries of the state or territory. Studies reporting HCC incidence in Australian states have referenced their respective cancer registries,\(^{293,73,294}\) while other studies have also used their registries to extract cases for linkage.\(^{289,295}\) Other examples of studies using state level registries include incidence studies from Osaka, Japan\(^{173,204}\) and England.\(^{296}\)

A recent example is a study published in 2014, after the completed capture of the 2012-2013 incident cohort. Parker et al\(^{73}\) examined the incidence and outcomes of HCC in the Northern Territory. Over the period 1991-2010, they identified 145 cases of HCC to derive an age-adjusted annual incidence of 22.7 per 100,000 Indigenous Australians and 4.0 per 100,000 non-Indigenous Australians, standardised to the Australian Standard Population. Remarkably, in contrast to incidence data from Australia and other developed, they found no significant change in annual age-adjusted incidence over this period.
The methodology of this paper comprised two parts with different data sources: the first was the epidemiological study for which data was sourced from the Northern Territory Cancer Registry, and the second was the clinical retrospective study which sourced data from the Royal Darwin Hospital medical records. Similar to other Australian registries, the Northern Territory Cancer Registry collects notifications of cancer via three main sources: histology reports, hospital discharge coding and death certificates. The authors “cross-checked with hospital records” to confirm HCC diagnosis, that is, they assessed the validity of the registry in its accuracy. Completeness was not addressed; they did not have independent sources from which to capture cases missed by the registry. Hence, with increasing clinical (non-histological) basis of diagnosis, and the remoteness of the region (failure to present to hospital for cases to appear via hospital coding), this may have explained the lack of increase in annual incidence over time.

National level

In Australia, HCC epidemiology at the national level has not been reported until very recently by Wallace et al\textsuperscript{273} in their 2018 study of rising incidence over the last three decades. This study collated data from the eight state/territory cancer registries in Australia. Prior to this, the only reports have been of total liver cancer incidence from the Australian Institute of Health and Welfare in their three-yearly reports.\textsuperscript{297} The data source for these AIHW publications are the combined state and territory cancer registries, without extraction of HCC-specific data.

In the United States, a number of national-level cancer registries have been referenced in HCC incidence studies. The population-based registries included in the National Cancer Institute’s Surveillance, Epidemiology, and End Results (SEER) Program are commonly used as the primary source for HCC incidence studies.\textsuperscript{272,291,298} SEER registries capture cancer cases from associated regions including statewide data from 10 states (California, Connecticut, Georgia, Hawaii, Iowa, Kentucky, Louisiana, New Jersey, New Mexico, and Utah) and select population groups (Alaskan, Native Americans, and a few city-based registries – Detroit, Seattle), which still only represents 28% of the US population.\textsuperscript{299} A more recent 2017 publication reports HCC incidence across all 50 US states using the United States
Cancer Statistics registry which covers 97% of the US population through combining other registries with the SEER program.\textsuperscript{299}

Other HCC incidence studies reporting national rates have included reports from developed countries including Japan,\textsuperscript{300} the Netherlands,\textsuperscript{301} Denmark,\textsuperscript{302} and Canada,\textsuperscript{303} each using their national cancer registry as the data source. In contrast, there are no incidence studies from countries with developing economies, which is a direct result of the lack of adequate cancer registration in those populations.\textsuperscript{304} Recent initiatives to develop a HCC research consortium between some African countries has sought to address this need.\textsuperscript{305}

Comparison of HCC incidence across different countries may difficult due to differences in the quality of the data, completeness of data collection as well as the age-standardisation used (2.2.3.9).

**Global level**

Incidence studies\textsuperscript{14,202,205,204} reporting on HCC epidemiology at the global level almost invariably reference the GLOBOCAN database. This is the collective data from cancer registries across the world maintained by the IARC, which also publishes this data in the 5 yearly Cancer in Five Continents volumes.\textsuperscript{15} While GLOBOCAN is a useful comprehensive source for incidence data, it should be remembered that at its core, it is a collection of data provided by its member registries; its population data can only be as robust as each source, and perhaps less so for the following reasons.

As previously mentioned, GLOBOCAN data only represents registries covering 21% of the world’s population, despite the IACR having 450 member registries. The reason for this is the disparity between developed but less populous Western countries where registry coverage of the population is near complete and developing, more populous, countries with poor registry coverage. For example, in Cancer in Five Continents Vol. X (2014), the world’s most populous country China only had 13 contributing registries representing some of the major cities. The entire continent of Africa had even fewer, with only eight registries included as less than half (44%, 8/18) of the submitted registry data were deemed of adequate quality for publication. This is in comparison to Asia (62%, 63/101), Central and South America (71%, 25/35), Europe (87%, 118/135), North America (94%, 66/70) and Oceania (91%, 10/11).
Consequently, this edition of Cancer in Five Continents was only able to represent 14% of world population.\textsuperscript{15}

Thus, where HCC incidence rate is reported for a country based on GLOBOCAN data, the data is only truly representative of cities/regions in that country with sufficient cancer registry data quality to have submitted and been accepted for publication. The unreported incidence, from regions without registry coverage or with poor quality data, may in fact be much higher.\textsuperscript{304}

Another issue with GLOBOCAN incidence rates relates to the values themselves and their derivation. Age-standardisation in GLOBOCAN is according to the World Standard Population which means incidence rates will tend to be lower compared to national incidence data from developed countries with older population distributions. This issue is further discussed in Section 2.2.3.9.
2.2.3.3 Cancer registration methodology

A cancer registry, by definition, is an information system that collects, stores, and analyses cancer epidemiology in a designated population. Its purposes are to provide accurate and timely data to assist interested bodies (government, health care providers, researchers, insurers) in the management and prevention of cancer. The methodology used for cancer registration must provide for complete data collection and enable comparisons to be made using recognised standards of data quality.

When comparing the methodology of different cancer registries, important characteristics relating to the registry background, case ascertainment procedures and information collected need to be noted.

Registry background

The population for which the registry is responsible can be described in terms of both numbers and geography. The population number used to calculate rates is provided generally from official census data, and interpolated between census or extrapolated from the last census. Larger populations are likely to give more accurate estimates of rates, provided that case capture is complete.

In addition to understanding aspects of the population geography such as population density and its urban or rural location, more specific details regarding the health facilities available within the area and beyond its boundaries can affect the registration completeness. If health services for consultation, diagnosis and treatment are located beyond the geographical boundaries of the population, there may be difficulty in capturing data from residents treated outside the area, leading to underestimation of the local incidence rates. Conversely, if the area has a renowned health facility that attracts non-residents, then incidence rates may be overestimated if non-residents are not excluded from analysis.

Many registries in developed countries are assisted by legislation that make cancer diagnosis reportable by health care facilities and/or health care workers. However, this may be variably applied and is not a guarantee for completeness.
Case ascertainment

Cancer cases are reported to the cancer registries from a number of sources including hospital inpatient and outpatient records (at public and private hospitals), radiotherapy departments, pathology laboratories, screening programs, autopsy and death certificates. Public hospital inpatient records and death certificates are the most frequent sources for case finding, at a near universal level, whereas reports from the outpatient and private settings can be variable, according to surveys published by GLOBOCAN. Notably, radiology departments do not report, and are not required to report cancer diagnoses in many jurisdictions, so uncommonly so as not to be included at all in these surveys of data sources.

In Victoria, for example, the Cancer Act 1981 has made it mandatory for all hospitals and pathology laboratories to notify cancer diagnoses to the Victorian Cancer Registry (VCR). Hospital notifications are based on coded diagnostic information extracted by trained hospital coders using discharge summaries of the inpatient admission. Note, therefore, that outpatient attendances are not coded, and hence not notified. Pathology labs send copies of all pathology reports (including histopathology, cytology, haematology, cytogenetics, and ancillary studies) that relate to a cancer diagnosis, progression or recurrence. The VCR also receives copies of all death certificates for deaths in Victoria which are then linked to previous notifications. Unlinked cases are traced back through to the source hospital for confirmation of coding. However, the VCR has no authority to question or validate the source data supplied by the hospital coders, which in turn, are dependent on accurate discharge summaries.

Cancer registration is thus dependent on primary sources forwarding notifications that are accurately coded. The first problem is the completeness of forwarding itself, which can often be a manual process by hospital information managers. In a review of 4613 cancer cases in the Health Information System in Sabah, Malaysia, only 84.3% had been registered with the local cancer registry. Other recent studies have confirmed this problem exists even at cancer registries with reputations of high data quality (see section 7.1.1.).

The second problem with case ascertainment relates to the coding practices performed at the data source, prior to being forwarded to the cancer registry. The World Health Organisation International Classification of Diseases (ICD) is the
standard used, although implementation of the various ICD editions is variable among the registries (see Section 2.1.1.2).

**Information recorded**

With each cancer report, the standard parameters forwarded to the cancer registry include:

1. basic demographics (name, sex, date of birth, ethnicity/race, residence, social security or Medicare number) to preclude double entry from other sources
2. cancer details (incidence date – generally diagnosis date, or first hospitalisation with diagnosis), primary site, histological type according to ICD coding.
3. stage of disease, as diagnosed by the physician
4. nature of the first treatment
5. follow-up status – death or living

It is interesting to note the variability in the information categories collected by different cancer registries across the world. The nature of the first treatment is the most variably collected, with almost universal collection in the US, UK, Japan and Korea, variable in mainland Europe and the rest of Asia, and not at all in Australia and South America. The stage of disease also follows a similar collection distribution, although with more registrations than that of treatments. Conversely, ethnicity/race was not collected by most registries apart from the US, UK and Australia – possibly a reflection of the greater multi-cultural nature of these societies compared to the rest of the world.
2.2.3.4 Changing diagnostic criteria and classifications

As discussed in section 2.1.2.7, the current accepted diagnostic criteria for HCC endorsed by international liver society guidelines involves a clinical and radiological diagnosis in most cases, with histological verification only required if the imaging is not diagnostic. Hence, an increasing proportion of HCCs in cancer registries have only a clinical basis for diagnosis. For example, in a study of HCC epidemiological trends over 20 years, data from the US SEER database revealed that the incidence of unconfirmed (non-histologically proven) HCC is rising at twice the rate of histologically confirmed HCC (annual percentage change 7.9 vs 3.2, respectively).³⁰⁹

![Incidence trends in histologically confirmed and unconfirmed HCC](image)

Figure 2-1. Incidence trends in histologically confirmed and unconfirmed HCC
Source: Altekruse et al 2012³⁰⁹

Data from registries such as the Surveillance, Epidemiology and End Results (SEER) program in the United States show that microscopically confirmed HCC has declined from 92.5% in 1976-1980 to 79.3% in 1996-2000 ³¹⁰ In contrast, radiologically diagnosed cases have increased to 12.5%.
Depending on the classification methodology of local cancer registries, non-histologically confirmed HCC may be coded as Liver Cancer Unspecified (ICD-10 C22.9). There are global disparities in this practice which can be seen in the GLOBOCAN database or Cancer Incidence in Five Continents with some registries coding more than 50% of their liver cancer cases as Liver Cancer Unspecified. A recent study reviewing the Swedish Cancer Registry showed that over the period 1975-2011, 22% of the liver cancers coded were unspecified. This is discussed further in section 0.

Hence, misclassification due to changing diagnostic criteria may contribute to underreporting of cancer incidence by cancer registries. This is an issue of validity that also creates problems for the assessment of registry completeness.
2.2.3.5 Registry Data Quality and Limitations

Indicators of registry data quality can be considered in four main areas: comparability, completeness, validity and timeliness. As this thesis is primarily concerned with assessing incidence rates, the discussion on completeness is most relevant and will be the focus of this section, following a brief overview of the other indicators.

Comparability

Data from registries must be comparable between different populations and different time periods in order for meaningful interpretation to be possible. A standard system of classification provides for this, with the WHO International Classification of Disease used since its first publication in the late 1940s and in its 10th edition at the commencement of this research. For neoplasms, an additional system is often used, the International Classification of Diseases for Oncology (ICD-O) which provides specific descriptors of cancer: topography (anatomical site), morphology (microscopic appearance and cellular origin), behaviour (malignant, benign, in-situ, uncertain) and grade (extent of differentiation), as well as basis of diagnosis (microscopy/histology, clinical).

Validity (accuracy)

Validity is the accuracy at which the cancer registry data set reflects the true situation. This can be determined through several methods.

Reabstracting and recoding audits involve performing an independent review of coding from the source medical records followed by comparison with the original coding. This evaluates both the validity of coding, and reproducibility among different data collectors.

Morphological verification (by histology, cytology or microscopy) is a means of validation of the diagnosis, considered to be most accurate. The percentage of morphologically verified cases can therefore be used as an indicator of data quality in the cancer registry. However, this value must be evaluated against the current practice for individual cancers. With advancing technology, tumours such as HCC are
increasingly diagnosed by radiology, and so without histology, the percentage of morphological verification should decrease. Hence, an inappropriately high percentage for certain cancers may suggest over-reliance on pathology rather than clinical data sources, and possibly leading to incomplete registration. Conversely, the rate of death certificate only notifications, whereby there is no other corroborating data source for registration, is associated with reduced validity.

**Timeliness**

The speed of access to cancer data is important for healthcare policymakers and researchers to respond to emerging trends and yet there may be a trade-off between timely availability and improving completeness and accuracy of registration. Smith-Gagen et al\textsuperscript{313} defined time to availability as the interval between the date of diagnosis and the date of availability in the registry for research. While there are no international guidelines for timeliness, several North American cancer registry bodies including SEER, Center for Disease Control, and North American Association of Central Cancer Registries have set standards of 95% registration of cases within 24 months of the end of the diagnosis year.\textsuperscript{312}

However, GLOBOCAN which is often the reference for epidemiology reports has significant delays in its reporting. The publications GLOBOCAN 2012\textsuperscript{314} and Cancer Incidence in Five Continents Vol X (2014)\textsuperscript{15} are actually reports of incidences from 2003-2007. This delay is a concern with rapidly changing cancer epidemiology such as that of HCC, which is influenced by the effects of migration, infections risk factors and new antiviral treatments. Public policy cannot be made on such delayed reporting but it may do so unwittingly.

**Completeness**

Possibly the most important indicator of data quality is completeness of registration as only with maximal case capture can incidence and mortality rates have meaningful significance. Completeness of registration is the proportion of all incident cases in the registry population which is accounted for in the registry. This value should approach 100% in order to adequately compare rates between populations. Methods to assess for completeness are presented below in section 2.2.3.6.
2.2.3.6 Methods of assessing cancer registration completeness

A number of methods have been used to evaluate or estimate the completeness of cancer registration, and can be broadly grouped into two categories: qualitative and quantitative methods.\(^{315}\)

**Qualitative methods**

Qualitative (or semi-qualitative) methods can indicate a level of completeness, relative to historical or regional data, without quantifying the number of missing cases. Several types of qualitative methods may be used:

**Historic data methods** compare registry incidence trends with stability of incidence rates over time and with other regional registries to assess for statistically significant changes that might suggest under or over-registration. This method is employed by Cancer Incidence in Five Continents.\(^{15}\) However, changes in diagnostic modalities, screening programs, or specific local/regional variations in risk factors may cause abrupt changes in incidence reflecting the true state, rather than incompleteness of registration.

**Mortality:incidence ratios** compares the number of deaths (independently sourced via the death registry) and the number of incidence cases (from the cancer registry) for a given year. This ratio should approximate the value of (1-survival probability), where the survival probability is taken at 5 years. Provided survival is relatively constant for a cancer and the mortality figures are accurate, then the ratio can indicate registration completeness. For example, if the mortality:incidence ratio is increasing when survival has been stable, then it suggests incidence is declining or being under-reported. This method however is reliant on a number of variables: accurate mortality reporting with the correct tumour identified on death certificates and assumption regarding 5-year survival probability in the context of rapidly improving medical therapy.
**Histological verification of diagnosis** as discussed previously for validity. If the rate is higher than expected (compared to clinical practice), this could suggest incompleteness of registration of clinically diagnosed cases.

**Proportion of cases with unknown basis of diagnosis.** Registries are required to note the basis of diagnosis: histology, cytology/haematology, radiology, autopsy, clinical diagnosis only or “unknown basis of diagnosis”. A rate greater than 20% has been used to suggest incompleteness and exclusion from publication by Cancer Incidence in Five Continents.\(^{15}\)

**Quantitative methods**

Quantitative methods provide a measure of registration completeness with a value generated. One of three methods are commonly used:

**Independent case ascertainment** can be done by reassessing the same sources used by the cancer registry to check for missing cases, and/or by using additional independent sources and comparing with registry results.

When this approach is employed by a single hospital, what is in fact occurring is an audit of the hospital’s reporting completeness, rather than true assessment of registry completeness which involves registration from multiple sources.

Some examples of studies assessing registry completeness using different types of independent sources include:

- Data linkage with a clinical study cohort. Comparing the cancer registry in Denmark with a cohort of cervical cancer patients recruited in a clinical study, the authors\(^ {316}\) found a 2.2% deficit of cancer registration in the registry. In another study, a cohort of patients with Hodgkin’s disease from the British National Lymphoma Investigation database was used to evaluate the national cancer registry completeness, which was found to be 89.7% complete.\(^ {317}\) It should be noted, however, that only one data source (clinical study patients) was
used in either examples, and thus the evaluation of registration completeness may not account for non-study patients in the population.

- Data linkage with a centralised general practice database. After the comparison, the Limburg (Netherlands) cancer registry was found to have captured 96.2% of the possible malignancies from the GP database.\textsuperscript{318} While this is laudable, the true completeness percentage is likely to be lower, considering that patients presenting to hospital with cancer, and either dying or managed through hospital outpatients would have been missed by the GP database.

- Prospective reporting from clinical cohort study of 17,000 women in the Oxford-FPA contraceptive study who informed study investigators of cancer development, of which 86.5% were eventually registered to the cancer registry, with a median lag-time of 2.5 years.\textsuperscript{319} This study revealed more about the nature of reporting of cancer than the actual completeness of the registry, as it also did not account for non-study patients.

- Cases identified in a multi-hospital case-control study in which the Kampala cancer registry in Uganda was found to be 89.6% complete.\textsuperscript{320}

- Retrospective analysis of hospital specialist clinic databases that are not accessed by coding found that the Estonian cancer registry was 90.8% complete.\textsuperscript{321}

- Cases identified by community survey. A survey was sent out to randomly selected areas of Chennai, India to ask households to identify cases of cancer incidence between 1982-1995 and then compared to the cancer registry for the same period and areas.\textsuperscript{322} More than half the residents had moved their residence but of those remaining, the cancer registry had registered 96% of the cancers. However, the authors did not account for the unknown, unregistered cancers in those previous residents; their denominator was purely the known remaining residents.

- Data-matching with the primary source. Reviews of the source of notification (usually hospital admissions database or national patient registry) have been compared with eventual cancer registry records with
finding of incomplete registration of about 80% in all cancers\textsuperscript{307} and under 50% in HCC.\textsuperscript{311} See sections 0 and 7.1.1.

From these examples, it can be seen that even using independent sources of case capture can have limitations; the ability of those sources to capture or represent the entire population needs consideration. Preferably, using multiple simultaneous independent sources would reduce this limitation. This has been a recent development which will be discussed in section 7.1.1.

**Capture-Recapture Methods**

This method was first developed to estimate the population of animals in a closed environment. In the ‘capture’ phase, animals were captured, tagged and released. This was repeated in a second, independent ‘recapture’. The numbers captured in each phase and the numbers common to both phases were used in a mathematical model to estimate the total population size.

This method has been used to estimate the completeness of cancer registries in general,\textsuperscript{323,324} as well as HCC in particular.\textsuperscript{311}

However, unlike the original context the modelling was designed for, cancer registrations involve a number of biases. The accuracy of the model is reliant upon two factors:

1. The independence of each capture source and each recapture attempt. The probability of being captured from one source in a multi-source model should not affect the likelihood of being captured from another source. Further, all individual cases must have the same probability of being captured.

2. The actual case is a true diagnosis. This is discussed further in Section 0 under Validity.

In cancer registration, especially with HCC, the stage of tumour at presentation or the performance status of the patient or a host of other factors can affect the
probability of the case being notified via any primary source (e.g. hospital admission, community palliative care facility, death certificate).

A number of methods have been formulated to resolve this issue of dependency between primary sources. Brenner,325 with further development by Crocetti,326 used pairs of primary sources to estimate interdependence, before comparing against a third source with known completeness to reduce variance in the estimates. Where all sources are dependent, a log-linear model has been applied such as that used by Törner et al in estimating completeness of HCC capture at the Swedish Cancer Registry.311

**Death certificate methods**

Cancer registries have a number of categories for notifications from death certificates:

- **Death Certificate Initiated (DCI)** – the death certificate was the first and independent source without which the case would not have been found. Often, information is traced back through hospital records that had failed to register the case in order to clarify the diagnosis.

- **Death Certificate Notification (DCN)** – The notification was first received from the death certificate, but other sources (later) also independently registered the case without requiring tracing back from the cancer registry

- **Death Certificate Only (DCO)** – No other sources apart from the death certificate were found that mention the case, despite all trace back efforts. High DCO rates may indicate incomplete case capture but may also be due to efficient tracing back efforts.

Two statistical methods using death certificate notification data have been used to estimate the completeness of cancer registration. The Death Certificate and Mortality:Incidence ratio method described by Parkin et al327 using DCN, DCO and mortality:incidence ratios estimate completeness. The Flow method developed by Bullard et al328 estimates the proportion of unregistered patients using three
probabilities: the probability of survival, the probability of cancer registration before death, and the probability of the death certificate mentioning cancer.

**Actual use**

A survey conducted to ascertain the methods used by 56 European cancer registries found the following methods used (at one point or another):\textsuperscript{329}

- Estimation of completeness – 48 registries
- Historic comparisons – 31 registries
- Comparison with a reference registry – 28 registries
- Capture-recapture method – 12 registries
- Flow method – 10 registries
2.2.3.7 Completeness of HCC and other cancer registration

HCC / Liver cancer registrations

There has never been any formal study evaluating the completeness of HCC registration prior to this research. The nearest comparator is a small study where liver cancer was used to investigate the completeness of a cancer registry. In a short correspondence, Kaczynski and Wallerstedt\textsuperscript{330} reported on their assessment of the completeness of the Swedish Cancer Registry. They chose to study liver cancer in Gothenburg, Sweden (population 395,000 – 444,000) reported during the period 1958 to 1970. This was an ideal subject as liver cancer had relatively low numbers and there was evidence of increasing incidence at the time. The authors searched patient discharge records from all hospitals in Gothenburg, biopsy and autopsy reports, and death certificates. Cases were extracted using the diagnostic code WHO 155.0 for primary liver cancer (n=295), and 156 for liver cancer of uncertain origin (n=50). Histological verification rate was 96% and the rate of incorrectly coded liver cancer was 8.5%. They only found two cases through other sources that had not been registered, such that the completeness of the registry was thought to be 99%.

Contrasting this with the recent study of the same Swedish Cancer Registry by Törner et al\textsuperscript{311} finding only 47% of HCCs being registered, it is apparent that this earlier study was erroneous. While the reported completeness rate appeared reassuring, the reality of the underreporting was concealed by the inadequate capture of clinical cases at the time. This is discussed further in Section 7.1.1.

Apart from this study by Kaczynski and Wallerstedt, there have not been any other study specifically of liver cancer/HCC registration completeness using independent case ascertainment. All other studies have assessed the entire cancer registry (all cancers) using the various modelling methods discussed in section 2.2.3.6, with liver cancer included in the results.

Using the Flow Method, Lorez et al\textsuperscript{331} evaluated the completeness of case ascertainment of all cancers at the Swiss cancer registry. They found that liver cancer had one of the lowest completeness of registration rate at 89.8%, with a histological verification rate of 56.7% which was the lowest by far (most cancers greater than 95%, next closest was pancreatic cancer at 73.7%).
Other cancer registrations

Presented here are examples of studies reporting underreporting of cancer incidence or incomplete registrations by cancer registries. Cancers that are difficult to diagnose, with lower rates of histological verification and high rates of clinical diagnoses (such as pancreatic cancer and liver cancer) are more likely to be underreported.

In a recent review of the Swedish Cancer Register which has traditionally been of high quality, Kilander et al\textsuperscript{332} compared the cancer registry data with that of the Swedish Patient Register through record linkage. They found that both pancreatic and biliary tract cancers were not reported to the cancer registry in 44\% of cases. The concordance between the two registries has only worsen over time, dropping from 63\% in 1990-1994 to 44\% in 2005-2009.
2.2.3.8 Types of studies of HCC incidence

This section summarizes the types of studies in the literature reporting HCC incidence, their features, advantages and disadvantages and provides examples of each type.

Population-based studies

• Population-based are studies where cases are ascertained from the entire population.

• Requires a geographically defined population to use as the denominator and all cases that fulfill diagnostic criteria in that population are used as the numerator. They should be differentiated from cohort-based incidences, see Cohort-based studies, below.

• Types of source data:
  
  o Primary case capture: None in the literature. This research will be the first to report HCC incidence based on primary case capture

  o Cancer Registry data: Current HCC incidence studies report from this source, within the limits of the cancer registry methodology as discussed above. Examples: 298,333

  o Hospital databases, National patient registry, death certificate: This requires a defined geographical region in order to calculate population incidence. Examples: 311,334,335

• Modelling:
  
  o E.g. Sartorius et al\textsuperscript{304} used HBV and HCV population-data in a model to estimate the degree of underestimation of HCC incidence compared to GLOBOCAN reported incidence. This is of course reliant on the accuracy of both GLOBOCAN (and local) registry data and HBV/HCV data.

• Advantages:
  
  o Provides incidence (and other data) across the spectrum of tumour presentations, tumour stages, performance status and social demographics

  o Accurate due to directly observed results rather than modelling results, provided the methodology of case capture is complete
• Disadvantages:
  o Labour intensive with primary case capture
  o Dependent on the limitations of the source registry (as discussed above)

  **Cohort-based studies**

  • The study population is based on an institution or a group recruited for a purpose such as a clinical trial or observational study
    o Reporting the cohort incidence uses the cohort size as the denominator, and the cases identified as the numerator.
    o Sometimes, the cohort come from the general population, but the findings of the study, i.e. HCC incidence, becomes cohort-based. For example, linkage studies between HCC registrations and HBV/HCV notifications\(^{295}\) can only report the incidence of HCC in HBV/HCV infected patients, and not the population incidence of HCC. In another study, Hallager et al\(^{336}\) correctly titles their study “A nationwide cohort study” as they estimated HCC incidence in a cohort of chronic HCV infected patients with cirrhosis, rather than from the general Danish population.
  
  • The cohorts range in size from clinical trial or observational study size,\(^{137}\) to single or multicentre cohorts\(^{295,337}\) to nationwide cohorts with particular risk factors.\(^{336}\)

  • Advantages:
    o Provides specific information on the risk group of interest rather than the general population risk
    o Easier to perform as the cohort is often already recruited
    o Accurate as the cohort is often well described

  • Disadvantage:
    o Unable to define population incidence
    o Cannot be generalised to other risk groups
2.2.3.9 Age-standardisation

As incidence and mortality rates vary significantly within a population between age-groups, a summary rate (conceptually this can be considered an ‘average’) is required when comparing populations. For example, the age-specific incidence of HCC is much higher in 70-year-old compared to 20-year-old Australian men, but how does the ‘average’ Australian’ man compare with the ‘average’ Chinese man?

The simplest method would be to present a crude rate, which is calculated as the number of disease cases divided by the total population. For example, 200 cases in a city with a population of 1 million, would give a crude incidence rate of 20 per 100,000 people.

Surprisingly, this crude incidence rate was the only method used by a recent large population-based study derived from the entire French population. Using national patient records, this was the first study of HCC epidemiology at the population-level in France and yet Goutte et al\textsuperscript{334} described their calculation of HCC incidence as “dividing the annual counts of incident HCC by the annual adult French population size”.

This is problematic because the age distribution of the population can profoundly influence the application of crude rates. For diseases such as HCC which rarely affects children, and has increasing incidence with progressive age, this summary incidence rate must take into account the age distribution of the population. Where the population tends to be younger than that of the typical age in disease, the age-standardised rate will be lower than the crude rate. Conversely, with a higher aged population such as in Australia, where the older population matches the older age of typical disease cases, then the age-standardised rate will be higher than the crude rate.

Age-standardisation is a fundamental process applied by cancer registries and epidemiological studies as a means of comparison between different populations.

There are several reference standard population age distributions that are used in the calculation of age-standardised rates. Table 2-2 shows the standard populations commonly used in the literature. The standard population developed by Segi\textsuperscript{338} in 1960 is often referred to as the “World” Standard Population, being the most often used by studies, including those based on International Agency for Research on Cancer’s GLOBOCAN database. It has a younger population (40% are less than 20 years old)
than another commonly used standards, the Scandinavian “European” Standard Population and WHO World Standard Population which have higher proportions of older ages.

Alternatively, national cancer registries may use standard populations derived from their own population, such as United States National Cancer Institutes’ Surveillance, Epidemiology and End Results (SEER) program which updates its standard population every decade.\textsuperscript{339} Similarly, the Australian Bureau of Statistics and the Australian Institute of Health and Welfare have recommended using an Australian Standard Population for age-standardisation of Australian data, which is updated every 25 years.\textsuperscript{340} Age-standardised rates using the standard population from which the data originates thus provide the most accurate summary data in applying incidence and mortality rates in the local setting.

Table 2-2. Standard Population Distributions (percentage)

<table>
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<th>Age group</th>
<th>Segi (&quot;world&quot;) standard</th>
<th>Scandinavian (&quot;European&quot;) standard</th>
<th>WHO World Standard</th>
<th>Australian Standard</th>
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<td>1.70</td>
</tr>
<tr>
<td>85+</td>
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<td>1</td>
<td>0.63</td>
<td>1.37</td>
</tr>
<tr>
<td>Total</td>
<td>100</td>
<td>100</td>
<td>100</td>
<td>100</td>
</tr>
</tbody>
</table>
2.2.3.10 Problems with HCC classification at the VCR

In 2012, only 46% of registered HCC in the Victorian Cancer Registry had histological verification, the lowest compared to all cancers recorded by the registry with most cancers having greater than 90% histological verification. Conversely, liver cancer had the highest percentage (4.8%) of Death Certificate Only registrations. Both of these indices of data quality suggest an incomplete registration of HCC using current registration methodology.

<table>
<thead>
<tr>
<th>Site</th>
<th>DCO%</th>
<th>HV%</th>
<th>M/I%</th>
</tr>
</thead>
<tbody>
<tr>
<td>All malignant tumours</td>
<td>1.7</td>
<td>93</td>
<td>37</td>
</tr>
<tr>
<td>Head &amp; neck</td>
<td>0.8</td>
<td>97</td>
<td>32</td>
</tr>
<tr>
<td>Oesophagus</td>
<td>1.2</td>
<td>92</td>
<td>68</td>
</tr>
<tr>
<td>Stomach</td>
<td>1.7</td>
<td>95</td>
<td>63</td>
</tr>
<tr>
<td>Bowel</td>
<td>1.4</td>
<td>95</td>
<td>38</td>
</tr>
<tr>
<td>Liver</td>
<td>4.8</td>
<td>46</td>
<td>79</td>
</tr>
<tr>
<td>Gallbladder</td>
<td>0.0</td>
<td>79</td>
<td>82</td>
</tr>
<tr>
<td>Pancreas</td>
<td>4.4</td>
<td>67</td>
<td>89</td>
</tr>
<tr>
<td>Lung</td>
<td>3.4</td>
<td>86</td>
<td>73</td>
</tr>
<tr>
<td>Melanoma</td>
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<td>99</td>
<td>14</td>
</tr>
<tr>
<td>Breast</td>
<td>0.6</td>
<td>99</td>
<td>20</td>
</tr>
<tr>
<td>Cervix</td>
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</tr>
<tr>
<td>Uterus</td>
<td>0.9</td>
<td>98</td>
<td>18</td>
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<tr>
<td>Ovary</td>
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<td>66</td>
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<td>96</td>
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<tr>
<td>Testis</td>
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<td>98</td>
<td>2</td>
</tr>
<tr>
<td>Kidney</td>
<td>1.8</td>
<td>89</td>
<td>28</td>
</tr>
<tr>
<td>Bladder</td>
<td>2.1</td>
<td>91</td>
<td>41</td>
</tr>
<tr>
<td>Brain &amp; CNS</td>
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<td>87</td>
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<tr>
<td>Thyroid</td>
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<tr>
<td>Unspecified site</td>
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<td>68</td>
<td>96</td>
</tr>
<tr>
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<td>99</td>
<td>26</td>
</tr>
<tr>
<td>Multiple myeloma</td>
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<td>99</td>
<td>51</td>
</tr>
<tr>
<td>Leukaemia</td>
<td>3.6</td>
<td>96</td>
<td>52</td>
</tr>
</tbody>
</table>

Figure 2-2. Indices of data quality of cancers at the Victorian Cancer Registry in 2012.
DCO = Death certificate only, HV = Histological verification, M/I = Mortality to incidence ratio

Through personal correspondence with VCR, a break-down of liver cancer registrations for 2009 was obtained for study. When broken down into the different
subtypes of primary liver cancer, HCC (ICD-10 C22.0) only forms a third of the total, with a quarter being ICC (ICD-10 C22.1). The remainder is the largest group, classified as Liver Cancer Unspecified (ICD10 C22.9), meaning that there was no histological verification.

**VICTORIAN CANCER REGISTRY 2009**

<table>
<thead>
<tr>
<th>Morphology</th>
<th>C220</th>
<th>C221</th>
<th>C222</th>
<th>C223</th>
<th>C224</th>
<th>C229</th>
<th>Total</th>
</tr>
</thead>
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<tr>
<td>Carcinoma NOS</td>
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<td></td>
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<td>4</td>
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<tr>
<td>Adenocarcinoma</td>
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<td>12</td>
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<td></td>
<td></td>
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<td>24</td>
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<tr>
<td>Cholangiocarcinoma</td>
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<td>30</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>60</td>
</tr>
<tr>
<td>Klatskin tumour</td>
<td>2</td>
<td>2</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>4</td>
</tr>
<tr>
<td>Hepatocellular ca</td>
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<td>106</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>212</td>
</tr>
<tr>
<td>Hepatocellular ca, fibrolamellar</td>
<td>1</td>
<td>1</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>2</td>
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<tr>
<td>Hepatocellular ca, clear cell type</td>
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<td>1</td>
<td></td>
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<td></td>
<td></td>
<td>2</td>
</tr>
<tr>
<td>Hepatocellular ca, pleomorphic type</td>
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<td>2</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>4</td>
</tr>
<tr>
<td>Hepatoblastoma</td>
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<td>2</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>4</td>
</tr>
<tr>
<td>Embryonal sarcoma</td>
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<td>1</td>
<td></td>
<td></td>
<td></td>
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<td>2</td>
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<tr>
<td>Angiosarcoma</td>
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<td>1</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>2</td>
</tr>
<tr>
<td>Not microscopically confirmed</td>
<td>34</td>
<td></td>
<td>127</td>
<td></td>
<td>161</td>
<td></td>
<td>321</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td>108</td>
<td>80</td>
<td>2</td>
<td>1</td>
<td>1</td>
<td>129</td>
<td>321</td>
</tr>
</tbody>
</table>

**ICD10 code descriptors**

C220 = Hepatocellular carcinoma  
C221 = Intrahepatic cholangiocarcinoma  
C223 = Angiosarcoma of liver  
C224 = Other sarcoma of liver  
C229 = Liver cancer unspecified

Figure 2.3. Breakdown of Primary Liver Cancer subtypes at the Victorian Cancer Registry 2009

The incidence trends in males for these three coding groups over the last 10 years at the VCR are shown Figure 2.4. The greatest rise in incidence occurred with the C22.9 liver cancer unspecified group, suggesting that the changing diagnostic criteria for HCC may be impacting the way HCC is being registered by the cancer registry.
Figure 2-4. Trends in Incidence Rates of HCC, ICC and Unspecified liver cancers in Males (VCR).

Hence, while studies across the world are reporting rising incidence of HCC, this needs to be true rates of HCC alone and not of primary liver cancer, as this is confounded by rates of ICC which is also on the rise\textsuperscript{18}. And if they are in fact deriving HCC-specific data from cancer registries, the reader needs to know how that registry is dealing with the issue of non-histologically confirmed HCC. Do the reported HCC rates include this larger group of C22.9 Liver Cancer unspecified, many of which are HCCs as defined by current clinical-radiological criteria?

Importantly, as HCCs are becoming clinically diagnosed, how accurate and complete is cancer registry data, given the low histologically verified rates and the high Death Certificate Only registrations?
2.3 SURVEILLANCE OF HEPATOCELLULAR CARCINOMA

2.3.1 Defining screening and surveillance

Screening is the use of a test to detect disease in its asymptomatic phase in the individual. Surveillance is the application of the screening test at regular intervals to detect disease in still asymptomatic patients. The main objective of surveillance is to reduce the mortality associated with the disease, through detection of earlier stage disease amenable to cost-effective curative therapies.

Surveillance for HCC satisfies the principles proposed by the World Health Organisation for the provision of a surveillance service. HCC is an important global health problem with high morbidity and there are accepted treatments available and accessible to most patients. There is an early asymptomatic phase which is detectable using modalities acceptable to the screened population, one which has been clearly defined. The natural history of HCC is also well studied and treatment guidelines by international authorities help direct management at its various stages. HCC surveillance has been analysed from a cost-effectiveness perspective and found to be favourable for long-term application to reduce morbidity with earlier diagnosis. Some of these points have been discussed elsewhere in this literature review, and others will be further explored below.

2.3.2 The efficacy of HCC surveillance

The efficacy of HCC surveillance has been evaluated in a number of studies of various designs. The highest level of evidence available in this area is Level II being randomised controlled trial, of which two have been performed.

The first was a negative trial, in which Chen et al investigated the effectiveness of screening using AFP testing to reduce mortality from liver cancer in HBsAg positive men in China over the period 1989-1995. Participants were randomly assigned in clusters (by township of residency) to receive six monthly AFP testing or nothing. The screened group (n=3712), compared to the controls (n=1869), had better early survival (23.7% one-year survival, vs 9.7% respectively). However, there was
no difference in five-year survival between the groups, suggesting the presence of lead-time bias.

The second RCT used both ultrasound and AFP to screen patients at 6-month intervals. Zhang et al randomised clusters (whole factories and villages as one unit) of 18,816 subjects aged 35-59 in Shanghai, China into either screening with 6 monthly ultrasound and AFP or controls for follow-up. Participants had serology positive for HBV infection (including sAg negative but core Ab positive patients, and excluding vaccinated patients with sAb positive only) or chronic hepatitis (elevated ALT/AST for more than 6 months), regardless of cirrhosis status which was not examined. Consequently, this target population has a lower risk of HCC than those recommended for surveillance under current international guidelines. Despite only 58.2% attendance of screening appointments, the screened group achieved a relative mortality reduction of 37% with 1-, 3-, and 5- year survival rates at 65.9%, 52.6%, 46.4% compared to 31.2%, 7.2%, 0%, respectively, in the controls.

Strangely however, while screening is generally expected to identify more patients with earlier stage disease, the control arm did not include a single person found with stage I HCC (zero vs 60.5% in those screened) or small HCC (zero vs 45.3%); in other words, no incidental diagnoses occurred among the 9,443 control patients over the entire follow-up period. This does raise questions regarding the validity of the results.

No further RCTs have been performed due to a number of reasons, one of which is the ethical dilemma of randomisation in light of an increasing number of observational studies with outcomes favouring surveillance. (Discussed further in section 2.3.4)

These studies have addressed the major limitation of the RCTs when applied to the Western population in which cirrhosis, due to a number of aetiologies other than chronic HBV infection, is the most important risk factor for HCC. Given the lack of RCT data for surveillance in cirrhosis, the level of evidence from these observational studies may be strengthened through meta-analysis.

Singal et al\textsuperscript{143} analysed the pool data from 47 studies of surveillance by ultrasound with/without AFP in patients with cirrhosis, for the outcomes of early detection, receipt of curative therapy and/or overall survival. Nearly half (41.4%) of
the 15,158 patients studied had HCC detected by surveillance, which was associated with improved early stage detection (odds ratio [OR] 2.08, 95% CI 1.80–2.37) and curative treatment rates (OR 2.24, 95% CI 1.99–2.52). Surveyed patients also had significantly better survival (OR 1.90, 95% CI 1.67–2.17), remaining significant in studies adjusted for lead-time bias.

2.3.3 Potential bias from non-randomised studies

The use of non-randomised data can lead to bias, which can be especially important when evaluating the efficacy of cancer screening. The major types of biases are addressed below in relations to surveillance for HCC.

2.3.3.1 Lead-time bias

Lead-time is the length of time between when a disease is diagnosed by screening in its asymptomatic phase and when it would have presented symptomatically without screening. Hence, lead-time bias may occur when the improved survival from surveillance is incorrectly attributed to the screening intervention; only an earlier diagnosis of asymptomatic disease is achieved rather than a change to its natural history.

For example, suppose person A is diagnosed with HCC at age 70, presenting with weight loss, and dies at age 72 - his survival time, defined as the time between diagnosis of cancer and death, is 2 years. Another Person B is diagnosed with HCC by screening at age 68 while still asymptomatic, then becomes symptomatic at age 70, and dies at 72 - his survival time is 4 years from diagnosis. Here, screening has led to lead-time bias with Person B noted to have longer ‘survival’ whereas in reality, Person B lived with a known diagnosis for longer but died at the same time as Person A, that is, the natural history has not been changed by earlier diagnosis.

Randomisation removes lead-time bias by setting the start time (time=0) at the point of randomisation, rather than time of diagnosis. Hence, if Persons A and B were randomised at age 65, then randomisation enables the correct conclusion to be made, that there is no difference in their survival times (7 years each).
If earlier diagnosis from screening does improve survival by enabling therapies that influence natural history, randomisation would also make this apparent. For example, if Person B was diagnosed with earlier stage HCC at age 68, allowing curative therapy to given, and lived to age 75 whereas Person A was diagnosed at late stage with no therapy provided leading to death at age 72, then their survival times, taken from time of randomisation, would be 10 years and 7 years respectively. Hence, screening provides a 3-year survival benefit, adjusted by randomisation for lead-time bias.

In the absence of RCTs in HCC surveillance, the effect of lead-time bias has been studied by several groups. Cucchetti et al\textsuperscript{344} used HCC doubling times described in the literature to perform a probalistic analysis of 1,380 patients with Childs A/B cirrhosis from the ITA.LI.CA (Italian Liver Cancer Group) database. Patients who underwent 6 monthly surveillance by ultrasound +/- AFP had a 5-year survival rate of 32.7% compared to 12.2% in non-screened symptomatic patients (p<0.001). The median lead-time calculated for 6 monthly surveillance was 6.5 months, which translated to lead-time bias accounting for survival benefit until the third year from HCC diagnosis, after which survival benefits of surveillance became apparent.

Another Italian group, Trevisani et al\textsuperscript{345} found a similar lead-time of 239 days in those receiving 6 monthly ultrasound surveillance, resulting in greater 5-year survival than the symptomatic presentation group after adjusting for lead-time bias. Wong et al\textsuperscript{346}, in a Hong Kong study of HCC surveillance in patients with chronic viral hepatitis found that adjustments for doubling times of less than 90 days, resulted in lead-time of 236 days for the surveillance group, and significant survival difference at 2 years (49.4% vs 28.6% in non-surveillance, p=0.035).
2.3.3.2 Length-time bias

With the aim of detecting asymptomatic disease, screening preferentially detects slow-growing tumours rather than aggressive tumours that would otherwise present symptomatically. By their nature, these indolent screen-detected tumours would tend towards a greater length of time between diagnosis and death, that is, a better prognosis. Hence, screen-detected tumours may have better survival by their nature, rather than by the intervention of screening itself. The length-time bias is this artificial survival benefit attributed to screening. At its extreme end, length-time bias results in an overdiagnosis bias, whereby the screen-detected cancer would not have led to clinical detection in the subject’s lifetime.

Hepatocellular carcinoma is well known for its heterogeneous biology and prognosis (ref) and thus prone to length-time bias in the evaluation of HCC surveillance efficacy. Unlike lead-time bias, there is a paucity of studies addressing the issue of length-time bias in HCC surveillance.

In the largest study to address length-time bias, Mittal et al 347 followed 887 patients with HCC in the Veterans Administration population in the United States of whom only 46.5% received any surveillance prior to HCC diagnosis. To adjust for length-time bias, the authors excluded HCC diagnosed within 12 months of cirrhosis recognition. Even after adjustments for length-time bias, they found that patients who underwent regular HCC surveillance had lower mortality than those who did not, adjusted HR 0.61 (0.49-0.76).

Among patients undergoing surveillance, Cucchetti et al 348 found in their semi-Markov model with Monte Carlo simulation that 18% would present with symptoms in-between surveillance appointments. These patients were estimated to have tumour doubling times of 42 days compared to 100 days in those diagnosed with HCC at their scheduled appointments (without symptoms). In order to avoid length-time bias when reporting surveillance outcomes, they suggest that analysis be performed on an ‘intention-to-screen’ basis, inclusive of these faster growing tumours that present symptomatically in-between surveillance times.
2.3.3.3 Selection bias

Finally, randomised controlled trials can eliminate the effects of selection bias which can be present in all interventional studies. Participants may have certain characteristics in themselves that may influence results beyond that of the expected outcomes of the intervention. For example, patients with alcoholic liver disease may have other barriers to healthcare such as socioeconomic disadvantage that affect their compliance with surveillance. Hence, observational studies may bias such patients towards the non-surveillance group, whereas randomisation would facilitate an even distribution between the intervention (surveillance) and the control groups.

2.3.4 Randomised controlled trials may no longer be feasible

Randomised controlled trials are often presented as the epitome of scientific evidence for a proposed intervention to reduce lead-time, length-time and selection bias. However, the very nature of their robust methodology leads to potential problems in their applicability to other patient populations. The one RCT by Zhang et al\textsuperscript{349} looking at HCC surveillance using ultrasound has been questioned for its applicability to other non-HBV populations, including cirrhotic patients and non-Asians. In the current era, it would be difficult to conduct other RCTs merely to confirm applicability in different target populations as there are sufficient observational data available. It is likely impossible to surmount the ethical dilemma of proposing randomisation for a non-invasive intervention for which substantial non-randomised evidence suggest significant survival benefits.

Beyond ethical issues, the practicality of such an attempt has been addressed in a feasibility study from Australia. Poustch et al\textsuperscript{350} proposed randomised allocation to a screening program of ultrasonography 6 monthly and serum AFP 3 monthly to a group of 205 patients with cirrhosis attending liver clinics. After receiving information outlining the risks and benefits of surveillance in the process of informed consent, nearly all patients (99.5\%) declined to be randomised.
2.3.5 Cost-effectiveness of HCC surveillance

Where efficacy in HCC surveillance relates to its ability to significantly affect outcomes in earlier stage tumour detection and ultimately improved survival, cost-effectiveness is concerned about whether such an intervention is financially justified at the population level.

An intervention is considered effective if it increases life expectancy by at least 3 months, and cost-effective if it can do so at a cost less than $50,000 per quality-adjusted life-year gained. This standard has been utilised across many fields in medicine, in both diagnostic and therapeutic interventions, although in the current era, it has been suggested that the cost threshold needs to be increased.

Based on these principles, several studies have applied decision analysis to assess the cost-effectiveness of HCC surveillance. Markov modelling forms the basis for these analyses, with the important variables assessed being:

- The incidence of HCC in the target population
- The natural history of the underlying liver disease predisposing to HCC
- The therapeutic options available and their costs
- The diagnostic modality used for surveillance and its cost
- The surveillance interval

While all studies have affirmed its cost-effectiveness to some degree or other, the interplay of the above variables is important in prescribing guidelines for surveillance.
2.3.6 Target population for HCC surveillance

2.3.6.1 Cirrhotic patients

In one of the earliest studies, Sarasin et al. in 1996 applied a decision analysis model for HCC surveillance using 6 monthly ultrasound and AFP compared to tumours presenting clinically. The target population was Western patients with Child-Pugh A cirrhosis, and the treatment assessed was partial hepatectomy (liver transplantation was not considered). The authors found that cost-effectiveness was attained with a minimum HCC incidence of 1.5% per year to achieve an increase of 3 months life expectancy, and up to 9 months with incidence of 6% per year. This was provided cirrhosis-related survival was 80% at 5 years (as suggested by Child-Pugh A prognosis), with surgical survival rate of 40-60% at 3 years. While these parameters are not representative of the current practice with a breadth of curative treatments available and reduced therapy-related mortality, the principles provided a sound framework for guideline development and further studies.

Arguedas et al. applied modelling to hepatitis C-related compensated cirrhosis inclusive of liver transplantation as a treatment option and found 6 monthly surveillance using ultrasound and AFP, or CT and AFP as being cost-effective at annual HCC incidence greater than 1.4% per year.

Conversely, Lin et al. found that HCC surveillance was effective regardless of the underlying HCC incidence risk in their model applied to hepatitis C-related compensated cirrhosis. However, this was provided ultrasound was performed annually with AFP 6 monthly. If both ultrasound and AFP were used 6 monthly, then the cost-effectiveness ratio was $73,789 per QALY, which is more than the traditional $50,000 per QALY.

The major international guides from the American, European and Asia-Pacific liver societies have recommended HCC surveillance be offered to all patients irrespective of aetiology of cirrhosis. While some cirrhotic patients may be at lower risk of HCC, such as suggested by a recent Danish cancer registry study where the 5-year cumulative risk was only 1.0% in alcohol-related cirrhosis, exclusions based on aetiology have not been recommended due to insufficient evidence.

However, cost-effectiveness of HCC surveillance is predicated upon improved patient survival on cancer detection, which is in-turn dependent on their ability to
tolerate the treatment offered. In decompensated cirrhotic patients, Child-Pugh C or Child-Pugh B with extensive ascites, encephalopathy, hepato-renal syndrome or clinical jaundice) only liver transplantation can be offered. Hence, when liver transplantation is not an option, surveillance is not cost-effective in these patients.\(^{357}\)

### 2.3.6.2 Non-cirrhotic patients

The majority of HCC that develops in non-cirrhotic patients are due to chronic HBV infection, hence HBV has the strongest evidence and recommendations in guidelines for HCC surveillance in non-cirrhotics. These patients are more suitable for curative surgical treatments due to their functional liver reserve. The resultant improved survival rates and lower risk of recurrence allows the decision analysis modelling to require a lower HCC incidence risk to achieve cost-effectiveness. Expert opinion, including that from international guidelines, indicate that in non-cirrhotic HBV patients, HCC surveillance would become effective at an incidence of at least 0.2% per year.\(^{52,358}\)

As previously discussed in (Section…), the risk of HCC in chronic HBV is influenced by viral load, degree of hepatitis, age, sex, geographical region, ethnicity, family history and other variables. Thus, individual patients can be assessed using tools such as HCC risk calculators to determine when HCC surveillance might be appropriate when the annual incidence exceeds 0.2%. Recommendations have been made by the various international liver societies for groups of patients for whom this risk is exceeded and warrant surveillance. See Table 2-3

Advanced fibrosis (bridging fibrosis, Metavir F3) in chronic hepatitis C patients can also lead to HCC development, with an annual incidence of 0.8% in a US study of HCV patients who had failed peginterferon and ribavirin, and followed up for HCC incidence.\(^{137}\) Another study of a Japanese cohort of chronic HCV patients with mild fibrosis (F0 or F1) also suggested the annual incidence of HCC was 0.5%.\(^{359}\) While these figures fall under the 1.5% annual incidence for cost-effectiveness in cirrhotics, the European Association for the Study of the Liver still recommended surveillance,\(^ {52}\) possibly as their non-cirrhotic state and its improved therapy outcomes may alter the decision analysis model towards a lower acceptable incidence. They note also that the transition from advanced fibrosis to cirrhosis is difficult to accurately define, and
hence erred on the side of caution. This recommendation has not been made by other liver societies, with the benefit of surveillance considered uncertain based on current evidence. In addition, as previous HCV studies involved biopsy-proven fibrosis grading, it is difficult to apply to the current era in which fewer biopsies are performed and advanced fibrosis may be based upon less accurate, non-invasive tests such as elastography. Finally, with the advent of direct-acting antiviral therapy which allows cure of almost all HCV infections, including previously failed peginterferon and ribavirin patients, the ongoing annual HCC incidence in advanced fibrosis is likely to be even lower than that quoted in previous studies.

There is increasing evidence of HCC developing in NASH without cirrhosis; one study with 50% of 145 Italian NALFD-related patients and another study with 65% of 31 French patients with metabolic syndrome and HCC. However, no recommendations have been made regarding surveillance in this risk group due to a number of barriers to cost-effectiveness. The high prevalence of NAFLD in the general population makes it difficult to identify those with fibrosis, and ascertain annual HCC incidence risk. Universal surveillance for the entire NAFLD population would not be cost-effective. In addition, obesity reduces sensitivity for ultrasound-based screening, whereas the use of more sensitive modalities such as CT or MRI makes the process not cost-effective. Also impacting the decision analysis is the increased surgical risk of such patients, who may also have associated cardiovascular disease. More data is required to risk-stratify NAFLD patients appropriately to recommend surveillance.

With other chronic liver diseases due to autoimmune hepatitis, haemochromatosis, alcoholic liver disease and other causes, there is lack of evidence of HCC incidence in non-cirrhotic patients. Hence, there are no recommendations for surveillance in these groups, unless cirrhosis develops.
## 2.3.6.3 Comparison HCC surveillance guidelines

Table 2-3. HCC surveillance guidelines from international liver societies

Source: AASLD, EASL, APASL

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<thead>
<tr>
<th>Cirrhosis (Child-Pugh A/B), from:</th>
<th>AASLD</th>
<th>EASL</th>
<th>APASL</th>
</tr>
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</tr>
<tr>
<td>HCV</td>
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</tr>
<tr>
<td>NASH</td>
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<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Primary biliary cholangitis</td>
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<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Genetic haemochromatosis</td>
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<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Autoimmune hepatitis</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Alcoholic cirrhosis</td>
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<td>Yes</td>
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</tr>
<tr>
<td>Child-Pugh C cirrhosis - not transplant candidate</td>
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**Non-cirrhosis:**

Chronic hepatitis B patients, with:

<table>
<thead>
<tr>
<th></th>
<th>AASLD</th>
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<th>APASL</th>
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<tr>
<td>Asian males &gt;40 years</td>
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</tr>
<tr>
<td>Asian females &gt;50 years</td>
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<td>Yes</td>
</tr>
<tr>
<td>Africans &gt; 20 years</td>
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<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Family history of HCC</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Advanced F3 fibrosis in HCV</td>
<td>Yes</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Test / Interval recommended:**

<table>
<thead>
<tr>
<th></th>
<th>AASLD</th>
<th>EASL</th>
<th>APASL</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ultrasound - 6 monthly</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Ultrasound - 6 monthly + AFP</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
</tr>
</tbody>
</table>
2.3.7 Surveillance test

The current standard test used for HCC surveillance is ultrasound, which is recommended by the international guidelines. The benefits of ultrasound includes its non-invasiveness, absence of discomfort and risks, relatively moderate costs, and ready availability in local settings, especially in regional areas. It can detect subclinical HCC disease as well as provide additional information on cirrhosis complications such as portal hypertension, ascites, varices and portal vein thrombosis.

However, ultrasound is an operator dependent test, meaning that accuracy can range between sonographers and even between visits by the same sonographer. Detection of small lesions in a cirrhotic liver is difficult as the echotexture of a coarse liver can impair sensitivity. Further, NAFLD is increasingly frequent as the cause for cirrhosis in the West, and the concurrent obesity will further reduce diagnostic accuracy. Hence, operator expertise and the quality of the ultrasound equipment can cause variations in performance outcomes. Guidelines suggest referral to experienced ultrasound centres for HCC surveillance, which is prudent, but the balance between accuracy and compliance with regular visits can be difficult to achieve if access is restricted to tertiary centres only.

Used in the context of surveillance, ultrasound has been shown to yield acceptable accuracy with sensitivity ranging from 58-89% and specificity greater than 90%. The pooled sensitivity of ultrasound was 94% in a meta-analysis of 19 studies examining US surveillance in the cirrhotic patients only. The majority of HCC tumours were detected before they presented clinically, although the sensitivity for the detection of early stage HCC was reduced at 63%. As noted in their discussion, these studies in the meta-analysis were from tertiary centres in Europe and Asia and so outcomes may be poorer in countries where obesity is more prevalent, or where ultrasound is conducted in the community setting.

While ultrasound sensitivity is lower for smaller lesions, the majority are still detected at a pre-clinical stage, at a tumour size that remains amenable to curative treatment. In a study of 1,431 patients undergoing ultrasound surveillance for chronic HCV, Sato et al. found only 1.4% of tumours found were greater than 30mm, whereas the overall mean tumour size was 16mm +/- 6mm.
Cross-sectional imaging with CT or MRI has not been recommended for HCC surveillance by any of the guidelines due to lack of evidence of superiority over ultrasound in cost-effectiveness, in addition to the invasive nature of radiation and/or contrast allergies and end-organ damage risk from contrast such as gadolinium. A randomised trial of 163 patients with compensated cirrhosis underwent surveillance, with biannual ultrasound or annual CT, with 6 monthly AFP in both groups. Ultrasound proved to be marginally better than CT with sensitivity and specificity 71.4% and 97.5%, respectively, for ultrasonography vs. 66.7% and 94.4%, respectively, for CT. 365

Alpha-fetoprotein (AFP) is the most frequently used biomarker for HCC, and one of the earliest used as a surveillance test. Its benefits include wide availability, inexpensive cost and ease of use. While its persistent elevation as well as its level are risk factors for HCC development, 366 the use of AFP in surveillance is contentious.

There is conflicting data on its efficacy. The randomised trial in Chinese HBV patients found that surveillance with 6 monthly AFP alone resulted in a sensitivity of 55.3% overall (80% in patients who attended all scheduled screening visits), but did not affect mortality rates. 342 It was suggested that therapy for HCC diagnosed by screening was ineffective, possibly due to AFP tendency to detect larger (non-curable) tumours. In contrast, an observational study of Alaskan HBV patients followed for 16 years with 6 monthly AFP found a survival benefit, 235 albeit compared with historical controls (who received less effective therapeutic options at the time).

The performance characteristics of AFP were developed in diagnostic testing, and hence its applicability to surveillance has been questioned. 52 Nevertheless, receiver operative curve analysis suggests a cut-off of 20ng/mL would provide the optimal balance with sensitivity and specificity. In the setting of viral hepatitis, this cut-off produced a sensitivity of 60% which was thought to be too insensitive, and missed many HCCs. 367 Combined with ultrasound surveillance, AFP provides an additional detection of only 6-8% of cases. 368

AFP is frequently normal with smaller HCCs; only 10-20% of early stage tumours present with abnormal AFP (these however are thought to be of an aggressive subclass). 369 Instead, AFP is noted to be more commonly elevated with larger tumours, with higher rates of portal vein invasion and poor histological differentiation. This
would make it a poor choice for surveillance testing, where the objective is to detect early stage disease.

The shortcomings of AFP in surveillance use has been addressed in more recent studies. False positive results are now understood to be due to fluctuations in AFP level which increase with recent viral flares of HBV or HCV infection or underlying liver disease exacerbations, and decline after antiviral therapy. Consequently, with antiviral therapy for HBV for example, the diagnostic accuracy of AFP has improved with the reduction of false positive findings, despite using even lower cut-off levels of 13 ng/mL. Using a cut-off level of 6ng/mL, AFP can be used as surveillance in HBV patients on entecavir with a sensitivity increased to 80.7%, and specificity of 80.4%. Due to the recent introduction of direct-acting antivirals for HCV, similar studies for AFP in this context have not been performed.

### 2.3.8 Surveillance interval

The ideal surveillance interval was initially chosen based on older studies that showed the median tumour doubling time to be about 6 months. Subsequent studies using 6 monthly intervals have proven to be cost-effective, as discussed previously. When the surveillance interval is lengthened to annually, meta-analysis shows that pooled sensitivity drops from 70% for bi-annual to 50% for annual surveillance. Intervals greater than 6 months also led to poorer survival, in a 15 year prospective study of over 10,000 patients. Conversely, shorter intervals of 3 months was not shown to improve detection of HCC compared to 6 months in a randomised trial involving 1,278 patients. Thus, the international guidelines have recommended 6 monthly surveillance intervals.
2.3.9 Surveillance in practice

The rate of surveillance can vary markedly in different settings, and it is important to note what is actually presented by studies.

As would be expected, the highest rates of surveillance occur in studies whose primary aim is to study the effects of surveillance. Thus, randomised control trials or cohort studies prospectively comparing the outcomes of surveillance in isolation or in comparison with a control cohort would have researchers actively involved in retaining patients in the study. Yet even in this context, surveillance rates are not optimal. Adherence in the large Chinese randomised study of ultrasound-based surveillance was only 58.2% while another prospective cohort study using 6 monthly AFP found adherence 25-38%.

In cohort studies of HCC, all patients will have HCC, hence the surveillance rate is in fact the proportion of HCC patients who underwent surveillance prior to diagnosis, as compared to the proportion presenting with symptoms or diagnosed incidentally. For example, a study based at a liver transplant centre reviewed 319 cases of HCC, of which 30.7% were diagnosed by surveillance. Such studies of course miss the patients with indications for surveillance in the community who never present with HCC. Even literature reviews of surveillance can fail to distinguish the importance of separating surveillance rates in all patients at risk, from the surveillance proportions in those already diagnosed with HCC.

Consequently, true surveillance rate is represented by studies that assess all patients in the studied population who are indicated to have surveillance. For example, a small Australian study of general practice patients with chronic HBV with indications for surveillance found that only 27% of patients were able to adhere to the surveillance program. Results were similar poor at prestigious tertiary centres such as Duke University Medical Centre with only 24.4% of chronic HCV cirrhotic patients adhering to 6 monthly surveillance, and 44% having at least annual surveillance. Similarly, the Mayo Clinic reports that only 14% of its cirrhotic patients received uninterrupted semi-annual surveillance, 30% attended most of the time (>75%), and 59% attended at least half the time. In the community setting, a cohort of 557 patients treated by gastroenterologists only adhered to 6 monthly surveillance in 9% of cases, with suboptimal (6-12 monthly) surveillance at 50.5%. In larger study of
9,369 patients, Davila et al\textsuperscript{383} analysed the US Veteran Administration HCV Clinical Cases Registry and found 42\% of patients had at least the first screening test after cirrhosis diagnosis, but consistent surveillance rates were only 12\% in the four years of follow-up. Overall, whether it is in the primary care physician or specialist setting, community practice or tertiary referral centre, true surveillance rates do appear to be quite poor.

Once patients have received their initial screening test, subsequent surveillance is poor with less than half attending their second visit within 1 year.\textsuperscript{384} A study of screening practices in HBV-infected Asian Americans found that surveillance decreased from 67\% to 47\% to 24\% from the 1st to 2nd to 10th year after HBV diagnosis, respectively.\textsuperscript{385}

In South Korea, there is a national funded 6 monthly HCC surveillance program with ultrasound and AFP for patients over 40 years with HBV or cirrhosis. Despite being free (for incomes less than 50\textsuperscript{th} percentile) or grossly subsidized (90\% subsidize for everyone else), the screening rate is only 22.9\%. From 2004 when the program was initiated until 2011, only half of those surveyed had ever had any surveillance.\textsuperscript{386}

In contrast, Japan which developed the world’s first nationwide HCC surveillance program, provides a 6-monthly surveillance for most patients (non-viral cirrhosis, chronic HBV without cirrhosis) and a more intense 3-4 monthly program for those deemed at higher risk (cirrhosis with HBV or HCV). The surveillance rate in this population was 42.3\% in patients with chronic viral hepatitis, 56.5\% with viral cirrhosis and 26\% with non-viral cirrhosis.\textsuperscript{387}
2.3.9.1 Improving surveillance

Several authors have implemented various strategies to address the poor rates of surveillance. Beste et al. found that a reminder implemented into the electronic medical record for primary care physicians at one facility increased the baseline surveillance rate from 18.2% to 27.6%. Similarly, Aberra et al incorporated automatic reminders for HCC surveillance into their chronic disease management program at a tertiary care facility. Surveillance rates improved from 74% to 93% although these were cross-sectional rates in the 12 months prior to and after implementation, and would be expected to decline in subsequent years.

McMahon et al. sent reminder letters every 6 months to both patients and primary care physicians in their 16 year Alaskan community-based HCC surveillance study with 6 monthly AFP. Despite the remoteness and difficulty of access, adherence with at least annual tests were 61-79% and with biannual tests 25-38%.

Using a nurse-led HCC surveillance clinic that received referrals from a medical hepatology clinic for patients indicated of surveillance by international guidelines, Australian authors followed surveillance adherence over 6 years. They found that ultrasound surveillance was attended within 6 months of the last visit in 30.3% of cases and within 7 months in 71.2% of cases. The average interval between ultrasound visits was less than 7 months in 65% of patients. None had a mean interval of greater than 12 months.
2.4 DIRECT COSTS OF HEPATOCELLULAR CARCINOMA MANAGEMENT

2.4.1 Rationale

With the incidence of HCC projected to increase in many developed countries, policymakers need to plan for the expected costs of the disease burden. Core aspects of disease burden including incidence and mortality have been discussed previously. Attention will now be drawn to the economic costs of disease burden.

Broadly speaking, these may be grouped into:

1) direct costs of treatment of disease and its complications
2) indirect costs which include:
   - morbidity costs, disability, loss of income
   - mortality costs - loss of income due to premature death

The focus of the following discussion will be on the direct costs of HCC.

While the literature is sparse on the economic burden of HCC, there is growing interest from a number of key stakeholders. Governments, especially in developed countries where there is universal state-funded healthcare, must act upon alarming trends in epidemiology to maximise the effectiveness of their health budgets. In HCC, where prevention of cirrhosis through treating modifiable risk factors such viral hepatitis is possible, ascertainment of costs related to late stage disease provides greater imperative for earlier interventions. Insurers and other payers, similarly, need to justify the cost of funding expensive treatments such as direct-acting antiviral drugs for hepatitis C infection.
### Table 2-4. Comparison of HCC costs studies in the literature

<table>
<thead>
<tr>
<th>Study</th>
<th>Description</th>
<th>Results (Currency US Dollars)</th>
</tr>
</thead>
</table>
| Lang et al<sup>391</sup> 2008 Taiwan 1999-2002 N = 2873 | **HCC patient:** all comers  
**HCC source:** single-centre (Taipei Veterans General Hospital  
**Cost source:** hospital claims data  
**Phases:** Costs were averaged for each group:  
- Group 1 (Initial): Patients surviving less than 1 year  
- Group 2 (Terminal): Patients surviving from 1 year to end of study (2002), i.e. died during the follow-up  
- Group 3 (Continuing): Patients surviving beyond 2002  
**Costing method:** Each patient’s cost calculated by determining survival, and using the average costs above. Thus, these are not direct costs of each patient  
**Controls:** Non-cancer patients, propensity matched | Mean Net (HCC) Total costs:  
- Group 1: $6260 p.a.  
- Group 2: $7182 p.a.  
- Group 3: $263 p.m.  
Lifetime (10 year) cost is a weighted average of all three groups = $12,683 |
| Yabroff et al<sup>392</sup> 2008 United States 1999-2003 N = Initial 502 Continuing 609 Terminal 1767 | Study of costs of all cancers, not just liver cancer  
**Liver cancer patients:** Medicare, age > 65 years  
**Cancer source:** SEER database, population-based  
**Cost source:** Medicare  
**Phases:** Costs were averaged for each group:  
- Initial: 12 months after diagnosis  
- Last Year: final 12 months of life  
- Continuing: All months between first and last year  
**Costing method:** Costs for all patients in each phase summed, then averaged. No individual level costs  
**Controls:** Non-cancer patients, matched by sex, age, geography, phase of care | Mean net costs  
- Men  
  - Initial: $41,284 p.a.  
  - Continue: $5,456 p.a.  
  - Last year: $50,917 p.a.  
- Women  
  - Initial: $38,847 p.a.  
  - Continue: $6,580 p.a.  
  - Last year: $58,076 p.a. |
| Thein et al<sup>280</sup> 2013 Canada 2002-2008 N = 2341 | **HCC patients:** All comers > 18 years  
**Cancer source:** Ontario Cancer Registry, population-based  
**Cost source:** Hospital, insurance, government databases  
**Phases:** Costs were averaged for each group:  
- Initial: 3 months prior to, and 1 month after diagnosis  
- Terminal: final 6 months of life  
- Continuing: Interval between  
**Costing method:** Costs for individual patients followed from diagnosis to death or last follow-up.  
**Controls:** Non-cancer patients, matched by sex, age, geography, phase of care | Mean net costs  
- Initial: $3,204 p.m.  
- Continue: $2,055 p.m.  
- Last year: $7,776 p.m. |
| Tapper et al<sup>393</sup> 2016 United States 2003-2013 N = 100 | **HCC patients:** HCV cirrhosis at transplant centre  
**Cancer source:** US transplant centre, institution-based  
**Cost source:** Publicly available schedules for fees, procedures, hospitalisation  
**Phases:** Not studied  
**Costing method:** Costs for individual patients calculated from the patient experience level, for each procedure or treatment  
**Controls:** None | Median costs  
- Overall: $6,279 p.m.  
- Transplant: $7,492 p.m.  
- Non-transplant: $4,830 p.m. |
| Thein et al<sup>393</sup> 2016 Canada 2002-2009 N = Pre-diagnosis 2808 Initial 1914 Terminal: Short-term 686 Long-term 947 | **HCC patients:** All comers > 18 years  
**Cancer source:** Ontario Cancer Registry, population-based  
**Cost source:** Hospital, insurance, government databases  
**Phases:** Costs were averaged for each group:  
- Pre-diagnosis: 12 months before diagnosis  
- Initial: 12 months after diagnosis  
- Terminal: 6 months before death  
**Costing method:** Costs for individual patients followed from diagnosis to death or last follow-up.  
**Controls:** Non-cancer patients, matched by propensity score, income quintile, Charlson-Deyo Comorbidity Index | Mean net costs  
- Pre-diagnosis: $586 p.m.  
- Initial: $7,812 p.m.  
- Terminal: Short-term $25,613 p.m.  
- Long-term -$452 |
2.4.2 Study Methodology Comparison

The current literature on HCC healthcare costs is dichotomised in its methodology on a number of fronts - in the general perspective, the ascertainment of study subjects, the derivation of cost data and the estimation of costs.

The study may take a prevalence-based or incidence-based approach to costing. Prevalence-based costing estimates the total cost of the disease over a given year including direct costs of medical treatment and indirect costs of lost of income due to morbidity and mortality. This global view is helpful for governments to assess the economic burden. Alternatively, the incidence-based approach to costing follows the direct costs of treatment incurred at the individual patient level, through the patient journey from diagnosis, treatment, possible complications and outcomes. This is useful for insurers, for cost-effective modelling and for planning of preventative strategies to high-cost sub-groups.

Study cohorts may also either be population-based or institution-based, with cost data retrieved from either administrative databases or recorded with patient experience. The costs themselves may be actual costs (retrospective) or projected costs using Markov modelling.

There are only a handful of costs studies in HCC in the literature. They are summarised in Table 2-4 and discussed in detail according to different aspects of their methodology in the following sections.
2.4.3 Types of study population

Population-based studies

The largest studies that examine the cost of HCC management are population-based studies that rely on the relevant cancer registries to identify HCC cases from the general population. The largest cost analysis of HCC in the East comes from Taiwan, where HCC is the top cancer in males in both incidence and mortality rates.\textsuperscript{391} A total of 2,873 HCC patients were sourced from the cancer registry over the period 1999-2002.

In the West, the 2016 study by Thein et al, the largest to date, identified 2,832 cases of HCC from Ontario, Canada obtained from the Ontario Cancer Registry diagnosed between 2002 and 2009.\textsuperscript{393} This was an extension of their earlier 2013 study which examined 2,341 HCC patients from the same population diagnosed between 2002 and 2008.\textsuperscript{393}

Significantly, there were 2,218 cases of non-histology confirmed HCC excluded from the 2016 study, thereby demonstrating again the limitations of cancer registry data as discussed earlier (section 0). It would be expected that non-histology confirmed HCC would more likely be later stage disease compared to their histology confirmed counterparts. Hence, given that later stage diagnoses are associated with higher costs, these population-based studies that are reliant on cancer registries may also underestimate the overall cost of HCC management.

Further, cancer registry derived population-based studies also lack detailed clinical information regarding HCC cases such as aetiological risk factors of cirrhosis and cancer staging. These are potentially important determinants of cost as they may help identify preventable costs as well as provide impetus for funding of surveillance programs or therapies directed at earlier stages.

Earlier on, in the United States, Yabroff et al conducted a population-based study to estimate the cost of care for elderly patients diagnosed with the 18 most prevalent cancers, sourced from the SEER cancer registries and linked to Medicare claims.\textsuperscript{392} Of the 718,907 cancer patients captured from 1999-2003, it is unclear exactly how many patients had HCC due to the failure to categorise liver cancer into its subtypes: HCC, ICC etc as discussed in (reference thesis segment). Further, patients with liver cancers were grouped into phases of care which were not mutually exclusive. There
were probably at least 1767 liver cancer patients (in the terminal phase of care), of whom one can probably expect 75-80% to be HCC rather than ICC or other primary liver malignancies. Few curative therapeutic options exist for ICC and so predominantly palliative management may account for underestimation of the cost of care. Also, as this study was based on Medicare recipients older than 65 years, it would have failed to capture the cost of more expensive curative treatments offered to younger patients, in whom HCC frequently occurs.

These selection biases possibly account for the lower mean cost per month of $564 and $1282 in the Yabroff and Thein studies, respectively, as compared to the cost calculated by Tapper et al. 394

Cohort-based studies

At the other end of the spectrum are the clinical cohort studies, of which there are similarly few in the current literature. The most recent is a retrospective, longitudinal cohort study by Tapper et al which analysed the costs of managing HCC in patients with HCV cirrhosis at a liver transplant centre in the United States. 394 Of 421 patients attending the centre over a period of 10 years, 100 patients were randomly selected for cost analysis and followed until death or end of study. All costs of care in the diagnostic, therapeutic and palliative stages of progress were calculated. Other cohort studies choose to only calculate costs directly attributed to the intervention, often comparing one therapy to another. 395,396 Other stages of management, including diagnosis, treatment of complications and terminal care are not accounted for.

Clinical studies such as these have the advantage of access to data such as aetiology of liver disease, liver function and cancer staging. Cost analysis according to these factors informs policy for funding of screening programs, drugs such as antivirals to prevent fibrosis progression and therapeutic interventions which are aligned to cancer stage (BCLC stage).

Conversely, they are also prone to selection bias as cohorts are derived from institutions with expertise (liver transplant centres), single aetiology (HCV infection) or with only certain therapeutic measures compared. Hence, they do not account for the breadth of costs associated with HCC management in the population, of which government is more interested in.
2.4.4 Phases of treatment

It is intuitive that the costs of managing chronic disease would vary at different stages of its natural history and as a result of therapeutic interventions to that process. A number of studies have divided this cost continuum for HCC management into defined phases of care such as initial, continuing and terminal phases.\textsuperscript{280,391,393}

In the large SEER cancer registry based study by Yabroff et al\textsuperscript{392} which assessed cost of care in all cancer types, the initial phase was defined as the first 12 months after diagnosis, the terminal phase as the last 12 months of life and the continuing phase as the remaining time between these two phases. Not all patients contributed to all three phases due to shorter survival times, in which case time is preferentially allocated to the terminal phase for analysis. This is consistent with other studies.\textsuperscript{397}

However, in the case of HCC, where survival time is poor compared to many cancers, perhaps phases with shorter duration might be more instructive. Thein et al set out to determine more accurately the optimal duration for definition of the phases.\textsuperscript{280} They performed a joint point regression of the log-linear trends in the average cost of HCC care per 30 patient-days from HCC diagnosis to death. They found a significant trend of increased costs 3 months prior to diagnosis until 1 month after diagnosis. Costs then declined until the months approaching death when costs again increased gradually, without significant trend. Thus, they defined the initial phase as 3 months prior to 1 month after diagnosis, the terminal phase as 6 months prior to death and the continuing phase as the time in between.

In their later 2016 paper, Thein et al extended their earlier work, assessing costs of HCC care of the same population over an extra year of capture.\textsuperscript{393} In this study, they redefined the phases, introducing a prediagnosis phase of 12 months prior to diagnosis to account for costs of surveillance. The initial phase was redefined as the first 12 months after diagnosis whereas the terminal phase remained defined as the 6 months prior to death.

Hence, it is important to note these differences in durations in the definitions of phases of care when comparing costs between studies. Initial therapies for newly diagnosed HCC often occur over a longer period than 1 month, especially with therapies such as TACE that may require several sessions to produce an adequate response. The shorter definition of the initial phase (up to 1 month post-diagnosis) in
the earlier study by Thein et al\textsuperscript{280} likely accounts for the lower net costs per 30 days of $3204 compared with $7,812 for the initial phase as defined by their later study of essentially the same population.\textsuperscript{393}

### 2.4.5 Net costs and comparisons with controls

The population based studies using administrative costing data present both the total costs of HCC care as well as the net cost as compared to controls without HCC.\textsuperscript{280,392,393}

Potential controls were obtained from government population databases and matched to cases, with varying levels of matching between studies. Thein et al matched controls on socio-demographic factors such as age, sex, income, and rural residence, and baseline clinical factors using indexes such as the Charlson-Deyo Comorbidity Index (CCI). This is an algorithm which calculates a score for baseline co-morbidities listed on hospitalisation records.\textsuperscript{280} They also used propensity scores to estimate the probability of HCC in an individuate with the observed covariates. The earlier study by Yabroff et al involved a simpler matching system of sex, age and residential area, without attention to levels of comorbidity or other clinical factors.

The bias raised by these types of controls is a point of discussion, given that these studies are based on cancer registry and Medicare data that do not have clinical details important in HCC care such as liver function, Child-Pugh status and MELD scores. HCC occurs mostly in the presence of cirrhosis, and subsequent to diagnosis, it is difficult to ascertain what costs arise due to complications of HCC therapy as opposed to complications arising from the progressive cirrhosis. Hence controls that are not adequately matched according to liver function may confound results.
2.4.6 Differences in cost calculations

Studies differ in the derivation of their costs data. The larger population-based studies employ a top-down approach from the perspective of paying bodies, with costings obtained from linkage to administrative databases. These include government health services databases such as that of the Ontario Ministry of Health and Long-Term Care\textsuperscript{393} or the US Medicare claims database\textsuperscript{392}.

In some studies, this top-down approach loses granular information due to early summation and average calculations, to the point of become a modelling procedure. For example, in the study by Lang et al\textsuperscript{391}, the average cost per phase of care is calculated for the group first and then modelled for each patient according to their survival times. Hence, the final result is longer the direct cost for that patient, but the estimated cost calculated using the pre-calculated average cost for that phase. In the study by Yabroff et al,\textsuperscript{392} all Medicare claims were simply summed after separating into the phases of care. There are no further descriptions of patient characteristics and associations with costs. Of course, as a top-down approach, the authors may not have had the primary data regarding patient and tumour features.

Studies with institution-based cohorts\textsuperscript{394,398} obtain costs data from the patient level or bottom-up approach. This involves looking at the patient experience and costs are calculated for items encountered in this process. How each cost is derived may vary. For example, costs of outpatients physician visits may be calculated from a standard fee schedule\textsuperscript{394}, whereas inpatient costs may be derived from hospital financial departmental calculation based on length of stay and issues addressed. Costs for procedures may also be calculated likewise by hospitals using formulae, although some studies are more mechanistic and break down all costs individually before tallying. For example, in their paper on the cost of TACE, Beheshti and Meek\textsuperscript{396}, accounted for direct costs of the equipment and clinical staff time, as well as indirect costs of overheads, fixed costs, depreciation, and non-clinical staff administration.

The comparability of the top-down versus bottom-up approaches to cost calculations was addressed in a paper that utilised the US Veterans Affairs costing system which could perform both analyses.\textsuperscript{399} The study analysed the total annual costs for 14,915 patients at 72 facilities, including the costs of inpatient treatment, outpatient encounters and investigations. Correlation between the two approaches was poorest
for individual outpatient encounters ($r = 0.24$) but improved with estimation of the
total annual outpatient cost ($r = 0.61$). Inpatient costings was better correlated for both
individual admissions and total annual admission costs ($r = 0.77$ and $r = 0.85$,
respectively).

The costs of HCC care can be presented in a number of ways: with reference to
measures of spread, treatments offered or comparisons to controls. For example,
Tapper et al$^{394}$ presents costs of patients undergoing either transplantation or non-
transplantation pathways, grouped by the first treatment modality provided. A
transplanted patient who has had bridging therapy with resection has a median cost of
$8,931 per month. This might be compared to the Thein et al$^{280}$ study in which a
similar patient would have a mean net cost of $11,249 per month in the initial phase,
$3,395 in the continuing phase and $13,267 in the terminal phase. Note that these are
net costs, that is, the difference between the HCC patient and the non-HCC control.
This is different from the cost presented by Tapper which is the total, unmatched cost.
A mean cost may be influenced by extreme outliers. The Thein study mean net cost
for transplant only patients was $29,865 with a wide 95% confidence interval of
$1,243 to $58,487 suggesting that outliers may have contributed to the higher mean
costs.

The mean net costs for the terminal phases, across the different HCC treatments,
presented by Thein et al are also difficult to conceptualise. Here, patients receiving
surgical resection or transplantation only have terminal phase mean net costs per
month of $32,712 or $29,865 respectively. Conversely, patients receiving RFA, TACE
or ethanol injections are less costly than the non-HCC patients in their terminal phases.
It is reasonable to assume most patients dying from HCC do so as a result of
progression of disease or decompensation, such that the costs is likely to be similar
across treatment modalities. Certainly, it is hard to explain how such patients are less
costly than the average patient without HCC or liver disease.

Further, it would be expected that surgical resection or transplantation would
incur most costs during the initial phase of therapy. They are also likely to have longer
survival and in their terminal phases, their costs should be similar to other treatment
pathways. Instead, this study shows that they are most costly in their terminal phases
which is counter-intuitive.
One possible reason for this discrepancy is that analysis for terminal phase only occurs for those who have died during the study period. Patients who have surgical resection or transplantation are likely mostly still alive at study conclusion and hence the high costs presented are attributable to the few who die from early complications.

2.4.7 Markov modelling

Various studies used modelling as a mean to estimate costs of HCC management. Lim et al \(^{400}\) applied the Markov Model to assess the cost-effectiveness of liver resection compared to cadaveric liver transplantation in three different geographical cost settings (Singapore, Switzerland and United States). Naugler and Sonnenberg\(^{401}\) used Markov Modelling to compare early intervention for small HCCs with TACE or RFA with waitlisting for transplantation. For these studies, both the costs of procedures and the probability of transition to subsequent stages of care were obtained from systematic literature reviews.

Such models are limited by the presumptions made in study design with only certain situations accounted for and many other presumptions made. For example, costs of post-resection recurrence management are estimated either using palliative cost estimates or in this study, assumed to equate to the cost of three TACE sessions. \(^{400}\) The costs of complications from therapy or complications of liver disease or HCC due to unsuccessful therapy are also not accounted for by these models. \(^{401}\)
2.4.8 Applicability of the data

As with the practice of evidence-based medicine in other areas, the applicability of the data to the local context needs to be considered.

Firstly, the patient population in HCC and cirrhosis can be quite variable and is likely to greatly influenced the cost of management. Patients who present at a younger age, with fewer comorbidities and with localised HCC are more likely to receive liver transplantation which is costly. Hence, studies which recruit patients from the SEER or US Medicare system will have older patients (age greater than 65) with comorbidities for whom liver transplantation is unlikely to be available. The costings from such studies may be biased towards a lower value. Conversely, the Tapper study of patients with HCV cirrhosis at a liver transplant centre may not be applicable for non-cirrhotic HBV patients who are generally good surgical resection candidates with good cure rates and low long term costs.

At the other extreme from the study with a focused patient group (Tapper), are studies with large diverse populations that provide total and mean costs without individual patient features. This is the case of the remainder of the papers (Thein et al,280 Lang et al,391 Yabroff et al392). It then becomes impossible to apply the results to a select group, such as when designing cost-effective analyses or targeted prevention programs.

Beyond the patient level, the data must also be applicable to the healthcare system which can be diverse in terms of public/private funding, availability of therapeutics, health literacy and other factors. Hence, it would be ideal that costings analyses are performed in the same healthcare settings to which they will be utilised.
2.5 SUMMARY AND IMPLICATIONS

The research literature on HCC epidemiology is currently nearly entirely dependent on cancer registry data. In developed countries, there is historical reassurance of cancer registry data quality due to the presence of mandatory reporting laws, shared coding practices, modern information technology systems and collaboration between different government registries and departments.

However, changing diagnostic algorithms for HCC and the emergence of HCC risk factors in new settings has challenged the accuracy of local cancer registries reporting of HCC incidence. The underreporting problem may be one of incomplete capture of new sources or missed reports from current sources, or it may be due to misclassification of already registered cases. There is a lack of contemporary evaluation of cancer registry data quality in general, while in HCC there is a complete absence of independent evidence to validate reported incidence.

In terms of the clinical features of HCC, its risk factors, treatment and outcomes, the literature is comprehensive in depth and range, especially in its coverage of many East Asian, European and North American populations. What is apparent from these studies is that the HCC disease burden is heterogeneous in nature, with local epidemiology greatly affecting outcomes. Hence, it is important that HCC management be guided by local data.

In Australia, there are limited clinical studies of HCC presentation and outcomes, most of which are institution-based or linked to a particular clinical trial or risk factor which may have selection-bias. There is an absence of clinical data at the population-based level which would provide data across all patient types and presentations.

Similar to its epidemiology, the costs of HCC treatment are very sensitive to the characteristics of the local setting, which in this case is the Australian universal healthcare system. There are limited studies on HCC directs costs worldwide and there is no evidence of costs in Australia. This is despite the recent government funding of expensive direct acting antiviral therapy for chronic HCV which presumably is based on cost-effectiveness analyses inclusive of complications of HCV such as cirrhosis and HCC. While overall costs can be obtained through modelling or government/insurance claims data, there is lack of granular, patient-level clinical details that would inform
local policy and target particular elements of the patient experience to improve outcomes cost-effectively.

Hence, with the novel methodology proposed by this research, it is hoped that these gaps in the HCC epidemiology literature can be addressed.
3 Research Design

The study of hepatocellular carcinoma is of interest to many researchers, clinicians and governing bodies because of its significance in mortality and mortality, as well as its emergence in regions and populations previously thought to be at low risk. Newer technologies in diagnostic imaging and therapeutic options have provided better treatment and improved outcomes for patients. Experimental studies of varying designs, including randomised controlled trials, have further defined cause and effect relationships between treatment and tumour outcomes. Epidemiological studies which initially defined the problem may in fact be outdated as populations are migrating, risk factors are changing and newer therapies are being applied outside of the controlled trial settings. Hence, an updated study is needed to describe the current epidemiology and management of HCC in the local setting.

This study, also known as The Hepatomas of Melbourne Epidemiological Research (HoMER) study, is the first population-based study in Australia, if not worldwide, to determine the incidence of hepatocellular carcinoma using clinical case capture, independent of the cancer registry. The strength of the study lies in its unique methodology to improve case capture and accuracy of diagnosis. The study aims to address the gaps in the literature as discussed previously, and in particular examine the influence of the local Australian context on epidemiology.

Each of the three studies in this thesis have been published or submitted and contain their own methodology segment. This chapter of the thesis is presented to provide any detail that may be lacking due to the word limitations imposed by the journals.

3.1 AIMS

1. To determine the incidence rate of hepatocellular carcinoma in Melbourne using independent clinical case capture

2. To describe the cohort survival outcomes and its determinants, in particular the role HCC surveillance participation

3. To describe the costs of hepatocellular carcinoma management in Australia


3.2 STUDY DESIGN

As an epidemiological study, this study design is observational by nature. Different hospitals have different patient demographics and also different treatment options available. The observational nature of the study provides opportunity for an exploration of the disease and its management across the population. There is no interventional aspect to the study with all clinical history, investigations or treatment offered to participants being standard of care for that institution.

Specifically, the three studies comprising this thesis all have research designs of a quantitative, observational nature. The methodology of each study is detailed within each study chapter / publication. Other relevant aspects of research design and methodology not included in the publications due to word limit restrictions are included here also for completeness. A summary of the research design and the background to its development is presented below.

3.2.1 Background to research design

The first study is a population-based incidence study of HCC diagnoses in the geographically defined area of Melbourne over a period of 12 months. The original concept arose from observations made by clinicians from the Melbourne collaboration for the Study of Hepatocellular Carcinoma (MeSH), a special interest group of the Melbourne Liver Group. MeSH members include gastroenterologists, surgeons and radiologists who treat HCC and represent all tertiary hospitals in Melbourne. It was noted that referrals to HCC clinics had been increasing in recent years, with many hospitals having to increase their operational capacity. Given the unique clinicoradiological basis of diagnosis for the majority of HCCs in current management, MeSH members hypothesised that HCC incidence may be underreported by the cancer registry.

Hence, a population-based study of HCC incidence was proposed, with diagnoses made by clinicians as the primary source of data, rather cancer-registry sourced as in most of the literature discussed previously. Due to the close collaboration between hospitals, the complete representation of all tertiary hospitals within the geographically defined area and the presumption that HCC management is almost entirely referred to tertiary hospitals, MeSH believed adequate case capture would be
possible to provide an accurate estimate of incidence. Associate professor Sally Bell, who is both a MeSH member and co-author of a similar study, the first Australian population-based incidence study of inflammatory bowel disease,\textsuperscript{402} became the principal supervisor for this thesis to provide guidance.

The development of the population-based incident cohort then provided a unique opportunity to study outcomes of HCC management at a population level. Few studies examine clinical aspects of HCC management at the population level as most clinical studies are institution-based (such as an earlier study by some MeSH members)\textsuperscript{27} or therapy-based (one modality in comparison with placebo or another modality). Conversely, population-based studies using cancer registry and administrative data do not record clinical risk factors and thus cannot associate these with outcomes.

Finally, this well characterised and diverse population-based cohort allowed us to describe the cost of HCC management in the Australian healthcare setting. This important area has yet to be addressed in the Australian literature, and is particularly relevant with the advent of publicly funding of hepatitis C antiviral therapy and advanced HCC treatments. While the intension was to include all hospitals in the cost analysis, there was difficulty with assessing the required data from certain hospitals within the time restrictions for completion of this thesis. Hence, findings of only half the cohort are presented.
3.2.2 Research design summary

**Study 1 - Chapter 4: Hepatocellular Carcinoma Incidence in Melbourne**

*Publication*: Novel population-based study finding higher than reported hepatocellular carcinoma incidence suggests an updated approach is needed

*Study type*: Population-based incidence study

*Source Population*: Residents of the geographical region defined as the Melbourne Statistical Division by the Australian Bureau of Statistics

*Risk period*: 12-month period from 1 July 2012 to 30 June 2013

*Participants*: 272 patients diagnosed with HCC by AASLD criteria

*Methodology*: Prospective case ascertainment using multiple capture sources

*Analysis*: Cross-reference of cases identified by the study and those collected by the cancer registry. Calculation of age-standardised incidence rate, by direct age standardisation using the Australian Standard Population 2001, and compared with cancer registry rates.

*Key outcome measure*: Incidence rate of HCC in Melbourne

**Study 2 – Chapter 5: Surveillance Improves Survival Outcomes of Hepatocellular Carcinoma**

*Publication*: Surveillance improves survival of patients with hepatocellular carcinoma: a prospective population-based study

*Study type*: Prospective cohort study

*Source population*: Population-based incidence cohort from Study 1

*Follow-up period*: 24 months from date of HCC diagnosis

*Participants*: 272 patients diagnosed with HCC by AASLD criteria

*Methodology*: Observation of overall survival outcomes in the incidence cohort
Analysis: Description of survival statistics using Kaplan-Meier survival function. Multivariate regression analysis of the risk factors associated with overall survival

Key outcome measures: Overall survival at 24 months. Risk factors associated with improved survival. Predictors of surveillance participation.

Study 3 – Chapter 6: Direct Costs of Hepatocellular Carcinoma Management in Australia

Submitted for publication: Direct Costs of Hepatocellular Carcinoma Management in Australia

Study type: Retrospective cohort analysis

Source population: Population-based incidence cohort from Study 1

Follow-up period: 24 months from date of HCC diagnosis

Participants: 142 patients diagnosed with HCC by AASLD criteria, from three of the seven tertiary hospitals involved in Study 1

Methodology: Costings data sourced from hospital data analysts for patient encounters in the first 24 months following diagnosis

Analysis: Description of costs of treatment by overall costs, treatment modality and phase of treatment (initial, continuing, terminal). Calculation of costs adjusted for survival duration. Multivariate regression analysis of the risk factors associated with higher costs of management.

Key outcome measures: Calculation of total costs and costs per month survived. Risk factors associated with higher costs.
3.3 PARTICIPANTS

3.3.1 Study population

The unique strength of this study lies in its population-based design, despite being a clinical study. For such a study aiming to determine disease incidence, it is important that the population is accurately defined in order to calculate an incidence rate.

The study population is defined as residents of the geographical region demarcated as the Melbourne Statistical Division (MSD) by the Australian Bureau of Statistics (ABS). A Statistical Division is an Australian Standard Geographical Classification representing a clearly defined geographical region, associated with a set of postcodes. Population records are accurately maintained from the Australian Census data, a nationwide compulsory population assessment which occurs every 5 years.

The MSD covers the region of metropolitan Melbourne as well as the surrounding urban fringe including the Dandenong Ranges, the Yarra Valley and the Mornington Peninsula. This land area is approximately 7694 square kilometres. The population of the MSD was 4.08 million in June 2010, according to the 2010 Census, which is 73.5% of Victoria's population.403

Within the MSD, there are seven tertiary referral University-teaching hospitals and their associated networks: St Vincent's Hospital (St Vincent’s Health), Austin Hospital (Austin Health), Royal Melbourne Hospital (Melbourne Health), Monash Medical Centre (Southern Health), Alfred Hospital (Alfred Health), Box Hill Hospital (Eastern Health) and Western Hospital (Western Health).

Figure 3-1. The Melbourne Statistical Division.
Adapted from ABS Maps (http://stat.abs.gov.au/itt/r.jsp?ABSMaps)
3.3.2 Case definition

Patients will be defined as having hepatocellular carcinoma if they have one of the following:

1. Histological diagnosis of Hepatocellular carcinoma (ICD-10 C22.0)

2. Clinical diagnosis based on AASLD 2010 criteria, in a patient with high risk of HCC and one dynamic imaging study (CT or MRI) showing a lesion greater than 1cm in diameter with characteristic imaging changes (arterial enhancement with portal-venous/delayed washout). This can be the initial or sequential modality (CT or MRI)

3. For difficult cases, patients will be included after arbitration by a panel of experts consisting of hepatologists and radiologists.

3.3.3 Case ascertainment

It is thought that most patients in the community who are suspected of having, or are newly diagnosed with hepatocellular carcinoma would be referred to one of the seven tertiary hospital networks for opinion, diagnosis, treatment or palliation. This assessment was based on expert opinion through personal communication and surveys of specialists with prominence in the management of HCC. For example, at the two major private hospitals in Melbourne (Cabrini and Epworth Hospitals), the hepatobiliary surgeons who manage HCC would discuss their cases at the multidisciplinary meetings of tertiary hospitals, (Alfred and Royal Melbourne Hospital respectively) where they also have public appointments. In other cases, especially in community private specialist and general practices, patients are referred directly to the Austin hospital, presumably as it has Victoria's only liver transplant unit.

Each of the seven tertiary referral hospitals have a weekly or fortnightly HCC multidisciplinary meeting. This is attended by representatives of the following disciplines:

1. Gastroenterology - with a hepatologist with special interest in HCC

2. Radiology - diagnostic and interventional radiologist

3. Hepatobiliary Surgery
4. Oncology

5. Clinical Nurse Co-ordinator

**Multiple Sources of Capture**

Multiple streams of data sources will be used to increase the probability of complete case capture required for accurate incidence estimation. This methodology has been employed successfully in previous similar population-based studies from St Vincent’s Hospital.\(^402,404\)

Patients will be captured via the following methods:

1. Hepatoma multidisciplinary meeting (MDM) for prospective registration of all new referrals to the MDM

2. Audits and databases of allied clinical units: Oncology, Hepatobiliary surgery, Palliative care

3. Database searches of pathology and radiology systems for key terms: "hepatocellular", "hepatoma", "liver primary malignancy"

4. Pharmacy dispensing database search for "sorafenib"

5. Hospital discharge coding for Hepatocellular Carcinoma and Liver Cancer
   Unspecified codes: ICD-10 C22.0, C22.9

**Private patients**

Using surveys to community-based specialists, we have found that patients managed by specialists in the private sector are likely to have some form of diagnostic modality (e.g. MRI, pathology) performed at a public hospital service. Thus, their diagnosis may be detected using the above database searches.

Once a diagnosis is made in the community, the specialist then generally refers the patient for opinion and ongoing management by the HCC multidisciplinary team at the local tertiary hospital service or where the specialist is associated. Attendance at the public hospital then provides further avenues for case identification as described
above. Rarely would a case of HCC be treated solely in the community as these practitioners feel that HCC is a complex disease that is best managed by a team approach.

In addition, as there is mandatory reporting of cancer diagnoses from pathology laboratories, nursing homes and palliative care facilities, these private patients may also be captured via the Cancer Registry and Death Registry if they have not been identified through the other systems.

3.3.4 Patient participation

As this is an observational study of what is essentially standard of care, patient participation is of a very limited nature. Specifically, this participation entails:

a. Providing opt-out consent for their health information to be accessed and stored in the study database for current and future ethically approved use.

b. They may be contacted by study personnel if they are lost to follow-up from their local health service.

Patient confidentiality

As this is an incidence study, it is important that the same patient is not recorded or captured more than once from the various possible sources of patient contact. Furthermore, as treatment and survival outcomes are measured, it is important that patients can be tracked, especially when their treatment may span several specialist centres across Melbourne. Consequently, their medical information needs to be in a re-identifiable format. At the same time, issues of privacy and confidentiality are important and need to be adequately addressed. Consequently, the methodology regarding data entry and access will ensure this.

After the patients are recruited, their identity will be coded in a re-identifiable manner before registration on the research database which only contains de-identified data. Patients may be re-identified for the purposes of data matching, excluding duplication and follow-up. Their identity will never be publicly available. The code
table for re-identification will be stored separately, password encrypted and only accessible by the primary study investigators. At end of the study period, access to the database and the re-identification table will be under the care of the Head of Gastroenterology at St Vincent's Hospital.

**Patient consent**

Opt-out consent will be obtained by one of three methods:

1. Directly from patients who are able to give consent

2. Indirectly from the carer or next-of-kin of patients who are deemed incompetent to consent (e.g. cognitive impairment)

3. A waiver of consent for patients who are not contactable and have an uncontactable next-of-kin, or are deceased.

**Opt-out consent**

Given the extensive coverage of this study (Melbourne Statistical Division with a population of more than 4 million), it was difficult to directly consent each patient in a written consent method. Complete case capture and accuracy are paramount for an incidence study, and so all methods that reduce administrative burden is important to facilitate registration.

As this study is observational with a low risk profile, we have chosen an opt-out consent as the method of consent for situations where patients are seen prospectively by local clinicians or contactable by telephone (methods 1 & 2 above). This method is routinely used by three quarters of clinical registries in Australia. 405

Using this approach, participants are provided with a Patient Information and Consent Form describing the purpose and procedures of the study. They are also provided with information to enable them to request more details about the study or to have their personal identifying information removed from the study. Opt-out consent is the preferred model of obtaining consent as it provides the following benefits:

- Patients are informed that their identifying data will be kept by a third party and maybe linked to other registries such as the cancer and death registries.
• Patients who are opposed to having their data collected or used by a third party have provision to remove their details from the study. There is evidence that this right is rarely exercised. The Victorian Trauma Registry which holds details on more than 15,000 patients and routinely follows up all patients at six months following discharge has a less than 0.5% patient withdrawal rate, with even lower rates recorded by the National Joint Replacement Registry;

• Patients may withdraw by notifying the study investigators without fearing that their decisions may influence their relationship with their treating clinicians who initially enrolled them.

• It enables optimal case catchment with minimal work burden to clinicians at the time of case identification. Most of these clinicians are not otherwise involved in the study. Some patients will be found on database and registry searches, and will only be contacted by telephone. This Opt-Out consent methodology will allow for study investigators to enrol patients without the need for direct (in-person) contact to obtain and witness signatures.

**Waiver of Consent**

Some patients will be found through pathology, radiology, and registry (cancer, death) searches and so may not have had contact with clinicians associated with the study. These patients will be contacted and consented by Opt-out methodology as defined above.

A waiver of consent is requested for patients who cannot be contacted and have a next-of-kin who is also not contactable. The request for waiver is also made for those patients who are deceased or who are incompetent to consent and do not have a next-of-kin to consent for them.
3.4 DATA COLLECTION

The following parameters will be collected from multiple sources (as discussed in Case Ascertainment) for the defined cases:

- Personal details: Initials, Age, Sex, Date of Birth, Ethnicity, Residential Postcode
- Medical History: co-morbidities, family history, medications, ECOG
- Liver disease history: aetiology of liver disease, treatment history, staging of liver disease (fibrosis score, Child-Pugh score, MELD score)
- Pathology results: Full blood examination, Electrolytes, Creatinine, Urea, Coagulation profile, Liver function tests, AFP
- Tumour features: size, segment, imaging modality, histopathology, treatments
- Outcomes: tumour outcomes, survival at 12 months

Data collection will occur at case ascertainment, and at 6- and 12-months post-diagnosis. Since this is an observational study, not all parameters may be available as the diagnostic work up is dependent upon the local treating clinician.

Data Security

The collection of personal identifying information imposes strict obligations on the organization acting as registry custodian. Data must be collected, processed, stored and released by the clinical quality registry in accordance with the Australian Code for the Responsible Conduct of Research and the National Statement on Ethical Conduct in Human Research and with any relevant legislative requirements or regulations which govern collection and storage of health-related data.

Because of the complexities in ensuring data security, registries must be housed in an environment with extensive experience in handling confidential personal data. Data will be held under strict security arrangements and with procedures in place to ensure that access to data is restricted and released only to study personnel. The Department of Gastroenterology at St Vincent's Hospital fulfils these requirements. The database itself will be securely encrypted and stored on the St Vincent's Hospital network.
3.5 PROCEDURE AND TIMELINE

Study Time Frame

The population-based incidence study will recruit patients over a period of 12 months, between 1st July 2012 and 30th June 2013. The follow-up period will be to 24 months post-diagnosis.

Data Verification

At the end of the 12-month data collection period, the Victorian Cancer Registry and the Death Registry will be consulted for patients with diagnoses of "primary liver cancer" or "hepatocellular cancer". This will be done via a formal application process to the Cancer Council for collaboration of data. Data-matching with the VCR will through matching of de-identified data using Initials, Date of Birth and Residential postcodes.

3.6 ETHICS

Ethics approval was obtained with each of the Human Research Ethics Committees governing the associated tertiary hospital networks: St Vincent’s Health (reference, HREC-A 056.12), Melbourne Health (including Western Health; reference, 2012.150), Eastern Health (reference, E66-1112), Austin Health (reference, H2012/04713), Southern Health (reference, 12201A), and Alfred Health (reference, 357/12).
3.7 LIMITATIONS

Sources of Errors in Incidence Determination

The sources of error for the incidence rate calculation falls into two main categories: failure of case capture (sensitivity) and failure of accurate case diagnosis (specificity).

Failure of Case Capture

For any population-based study, the fringe areas bordering on other service jurisdictions are often where failure of complete capture can occur. All of Victoria's tertiary hospitals are located in the MSD. People living in the fringe areas of the MSD who attend a closer regional hospital outside the MSD, such as Geelong, Ballarat, Shepparton or Traralgon will in fact get referred to a tertiary hospital where their diagnosis is then captured. The reason for this is that the complexity of HCC management generally requires physicians in regional areas to refer to a tertiary centre.

The possible exception here is that certain cases of HCC such as those for palliative management may indeed be managed locally only. In this case, we will rely on the Victorian Cancer Registry picking up the case as part of mandatory reporting regulations.

For these cases, the errors are dependent on the intrinsic accuracy of the system, which include: incorrect coding, failure of case registration, leakage across the border to neighbouring states and patients dying in another state. In general, patients living at the Victorian border who might have their diagnosis made at an interstate hospital will not contribute to any error in the incidence calculation as we are only assessing the incidence within the central MSD area.

Within the MSD, failure of capture may also occur with patients who are treated entirely in the private sector and not through a public tertiary hospital system. In these cases, we anticipate that the treating doctor is someone prominent in their field, be it radiological, surgical or oncological intervention. Such a doctor is generally associated with a public tertiary hospital and we hope to reduce this leakage by communicating with these doctors to link their private practice patients.
Failure of accurate case diagnosis

As diagnostic criteria have become increasingly reliant on radiological criteria, there is a small degree of reduction in specificity. These errors fall within the constraints of these validated algorithms, though these may not be perfect.

Beyond these criteria, there are cases where the lesion may not entirely meet diagnostic criteria and diagnosis is made on clinical expert opinion. Reliance on the cancer registry is not helpful in this case, as their current coding system can only categorise histologically verified HCC. In fact, this study itself will seek to validate the cancer registry data for this group of lesions.

Other sources of errors and their implications are discussed within the relevant study chapters.
4 Hepatocellular Carcinoma Incidence in Melbourne

The main study of this thesis has been published in the international peer-reviewed journal *Hepatology*, (Impact Factor 13.246 in 2016, Rank 1 in the Hepatology category, Rank 4 in the GI category).

Reference:


The text in its entirety is included in this chapter. The print version from the journal is included as an appendix.
4.1 ABSTRACT

Novel population-based study finding higher than reported hepatocellular carcinoma incidence suggests an updated approach is needed

Thai Hong¹, Paul Gow²,¹⁰, Michael Fink³, Anouk Dev⁴, Stuart Roberts⁵, Amanda Nicoll⁶,⁷,¹¹, John Lubel⁶,¹¹, Ian Kronborg⁸, Niranjan Arachchi⁹, Marno Ryan¹, William Kemp⁵, Virginia Knight⁴, Helen Farrugia⁹, Vicky Thursfield⁹, Paul Desmond¹, Alexander Thompson¹, Sally Bell¹

Departments of Gastroenterology & Hepatology: ¹St Vincent's Hospital, Melbourne, Australia. ²The Austin Hospital, Melbourne, Australia. ³Department of Surgery, The Austin Hospital, Melbourne, Australia. ⁴Monash Medical Centre, Melbourne, Australia. ⁵The Alfred Hospital, Melbourne, Australia. ⁶Eastern Health, Melbourne, Australia. ⁷The Royal Melbourne Hospital, Melbourne, Australia. ⁸Western Health, Melbourne, Australia. ⁹Victorian Cancer Registry, Cancer Council Victoria, Australia. ¹⁰Melbourne Medical School, University of Melbourne, Melbourne, Australia. ¹¹Eastern Health Clinical School, Monash University, Melbourne, Australia.

Hepatocellular carcinoma (HCC) incidence is rising rapidly in many developed countries. Primary epidemiological data have invariably been derived from cancer registries that are heterogeneous in data quality and registration methodology; many registries have not adopted current clinical diagnostic criteria for HCC and still rely on histology for classification. We performed the first population-based study in Australia using current diagnostic criteria, hypothesizing that HCC incidence may be higher than reported. Incident cases of HCC (defined by American Association for the Study of Liver Diseases diagnostic criteria or histology) were prospectively identified over a 12-month period (2012-2013) from the population of Melbourne, Australia. Cases were captured from multiple sources: admissions to any of Melbourne’s seven tertiary hospitals; attendances at outpatients; and radiology, pathology, and pharmacy services. Our cohort was compared to the Victorian Cancer Registry (VCR) cohort (mandatory notified cases) for the same population and period, and incidence rates were compared for both cohorts. There were 272 incident cases (79% male; median age: 65 years) identified. Cirrhosis was present in 83% of patients, with hepatitis C virus infection (41%), alcohol (39%), and hepatitis B virus infection (22%) the commonest aetiologies present. Age-standardized HCC incidence (per 100,000, Australian Standard Population) was 10.3 (95% confidence interval [CI]: 9.0-11.7) for males and 2.3 (95% CI: 1.8 to 3.0) for females. The VCR reported significantly lower rates of HCC: 5.3
(95% CI: 4.4 to 6.4) and 1.0 (95% CI: 0.7 to 1.5) per 100,000 males and females respectively (P < 0.0001).

Conclusions: HCC incidence in Melbourne is 2-fold higher than reported by cancer registry data owing to under-reporting of clinical diagnoses. Adoption of current diagnostic criteria and additional capture sources will improve registry completeness. Chronic viral hepatitis and alcohol remain leading causes of cirrhosis and HCC. (HEPATOLOGY 2016;63:1205-1212)
4.2 INTRODUCTION

Primary liver cancer (PLC) has become the second leading cause of cancer mortality worldwide and is also the fifth most common cancer. Hepatocellular carcinoma (HCC), the predominant type of primary liver cancer, mostly arise in the setting of cirrhosis, with the most common aetiologies being chronic viral hepatitis B and C, alcohol and non-alcoholic fatty liver disease.

The incidence of HCC has been widely reported to be increasing in regions with historically low incidence. In Australia, liver cancer is the fastest rising cause of cancer death. Multiple factors may contribute to this phenomenon, including increased migration from regions with high HCC and viral hepatitis prevalence, an increasing burden of cirrhosis as patients are surviving longer with better medical treatments, and the obesity epidemic causing rising prevalence of non-alcoholic steatohepatitis related cirrhosis.

The HCC epidemiology literature has been reliant upon cancer registries as the primary source of incidence data and hence is subject to the limitations of cancer registry data capture methodology. Cancer registries vary in a number of important features. Mandatory reporting laws that help improve registration completeness are not universal and where laws exist, not all potential sources of case identification are utilised. For example, in Victoria, Australia, cancers identified from hospital admissions and pathology services are registered but diagnoses made in outpatient settings and radiology services are not reportable, possibly leading to incomplete registration.

Differences also occur in the criteria for HCC classification. The traditional approach used by the Victorian Cancer Registry (VCR, Victoria, Australia) and many other registries across the world (e.g. China, Italy) relies upon histological verification for HCC classification; all clinically diagnosed PLC without histology are classified as Liver Cancer Unspecified. However, in current clinical practice, HCC is predominantly diagnosed using clinicoradiological criteria in subjects with cirrhosis rather than histology, as approved by current guidelines from Learned Societies. Hence, some registries (United States, some European countries) now accept clinical diagnosis as a basis for HCC classification.
Therefore, in this context, many studies have reported HCC incidence using total PLC rates as a surrogate marker. However, this is misleading as a significant proportion of primary liver cancers are intrahepatic cholangiocarcinoma (ICC), forming up to 45% of PLC figures as reported by some cancer registries (Figure 4-1). Compared to ICC, HCC has entirely different biologic, prognostic and management implications and hence epidemiological research needs to be HCC specific. Accurate and current epidemiology informs policy decisions by government concerning health resource utilization, identifies risk factors for HCC, and provides targets for prevention.

In Victoria, Australia, we hypothesised that HCC incidence rates may be higher than currently reported by the cancer registry, owing to incorrect classification of clinically diagnosed cases, and incomplete capture from non-reported sources. Therefore, our aim was to determine the incidence rate of HCC in an independent population-based study using current clinical diagnostic criteria. We then compared results with data from the VCR for the same period and population.

Figure 4-1. Disproportionate contributions of different types of Primary Liver Cancer, as classified by various national cancer registries, with heterogeneous distribution of liver cancer incidence in males worldwide.

4.3 MATERIALS AND METHODS

4.3.1 The study population

We performed a population-based study of HCC incidence in Melbourne, Australia, within the geographical region defined by the Australian Bureau of Statistics (ABS) as the Melbourne Statistical Division (MSD). This area has an estimated population of 4,300,207 (ABS Census 2011, projected for the 2012/2013 incident period), suitable for epidemiological study. The population is ethnically diverse with 35% born outside Australia including those from countries with high HCC incidence.

This region contains seven tertiary referral public health services, all of which were participating study sites. Each health service consists of a tertiary university teaching hospital, with associated secondary hospitals, as well as radiology and pathology services. There were no tertiary hospitals in Victoria outside the MSD. The VCR is the population-based registry responsible for the MSD. Patients residing outside the MSD (defined by residential postcodes) were excluded.

4.3.2 Case ascertainment

From July 1, 2012 to June 30, 2013, potential cases were screened from multiple concurrent and overlapping sources. These included patients attending HCC outpatient clinics or discussed at multidisciplinary meetings as well as those found on database searches of the radiology, pathology, pharmacy, and medical coding services of the hospitals involved. In addition, the tertiary hospital hepatology units kept prospective databases of patients diagnosed with HCC and these were also queried. Private physicians and surgeons managing HCC in the community were also invited and contributed to case finding.

Search parameters included radiological procedures (transarterial chemoembolisation, radio frequency, microwave or ethanol ablation), histological diagnoses of HCC (ICD-0-3 C22.0 M8170/3), sorafenib dispensing and medical admissions coding of International Classification of Diseases ICD-10 C22.0 Hepatocellular carcinoma, and C22.9 Liver Cancer Unspecified. American Association for the Study of Liver Disease (AASLD) clinicoradiological diagnostic
criteria and/or histology were used to define HCC cases. Cases of HCC recurrence or diagnosis dates outside the designated study period were excluded. Readmissions or attendance of a case at another site was only counted for the first instance.

Data collected included demographics, underlying aetiology of chronic liver disease, hepatic synthetic liver function, the presence of cirrhosis, Child-Pugh scores, mode of diagnosis, involvement in surveillance programs and tumour staging according to Barcelona Clinic Liver Cancer (BCLC) staging. The aetiology of chronic liver disease was defined by the consulting physician with verification from pathology or radiology results if it was not documented. Data were de-identified and recorded on a secure study database.

Independent human research ethics committees governing each of the associated tertiary health networks granted ethics approval.

### 4.3.3 Victorian Cancer Registry correlation

Current Australian legislation mandates notification of cancers from hospital admissions and pathology, but not outpatient attendances such as clinics or radiology. The VCR provided deidentified data for incident cases of all primary liver cancer subtypes (ICD-10 C22.0 to C22.9) notified during the study incident period. We excluded cases with residential postcodes outside the MSD. In 2012-2013, the VCR methodology required histological verification to code a liver cancer as HCC (C22.0). Clinically diagnosed HCC reported to the VCR without histology were coded as Liver Cancer Unspecified (C22.9). The deidentified information provided by the VCR included patient initials, dates of birth, residential postcode, diagnostic coding, and source of registration (public hospital, private hospital, pathology, or death certificate). Records were matched to our cohort using these parameters.

### 4.3.4 Statistical analysis

Age-standardised incidence rates were calculated using the direct-method for age-standardisation with 18 groups of 5-year age groups (0-, 5-, 10-,…, 85+) for each sex separately. The population data for each age group was derived from ABS Australian Census 2011, with the same figure used as denominator for both MSD and...
VCR rate calculations. Incidence rates were standardised to the Australian Standard Population, using the Australian Census 30 June 2001 standard population as recommended by the ABS\textsuperscript{340}. Incidence rates were reported with 95% confidence intervals (CIs), assuming a Poisson distribution. Categorical variables were compared using Chi-square test or Fisher's exact test, while continuous variables were compared using Mann-Whitney’s test with statistical significance assessed at the 0.05 level. Calculations were performed using StataCorp software (2011; Stata Statistical Software: Release 12; StataCorp LP, College Station, TX).
4.4 RESULTS

There were 327 new diagnoses of HCC captured across the study sites of which 272 cases fulfilled inclusion criteria for the study; 55 patients living outside the study region were excluded. Hospital HCC multi-disciplinary meetings and clinics were the source of most cases captured, with 82% (224 of 272) patients having attended or been referred for discussion. Searches of hospital admission coding captured 68% of patients whereas the combination of multidisciplinary meetings and coding search captured 97% (263 of 272) of cases. The remaining cases (3%) not captured by either of these means were sourced by radiology, pathology or pharmacy searches and private physician referrals.

The baseline characteristics of the cohort are reported in Table 4-1. The majority of HCC patients were male (79%). Patients had a median age of 65 years at diagnosis with men significantly younger than women (median age 64 (range 28-93) and 74 (range 39-91) respectively, p=0.0001).

4.4.1 Incidence rates

The age-standardized incidence rates of HCC in the MSD were 10.3 (95% CI: 9.0-11.7) and 2.3 (95% CI: 1.8-3.0) per 100,000 males and females, respectively.

In comparison, for the same period and population, the VCR recorded 138 cases of HCC (112 males, 26 females) equating to incidence rates of 5.3 (95% CI: 4.4-6.4) and 1.0 (95% CI: 0.7-1.5) per 100,000 males and females, respectively. This was significantly lower than the clinically diagnosed HCC incidence rates from our study (P < 0.0001 and P = 0.0014, respectively, Figure 4-2).
Table 4-1. Baseline Characteristics

<table>
<thead>
<tr>
<th>Total cohort, n</th>
<th>272</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex, males, n (%)</td>
<td>216 (79)</td>
</tr>
<tr>
<td>Age, median, years (range)</td>
<td>66 (28-93)</td>
</tr>
<tr>
<td>Males</td>
<td>64 (28-93)</td>
</tr>
<tr>
<td>Females</td>
<td>74 (39-91)</td>
</tr>
<tr>
<td>Race, n (%), median age (range)</td>
<td></td>
</tr>
<tr>
<td>Caucasian</td>
<td>201 (74), 66 (39-93)</td>
</tr>
<tr>
<td>Asian</td>
<td>59 (22), 63 (33-91)</td>
</tr>
<tr>
<td>African</td>
<td>10 (4), 56 (28-76)</td>
</tr>
<tr>
<td>Unknown</td>
<td>1%</td>
</tr>
<tr>
<td>Place of birth, %</td>
<td></td>
</tr>
<tr>
<td>Australia</td>
<td>39</td>
</tr>
<tr>
<td>Overseas</td>
<td>57</td>
</tr>
<tr>
<td>Unknown</td>
<td>4</td>
</tr>
<tr>
<td>Overseas born in Melbourne population^(13)</td>
<td>35</td>
</tr>
<tr>
<td>Risk factors for chronic liver disease present n (%)</td>
<td></td>
</tr>
<tr>
<td>Chronic hepatitis C</td>
<td>112 (41)</td>
</tr>
<tr>
<td>Alcoholic liver disease</td>
<td>107 (39)</td>
</tr>
<tr>
<td>Chronic hepatitis B</td>
<td>60 (22)</td>
</tr>
<tr>
<td>Fatty liver disease</td>
<td>39 (14)</td>
</tr>
<tr>
<td>Hemochromatosis</td>
<td>6 (2)</td>
</tr>
<tr>
<td>Primary biliary cirrhosis</td>
<td>5 (2)</td>
</tr>
<tr>
<td>Autoimmune hepatitis</td>
<td>3 (1)</td>
</tr>
<tr>
<td>Other/unknown</td>
<td>17 (6)</td>
</tr>
<tr>
<td>More than one risk factor</td>
<td>73 (27)</td>
</tr>
<tr>
<td>Mode of presentation n (%)</td>
<td></td>
</tr>
<tr>
<td>Surveillance program (6-12 monthly US)</td>
<td>110 (40)</td>
</tr>
<tr>
<td>Known cirrhotic but not screened</td>
<td>53 (19)</td>
</tr>
<tr>
<td>First presentation of cirrhosis or incidental</td>
<td>105 (39)</td>
</tr>
<tr>
<td>Unknown</td>
<td>4 (2)</td>
</tr>
<tr>
<td>Liver functional status n (%)</td>
<td></td>
</tr>
<tr>
<td>Cirrhosis present</td>
<td>225 (83)</td>
</tr>
<tr>
<td>Child Pugh A</td>
<td>125 (56)</td>
</tr>
<tr>
<td>Child Pugh B</td>
<td>67 (30)</td>
</tr>
<tr>
<td>Child Pugh C</td>
<td>33 (15)</td>
</tr>
<tr>
<td>Barcelona Clinic Liver Cancer staging n (%)</td>
<td></td>
</tr>
<tr>
<td>BCLC-A</td>
<td>70 (26)</td>
</tr>
<tr>
<td>BCLC-B</td>
<td>59 (22)</td>
</tr>
<tr>
<td>BCLC-C</td>
<td>98 (36)</td>
</tr>
<tr>
<td>BCLC-D</td>
<td>41 (15)</td>
</tr>
</tbody>
</table>

Abbreviation: US, ultrasound.
4.4.2 Adjusted VCR cohort

At the time of study (2012-2013), only cases with histology were classified as HCC (ICD-10 C22.0) by the VCR (138 cases). For the same period, a further 162 cases (118 males, 44 females) without histology were registered by the VCR and coded as Liver Cancer Unspecified (ICD-10 C22.9). Prompted by this study, the VCR reviewed these 162 Liver Cancer Unspecified cases and reclassified them using clinical (non-histological) information supplied at the time of initial cancer registration, resulting in 123 reclassified as HCC, 24 as ICC, 1 as other, and 14 remained Liver Cancer Unspecified. Therefore, for the 12-month period of comparison (2012-2013), it was possible to define an adjusted total of 261 cases of HCC recorded by the VCR, consisting of 123 newly reclassified HCC and the original 138 histologically coded HCC.

We cross-referenced the new adjusted VCR cohort (n = 261) with our study cohort (n = 272) and matched 205 cases of incident HCC common to both cohorts (see Fig. 3). Of the 56 VCR cases that were not identified in our study, there were 5 verifiable HCC incidence cases missed by our capture method, equating to 1.8% of our cohort size. There were 25 non-incident HCC cases with clinical diagnosis dates outside our study inclusion period (i.e., clinical diagnosis before July 1, 2012, but delayed registration in the VCR or diagnosed after July 30, 2013 and yet still incorrectly included in the VCR incidence cohort) and 3 cases of incorrect diagnoses (not HCC). The remaining 23 cases were notified to the VCR by sources beyond our study sites, including private hospitals (12 cases), other public hospitals not associated with our study (8 cases), pathology laboratories (2 cases), and death-certificate-only notifications (1 case). We were not able to verify these diagnoses because our ethics approvals were site specific and did not allow case identification at non-study sites.

4.4.3 Adjusted VCR rates

If we were to presume that all of the 23 unverified cases of the VCR cohort would have met inclusion criteria, then the composite VCR group of likely incident HCC cases would be 233 cases (including the 205 matched cases and 5 cases we missed). For this composite group, the HCC incidence rates are 8.8 (95% CI: 7.6 to 10.2) and 1.9 (95% CI: 1.4 to 2.5) per 100,000 males and females, respectively. These
rates remain lower than our rates, but not significantly so (P = 0.0981 for males and P = 0.3729 for females).

### 4.4.4 Cases missed by VCR registration

Our study captured 67 HCC cases (25% of cohort) that were not registered by the VCR. There were 37 patients who were admitted and coded as HCC, but not reported to the VCR by hospitals. Another 16 patients were admitted for HCC treatment (liver transplantation 2, resection 1, transarterial chemo-embolization 8, and radiofrequency ablation 5), but not did not receive the correct HCC coding on discharge to trigger notification. There were also 14 outpatients receiving palliative treatments (sorafenib or best supported care) who would not have been reportable under current mandatory reporting methods.

To account for cases that may have been notified subsequent to our study period and registered with incorrect diagnosis dates (date of admission rather than date of initial diagnosis), we matched these 67 cases with VCR registrations to March 4, 2015. There were 26 cases registered incorrectly, only 2 cases of late registration and 39 cases remained unaccounted for.

### 4.4.5 Differences between histology defined and clinically diagnosed HCC in the VCR cohort

We examined the 205 matched VCR cases for which we had clinical information from our independent data collection and compared the 100 cases defined by histology with the 105 cases diagnosed clinically (see Supporting Table 4-2). The clinically diagnosed cases were significantly different in racial background (higher proportion of Caucasian [P = 0.0315], lower Asian [P = 0.0387]), and more likely to have advanced disease (presence of cirrhosis [P = 0.0004], higher Child-Pugh scores [P = 0.0021], and later BCLC staging [P = 0.0001]). They were also less likely to be undergoing surveillance despite fulfilling indications for screening (P = 0.0254).
Figure 4-2. Comparison of HCC incidence rates between this study and VCR groups according to histology and composite (clinical and histology) classifications. Age-standardized incidence rate per 100,000 (Australian Standard Population) with 95% CIs.

Figure 4-3. Case matching the study cohort (n = 272) with the VCR cohort (n = 261).
Table 4-2. Baseline Characteristics of VCR HCC cases defined by histology or clinical diagnosis.

<table>
<thead>
<tr>
<th></th>
<th>VCR HCC cases (histology)</th>
<th>VCR Unspecified cancer (clinical only)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of cases</td>
<td>100</td>
<td>105</td>
<td>NS</td>
</tr>
<tr>
<td>Sex: males, n (%)</td>
<td>83 (83%)</td>
<td>83 (79%)</td>
<td>NS</td>
</tr>
<tr>
<td>Age: median, years (range)</td>
<td>64 (28 - 91)</td>
<td>65 (40 - 91)</td>
<td>NS</td>
</tr>
<tr>
<td>Males</td>
<td>63 (28 - 87)</td>
<td>63 (44 - 91)</td>
<td>NS</td>
</tr>
<tr>
<td>Females</td>
<td>68 (39 - 91)</td>
<td>77 (40 - 89)</td>
<td>NS</td>
</tr>
<tr>
<td>Race: n (%), median (years): age (range)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Caucasian</td>
<td>69 (69%), 66 (39 - 87)</td>
<td>86 (82%), 65 (40 - 89)</td>
<td>0.0315</td>
</tr>
<tr>
<td>Asian</td>
<td>27 (27%), 56 (33 - 91)</td>
<td>16 (15%), 75 (44 – 90)</td>
<td>0.0387</td>
</tr>
<tr>
<td>African</td>
<td>3 (3%), 52 (28 - 74)</td>
<td>2 (2%), 63 (52 - 76)</td>
<td>NS</td>
</tr>
<tr>
<td>Other (Unknown)</td>
<td>1 (1%)</td>
<td>1 (1%)</td>
<td></td>
</tr>
<tr>
<td>Place of birth, %</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Australia</td>
<td>36%</td>
<td>43%</td>
<td>NS</td>
</tr>
<tr>
<td>Overseas</td>
<td>57%</td>
<td>54%</td>
<td>NS</td>
</tr>
<tr>
<td>Unknown</td>
<td>7%</td>
<td>3%</td>
<td>NS</td>
</tr>
<tr>
<td>Risk factors for chronic liver disease present</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chronic hepatitis C</td>
<td>33 (33%)</td>
<td>48 (46%)</td>
<td>0.0627</td>
</tr>
<tr>
<td>Alcoholic liver disease</td>
<td>34 (34%)</td>
<td>48 (46%)</td>
<td>0.0870</td>
</tr>
<tr>
<td>Chronic hepatitis B</td>
<td>27 (27%)</td>
<td>18 (17%)</td>
<td>0.0883</td>
</tr>
<tr>
<td>Fatty liver disease</td>
<td>16 (16%)</td>
<td>15 (14%)</td>
<td>NS</td>
</tr>
<tr>
<td>Haemochromatosis</td>
<td>2 (2%)</td>
<td>4 (4%)</td>
<td>NS</td>
</tr>
<tr>
<td>Primary biliary cirrhosis</td>
<td>2 (%)</td>
<td>2 (2%)</td>
<td>NS</td>
</tr>
<tr>
<td>Autoimmune hepatitis</td>
<td>0</td>
<td>0</td>
<td>NS</td>
</tr>
<tr>
<td>Other / Unknown</td>
<td>6 (6%)</td>
<td>5 (5%)</td>
<td>NS</td>
</tr>
<tr>
<td>More than one risk factor</td>
<td>23 (23%)</td>
<td>34 (32%)</td>
<td>NS</td>
</tr>
<tr>
<td>Mode of presentation</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Surveillance program (6-12 monthly US)</td>
<td>40 (40%)</td>
<td>39 (37%)</td>
<td>NS</td>
</tr>
<tr>
<td>Known cirrhotic but not screened</td>
<td>15 (15%)</td>
<td>29 (28%)</td>
<td>0.0254</td>
</tr>
<tr>
<td>First presentation of cirrhosis or incidental</td>
<td>43 (43%)</td>
<td>36 (34%)</td>
<td>NS</td>
</tr>
<tr>
<td>Unknown</td>
<td>2 (2%)</td>
<td>1 (1%)</td>
<td>NS</td>
</tr>
<tr>
<td>Liver functional status</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cirrhosis present</td>
<td>71 (71%)</td>
<td>95 (90%)</td>
<td>0.0004</td>
</tr>
<tr>
<td></td>
<td>Child Pugh A</td>
<td>Child Pugh B</td>
<td>Child Pugh C</td>
</tr>
<tr>
<td>------------------</td>
<td>--------------</td>
<td>--------------</td>
<td>--------------</td>
</tr>
<tr>
<td></td>
<td>50 (70%)</td>
<td>41 (43%)</td>
<td>4 (6%)</td>
</tr>
<tr>
<td>Child Pugh B</td>
<td>17 (24%)</td>
<td>32 (34%)</td>
<td>22 (23%)</td>
</tr>
<tr>
<td>Child Pugh C</td>
<td>4 (6%)</td>
<td>22 (23%)</td>
<td>22 (23%)</td>
</tr>
</tbody>
</table>

**Barcelona Clinic Liver Clinic Staging**

<table>
<thead>
<tr>
<th></th>
<th>BCLC-A</th>
<th>BCLC-B</th>
<th>BCLC-C</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>34 (34%)</td>
<td>14 (13%)</td>
<td>33 (33%)</td>
<td>0.0005</td>
</tr>
<tr>
<td>BCLC-B</td>
<td>24 (24%)</td>
<td>22 (21%)</td>
<td>44 (42%)</td>
<td>NS</td>
</tr>
<tr>
<td>BCLC-C</td>
<td>33 (33%)</td>
<td>44 (42%)</td>
<td>44 (42%)</td>
<td>NS</td>
</tr>
<tr>
<td>BCLC-D</td>
<td>5 (5%)</td>
<td>25 (24%)</td>
<td>25 (24%)</td>
<td>0.0001</td>
</tr>
</tbody>
</table>
4.5 DISCUSSION

The management of HCC is complex and costly, requiring involvement of tertiary health care and the use of advance diagnostic modalities and therapeutics, including liver transplantation. Accurate representation of HCC epidemiology is required to adequately address the increasing burden of disease on the health system. This is the first study in Australia to independently define the problem at the population-based level using current clinicoradiological diagnostic criteria, thus addressing the shortcomings of current epidemiological literature that is primarily dependent upon cancer registries.

We have shown that HCC incidence rates in Melbourne are two-fold higher than those reported by the Victorian Cancer Registry using histology as a basis for classification. The data demonstrate the importance of using current diagnostic criteria for registry classification of HCC in cancer registries. HCC is no longer diagnosed histologically but based on clinicoradiological criteria. These criteria have been validated and accepted by international liver societies; histology is reserved for indeterminate cases.

As a direct result of our study, the VCR have adopted new methodology to classify HCC by both histological and/or clinicoradiological criteria as of 1 January, 2014. Indeed, cancer registries across the world are starting to recognise the need for a change in classification of HCC to a broader diagnostic criterion consisting of both clinical and radiological bases of diagnosis. Comparing reports from the International Association of Cancer Registries in Cancer Incidence in Five Continents Vol IX (2007) and Vol X (2014) many registries from China, South East Asia, Italy and other regions are gradually implementing clinical criteria, resulting in lower rates for unspecified primary liver cancer and higher rates for HCCs. As with Victoria from 2014 onwards, incidence rates for HCC will be higher than previously reported.

We then tested whether a population-based incidence study, using multiple capture methods to diagnose cases identified through comprehensive clinical case collection, would identify a greater number of incident HCCs compared to our local cancer registry. For the comparator we used the adjusted VCR incident data for the matching time period, after reclassification of cases that were originally classified as Liver Cancer Unspecified, but which on review, had been given a clinical diagnosis of
HCC at the point of notification. We still identified higher incidence rates than the adjusted registry incidence rates for clinically diagnosed HCC. This difference did not meet statistical significance, possibly owing to our conservative approach in presuming that all 23 cases notified to the VCR from non-study sources were indeed HCC.

Nevertheless, the fact remains that a quarter of the total HCC cases identified in our study were not notified to the VCR (including those notified incorrectly and thus not included in published incidence figures). In contrast, using this capture method, our missed rate was less than 2%. This highlights both the importance of identifying appropriate sources of case capture to optimise cancer registration completeness, as well as the need to be familiar with the methodology of the local registry, especially in light of newer clinical diagnostic criteria. Best practice management of HCC should involve multi-disciplinary case review meetings involving hepatologists, radiologists, surgeons and oncologists. On the basis of our findings, we propose that mandatory notification from multi-disciplinary meetings to cancer registries should be required and supported.

In addition to correctly classifying HCC using current diagnostic criteria, it is also important for researchers to differentiate HCC epidemiology from that of ICC. Many studies have used HCC and PLC interchangeably, quoting total PLC rates from cancer registries for incidence and mortality when, in fact, the discussion relates to HCC. Greater emphasis needs to be made of the significant contribution ICC rates make to PLC figures in different populations. For example, ICC make up between 5% and 25% of total PLC rates across United States registries, and up to 45% in UK registries (IACR). ICC incidence and mortality rates have also risen in recent times, suggesting that trends in PLC incidence need to account for changes in both HCC and ICC rates independently, particularly given that the biological behavior, clinical management, prognosis and survival rates differ significantly between HCC and ICC. Hence, more accurate representation will assist planning of education and preventative screening practices as well as allow appropriate utilization of health care resources.

While tertiary referral bias may be a concern in terms of adequate population representation, the unique nature of HCC management reduces this limitation. HCC is a complex disease with a poor prognosis, mostly referred to specialists and generally
requiring a tertiary hospital service for diagnosis or treatment at some point. In addition, as a cancer, HCC is mandatorily reportable in Australia; patients, including those with terminal disease and palliative needs, who present elsewhere (e.g. private hospitals, nursing homes, death certificate only notifications) are captured by the population-based VCR. Our favourable comparison with the VCR data suggests that tertiary referral bias has not negatively influenced our reported incidence rates. Instead, the cases missed by the VCR did in fact present to a tertiary hospital as hypothesized and were captured by our methods. Moreover, any residual failure of capture on our part would serve to further strengthen our suggestion that incidence is currently under-reported.

We recognize that the two-fold discrepancy between our HCC incidence and the local registry rates examined over a one-year period in Melbourne may not be generalizable to other populations. Incidence rates in any population will depend upon the prevailing risk factors present; in the case of developed countries with historically low incidence, migrants from countries with high HCC incidence play an important role. Our data shows that people born overseas are overrepresented in HCC cases in Melbourne. We suggest that our methodology could be validated in other cities, such as those in Australia, the United States, Canada and Europe, which have similarly high proportions of overseas-born residents. Furthermore, the degree of discrepancy between rates from an independent, population-based study such as this and that of the local registry, will also depend upon individual cancer registry practices as well as local epidemiology. Particularly important would be populations where the local registry is yet to adopt clinical criteria in cancer registrations and is still reporting disproportionately high rates of unspecified PLCs (Figure 4-1). Although our results based on a capture period of only one year may not reflect longer term trends, and may not be reproducible in all populations, our methodology may nevertheless help other regions improve case ascertainment to better inform health policies.
4.6 CONCLUSION

This study is the first Australian study to describe HCC incidence at a population-based level using current accepted clinicoradiologic and pathologic criteria, independent of cancer registry data. Our HCC incidence rates are two-fold higher than that reported by the cancer registry, suggesting that the revision of cancer registration methodology in line with current diagnostic criteria was required. Furthermore, the inclusion of additional clinical sources of cases may improve data capture and estimates. Finally, we reiterate the importance of using HCC specific data in publications and discussion of epidemiologic data, which requires having a full understanding of registration methodologies of the local reporting cancer registry. Accurate epidemiological data will assist policy makers to implement public health interventions such as education, screening for viral hepatitis and cancer, and allow effective resource allocation.
5 Surveillance Improves Survival Outcomes of Hepatocellular Carcinoma

This is a longitudinal study of the population-based cohort of incident HCC in Melbourne, captured as described in Chapter 4. This study has been published in Australia’s highest ranking peer-reviewed medical journal, *the Medical Journal of Australia* (Impact Factor 4.227 in 2017, rank 19th in the General and Internal Medicine category).418

Reference:


The text in its entirety is included in this chapter. The print version from the journal is included as an appendix.
5.1 ABSTRACT

Surveillance improves survival of patients with hepatocellular carcinoma: a prospective population-based study

Thai P Hong¹, Paul J Gow², Michael Fink³, Anouk Dev⁴, Stuart K Roberts², Amanda Nicoll⁵, John S Lubel⁶, Ian Kronborg⁷, Niranjan Arachchi³, Marno Ryan¹, William W Kemp⁸, Virginia Knight⁵, Vijaya Sundararajan¹, Paul Desmond¹, Alexander JV Thompson¹, Sally J Bell¹

¹ St Vincent's Hospital Melbourne, Melbourne, VIC. ² Austin Hospital, Melbourne, VIC. ³ University of Melbourne, Melbourne, VIC. ⁴ Austin Health, Melbourne, VIC. ⁵ Monash Health, Melbourne, VIC. ⁶ Eastern Health, Melbourne, VIC. ⁷ Western Health, Melbourne, VIC. ⁸ Alfred Hospital, Melbourne, VIC.

Objectives: To determine the factors associated with survival of patients with hepatocellular carcinoma (HCC) and the effect of HCC surveillance on survival.

Design, setting and participants: Prospective population-based cohort study of patients newly diagnosed with HCC in seven tertiary hospitals in Melbourne, 1 July 2012 e 30 June 2013.

Main outcome measures: Overall survival (maximum follow-up, 24 months); factors associated with HCC surveillance participation and survival.

Results: 272 people were diagnosed with incident HCC during the study period; the most common risk factors were hepatitis C virus infection (41%), alcohol-related liver disease (39%), and hepatitis B virus infection (22%). Only 40% of patients participated in HCC surveillance at the time of diagnosis; participation was significantly higher among patients with smaller median tumour size (participants, 2.8 cm; non-participants, 6.0 cm; P < 0.001) and earlier Barcelona Clinic Liver Cancer (BCLC) stage disease (A/B, 59%; C/D, 25%; P < 0.001). Participation was higher among patients with compensated cirrhosis or hepatitis C infections; it was lower among those with alcohol-related liver disease or decompensated liver disease. Median overall survival time was 20.8 months; mean survival time was 18.1 months (95% CI, 16.6e19.6 months). Participation in HCC surveillance was associated with significantly lower mortality (adjusted hazard ratio [aHR], 0.60; 95% CI, 0.38e0.93; P 1/4 0.021), as were curative therapies (aHR, 0.33; 95% CI, 0.19e0.58). Conversely, higher Child-Pugh class, alpha-fetoprotein levels over 400 kU/L, and later BCLC disease stages were each associated with higher mortality.
**Conclusions:** Survival for patients with HCC is poor, but may be improved by surveillance, associated with the identification of earlier stage tumours, enabling curative therapies to be initiated.

**Summary Box**

**The known**

The incidence and mortality of hepatocellular carcinoma (HCC) are rising more rapidly in Australia than those of other cancer types.

**The new**

Survival for patients with HCC is poor, with a median survival time of 20.8 months. Surveillance is associated with improved survival, but participation rates are low (40%), despite 89% of patients with HCC qualifying for surveillance. Risk factors for HCC, such as cirrhosis and viral hepatitis, are underdiagnosed, and are often first identified when HCC is diagnosed.

**The implications**

Strategies for increasing the recognition of risk factors for HCC and for improving surveillance rates among people at risk, in line with established international guidelines, are needed.
5.2 INTRODUCTION

On a global basis, liver cancer is the fifth most frequently diagnosed cancer type, and causes the second highest number of cancer-related deaths.\textsuperscript{15} Incidence and mortality are both highest in East and South-East Asia, Africa, and developing nations, but are rising in Western countries; the increase in the number of liver cancer-related deaths has been the most rapid for any cancer type in Australia over the past 40 years.\textsuperscript{276}

Hepatocellular carcinoma (HCC) accounts for about 82% of primary liver cancer in Australia\textsuperscript{15}. HCC is most frequently identified in patients with cirrhosis, typically caused by chronic hepatitis B (HBV) or C virus (HCV) infections, alcohol-related liver disease, or non-alcoholic fatty liver disease.\textsuperscript{243,274,295} A variety of treatments are available, including curative therapies (liver transplantation, surgical resection, percutaneous and laparoscopy-assisted ablation) and palliative measures, such as transarterial chemoembolisation, a kinase inhibitor (sorafenib), selective internal radiation therapy, and best supportive care. Despite advances in therapy, overall survival remains poor,\textsuperscript{281} partly because late presentation with advanced disease\textsuperscript{282} limits treatment options.

HCC surveillance facilitates diagnosis at a stage of disease when curative treatments are effective, and is associated with reduced mortality.\textsuperscript{349} International guidelines\textsuperscript{51,52,104} recommend surveillance as standard practice, but uptake is poor and its implementation varies between institutions and physicians.\textsuperscript{383,419} Barriers to surveillance include lack of awareness of the underlying risks, low rates of screening for cirrhosis and viral hepatitis, cultural and linguistic difficulties, and cost and resource limitations.

We recently reported the first Australian population-based study of incident HCC.\textsuperscript{420} We found that age-standardised incidence rates of HCC in Melbourne were twice as high as reported by the Victorian Cancer Registry: 10.3 cases (95% confidence interval [CI], 9.0-11.7) per 100 000 men and 2.3 cases (95% CI, 1.8-3.0) per 100 000 women.

In this new study, we aimed to determine overall survival for patients with HCC and to identify factors that influence survival. We hypothesised that participating in an
HCC surveillance program would be associated with diagnosis of HCC at an earlier stage and consequently with improved survival.
5.3 METHODS

5.3.1 Study cohort

Data for the prospective clinical cohort of patients in the Melbourne statistical division newly diagnosed with HCC during 1 July 2012 - 30 June 2013, identified in our earlier study, were analysed. The Melbourne statistical division has an estimated population of 4 300 207 (projected population for 2012-13) that is ethnically diverse; 35% of residents were born outside Australia. Patients residing outside the division (defined by residential postcodes) were excluded.

The population-based Victorian Cancer Registry collects data for all patients with cancer in the Melbourne statistical division. The region includes seven tertiary referral public health services, all of which were participating study sites. Each health service includes a tertiary university teaching hospital, with associated secondary hospitals and radiology and pathology services.

5.3.2 Data collection

Our case ascertainment methodology was reported previously. Data for patients at all study sites were captured (with the informed consent of the patients) and cross-referenced with Victorian Cancer Registry data. Data were de-identified and stored on a secure database.

Data collated from patient records included demographic information (including ethnic background and place of birth), residential postcode, aetiology of chronic liver disease, the presence of cirrhosis, Child-Pugh scores, alpha-fetoprotein levels, mode of presentation, participation in a surveillance program, Barcelona Clinic Liver Cancer (BCLC) stage, and treatment modality. The aetiology of chronic liver disease was defined by the consulting physician, and verified by pathology or radiology results if the cause was not documented. Cirrhosis status was determined after a review of histology, transient electrography, radiology, and biochemistry findings. Treatment modality was defined as the first treatment given, except for patients who were downstaged when more curative therapy was later assigned.

Three ethnic groups were defined for the purposes of our analysis: white (including Egypt, Middle East), African (sub-Saharan Africa), and Asian (mainly East
and South-East Asia, with three patients from India or Sri Lanka). Indigenous status was not recorded.

Participation in a surveillance program was defined as patients with risk factors defined in international guidelines — cirrhosis of any cause; chronic HBV infection in Asian men over 40, Asian women over 50, African patients over 20 years of age, and people with a family history of HCC — undergoing 6-monthly ultrasound assessment with or without alpha-fetoprotein assessment.

The primary study outcome was overall survival. Survival time was calculated from the date of diagnosis until the date of notified death, as retrieved from hospital records, the Victorian Cancer Registry, and the Registry of Births, Deaths and Marriages Victoria. Patients were censored at last known medical attendance (consultation, radiology, pathology, other records), with a maximum follow-up period of 24 months.

5.3.3 Statistical analysis

Descriptive statistics are presented for continuous factors (medians with interquartile ranges [IQRs]) and categorical variables (numbers, proportions). Standardised HCC incidence ratios were calculated, comparing rates by country of birth with those for Australian-born patients (projected population for 2012-13). Correlations of clinically relevant variables were assessed as Spearman rank correlation coefficients (not reported); if the correlation of two variables was statistically significant, for the purposes of regression analysis they were either combined (e.g., cirrhosis and Child-Pugh class combined as the new variable, “liver function”) or one variable was omitted (e.g., BCLC stage but not tumour size retained).

To assess factors associated with surveillance participation, crude and adjusted odds ratios (ORs, aORs) were respectively estimated in logistic regression and multiple logistic regression models.

Survival was estimated with the Kaplan-Meier method. As the upper confidence bound for median survival time could not be calculated (the point 95% CI never dropped below 0.5 during the 24-month maximum follow-up period), mean survival time — calculated as the area under the Kaplan-Meier survivor function with the Stata
option \textit{rmean} — is also presented. Cox proportional hazards models were fitted for individual factors associated with survival nominated by specialist hepatologists (crude hazard ratio [HR]); factors for which $P < 0.1$ in the univariate analysis were included in the multiple regression Cox proportional hazards model (adjusted HR [aHR]). Violations of the proportional hazards assumption were assessed by visual inspection of Kaplan-Meier curves and in Schoenfeld residuals tests. $P < 0.05$ was deemed statistically significant. All analyses were performed in Stata Statistical Software 12 (StataCorp).

5.3.4 Ethics approval

Human research ethics committees for each health network granted approval for the study: St Vincent’s Health (reference, HREC-A 056.12), Melbourne Health (including Western Health; reference, 2012.150), Eastern Health (reference, E66-1112), Austin Health (reference, H2012/04713), Southern Health (reference, 12201A), and Alfred Health (reference, 357/12).
5.4 RESULTS

A total of 272 people in the Melbourne statistical division were diagnosed with incident HCC during 1 July 2012 - 30 June 2013, including 216 men (79%). The most frequent risk factors for liver disease were HCV infection (112, 41%), alcohol (107, 39%), HBV infection (60, 22%), and non-alcoholic fatty liver disease (39, 14%); 73 patients (27%) had more than one risk factor (Table 5-1). Of 225 patients (83%) with cirrhosis, 72 (32%) were first diagnosed with cirrhosis at the time of HCC diagnosis.

Most patients (166, 61%) were born overseas (Table 5-1). The standardised incidence of HCC was higher for overseas-born than for Australian-born people, and particularly high for those born in sub-Saharan Africa, Italy, Vietnam, or Egypt (Figure 5-1). Significantly more overseas-born patients had viral hepatitis-related HCC (108 of 166, 65%) than Australian-born patients (55 of 106, 52%; P < 0.031); significantly more Australian-born patients had alcohol-related HCC (65 of 106, 61% v 42 of 166, 25%, P < 0.001).

Treatment with curative intent was provided to 87 patients (32%) — liver transplantation (3%), resection (13%), and ablative therapies (radio-frequency, microwave, percutaneous alcohol; 16%) — and 180 patients (66%) were offered treatment with palliative intent — trans-arterial chemo-embolisation (24%), selective internal radiation radiotherapy (1.8%), systemic targeted therapy (sorafenib, 13%), and best supportive care (28%) (Table 5-1). Follow-up treatment for five patients with late stage disease was not recorded because they were overseas or otherwise lost to follow-up.

Figure 5-1. Standardised incidence ratios for hepatocellular carcinoma (compared with incidence among Australian-born people), by country/region of birth (Countries of birth providing fewer than three patients not shown)
Table 5-1. Baseline Characteristics

<table>
<thead>
<tr>
<th>Total cohort, n</th>
<th>272</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Sex: males, n (%)</strong></td>
<td>216 (79%)</td>
</tr>
<tr>
<td><strong>Age: years, median (IQR)</strong></td>
<td></td>
</tr>
<tr>
<td>Males</td>
<td>64 (56 - 74)</td>
</tr>
<tr>
<td>Females</td>
<td>74 (64 - 80)</td>
</tr>
<tr>
<td><strong>Race: n (%), median age (IQR)</strong></td>
<td></td>
</tr>
<tr>
<td>Caucasian (Australian-born)</td>
<td>105 (39%), 60 (56 - 71)</td>
</tr>
<tr>
<td>Caucasian (Overseas-born)</td>
<td>96 (36%), 70 (61 - 78)</td>
</tr>
<tr>
<td>Asian</td>
<td>59 (22%), 63 (54 - 75)</td>
</tr>
<tr>
<td>African</td>
<td>10 (4%), 56 (53 - 74)</td>
</tr>
<tr>
<td>Unknown</td>
<td>2 (1%), 65 (55 - 75)</td>
</tr>
<tr>
<td><strong>Place of birth, n (%)</strong></td>
<td></td>
</tr>
<tr>
<td>Australia</td>
<td>105 (39%)</td>
</tr>
<tr>
<td>Overseas</td>
<td>155 (57%)</td>
</tr>
<tr>
<td>Unknown</td>
<td>12 (4%)</td>
</tr>
<tr>
<td><strong>Risk factors for chronic liver disease present, n (%)</strong></td>
<td></td>
</tr>
<tr>
<td>Chronic hepatitis C virus (HCV)</td>
<td>112 (41%)</td>
</tr>
<tr>
<td>Alcohol-related liver disease</td>
<td>107 (39%)</td>
</tr>
<tr>
<td>Chronic hepatitis B virus (HBV)</td>
<td>60 (22%)</td>
</tr>
<tr>
<td>Non-alcohol fatty liver disease (NAFLD)</td>
<td>39 (14%)</td>
</tr>
<tr>
<td>Haemochromatosis</td>
<td>6 (2%)</td>
</tr>
<tr>
<td>Primary biliary cirrhosis</td>
<td>5 (2%)</td>
</tr>
<tr>
<td>Autoimmune hepatitis</td>
<td>3 (1%)</td>
</tr>
<tr>
<td>Other / Unknown</td>
<td>17 (6%)</td>
</tr>
<tr>
<td>More than one risk factor</td>
<td>73 (27%)</td>
</tr>
<tr>
<td><strong>Mode of presentation, n (%)</strong></td>
<td></td>
</tr>
<tr>
<td>Surveillance program (6-12 monthly ultrasound)</td>
<td>110 (40%)</td>
</tr>
<tr>
<td>Known indication but not screened</td>
<td>53 (19%)</td>
</tr>
<tr>
<td>First presentation of cirrhosis /other risk factor</td>
<td>32 (12%)</td>
</tr>
<tr>
<td>Incidental HCC finding</td>
<td>73 (27%)</td>
</tr>
<tr>
<td>Unknown</td>
<td>4 (2%)</td>
</tr>
<tr>
<td><strong>Liver functional status, n (%)</strong></td>
<td></td>
</tr>
<tr>
<td>Cirrhosis present</td>
<td>225 (83%)</td>
</tr>
<tr>
<td>Child Pugh A</td>
<td>125 (56%)</td>
</tr>
<tr>
<td>Child Pugh B</td>
<td>67 (30%)</td>
</tr>
<tr>
<td>Child Pugh C</td>
<td>33 (15%)</td>
</tr>
<tr>
<td><strong>Barcelona Clinic Liver Cancer Staging, n (%)</strong></td>
<td></td>
</tr>
<tr>
<td>BCLC-A</td>
<td>70 (26%)</td>
</tr>
<tr>
<td>BCLC-B</td>
<td>59 (22%)</td>
</tr>
<tr>
<td>BCLC-C</td>
<td>98 (37%)</td>
</tr>
<tr>
<td>BCLC-D</td>
<td>41 (15%)</td>
</tr>
<tr>
<td><strong>Treatment modality, n (%)</strong></td>
<td></td>
</tr>
<tr>
<td>Best supportive care</td>
<td>76 (28%)</td>
</tr>
<tr>
<td>Sorafenib</td>
<td>34 (13%)</td>
</tr>
<tr>
<td>Selective Internal Radiation Therapy</td>
<td>5 (1.8%)</td>
</tr>
<tr>
<td>Transarterial Chemoembolisation</td>
<td>65 (24%)</td>
</tr>
</tbody>
</table>
Table 5-2. Logistic regression analysis of factors influencing surveillance participation

<table>
<thead>
<tr>
<th>Risk factor</th>
<th>Surveillance participation</th>
<th>Odds ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Number of participants</td>
<td>110 (40%)</td>
<td>158 (58%)</td>
</tr>
<tr>
<td>Age (years), median (IQR)</td>
<td>64 (56–74)</td>
<td>66 (56–77)</td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Women</td>
<td>27</td>
<td>28</td>
</tr>
<tr>
<td>Men</td>
<td>83</td>
<td>130</td>
</tr>
<tr>
<td>Ethnic background/place of birth</td>
<td></td>
<td></td>
</tr>
<tr>
<td>White/overseas-born</td>
<td>52</td>
<td>45</td>
</tr>
<tr>
<td>White/Australian-born</td>
<td>36</td>
<td>67</td>
</tr>
<tr>
<td>African</td>
<td>3</td>
<td>7</td>
</tr>
<tr>
<td>Asian</td>
<td>19</td>
<td>39</td>
</tr>
<tr>
<td>Liver function</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Non-cirrhotic</td>
<td>6</td>
<td>32</td>
</tr>
<tr>
<td>Child–Pugh A</td>
<td>66</td>
<td>57</td>
</tr>
<tr>
<td>Child–Pugh B</td>
<td>26</td>
<td>41</td>
</tr>
<tr>
<td>Child–Pugh C</td>
<td>11</td>
<td>22</td>
</tr>
<tr>
<td>Decompensated cirrhosis (Child–Pugh B/C)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>73</td>
<td>85</td>
</tr>
<tr>
<td>Yes</td>
<td>37</td>
<td>73</td>
</tr>
<tr>
<td>Chronic hepatitis B</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>88</td>
<td>120</td>
</tr>
<tr>
<td>Yes</td>
<td>22</td>
<td>38</td>
</tr>
<tr>
<td>Chronic hepatitis C</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>52</td>
<td>105</td>
</tr>
<tr>
<td>Yes</td>
<td>58</td>
<td>53</td>
</tr>
<tr>
<td>Alcohol-related liver disease</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>74</td>
<td>88</td>
</tr>
<tr>
<td>Yes</td>
<td>36</td>
<td>70</td>
</tr>
<tr>
<td>Non-alcohol fatty liver disease</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>97</td>
<td>132</td>
</tr>
<tr>
<td>Yes</td>
<td>13</td>
<td>6</td>
</tr>
</tbody>
</table>

CI = confidence interval; IQR = interquartile range. * Includes factors for which P < 0.1 in univariate analysis. † Based on an alternative model not including the variable “liver function.”
5.4.1 Surveillance at the time of hepatocellular carcinoma diagnosis

One hundred and ten patients (40%) were participating in surveillance at the time of HCC diagnosis; surveillance data were incomplete for four patients. Most non-participating patients had guideline indications for surveillance: cirrhosis (120 of 158, 76%) or chronic HBV infection without cirrhosis (17, 11%); 120 of 225 patients with cirrhosis (53%) were not participating in surveillance, including 72 (60%) who were diagnosed with cirrhosis at the time of HCC diagnosis. Non-participation was most marked among those with chronic HBV infections but not cirrhosis (17 of 21, 81%), including 12 patients in whom the infection was first detected at the time of HCC diagnosis. Overall, 242 of 272 patients (89%) would have qualified for surveillance (225 with cirrhosis, 17 without cirrhosis but with chronic HBV infections).

The multivariable analysis indicated that Australia-born (aOR, 0.45; 95% CI, 0.24 - 0.85; P = 0.014) and Asian patients (aOR, 0.42; 95% CI, 0.20 - 0.91; P = 0.029) were less likely to participate in surveillance than white patients born overseas. Participation in surveillance by patients with compensated cirrhosis (Childs-Pugh A) was higher than for those without cirrhosis (aOR, 5.70; 95% CI, 2.10 - 15.5; P = 0.001), but decompensated cirrhosis (Childs-Pugh B or C) was associated with a lower surveillance rate than that for patients with compensated cirrhosis or without cirrhosis (aOR, 0.53; 95% CI, 0.30 - 0.95; P = 0.033). Surveillance was higher among patients with HCV-related HCC (aOR, 1.95; 95% CI, 1.11 - 3.42; P = 0.020) and lower among those with alcohol-related HCC (aOR, 0.53; 95% CI, 0.29 - 0.95; P = 0.034) (Table 5-2).

Participation in surveillance was higher for patients with earlier than later stage disease (BCLC A/B, 75 of 127, 59%; BCLC C/D, 35 of 139, 25%; P < 0.001), with smaller tumour size (participants: median, 2.8 cm; IQR, 2.0 - 4.0 cm; non-participants: median, 6.0 cm; IQR, 3.6 - 10 cm; P < 0.001), or receiving curative treatment (59 of 99, 60%; not receiving curative treatment, 51 of 169, 30%; P < 0.001).
5.4.2 Survival analysis

Median overall survival time was 20.8 months (lower end of 95% CI, 16.6 months; upper limit not calculable because point 95% CI did not fall below 0.5 during 24-month follow-up), with 12-month and 24-month survival rates of 62% and 47% respectively (Figure 5-2A). Mean survival time was 18.1 months (95% CI, 16.6 - 19.6 months).

In the multivariable analysis, poor survival was predicted by higher Childs-Pugh class, alpha-fetoprotein level exceeding 400 kU/L (aHR, 2.06; 95% CI, 1.38 - 3.08; P < 0.001), and later BCLC stage at HCC diagnosis (BCLC C/D v BCLC A/B: aHR, 2.59; 95% CI, 1.57 - 4.27; P < 0.001) (Figure 5-2B; Table 5-3); increased survival was associated with participation in surveillance programs (aHR, 0.60; 95% CI, 0.38 - 0.93; P = 0.021) and curative treatment (aHR, 0.33; 95% CI, 0.19 - 0.58; P < 0.001) (Table 5-3). Survival rates for surveillance participants were 79% at 12 months and 66% at 24 months, compared with 49% and 33% respectively for non-participants (Figure 5-2C).

Table 5-3. Logistic regression analysis of factors influencing survival

<table>
<thead>
<tr>
<th>Factor</th>
<th>Value</th>
<th>Univariate</th>
<th>P</th>
<th>Multivariable*</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years), median (IQR)</td>
<td>65 (56–76)</td>
<td>1.02 (1.00–1.03)</td>
<td>0.010</td>
<td>1.01 (0.99–1.02)</td>
<td>0.43</td>
</tr>
<tr>
<td>Sex (men)</td>
<td>216 (79%)</td>
<td>0.77 (0.51–1.17)</td>
<td>0.22</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ethnic background</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>201 (74%)</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>African</td>
<td>10 (37%)</td>
<td>0.70 (0.26–1.90)</td>
<td>0.48</td>
<td>0.62 (0.23–1.72)</td>
<td>0.36</td>
</tr>
<tr>
<td>Asian</td>
<td>59 (22%)</td>
<td>0.56 (0.34–0.92)</td>
<td>0.023</td>
<td>0.76 (0.44–1.32)</td>
<td>0.33</td>
</tr>
<tr>
<td>Liver function</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Non-cirrhotic</td>
<td>38 (14%)</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>0.63</td>
</tr>
<tr>
<td>Child–Pugh A</td>
<td>125 (48%)</td>
<td>1.22 (0.59–2.52)</td>
<td>0.59</td>
<td>1.21 (0.55–2.64)</td>
<td></td>
</tr>
<tr>
<td>Child–Pugh B</td>
<td>67 (27%)</td>
<td>3.82 (1.87–7.81)</td>
<td>0.001</td>
<td>3.06 (1.36–6.89)</td>
<td>0.007</td>
</tr>
<tr>
<td>Child–Pugh C</td>
<td>33 (13%)</td>
<td>6.36 (2.96–13.7)</td>
<td>0.001</td>
<td>5.26 (2.13–13.0)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Risk factor for cirrhosis</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chronic hepatitis C</td>
<td>112 (41%)</td>
<td>0.68 (0.47–0.99)</td>
<td>0.042</td>
<td>0.67 (0.43–1.05)</td>
<td>0.08</td>
</tr>
<tr>
<td>Chronic hepatitis B</td>
<td>60 (22%)</td>
<td>0.86 (0.55–1.32)</td>
<td>0.48</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Alcohol</td>
<td>107 (39%)</td>
<td>1.29 (0.91–1.83)</td>
<td>0.15</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Non-alcohol fatty liver disease</td>
<td>39 (14%)</td>
<td>0.77 (0.45–1.29)</td>
<td>0.32</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Alpha-fetoprotein (&gt; 400 kU/L)</td>
<td>81 (30%)</td>
<td>3.13 (2.20–4.46)</td>
<td>&lt; 0.001</td>
<td>2.06 (1.38–3.08)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>BCLC staging (stages C/D v A/B)</td>
<td>139 (52%)</td>
<td>6.53 (4.24–10.1)</td>
<td>&lt; 0.001</td>
<td>2.59 (1.57–4.27)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Curative treatment (provided)</td>
<td>85 (31%)</td>
<td>0.38 (0.11–0.30)</td>
<td>&lt; 0.001</td>
<td>0.33 (0.19–0.58)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Surveillance (participated)</td>
<td>110 (40%)</td>
<td>0.33 (0.22–0.50)</td>
<td>&lt; 0.001</td>
<td>0.60 (0.38–0.93)</td>
<td>0.021</td>
</tr>
</tbody>
</table>

BCLC = Barcelona Clinic Liver Cancer; CI = confidence interval; IQR = interquartile range. * Includes factors for which P < 0.1 in univariate analysis.
Figure 5-2. Survival functions (with 95% confidence envelopes) for 272 people in Melbourne diagnosed with incident hepatocellular carcinoma, July 2012 - June 2013.
A. Overall; B. by BCLC stage; C. by participation in hepatocellular carcinoma surveillance
B. BCLC = Barcelona Clinic Liver Cancer
5.5 DISCUSSION

The incidence of HCC in Australia is increasing. \(^{276,279}\) The parallel rises in incidence and population-attributable mortality rates \(^{279}\) suggest that the rise in incidence is not driven by detection of earlier tumours during surveillance alone, but may be related to demographic changes and the increased prevalence of underlying risk factors. \(^{27}\) Survival remains poor; our 12-month survival rate of 62% is similar to recent estimates for other developed countries. \(^{281,282}\)

We found that survival was better for patients who presented with earlier stage disease, smaller tumours, and compensated liver disease. These factors all predict eligibility for treatment with curative intent, the factor with the greatest positive influence on survival.

Surveillance was associated with improved survival. Despite the acknowledged role of HCC surveillance in managing cirrhosis, only 40% of patients were participating in surveillance when diagnosed with HCC, a proportion similar to the 38% reported for one Melbourne tertiary centre more than a decade ago. \(^{27}\) Surveillance is particularly infrequent among patients of Asian or Australian-born backgrounds and those with alcohol-related liver disease. The emergence of non-alcoholic fatty liver disease-related HCC, linked with the rise of the metabolic syndrome in developed countries, is particularly challenging for surveillance because of the large population at risk. \(^{422}\)

We identified two major barriers to increased uptake of surveillance: adherence to surveillance was poor for patients with certain recognised risk factors (decompensated cirrhosis, alcohol misuse) and, perhaps more importantly, a considerable number of patients diagnosed with HCC had hitherto undiagnosed cirrhosis or viral hepatitis. These findings indicate that a two-tiered approach may be needed to improve outcomes.

Firstly, clinicians should be alert to risk factors for chronic liver disease, such as excessive alcohol use, chronic HCV and HBV infections, and non-alcoholic fatty liver disease in certain social groups (e.g., patients of low socio-economic status or with mental health problems, injecting drug users, migrants, patients with diabetes or metabolic syndrome). Patients with these risk factors should be screened for cirrhosis, and those with active liver disease should be screened longitudinally. An aspartate
transaminase to platelet ratio index (APRI) value greater than 1.0 predicts cirrhosis with 76% sensitivity and 72% specificity,\textsuperscript{423} and the test is simple to undertake. Community-based screening based on blood pathology and transient elastography identifies significant fibrosis in 16% of patients with hepatitis C.\textsuperscript{424}

HCC surveillance comprising 6-monthly liver ultrasound and alpha-fetoprotein assessment should be offered to all patients with cirrhosis, as well as to Asian men over 40, women over 50, Africans over 20 years of age, and patients with a family history of HCC without cirrhosis but with chronic HBV infections.\textsuperscript{51} This recommendation should be communicated during medical training and included in specialist society and jurisdictional guidelines.

Secondly, effective surveillance might be best achieved with a national HCC surveillance program. HCC fulfils many of the criteria for such programs: its incidence is high, a non-invasive and inexpensive screening method is available, and early detection is associated with improved survival when combined with effective therapy.

Preventive responses to known causes of chronic liver disease may also be beneficial as public health measures. Improving the diagnosis of viral hepatitis in at-risk populations, together with viral suppression (HBV) and eradication (HCV), could be cost-effective strategies for preventing HCC.\textsuperscript{425,426} As antiviral drugs for treating HBV and HCV infections are readily available in Australia, increased education and use of these drugs in community practice are important. Non-alcoholic fatty liver disease, a major indication for liver transplantation in many countries, may also be under-recognised as a risk factor by the general medical community.

\section*{5.5.1 Limitations}

Our study was limited by inherent biases that affect interpretation of survival outcomes in cancer screening. As cirrhosis, the major trigger for surveillance, is itself asymptomatic and underdiagnosed, lead time in HCC diagnosis varies widely; as the growth rate for HCC is quite variable, length time bias is also important. Randomised controlled trials could circumvent these biases. Two older trials found that HCC surveillance improved survival,\textsuperscript{349,342} but their methodological flaws limit the generalisability of their findings. Randomised controlled trials are now impracticable, as informed patients usually decline randomisation in preference of direct access to
surveillance. A number of studies have attempted to reduce lead time bias in HCC surveillance by adjusting for tumour growth during the asymptomatic phase; one such study found that the short term survival benefit of surveillance was markedly reduced after taking lead time into account, but not the long term survival benefits.\textsuperscript{344}
5.6 CONCLUSION

Survival for patients with HCC in Australia is poor. While surveillance allows the detection of smaller, early stage tumours, enabling curative therapies associated with significantly better survival to be initiated, the rate of participation in HCC surveillance programs is relatively low. Cirrhosis had not previously been detected in one-third of patients newly diagnosed with HCC. Improving the identification of cirrhosis in primary care and by other physicians and enrolling patients in surveillance programs may improve their outcomes. A national surveillance program for patients at increased risk of HCC, in accordance with the relevant international guidelines, should also be considered.
6 Direct Costs of Hepatocellular Carcinoma Management in Australia

This study will be submitted to a peer-review journal. It has also been presented at the national conference – Australian Gastroenterology Week 2017, Gold Coast, Australia – as an oral presentation.
6.1 ABSTRACT

Background

Hepatocellular carcinoma (HCC), a common complication of cirrhosis and chronic viral hepatitis, is an increasing burden of disease in Australia. Public funding for new therapeutics, prevention and early detection of disease is based on cost-effective analyses predicated on costs that are often derived from modelling. This is the first study of direct costs of HCC management in Australia.

Method

Patients with HCC recruited from a population-based incident cohort in Melbourne were followed for 24 months. Direct costs were extracted from the treating hospital claims database inclusive of all inpatient, outpatient and emergency attendances. Costs analyses were performed by phase of treatment (initial, continuing, terminal), by treatment given, and adjusted for overall survival. Multivariable analysis was performed to determine factors associated with higher costs.

Results

There were 142 patients analysed, with HCC management in the 24 months from HCC diagnosis costing a total of $7,823,126 (mean: $55,092, median: $33,065 IQR: $17,260-$62,796), with inpatient costs the largest component (75.6%). Liver transplantation accounted for 22% of total costs (most), followed by best supportive care (13%). The mean cost per month in the initial phase of care (3 months before diagnosis until 1 month after) was $3,403, the terminal phase (6 months before death) $6,419 and the continuing phase (interval between other two phases) $2,589. On multivariable analysis, the significant factors associated with higher costs were Child-Pugh class C, AFP >200 and treatment modality given.

Conclusion

HCC is expensive to treat relative to its poor overall survival. Earlier detection allows for curative options, which while costlier initially, provides better prognosis and may prove cost-effective in the long term. This study provides baseline costings for Australia, associated with clinical risk factors, to enable cost-effective analyses and planning of preventative strategies.
6.2 INTRODUCTION

Hepatocellular carcinoma (HCC) incidence and mortality is rising in many developed countries,\textsuperscript{276} becoming an increasingly important disease burden for the healthcare system. These trends in previously low incidence regions, such as Australia, are projected to continue in the coming decades, and are thought to be due to increasing prevalence of risk factors such as viral hepatitis, obesity and diabetes.\textsuperscript{274}

A vast array of therapies exists for HCC, ranging from liver transplantation, surgical resection and ablative therapies to loco-regional chemoradiotherapy and new targeted anti-tumour agents, with many patients requiring multiple treatments over time. However overall survival remains poor, at approximately 50% at 12 months and 16% at 5 years with most terminal patients eventually requiring inpatient palliative care.\textsuperscript{279}

A fundamental strategy to reduce disease burden involves disease prevention, risk factor identification and reduction, and early detection of disease to improve quality adjusted life years. For HCC, this includes prevention of cirrhosis through treatment of underlying risk factors (viral hepatitis B and C, metabolic syndrome) and surveillance programs to detect HCC at a curable stage. Implementation of such strategies at a population level requires a cost-effective analysis, which is predicated upon the cost of HCC management to be alleviated.

Hence, an understanding of the costs of HCC management would be useful in healthcare policymaking. A number of studies have used linkage between cancer registry and administrative data to estimate the costs of HCC treatment\textsuperscript{280}. Some recent studies have described direct costs but are limited by patient selection (in HCV patients only)\textsuperscript{394} or disease stage\textsuperscript{398}. Direct costs data extracted at a clinical level, across the breadth of different clinical presentations, liver disease risk factors, tumour stages and treatments, are still lacking. In particular, there are no costs data for HCC management in the Australian setting.

Our recent HCC incidence cohort\textsuperscript{420} provides the opportunity to describe the cost of HCC management in Australia. Further understanding of the determinants of higher costs will allow better planning and use of health resources.
6.3 METHODS

6.3.1 Study population

Patients with incident HCC diagnoses were recruited from the population of Melbourne, Australia over a period of 12 months (July 2012 to June 2013) to form the original study cohort. Patients were identified from multiple sources including public and private hospitals, cancer registry, radiology and pathology services, as previously described. There were 272 patients with HCC who met inclusion criteria, with their care primarily provided at one of seven tertiary hospital networks within the Melbourne metropolitan area.

For this study, we analysed the health care costs of patients attending three of these hospital networks (Austin Health, St Vincent's Health and Southern Health). These hospitals represent the breadth of treatment modalities available in Victoria (including liver transplantation) as well as the variety of patient demographics. Costs data were not readily available from the other hospitals involved in the initial cohort study. Table 1 shows the baseline characteristics and the comparison between patients included and not included in the costs analysis.

6.3.2 Data collection

Patients were followed up for at least 24 months. Clinical information was obtained from hospital, pathology and radiology records, physician letters and cancer registry data. Baseline demographics and patient factors included age, sex, race, country of birth and residential postcode. Clinical information collected included aetiology of liver disease, liver function (Child-Pugh score, MELD score) and tumour stage (BCLC stage). Diagnostic imaging and therapeutic interventions given after the date of diagnosis were also recorded. Hospital records and the cancer registry provided mortality data. Ethics approval was granted by the Human Research Ethics Committee of each of the institutions involved.
6.3.3 Health costings

Costing data was performed by the clinical costings analyst of the three hospitals separately, taking the perspective of the healthcare system costs. Costs were calculated in Australian dollars ($) for each patient from the date of diagnosis to last follow-up.

An analysis of costs according to phases of cancer care as defined by Thein et al was used with three phases defined: 1) Initial phase: three months prior to diagnosis to 1 month after, 2) Terminal phase: 6 months prior to death and 3) Continuing phase: the interval between the initial and terminal phases. For patients surviving at end of follow-up or censored without death, the Continuing phase encompassed the remainder of the analysis period following the Initial phase.

The treatment modalities offered across the three hospitals analysed include liver transplantation (at the Austin only), liver resection, ablative therapy (radio frequency or microwave), percutaneous ethanol injection, standard transarterial chemoembolisation, drug-eluting bead transarterial chemoembolisation, selective internal radiation therapy, sorafenib systemic chemotherapy and best supportive care. Patients were categorised according to the most curative therapy provided if there were more than one treatment modality.

6.3.4 Statistical analysis

Both mean and median costs were calculated, as the total costs were not normally distributed. Survival data are complete as correlation with the death registry was made at the time of last follow-up. Patients were censored at the time of last medical follow-up if mortality data was not available.

A dependent variable of cost per month for each patient was derived from the total cost for that patient divided by the number of months survived (or before censored). The association between cost per month and a number of independent variables were tested using Cox Proportional Hazards Model.

All analyses were performed in Stata Statistical Software 12 (StataCorp).
Table 6-1. Baseline Characteristics for Included and Excluded Hospitals

<table>
<thead>
<tr>
<th></th>
<th>All patients</th>
<th>Included Hospitals</th>
<th>Excluded Hospitals</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Number</strong></td>
<td>272</td>
<td>142</td>
<td>124</td>
<td></td>
</tr>
<tr>
<td><strong>Sex: males, n (%)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>216 (79%)</td>
<td>111 (78%)</td>
<td>99 (80%)</td>
<td></td>
</tr>
<tr>
<td><strong>Age: median, years (range)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Males</td>
<td>64 (28 - 93)</td>
<td>64 (28 - 89)</td>
<td>66 (38 - 93)</td>
<td></td>
</tr>
<tr>
<td>Females</td>
<td>74 (39 - 91)</td>
<td>72 (39 - 89)</td>
<td>75 (54 - 91)</td>
<td></td>
</tr>
<tr>
<td><strong>Race: n (%)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Caucasian</td>
<td>201 (74%)</td>
<td>97 (68%)</td>
<td>100 (81%)</td>
<td>0.0263</td>
</tr>
<tr>
<td>Asian</td>
<td>59 (22%), 63 (33 - 91)</td>
<td>39 (27%)</td>
<td>19 (15%)</td>
<td>0.0117</td>
</tr>
<tr>
<td>African</td>
<td>10 (4%), 56 (28 - 76)</td>
<td>5 (3%)</td>
<td>5 (4%)</td>
<td></td>
</tr>
<tr>
<td>Unknown</td>
<td>1%</td>
<td>1</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td><strong>Place of birth, %</strong></td>
<td></td>
<td></td>
<td></td>
<td>0.0342</td>
</tr>
<tr>
<td>Australia</td>
<td>39%</td>
<td>33%</td>
<td>46%</td>
<td></td>
</tr>
<tr>
<td><strong>Risk factors for chronic liver disease present</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chronic hepatitis C</td>
<td>112 (41%)</td>
<td>51 (36%)</td>
<td>57 (46%)</td>
<td>0.1736</td>
</tr>
<tr>
<td>Alcoholic liver disease</td>
<td>107 (39%)</td>
<td>27 (19%)</td>
<td>51 (41%)</td>
<td></td>
</tr>
<tr>
<td>Chronic hepatitis B</td>
<td>60 (22%)</td>
<td>38 (27%)</td>
<td>20 (16%)</td>
<td>0.0394</td>
</tr>
<tr>
<td>Fatty liver disease</td>
<td>39 (14%)</td>
<td>12 (5%)</td>
<td>18 (15%)</td>
<td></td>
</tr>
<tr>
<td>Haemochromatosis</td>
<td>6 (2%)</td>
<td>1 (1%)</td>
<td>3 (2%)</td>
<td></td>
</tr>
<tr>
<td>Other / Unknown</td>
<td>23 (8%)</td>
<td>13 (9%)</td>
<td>10 (8%)</td>
<td></td>
</tr>
<tr>
<td>More than one risk factor</td>
<td>73 (27%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Mode of presentation</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Surveillance program (6-12 monthly US)</td>
<td>110 (40%)</td>
<td>60 (42%)</td>
<td>47 (38%)</td>
<td>0.4586</td>
</tr>
<tr>
<td>Known cirrhotic but not screened</td>
<td>53 (19%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>First presentation of cirrhosis or incidental</td>
<td>105 (39%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Unknown</td>
<td>4 (2%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Liver functional status</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cirrhosis</td>
<td>225 (83%)</td>
<td>118 (84%)</td>
<td>103 (88%)</td>
<td></td>
</tr>
<tr>
<td>Child Pugh A</td>
<td>159 (58%)</td>
<td>94 (66%)</td>
<td>61 (49%)</td>
<td>0.0044</td>
</tr>
<tr>
<td>Child Pugh B</td>
<td>75 (28%)</td>
<td>34 (24%)</td>
<td>41 (33%)</td>
<td>0.0766</td>
</tr>
<tr>
<td>Child Pugh C</td>
<td>32 (12%)</td>
<td>14 (10%)</td>
<td>18 (15%)</td>
<td>0.2569</td>
</tr>
<tr>
<td><strong>Barcelona Clinic Liver Clinic Staging</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>BCLC-A</td>
<td>70 (26%)</td>
<td>43 (30%)</td>
<td>25 (21%)</td>
<td>0.0699</td>
</tr>
<tr>
<td>BCLC-B</td>
<td>59 (22%)</td>
<td>27 (19%)</td>
<td>30 (25%)</td>
<td>0.3786</td>
</tr>
<tr>
<td>BCLC-C</td>
<td>98 (36%)</td>
<td>53 (37%)</td>
<td>44 (36%)</td>
<td>NS</td>
</tr>
<tr>
<td>BCLC-D</td>
<td>41 (15%)</td>
<td>19 (13%)</td>
<td>22 (18%)</td>
<td>0.3081</td>
</tr>
</tbody>
</table>
6.4 RESULTS

There were 272 patients recruited in the HCC incidence cohort, of which 148 patients were from the representative three hospitals used for this study. There were 15 patients excluded from costs analysis for the following reasons: 13 patients had the majority of their treatment in the private sector, with minimal public costs data, and 2 patients were only diagnosed with HCC incidentally after liver transplantation. The remaining 142 patients were analysed. The baseline demographics, clinical and disease characteristics are presented in Table 6-1.

Comparison between the three included hospitals included in the costings cohort (n=142) and the four excluded hospitals (n=124) showed significant differences in racial groups with fewer Caucasians (68% vs 81%, respectively, p=0.0263) and more Asian patients (27% vs 15%, respectively, p=0.0117), and fewer patients born in Australia (33% vs 46%, respectively, p=0.0342). Chronic hepatitis B was more frequently a risk factor for underlying liver disease in patients from the included hospitals (27% vs 16%, p=0.0394). The severity of liver disease was lower in the included hospitals, with more patients in Child Pugh Class A status (67% vs 49%, p=0.0044).

6.4.1 Overall costs

The total overall cost of care for the 142 patients was $7,823,126 in the 24 months from the date of their HCC diagnosis. The mean total cost per patient was $55,092 with the median total cost $33,065 (IQR: $17,260 - $62,796).

Inpatient admissions which include (treatments, progressive, palliative care) accounted for most of the total costs over 24 months (75.6%), whereas outpatient management (20.1%) and emergency department without admission (4.3%) were less costly.
6.4.2 Cost by treatment received

The total cost of treatment was highest per patient receiving liver transplantation, with a median cost of $254,022 (IQR $161,148 - $285,111). See Table 6-2. The cost for the eight patients receiving liver transplantation was $1,737,482 which is 22% of total costs for all 142 patients. Patients receiving best supportive care had the second highest total cost of $1,009,448, making up 13% of total cohort costs.

Patients receiving treatment with curative intent (liver transplantation, Resection, RFA/MWA, PEI) incurred median total costs that were significantly higher than those with palliative intent (TACE/DCB, SIRT, Sorafenib, best supportive care) ($43,909 vs $27,403, respectively, p=0.022).

Table 6-2. Costs over 24 months, by treatment

<table>
<thead>
<tr>
<th>Treatment</th>
<th>n</th>
<th>Mean Total cost</th>
<th>Median Total cost</th>
<th>Mean Cost /m</th>
<th>Median Cost /m</th>
</tr>
</thead>
<tbody>
<tr>
<td>All patients</td>
<td>142</td>
<td>$55,092</td>
<td>$33,065</td>
<td>$6,419</td>
<td>$2,428</td>
</tr>
<tr>
<td>Best supportive care</td>
<td>33</td>
<td>$30,589</td>
<td>$22,715</td>
<td>$14,120</td>
<td>$7,641</td>
</tr>
<tr>
<td>Sorafenib</td>
<td>18</td>
<td>$28,725</td>
<td>$20,863</td>
<td>$4,321</td>
<td>$1,685</td>
</tr>
<tr>
<td>SIRT</td>
<td>4</td>
<td>$43,359</td>
<td>$48,116</td>
<td>$3,793</td>
<td>$2,927</td>
</tr>
<tr>
<td>TACE-DCB</td>
<td>7</td>
<td>$71,880</td>
<td>$57,986</td>
<td>$5,419</td>
<td>$2,416</td>
</tr>
<tr>
<td>TACE</td>
<td>28</td>
<td>$48,113</td>
<td>$44,082</td>
<td>$3,392</td>
<td>$2,266</td>
</tr>
<tr>
<td>PEI</td>
<td>4</td>
<td>$60,443</td>
<td>$54,902</td>
<td>$4,512</td>
<td>$2,999</td>
</tr>
<tr>
<td>RFA/MWA</td>
<td>20</td>
<td>$64,941</td>
<td>$33,815</td>
<td>$4,598</td>
<td>$1,626</td>
</tr>
<tr>
<td>Resection</td>
<td>20</td>
<td>$49,739</td>
<td>$46,171</td>
<td>$2,017</td>
<td>$1,924</td>
</tr>
<tr>
<td>Liver Transplantation</td>
<td>8</td>
<td>$217,185</td>
<td>$254,022</td>
<td>$8,660</td>
<td>$9,390</td>
</tr>
<tr>
<td>Non-Transplantation</td>
<td>134</td>
<td>$45,415</td>
<td>$30,673</td>
<td>$6,285</td>
<td>$2,335</td>
</tr>
<tr>
<td>Curative Treatments</td>
<td>57</td>
<td>$77,027</td>
<td>$43,909</td>
<td>$4,224</td>
<td>$1,947</td>
</tr>
<tr>
<td>Palliative Treatments</td>
<td>85</td>
<td>$40,383</td>
<td>$27,403</td>
<td>$7,687</td>
<td>$2,948</td>
</tr>
</tbody>
</table>
6.4.3 Costs outliers

There were 12 patients with costs considered to be outliers, defined as more than 1.5 times the interquartile range, above the 75th percentile of costs. Five patients managed by best supportive care had prolonged admissions due to their decompensated liver disease and other psychosocial problems, leading to total costs ranging from $47,663 to $140,468. This is in comparison to a median cost of $19,414 for all patients receiving best supportive care (inclusive of outliers), and a median cost of $14,845 if outliers are excluded. Likewise, other outliers included three patients receiving RFA or MWA (one of whom had a complicated diaphragmatic tear requiring ICU admission), and one each for the TACE, PEI and sorafenib groups. The total costs for outliers was $1,417,115, forming 23% of total costs.

Figure 6-1. Total costs over 24 months, by treatment
6.4.4 The effect of survival on cost

The median overall survival was 26.2 months, with 12 months and 24 months survival being 67% and 52%, respectively.

The mean cost per month survived was $6,419 (95%CI: $4,643-$8,195) with a median of $2,428 (IQR:$1141-$7641). See Table 6-2.

Grouped by phases of care, the Initial phase cost a mean of $3,403, the Continuing phase mean cost was $2,589 while Terminal phase mean cost was $6,419.

The median costs per month were highest for patients receiving liver transplantation, $9,390 (IQR: $6715 - $11,519) and best supportive care, $7,641 (IQR: $1471 - $15,425). Patients receiving curative were less expensive per month survived than those receiving palliative therapy (median cost $2,021 vs $2,886 respectively, p=0.082).

Median costs per month increased with increasing BCLC stage, Child-Pugh scores and MELD scores. The cost for treating patients with early stage disease (BCLC-A or B) was significantly less than for those with later stage disease (BCLC-C or D), (median cost per month survived $1,617 and $3,303, respectively, p=0.0008).

On multivariable analysis, the significant predictors of costs per month were Childs C liver function, AFP level greater than 200 and treatment modality.

![Cost per month, by treatment](image)

Figure 6-2. Cost per month, by treatment
Table 6-3. Multiple regression of factors associated with higher costs

<table>
<thead>
<tr>
<th>Variable</th>
<th>Numbers (n)</th>
<th>Mean cost/month</th>
<th>Univariate (p-value)</th>
<th>Multivariate (p-value)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>All</td>
<td>Non-Transplant</td>
<td>All</td>
<td>Non-Transplant</td>
</tr>
<tr>
<td>Liver Function</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Non-cirrhotic</td>
<td>24</td>
<td>24</td>
<td>$3,637</td>
<td>1</td>
</tr>
<tr>
<td>Childs A</td>
<td>73</td>
<td>71</td>
<td>$3,211</td>
<td>0.944</td>
</tr>
<tr>
<td>Childs B</td>
<td>31</td>
<td>29</td>
<td>$8,364</td>
<td>0.001</td>
</tr>
<tr>
<td>Childs C</td>
<td>14</td>
<td>10</td>
<td>$23,230</td>
<td></td>
</tr>
<tr>
<td>Barcelona Clinic</td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Liver Cancer Stage</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>A</td>
<td>43</td>
<td>41</td>
<td>$2,938</td>
<td>1</td>
</tr>
<tr>
<td>B</td>
<td>27</td>
<td>26</td>
<td>$3,743</td>
<td>0.117</td>
</tr>
<tr>
<td>C</td>
<td>53</td>
<td>53</td>
<td>$5,991</td>
<td>0.001</td>
</tr>
<tr>
<td>D</td>
<td>19</td>
<td>14</td>
<td>$19,292</td>
<td></td>
</tr>
<tr>
<td>AFP &lt;200</td>
<td>101</td>
<td>94</td>
<td>$5,201</td>
<td>0.033</td>
</tr>
<tr>
<td>&gt;200</td>
<td>41</td>
<td>40</td>
<td>$9,418</td>
<td></td>
</tr>
<tr>
<td>Treatment modality</td>
<td>142</td>
<td></td>
<td>0.001</td>
<td>0.0001</td>
</tr>
<tr>
<td>Curative treatment</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Palliative treatment</td>
<td>57</td>
<td>49</td>
<td>$4,571</td>
<td>0.063</td>
</tr>
<tr>
<td></td>
<td>85</td>
<td>85</td>
<td>$7,658</td>
<td></td>
</tr>
<tr>
<td>Surveillance</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Non-surveillance</td>
<td>60</td>
<td>53</td>
<td>$5,519</td>
<td>0.394</td>
</tr>
<tr>
<td></td>
<td>82</td>
<td>81</td>
<td>$7,077</td>
<td></td>
</tr>
<tr>
<td>Tumour size &lt; 5cm</td>
<td>89</td>
<td>81</td>
<td>$5,924</td>
<td>0.477</td>
</tr>
<tr>
<td>&gt;5cm</td>
<td>53</td>
<td>53</td>
<td>$7,249</td>
<td></td>
</tr>
</tbody>
</table>
6.5 DISCUSSION

The increasing incidence of HCC in developed countries heralds greater economic burden on limited healthcare resources. Understanding the costs of HCC management and the determinants of higher costs will assist policy makers and funders in health resource allocations.

While strategies to prevent cirrhosis and HCC development are available, implementation is variable and suboptimal. Hepatitis B virus (HBV) vaccinations have reduced the burden in epidemic countries but migration of the older unvaccinated population has seen this risk transferred to developed countries, where better public education and screening are required. Surveillance for the detection of early HCC in patients with cirrhosis or HBV is recommended by international guidelines but poorly implemented by health systems. Hepatitis C virus (HCV) infection is almost universally curable with new direct-acting antivirals but availability is limited by their high costs. The increasing burden of cirrhosis and HCC, on morbidity, mortality and economic costs, may provide cost-effective arguments for public funding of these preventative measures.

Our population-based clinical cohort provides the opportunity to assess the direct costs of HCC management across the breadth of aetiology of liver disease, tumour stage and treatment modalities.

We found the total costs of managing HCC highest at the extreme ends of the curative-palliative treatment spectrum, with those receiving liver transplantation and best supportive care accounting for 39% of total cohort costs. Likewise, the total costs viewed in terms of liver disease (Child-Pugh class) and tumour stage (BCLC stage) shows the same pattern of higher costs at both ends of the severity scale. Hence, the cost to the health system of late presentation is significant and yet the survival outcome is generally poor. This is in contrast to money spent at the other end of the spectrum that results in better patient outcomes.

The analysis of cost per month, taking into account survival, highlights the point that HCC diagnosed at earlier tumour stage with less severe liver disease provides the opportunity for therapies that will be cost-effective in the long term. This effect would be more clearly seen with longer follow-up; our short follow-up of 24 months does not
provide sufficient time for the high upfront cost of liver transplantation and resection to manifest cost-effectiveness.

Prolonged hospitalization was the common factor in cases with the highest costs, seen predominantly in liver transplantation, complications of therapy (mostly surgical), and progression of liver disease for patients treated palliatively. The 12 patients who were high-cost outliers for their particular treatment modality contributed nearly a quarter of overall costs.

The high costs of hospitalization and management of severe liver disease provides economic incentive for strategies to prevent cirrhosis and HCC development. The public funding of direct acting antivirals for hepatitis C treatment in Australia is a major undertaking, that despite high initial costs, is projected to reduce the long-term cost due to HCC and progressive liver disease. Further initiatives are needed to manage the risk factors of cirrhosis and HCC. This may include educational programs to increase hepatitis B screening in migrant populations, a national HCC surveillance program to detect earlier stage tumours and strategies to address risk factors such as obesity and alcohol excess.

This study provides important costing data for HCC management in the Australian setting where healthcare is publicly funded and universal. Our mean cost of AUD$6,419 per month is similar to the costs incurred in the recent 2018 US Veteran Affairs study which found a mean total cost of USD$154,688 over 3 years (USD$4,297 per month) in HCC patients. The Canadian Medicare study which used a phases of care approach also had similar results.

Limitations of this direct cost analysis include possible inaccuracies that may underestimate or overestimate true costs. As costs were hospital derived, the cost of investigations and treatments incurred outside of the public sector have not been included. In general, however, HCC is treated primarily in the public tertiary setting, and most costs are incurred post-diagnosis and after tertiary referral. Hence, we believe any underestimation would be insignificant.

Conversely, at risk of overestimation, these hospital-derived costs include all admissions following HCC diagnosis and may have included non-HCC-related admissions. Pathophysiologically, however, it would be hard to distinguish between pure liver-related admissions, compared to HCC-related admissions, and even non-
liver admissions, as HCC and cirrhosis would predispose to infection or other organ system failures. One way to mitigate these confounding costs would be using controls with matched liver disease but without HCC as has been done in other studies. However, this was beyond the resources of the study at the time and may be a direction to consider for future research.

6.6 CONCLUSION

This is the first report of Australian costs of HCC management, provided with patient-level clinical risk factors that can inform cost-effectiveness analyses. The highest costs are borne by the sickest patients with incurable disease. Strategies to prevent cirrhosis with antiviral treatment, improve early HCC diagnosis to enable the use of curative treatments, may reduce overall cost in the longer term.
7 Further Discussion

Each of the three studies in this thesis have their own discussion section contained in their respective chapters. The purpose of this chapter is to summarise the discussion and address other points related to this research that were not included in the papers due to word limit restrictions from the journals. This chapter will also review how our results compare with relevant literature published since the commencement of this research, and in particular the direct impact of this research.

The basis of this research was a simple observation from members of the Melbourne Liver Group that cases of hepatocellular carcinoma were presenting more frequently at their respective tertiary hospital liver clinics. What began as a local study to confirm clinical suspicion and present Australian data became a study with greater international impact than anticipated. This novel methodology of capturing clinical cases of HCC first-hand by clinicians from the same population as that covered by the relevant geographical cancer registry has not been previously performed anywhere. Further, despite a thorough literature search, no other study could be found that has assessed the completeness of cancer registration of any cancer using primary capture sources with clinical verification.

In addition to this independent case capture methodology, this research is also unique in that it has been able to describe clinical characteristics of an entire geographical population with incident HCC. This is in contrast to other clinical studies whose patient population is restricted to single or multiple institutions that do not cover a geographical region (and therefore are not population-based) or restricted to certain stages of HCC presentation (e.g. transplant centre patients only). Being population-based has the advantage of removing potential selection bias.
7.1.1 Establishing local HCC incidence using multiple sources of case capture

The HCC incidence study determined the age-standardised incidence of HCC in Melbourne using primary sources independent of the local cancer registry. The dependence of cancer registry data for HCC epidemiology has been discussed previously in section 0. The following are some contemporary studies that also aim to establish HCC incidence using various capture methods, while also reassessing of cancer registry dependence. Some of these studies were published since this research commenced while others were published afterwards, citing the incidence paper (Chapter 4).

Using multiple primary sources, a significantly higher number of cases was identified, with a quarter of the study cases not registered with the registry. Conversely, there were only 2% of cases that this capture methods did not pick up that appeared at the registry. The combination of multidisciplinary meeting and hospital coding sources captured 97% of cases with the rest captured through pathology, radiology or pharmacy records alone.

However, the completeness of capture using this methodology does rely upon the presence of established multidisciplinary centres and referral patterns. While this may not be applicable to other regions and healthcare settings without this, the principle of using multiple independent sources to establish incidence is an important one.

In their recent 2017 paper, Jepsen et al reported on the incidence of HCC in Denmark over the period 1994-2016 using a combination of the Danish Cancer Registry, National Patient Registry (hospital discharge coding) and Pathology Registry. They found that HCC incidence was stable at 3.0 per 100,000 in 1994-2007 (which was also reported in their earlier 2007 paper, but nearly doubled to 5.7 in 2008-2011 and remaining high at 5.0 in 2012-2016. Notably, the earlier study, which only used the Danish Cancer Registry as its incidence source, found a decreasing trend throughout 1978-2003. This would suggest that the recent study, with its multiple sources, increased case capture and contributed to the rise in reported incidence after 2007.
However, the concordance between the Danish Cancer Registry and National Patient Registry was less than perfect: 78% of HCC cases were in both registries, 8% in the Cancer Registry alone, and 15% in the National Patient Registry alone. Hence, the completeness of the Danish Cancer Registry was approximately 86%.

Remarkably, this Melbourne study found the same degree of completeness at the VCR; after adjusting for clinical (non-biopsy) diagnoses, the Victorian Cancer Registry had 233 of 272 study identified cases, meaning it was 85.7% complete (section 4.4.3). In both cases, this reinforces the need for multiple sources of case capture.

Another Scandinavian study, also published in *Hepatology* a year after this incidence study, used a combination of sources to validate the completeness of the Swedish Cancer Registry. Törner et al\(^{311}\), found that liver cancer incidence was underreported by the Swedish Cancer Registry, thus explaining previous reports of decreasing incidence over the last 30 years, in contrast to other Western countries.\(^ {428}\) The authors combined data from three registries, the Cancer Registry, the Cause of Death Registry and the National Patient Register (hospital discharge coding), to determine the distribution of reports of liver cancer. There were 13,749 liver cancer cases reported to at least one registry in 1998-2010: only 47% were registered to the Cancer Registry as liver cancer, 69% to the Patient Register and 64% to the Death Registry. This is in comparison to registrations to the same Cancer Registry at 80% for colon cancer, and 82% for lymphoma as examples given by the authors. They then used a log-linear capture-recapture model based on the overlap between the registries to estimate that the underestimation rate was 37-45%, that is, the registry completeness was 55-67%.

Concerning as this was, other elements suggest further underestimation. Firstly, the authors erred on the side of caution by excluding cases recorded as liver cancer on the Patient or Death Registry but recorded on the Cancer Registry as another cancer (3,548 cases, 25%), although it is likely some of these cases were true liver cancers. Secondly, their histological verification rate was 98% while they also report a declining proportion of clinical basis of diagnosis and liver cancer unspecified cases. This is in contrast to other registries which record decreasing histological verification rate (42% at the Victorian Cancer Registry in 2012) and ever-increasing clinical diagnoses. This would suggest, and the authors acknowledge this, that the Swedish
Cancer Registry may be missing reports of clinical diagnoses of liver cancer altogether, rather than merely misclassifying them. The misclassification rate and missed reporting rate (not registered at all, regardless of coding) at the Swedish Cancer was 26% (3,548 of 13,749) and 27% (3,762 of 13,749), respectively. In comparison, the respective rates from this Melbourne study were: misclassification (9.6%, 26 of 272 cases) and missed reporting (14%, 39 of 272 cases). See section 4.4.4.

The difference in methodology of both of these Scandinavian papers compared to this incidence study possibly accounts for this. Both papers depended on registries which have the common weakness of reliance on an external source to provide accurate coding. While increasing the number of sources will potentially increase case capture, a true assessment of completeness will only be valid if those sources contain correct diagnoses. Otherwise, there is risk of overcompensating, leading to overestimation of incidence due to the inclusion of non-HCC cases. Further discussion of validating registry coding is discussed in the next section.

Instead, this methodology of clinically verified case capture provides an accurate account of incidence at the expense of potentially missing cases. While every tertiary hospital in the region was included, there was limited access to private hospitals and other smaller hospitals. Having a national patient registry similar to the Scandinavian countries would assist improving capture for cancer cases in general. Of course, this is provided that hospitals forward coding diagnoses to the national registries, which was part of the problem with missed reports in the Swedish study. In terms of HCC case capture, the specialised nature of HCC treatment means that most patients are referred to a tertiary hospital at some point. The favourable comparison with the Victorian Cancer Registry and Death notifications suggest that this methodology is near complete for HCC incidence determination.
7.1.2 Validating HCC diagnoses in the cancer registry

In addition to the implicit assessment of the Victorian Cancer Registry’s completeness through comparison of independently determined and registry-derived HCC incidence rates, this study also addressed the issue of validity. The study discovered that nearly half (123, 47%) of the 261 HCC cases recorded in the VCR were initially misclassified as Liver Cancer Unspecified as they were clinically diagnosed HCC without histological verification. Prompted by this study, the VCR has reassessed all liver cancer diagnoses from 1982 onwards and reclassified cases as HCC if they were clinically diagnosed.

A recent 2018 study by Carville et al has analysed this completed dataset with the reclassified HCC diagnoses. They reviewed cases of HCC recorded in the VCR to examine incidence and survive trends over the last three decades (1984-2013). They found that incidence increased sixfold from 0.9 to 5.9 per 100,000, with an accelerated annual percentage change of 9.5% in the last five years. The proportion of clinically diagnosed cases increased from 1% in 1984-2004 to 43% in 2009-2013. Importantly, the revised clinical criteria for classifying HCC added 993 cases, or 27.3% to the total.

In the previously mentioned analysis of the Swedish Cancer Registry, Törner et al found that 22% of the 21,038 cases of liver cancer during 1975-2011 were registered as Liver Cancer Unspecified. This proportion dropped over time to less than 10%. In contrast, the histological verification increased to 98%, which as discussed before (in section 7.1.1) suggests incomplete registration of clinically diagnosed cases. This highlights the point that while histological verification is often the gold standard for diagnosis, and thus a measure of validity, an extremely high value that is out of keeping with contemporary clinical practice is a warning for reassessment of completeness.

However, allowing for both clinical and histological basis of diagnosis for classification does not guarantee completeness without validation. In the Danish registry study mentioned previously, Jepsen et al noted that this Melbourne study showed that the VCR was only 50% complete, a result of only classifying HCC with biopsy verification. In contrast, the authors point to the Danish Cancer Registry’s practice of registering HCCs without biopsy verification, and inferred that the Danish
registry was therefore complete, although they acknowledge that no formal validation has been performed.

This validation is, in fact, the important difference between the Danish and this incidence study: the Danish study relied on second-hand coding data whereas the Melbourne data was collected first-hand by clinicians. This difference possibly manifested in their finding that the proportion of non-cirrhotic HCCs decreased from 26% to 18% over the study period. This is in contrast to the literature which is reporting increasing incidence of non-cirrhotic HCCs (section 2.2.1.2). This may be explained by their reliance on discharge coding (absence of cirrhosis coding) and histology (which is also declining) to define non-cirrhosis. Instead, this likely suggest the underdiagnosis of cirrhosis in the earlier era, which is a known phenomenon as highlighted in the second paper of this thesis.
7.1.3 The need for population-based clinical data

Our second study (Chapter 5) is the first description of a clinical population-based cohort with HCC in Australia. Prior to this study, other clinical cohorts were institution-based, recruited for the purposes of a trial, or linked by particular aetiology of liver disease (e.g. linkage studies with viral hepatitis notifications). A population-based cohort provides information across the spectrum of demographics and presentations, thus assisting government and healthcare providers to target strategies to areas of need.

While many recognise the need for clinical data on HCC based on larger populations, there have been few studies that have managed to link epidemiology with clinical features of HCC and its management. One of the earliest to do so was the Liver Cancer Study Group of Japan which registered 11,379 patients with HCC diagnosed over 2 years (1990-1991) in 536 hospitals throughout Japan.\textsuperscript{300} This was a large undertaking in both geographical coverage and clinical depth, with the recording of HCC relevant data, often missing from registry-based epidemiological studies, such as aetiology of liver disease, degree of fibrosis/cirrhosis, tumour staging, treatment and causes of death (cancer or liver related, mechanism of death – e.g. liver failure, bleeding, etc).

More recently in 2017, the French have published the largest population-based clinical cohort to date with 31,927 patients with HCC diagnosed in 2009-2012.\textsuperscript{334} The study was made possible by the presence of the French Programme for the Medicalisation of Information Systems database which contains discharge information from all French hospitals. This study did not use any other primary source of case capture such as the Cancer Registry or Death Registry. Hence, patients who were not admitted to hospital may have been missed, although this is unlikely to have occurred over the 4-year period of study.

While the methodology is clear on the data parameters extracted, there is little detail on how data extraction was performed. It is likely this was achieved through discharge coding rather than individual chart review given the enormity of the study sample size. This may explain the fact that more than a third of the HCC cases had an unknown aetiology whereas HCV and HBV infection were only 8% and 3%
respectively. The simple explanation would be that the viral infection status was missing from the coding data.

Unfortunately, such gaps raise suspicion on the validity of the other data parameters, especially when there is no other parameter with which to cross-check as with the viral hepatitis example above. Cirrhosis was present in 73.4% of HCC cases according to the paper, but what is there to say there was another 10% of cirrhosis that was uncoded? This underlies the importance of a prospective data collection by clinicians such as the methodology in this incidence study.

Nevertheless, this nationwide population-based study was important in revealing the heterogeneity in incidence (range 12.8 to 24.9 per 100,000), access to curative treatments (1.3% to 28.8%) and median survival (5.7 to 12.1 months) between French regions and hospitals, which could not have been achieved with institution-based cohort studies.

Despite many African countries having among the highest HCC incidence and mortality rates in the world, there had been few studies of HCC epidemiology and clinical features apart from single centre studies with small sample sizes. A consortium, the Africa Network of Gastrointestinal and Liver Diseases, was formed to address this need. The findings from a multicentre, multicountry retrospective cohort study involving 2566 patients from 21 tertiary referral centres was recently published.\textsuperscript{305} Participating centres volunteered to be involved in the data collection; two centres were in Egypt and the rest from sub-Saharan African countries (nine centres from Nigeria, four from Ghana and other countries one centre each). Despite the request for data covering a ten-year period, 2006-2016, and with countries having populations of 40 to 100 million, many countries submitted data for only 20-50 patients per country. Hence, while there is need for representative population data, there are many barriers to its collection.
7.1.4 Using geographical mapping of risk factors to target surveillance strategies

A population-based cohort allows the opportunity to detect geographical clustering of clinical features that may be useful in preventative health strategies. In an earlier revision of the second paper (Chapter 5), the distribution of HCC incidence across Melbourne was examined. This was removed from the final version due to word limit requirements of the journal and will be presented here.

7.1.4.1 Geographic clustering of HCC incidence

HCC incidence (crude rate) was calculated for each local government area (LGA) in Melbourne use the population of that LGA as the denominator. The crude incidence rate across all of Melbourne (the entire study) was used as the comparator. Each LGA received a standardised incidence ratio, which is the ratio of its own incidence to that of Melbourne.

There was marked variation of HCC incidence rates between local government areas (LGA) – some areas had up to 2.8 times the expected rate based on the Melbourne average. Standardised incidence ratio of HCC in LGAs mapped geographically are shown in Figure 7-1A.
This mapping revealed that the high incidence areas of Melbourne were Greater Dandenong, Yarra and Maribyrnong, followed by Brimbank and Wyndham. These areas are significant for the higher numbers of migrant residents, especially those from high HBV prevalent countries including Vietnam, China, and sub-Saharan Africa countries.

These findings confirm a previous report from New South Wales showing geographic clustering of HCC incidence in metropolitan areas with higher proportions of overseas born patients.\textsuperscript{430}

In their recent paper reviewing VCR data of Melbourne HCC incidence over the last three decades, Carville et al\textsuperscript{429} also presented HCC incidence by LGAs, without using a standardised incidence ratio. They showed that over the period 2004-2013, the
high incidence was similarly high in Greater Dandenong, Yarra and Brimbank as in this study. Notably, the incidence in Wyndham was not elevated, which reflects the later settlement of African, Burmese and other migrants to this area in recent years. Importantly, their results over the longer term of 10 years confirms the validity of the finding that geographical clustering is a real and sustained phenomenon, rather than the incidental finding of a 12-month incidence study.

7.1.4.2 Correlation with geographic distribution of risk factors

Using Department of Health HBV notification data, the distribution of HBV notification incidence ratio was also mapped Figure 7-1B, using the same method as the standardised incidence ratio, i.e. the incidence of HBV notification in each LGA against the Melbourne average. There was significant correlation between the HBV incidence ratio with the HCC incidence ratio among the LGAs (r=0.63, p=0.0012), Figure 7-1D.

Similarly, the proportion of overseas born residents in each LGA was obtained from ABS Census data. This were mapped by LGAs as ratio of proportions compared to the Melbourne average proportion (Figure 7-1C). The distribution significantly correlated with the study HCC incidence distribution (r=0.56, p=0.029), Figure 7-1E.

In contrast, HCV notifications incidence did not correlate with the HCC incidence distribution. However, looking specifically at HCV associated HCC incidence, the relative rates were highest in inner city areas with higher injecting drug use (IDU) rates as well as state prisons. HCC with alcoholic liver disease in the absence of viral hepatitis was highest in areas with lower income (ABS Census), with a significant correlation (r= -0.409, p=0.0264).

7.1.4.3 Significance of geography

As reported in the results of the second study (section 5.4), this research provides new data on the comparative incidence of liver cancer in migrant groups in Australia. It supports the observation that migrants retain the HCC risk of their country of birth. In previous Australian studies, Asian and Italian migrants have had the highest HCC incidence. Here, the study presents the first reported incidence for African
migrants as the ethnic with the highest HCC incidence in Australia. Patients from sub-Saharan Africa have rates that are 16 times that of Australian-born patients in both males and females (Figure 5-1). Using census demographic data, culturally effective surveillance programs may be targeted to these high-risk populations.

The applicability of this targeted approach may be limited by the demographics of the region. It is best applied in developed cities in which migrant populations settle in geographical clusters. World events in recent decades have resulted in mass migration and resettlement of people from undeveloped countries to Western countries, where this clustering occurs as people seek familiarity in language and culture in a foreign country. Developed Western cities with high migrant populations are also the same cities with increasing HCC incidence and mortality rates, hence making this targeted approach potentially useful.

Knowledge of the geographical mapping of HCC incidence and risk factors may be used in a number of applications, as discussed in the recommendations in section 8.2.
7.1.5 Clinical determinants of HCC costs of treatment

Despite using a top-down approach to the derivation of costs, this Australian cost study had the benefit of a well-characterised clinical cohort to provide important associations with relevant risk factors. This has been the shortcoming of much of the HCC costs literature to date as the large administrative databases lack patient-level detail.

Interestingly, a study published recently in 2018 (after the completion of the Melbourne cost data) has comprehensively described the costs of HCC management from the top-down approach but also with detailed clinical risk factor analysis. Kaplan et al.\textsuperscript{27} analysed the cost of HCC management over three years in 3188 HCC patients treated through the US Veterans Affairs health system. HCC cases were identified through the VA Corporate Data Warehouse using the older and less accurate ICD-9 coding (155.0 and 155.2). However, as all the patient charts were reviewed by extractors, it is likely any non-HCC cases (155.2 secondary cancers) were excluded in the final cohort. Cases were matched 1:4 with non-HCC cirrhotic control patients.

While there was no control group, the mean total costs in Australia were very similar to the mean total US cost – AUD$231,084 ($6,419 per month) versus USD$154,688 over three years. This would suggest that the Australian net costs would likely have been similar with a control group.

The authors also performed a multivariable analysis to predict higher costs, similar to this study. They found that the factors associated with higher cost were liver transplantation, early BCLC stage and multidisciplinary board review, all of which correlated with improved survival and lower costs, once adjusted for survival. This is also similar to the Melbourne findings although in both studies, the relatively short follow-up (2 years and 3 years) bias results towards factors associated with high upfront costs. Longer follow-up is required for the cost-effectiveness findings to manifest more significantly.

Nevertheless, it is reassuring to see that this resource-limited study had comparable findings to a robust well-resourced study, which is the largest HCC study to date.
7.1.6 Impact of this research

7.1.6.1 Changes to the Victorian Cancer Registry classification of HCC

This research was performed with collaboration from the Victorian Cancer Registry (the two of the co-authors of the HCC incidence paper are the Director and the Reporting and Quality Assurance Manager of the VCR). Even before completing the capture of the incident cohort (July 2012 to June 2013), it became apparent that the VCR was missing HCC diagnoses. The second part of the research hypothesis, that the registry’s underreporting is partly due to misclassification of clinically diagnosed cases as Liver Cancer Unspecified cases, was confirmed through cross-checking of these cases with the registry.

To the registry’s credit, they promptly made changes to their registration protocols. From 1 January 2014, HCCs would be classified correctly without the need for histological verification. Further, the registry proceeded to a retrospective reclassification of previously registered cancer, as discussed in section 0. Hence, this research was able to make an impact on the local epidemiology reporting before the first paper was published.

7.1.6.2 Impact on other studies

Establishing complete case capture, correct classification and thus accurate incidence reporting at the official cancer registry is important for other studies that use this empirical data. For example, The Polaris Observatory HCV Collaborators\textsuperscript{433} recently published a modelling study of global HCV prevalence using country-level disease burdens with model outputs validated against local empirical data. The authors cited this research study and that of the Swedish study by Törner et al\textsuperscript{311} in their research limitations, acknowledging that inaccurate local data could impair their model.

Closer to home, a 2018 Australian study by Wallace et al\textsuperscript{273} reported on HCC incidence and survival in Australia from 1982 to 2014. They extracted HCC cases from the Australian Cancer Database which contains cancer registrations from the registries for each of the six states and two territories of Australia. Informed by this study’s
findings, they noted that two of the eight Australian registries had the same problem of not correctly coding clinically diagnosed HCCs. As this was a registry-based study, they made assumptions that all Liver Cancer Unspecified cases were HCC for their analysis which may have caused an overestimation in their incidence rate.

7.1.6.3 International research community reception

This research study has been well received by the international community, with 25 citations in the literature to date, from publications in international journals including The Lancet Gastroenterology & Hepatology, Gastroenterology, Hepatology, Journal of Hepatology, and Liver International. These citations are provided in Appendix B.

The first study was published Hepatology with an editorial highlighting the important questions it raised with regards to case ascertainment and diagnostic coding in the new era of clinically diagnosed HCC.

The studies by Törner et al311 and Jepsen et al302 are significant not only for their findings of underreporting of HCC incidence in their respective cancer registries. Equally important is the fact that these two Scandinavian countries, which have reputations for having robust epidemiological data, have found flaws in their HCC data. As the Hepatology editorial suggests, this study heralds the need for registries (even well-regarded ones) to reassess their methodology so that the downstream effects of underestimating HCC burden can be avoided.
8 Conclusion

The burden of liver cancer is increasing in developed countries such as Australia. Hepatocellular carcinoma, the predominant form of liver cancer, is a complex disease in its epidemiology and management. HCC occurs mostly in cirrhosis which is commonly secondary to chronic viral hepatitis B and/or C, alcohol-related liver disease, non-alcoholic fatty liver disease and other causes. Recent changes to diagnostic practice allow HCC diagnoses to be made by clinical and radiological criteria, without histological verification. A number of treatment options are available for HCC, the choice of which is dependent on stage of tumour presentation and underlying liver disease. Survival outcomes may be related to any these factors.

The interplay between rapidly evolving trends in HCC risk factors and changes in its diagnostic criteria suggested the possibility that HCC incidence may be underreported by official cancer registry figures. Such underestimation has repercussions for adequate health resource allocations for prevention and early detection of HCC, anticipating the costs of the disease burden, and funding of treatment options and research.

A population-based study was designed to capture cases from multiple primary sources and determine HCC incidence, independently from the cancer registry. To the best of my knowledge, this novel methodology is the first in the world to determine population incidence of HCC using clinical diagnostic criteria applied by clinicians themselves.

This study found a two-fold higher age-standardised incidence of HCC in Melbourne than reported by the cancer registry. Further, the research revealed outdated registry classification practices that partly contributed to the underreporting of HCC incidence. As a direct result of this study, the cancer registry coding practices were updated to align with current clinical diagnostic criteria for HCC. The development of a clinical HCC registry with multiple primary sources of case capture, including multidisciplinary discussion/clinic attendance, hospital discharge coding databases and cancer registry notifications, may allow for ongoing completeness and accuracy of epidemiological data to enable prompt responses to rapid trends.
The clinical cohort recruited from the incidence study provided the opportunity to describe the clinical features of HCC presenting at the population level. It also allowed for longitudinal clinical study of survival outcomes and determine the effect of surveillance participation on survival.

The clinical cohort study findings were that cirrhosis in Australia is mainly due to chronic hepatitis C and alcohol-related liver disease, followed by chronic hepatitis B which is common in migrants. Survival outcomes for HCC remains poor despite the breadth of therapeutic options available. Participation in HCC surveillance was associated with the detection of earlier stage tumour that was amenable to curative treatment, leading to improved survival. A national HCC surveillance program targeting high-risk groups should be considered as a cost-effective measure to reduce burden of disease.

Lastly, the longitudinal clinical cohort also allowed us to study the direct costs of HCC management in Australia, the first report of its kind. The study described costs according to stage of disease, phase of treatment and by the treatment applied. Most of the costs are borne by the sickest patients. Hence, strategies to improve earlier diagnosis rates and prevent progression of liver disease will be cost-effective in the long-term by reducing disease burden.
8.1 FUTURE DIRECTIONS FOR RESEARCH

Epidemiology has always been critical to understanding disease and its management, especially in the local setting. The high dependency of the HCC literature on cancer registries is testament to both the importance of epidemiology but also to the need for its ongoing review, as this research has highlighted. Continued research with innovative approaches is required to ensure epidemiology remains relevant.

As has been performed in Sweden and Denmark, reappraisal of the local cancer registry practices and data quality in many developed countries with rising HCC incidence could contribute to a global effort to consolidate current HCC epidemiology.

In Australia, an independent evaluation of HCC incidence could be performed as a national research study. Given the findings from this research that most HCC cases may be captured with the combination of multidisciplinary meeting and hospital discharge records, a retrospective multi-centre study could be performed without onerous effort.

While such a cross-sectional incidence study will help inform and validate cancer registry practices, recruiting and maintaining population-based clinical cohorts will require much more resources. Nevertheless, the research value of such cohorts in allowing observation of the effects of health interventions on outcomes across the HCC disease spectrum will be immense. A clinical HCC registry could be a first step in providing longitudinal clinical data, but it needs to be population-based to be fully useful for epidemiological research purposes.

This Melbourne incident cohort is a great opportunity to study long-term outcomes such as 5-year survival and the cost-effectiveness of treatments. The use of non-HCC controls will make the cost-effective analyses more robust.
8.2 RECOMMENDATIONS

A number of recommendations can be made from the results of this research for the relevant research and government bodies. Some of these points have been discussed previously and will be summarised here.

1. **Cancer registries need to review their classification methodology for HCC.** This research and that of others show that even historically robust cancer registries in developed countries can have inherent errors due to changes in diagnostic practices. This may apply to other cancers that are clinically diagnosed with low histological verification rates.

2. **Better linkage between hospital coding (admission registries) and cancer registries to reduced missed reports.** A significant number of HCC cases were correctly coded at the hospital end but missed being reported to the cancer registries. This was also experienced by other studies. Improvements in information systems may help this process.

3. **Hospital HCC multidisciplinary clinics should forward diagnoses to the cancer registry.** This primary source was both complete and accurate. It allows capture of outpatients, both public and private.

4. **Cancer registries should publish or make readily available separate HCC data.** GLOBOCAN is able to publish separate HCC rates in Cancer in Five Continents because that data is available for extraction from its source registries. Yet most publicly available data published by the local registries themselves are of primary liver cancer as a whole.
5. **Studies of HCC epidemiology should specifically extract and report on HCC incidence.** It would be important that where HCC incidence is reported, the data is sourced from true HCC data and not extrapolated from liver cancer data used as a surrogate. Perhaps such data extraction is currently difficult, since even international guidelines on HCC still quote incidence of liver cancer rather than specific HCC incidence. Studies also need to use age-standardised incidence rates that have been standardised to both the World Standard Population and local standard population, which may give quite different results.

6. **Consider establishing a clinical HCC registry.** Through electronic linkage of records from multidisciplinary clinics, hospital discharge coding and cancer registry notifications, a highly complete and accurate clinical HCC registry could be created and maintained. This would enable rapid responses to changing HCC epidemiology and provide robust data for research, helping overcome the registry barriers of timeliness and accuracy. The linkage to clinic and discharge coding would also allow the cancer registry to record aetiology of liver disease, liver functional status, treatment and other staging data, which it currently does not record.

Starting on a smaller scale with a pilot city-based registry could be an option. One example comes from a Belgian group that asked treating physicians to voluntarily report prospective incident HCC cases with 6 monthly reminders for survival data updates.

7. **Government should develop an HCC surveillance program for high risk groups.** Consider the lifetime risk of HCC in a HCV/HBV cirrhotic patient is one in four, compared to the lifetime risk of breast cancer, which is one in 12 women. Hence, for these high-risk groups for whom surveillance is cost-effective, there needs to be a national screening program like with bowel or breast cancer. High risk groups can be identified through the HBV/HCV notifications databases, hospital clinic or GP referrals, or through self-registration.
8. **Better public health education, especially in areas with high migrant populations.** Using census data, these areas can be identified and given increase public and health professional education regarding risk factors for liver disease, screening for cirrhosis, and participating in HCC surveillance if indicated.

9. **Cost-effective analyses should be performed using HCC costs associated with clinical risk factors.** The high costs of HCC management in both good and poor prognosis patients should be an incentive to invest in the former group as the longer-term results (improved survival, reduced morbidity) will be cost-effective. That investment could take the form of some of the recommendations made above.
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Appendices

Appendix A

Citations (to January 2019)


Appendix B

Print versions of the publications will follow here.
Novel Population-Based Study Finding Higher Than Reported Hepatocellular Carcinoma Incidence Suggests an Updated Approach Is Needed

Thai P. Hong,1 Paul Gow,2,3 Michael Fink,4 Anouk Dev,5 Stuart Roberts,6 Amanda Nicoll,7–9 John Lubel,7,9 Ian Kronborg,10 Niranjan Arachchi,10 Marno Ryan,1 William Kemp,6 Virginia Knight,5 Helen Farrugia,11 Vicky Thursfield,11 Paul Desmond,1 Alexander J. Thompson,1 and Sally Bell1

Hepatocellular carcinoma (HCC) incidence is rising rapidly in many developed countries. Primary epidemiological data have invariably been derived from cancer registries that are heterogeneous in data quality and registration methodology; many registries have not adopted current clinical diagnostic criteria for HCC and still rely on histology for classification. We performed the first population-based study in Australia using current diagnostic criteria, hypothesizing that HCC incidence may be higher than reported. Incident cases of HCC (defined by American Association for the Study of Liver Diseases diagnostic criteria or histology) were prospectively identified over a 12-month period (2012-2013) from the population of Melbourne, Australia. Cases were captured from multiple sources: admissions to any of Melbourne’s seven tertiary hospitals; attendances at outpatients; and radiology, pathology, and pharmacy services. Our cohort was compared to the Victorian Cancer Registry (VCR) cohort (mandatory notified cases) for the same population and period, and incidence rates were compared for both cohorts. There were 272 incident cases (79% male; median age: 65 years) identified. Cirrhosis was present in 83% of patients, with hepatitis C virus infection (41%), alcohol (39%), and hepatitis B virus infection (22%) the commonest etiologies present. Age-standardized HCC incidence (per 100,000, Australian Standard Population) was 10.3 (95% confidence interval [CI]: 9.0-11.7) for males and 2.3 (95% CI: 1.8 to 3.0) for females. The VCR reported significantly lower rates of HCC: 5.3 (95% CI: 4.4 to 6.4) and 1.0 (95% CI: 0.7 to 1.5) per 100,000 males and females respectively (P < 0.0001). Conclusions: HCC incidence in Melbourne is 2-fold higher than reported by cancer registry data owing to under-reporting of clinical diagnoses. Adoption of current diagnostic criteria and additional capture sources will improve registry completeness. Chronic viral hepatitis and alcohol remain leading causes of cirrhosis and HCC. (HEPATOLOGY 2016;63:1205-1212)

Primary liver cancer (PLC) has become the second leading cause of cancer mortality worldwide and is also the fifth-most common cancer.1 Hepatocellular carcinoma (HCC), the predominant type of primary liver cancer, mostly arises in the setting of cirrhosis, with the most common etiologies being chronic viral hepatitis B and C, alcohol, and nonalcoholic fatty liver disease.

Abbreviations: ABS, Australian Bureau of Statistics; BCLC, Barcelona Clinic Liver Cancer; CI, confidence interval; HCC, hepatocellular carcinoma; ICC, intrahepatic cholangiocarcinoma; ICD, International Classification of Diseases; MSD, Melbourne Statistical Division; PLC, primary liver cancer; VCR, Victorian Cancer Registry.

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The incidence of HCC has been widely reported to be increasing in regions with historically low incidence.\(^{(2,3)}\) In Australia, liver cancer is the fastest rising cause of cancer death.\(^{(4)}\) Multiple factors may contribute to this phenomenon, including increased migration from regions with high HCC and viral hepatitis prevalence, an increasing burden of cirrhosis as patients are surviving longer with better medical treatments, and the obesity epidemic causing rising prevalence of nonalcoholic steatohepatitis-related cirrhosis.\(^{(5)}\)

The HCC epidemiology literature has been reliant upon cancer registries as the primary source of incidence data\(^{(6)}\) and hence is subject to the limitations of cancer registry data capture methodology. Cancer registries vary in a number of important features. Mandatory reporting laws that help improve registration completeness are not universal, and where laws exist, not all potential sources of case identification are utilized. For example, in Victoria, Australia, cancers identified from hospital admissions and pathology services are registered, but diagnoses made in outpatient settings and radiology services are not reportable, possibly leading to incomplete registration.

Differences also occur in the criteria for HCC classification. The traditional approach used by the Victorian Cancer Registry (VCR; Victoria, Australia) and many other registries across the world (e.g., China and Italy\(^{(7,8)}\)) relies upon histological verification for HCC classification; all clinically diagnosed PLC without histology are classified as Liver Cancer Unspecified. However, in current clinical practice, HCC is predominantly diagnosed using clinicoradiological criteria in subjects with cirrhosis rather than histology, as approved by current guidelines from Learned Societies.\(^{(9,10)}\) Hence, some registries (United States and some European countries) now accept clinical diagnosis as a basis for HCC classification.\(^{(7)}\)

Therefore, in this context, many studies have reported HCC incidence using total PLC rates as a surrogate marker.\(^{(11,12)}\) However, this is misleading given that a significant proportion of primary liver cancers are intrahepatic cholangiocarcinomas (ICCs), forming up to 45% of PLC figures as reported by some cancer registries\(^{(8)}\) (Fig. 1). Compared to ICC, HCC has entirely different biological, prognostic, and management implications and hence epidemiological research needs to be HCC specific. Accurate and current epidemiology informs policy decisions by government concerning health resource utilization, identifies risk factors for HCC, and provides targets for prevention.

In Victoria, Australia, we hypothesized that HCC incidence rates may be higher than currently reported by the cancer registry, owing to incorrect classification of clinically diagnosed cases, and incomplete capture from nonreported sources. Therefore, our aim was to determine the incidence rate of HCC in an independent population-based study using current clinical diagnostic criteria. We then compared results with data from the VCR for the same period and population.

**Materials and Methods**

**THE STUDY POPULATION**

We performed a population-based study of HCC incidence in Melbourne, Australia, within the geographical region defined by the Australian Bureau of Statistics (ABS) as the Melbourne Statistical Division (MSD). This area has an estimated population of 4,300,207 (ABS Census 2011, projected for the 2012-2013 incident period), suitable for epidemiological study. The population is ethnically diverse with 35%
born outside Australia, including those from countries with high HCC incidence.

This region contains seven tertiary referral public health services, all of which were participating study sites. Each health service consists of a tertiary university teaching hospital, with associated secondary hospitals, as well as radiology and pathology services. There were no tertiary hospitals in Victoria outside the MSD. The VCR is the population-based registry responsible for the MSD. Patients residing outside the MSD (defined by residential postcodes) were excluded.

CASE ASCERTAINMENT

From July 1, 2012 to June 30, 2013, potential cases were screened from multiple concurrent and overlapping sources. These included patients attending HCC outpatient clinics or discussed at multidisciplinary meetings as well as those found on database searches of the radiology, pathology, pharmacy, and medical coding services of the hospitals involved. In addition, the tertiary hospital hepatology units kept prospective databases of patients diagnosed with HCC and these were also queried. Private physicians and surgeons managing HCC in the community were also invited and contributed to case finding.

Search parameters included radiological procedures (transarterial chemoembolisation, radio frequency, microwave, or ethanol ablation), histological diagnoses of HCC (International Classification of Diseases [ICD]-0-3 C22.0 M8170/3), sorafenib dispensing and medical admissions coding of ICD-10 C22.0 Hepatocellular carcinoma, and C22.9 Liver Cancer Unspecified. American Association for the Study of Liver Diseases (AASLD) clinico-radiological diagnostic criteria and/or histology were used to define HCC cases. Cases of HCC recurrence or diagnosis dates outside the designated study period were excluded. Readmissions or attendance of a case at another site was only counted for the first instance.

Data collected included demographics, underlying etiology of chronic liver disease, hepatic synthetic liver function, presence of cirrhosis, Child–Pugh scores, mode of diagnosis, involvement in surveillance programs, and tumor staging according to Barcelona Clinic Liver Cancer (BCLC) staging. The etiology of chronic liver disease was defined by the consulting physician with verification from pathology or radiology results if it was not documented. Data were deidentified and recorded on a secure study database.

Independent human research ethics committees governing each of the associated tertiary health networks granted ethics approval.
VICTORIAN CANCER REGISTRY CORRELATION

Current Australian legislation mandates notification of cancers from hospital admissions and pathology, but not outpatient attendances such as clinics or radiology. The VCR provided deidentified data for incident cases of all primary liver cancer subtypes (ICD-10 C22.0 to C22.9) notified during the study incident period. We excluded cases with residential postcodes outside the MSD. In 2012-2013, the VCR methodology required histological verification to code a liver cancer as HCC (C22.0). Clinically diagnosed HCC reported to the VCR without histology were coded as Liver Cancer Unspecified (C22.9). The deidentified information provided by the VCR included patient initials, dates of birth, residential postcode, diagnostic coding, and source of registration (public hospital, private hospital, pathology, or death certificate). Records were matched to our cohort using these parameters.

STATISTICAL ANALYSIS

Age-standardized incidence rates were calculated using the direct method for age standardization with 18 groups of 5-year age groups (0-, 5-, 10-, ..., 85+) for each sex separately. The population data for each age group were derived from ABS Australian Census 2011, with the same figure used as denominator for both MSD and VCR rate calculations. Incidence rates were standardized to the Australian Standard Population, using the Australian Census June 30, 2001 standard population as recommended by the ABS. (14) Incidence rates were reported with 95% confidence intervals (CIs), assuming a Poisson distribution. Categorical variables were compared using chi-square test or Fisher’s exact test, whereas continuous variables were compared using Mann-Whitney’s test with statistical significance assessed at the 0.05 level. Calculations were performed using StataCorp software (2011; Stata Statistical Software: Release 12; StataCorp LP, College Station, TX).

Results

There were 327 new diagnoses of HCC captured across the study sites, of which 272 cases fulfilled inclusion criteria for the study; 55 patients living outside the study region were excluded. Hospital HCC multidisciplinary meetings and clinics were the source of most cases captured, with 82% (224 of 272) of patients having attended or been referred for discussion. Searches of hospital admission coding captured 68% of patients whereas the combination of multidisciplinary meetings and coding search captured 97% (263 of 272) of cases. The remaining cases (3%) not captured by either of these means were sourced by radiology, pathology, or pharmacy searches and private physician referrals.

The baseline characteristics of the cohort are reported in Table 1. The majority of HCC patients were male (79%). Patients had a median age of 65 years at diagnosis, with men significantly younger than women (median age: 64 [range, 28-93] and 74 [range, 39-91] respectively; $P = 0.0001$).

<table>
<thead>
<tr>
<th>Table 1. Baseline Characteristics</th>
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<tbody>
<tr>
<td>Total cohort, n</td>
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<tr>
<td>Sex, males, n (%)</td>
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<tr>
<td>Age, median, years (range)</td>
</tr>
<tr>
<td>Males</td>
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<tr>
<td>Females</td>
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<tr>
<td>Race, n (%), median age (range)</td>
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<tr>
<td>Caucasian</td>
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<tr>
<td>Asian</td>
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<td>African</td>
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<tr>
<td>Place of birth, %</td>
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<tr>
<td>Australia</td>
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<tr>
<td>Overseas</td>
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<tr>
<td>Unknown</td>
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<tr>
<td>Overseas born in Melbourne population (13)</td>
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<tr>
<td>Risk factors for chronic liver disease present n (%)</td>
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<tr>
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<td>Chronic hepatitis B</td>
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<td>Fatty liver disease</td>
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<td>Hemochromatosis</td>
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<td>Primary biliary cirrhosis</td>
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<tr>
<td>Autoimmune hepatitis</td>
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<tr>
<td>Other/unknown</td>
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<td>More than one risk factor</td>
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<tr>
<td>Mode of presentation n (%)</td>
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<tr>
<td>Surveillance program (6-12 monthly US)</td>
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<td>Known cirrhotic but not screened</td>
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<tr>
<td>First presentation of cirrhosis or incidental</td>
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<tr>
<td>Unknown</td>
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<tr>
<td>Liver functional status n (%)</td>
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<tr>
<td>Cirrhosis present</td>
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<tr>
<td>Child Pugh A</td>
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<td>Child Pugh B</td>
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<td>Child Pugh C</td>
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<td>Barcelona Clinic Liver Cancer staging n (%)</td>
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<td>BCLC-A</td>
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Abbreviation: US, ultrasound.
The age-standardized incidence rates of HCC in the MSD were 10.3 (95% CI: 9.0-11.7) and 2.3 (95% CI: 1.8-3.0) per 100,000 males and females, respectively.

In comparison, for the same period and population, the VCR recorded 138 cases of HCC (112 males, 26 females) equating to incidence rates of 5.3 (95% CI: 4.4-6.4) and 1.0 (95% CI: 0.7-1.5) per 100,000 males and females, respectively. This was significantly lower than the clinically diagnosed HCC incidence rates from our study ($P < 0.0001$ and $P = 0.0014$, respectively, Fig. 2).

**ADJUSTED VCR COHORT**

At the time of study (2012-2013), only cases with histology were classified as HCC (ICD-10 C22.0) by the VCR (138 cases). For the same period, a further 162 cases (118 males, 44 females) without histology were registered by the VCR and coded as Liver Cancer Unspecified (ICD-10 C22.9). Prompted by this study, the VCR reviewed these 162 Liver Cancer Unspecified cases and reclassified them using clinical (nonhistological) information supplied at the time of initial cancer registration, resulting in 123 reclassified as HCC, 24 as ICC, 1 as other, and 14 remained Liver Cancer Unspecified. Therefore, for the 12-month period of comparison (2012-2013), it was possible to define an adjusted total of 261 cases of HCC recorded by the VCR, consisting of 123 newly reclassified HCC and the original 138 histologically coded HCC.

We cross-referenced the new adjusted VCR cohort ($n = 261$) with our study cohort ($n = 272$) and matched 205 cases of incident HCC common to both cohorts (see Fig. 3). Of the 56 VCR cases that were not identified in our study, there were 5 verifiable HCC incidence cases missed by our capture method, equating to 1.8% of our cohort size. There were 25 nonincident HCC cases with clinical diagnosis dates outside our study inclusion period (i.e., clinical diagnosis before July 1, 2012, but delayed registration in the VCR or diagnosed after July 30, 2013 and yet still incorrectly included in the VCR incidence cohort) and 3 cases of incorrect diagnoses (not HCC). The remaining 23 cases were notified to the VCR by sources beyond our study sites, including private hospitals (12 cases), other public hospitals not associated with our study (8 cases), pathology laboratories (2 cases), and death-certificate-only notifications (1 case). We were not able to verify these diagnoses because our ethics approvals were site specific and did not allow case identification at nonstudy sites.

**ADJUSTED VCR RATES**

If we were to presume that all of the 23 unverified cases of the VCR cohort would have met inclusion criteria, then the composite VCR group of likely incident HCC cases would be 233 cases (including the 205 matched cases and 5 cases we missed). For this composite group, the HCC incidence rates are 8.8 (95% CI: 7.6 to 10.2) and 1.9 (95% CI: 1.4 to
2.5) per 100,000 males and females, respectively. These rates remain lower than our rates, but not significantly so ($P = 0.0981$ for males and $P = 0.3729$ for females).

## CASES MISSED BY VCR REGISTRATION

Our study captured 67 HCC cases (25% of cohort) that were not registered by the VCR. There were 37 patients who were admitted and coded as HCC, but not reported to the VCR by hospitals. Another 16 patients were admitted for HCC treatment (liver transplantation 2, resection 1, transarterial chemoembolization 8, and radiofrequency ablation 5), but not did not receive the correct HCC coding on discharge to trigger notification. There were also 14 outpatients receiving palliative treatments (sorafenib or best supported care) who would not have been reportable under current mandatory reporting methods.

To account for cases that may have been notified subsequent to our study period and registered with incorrect diagnosis dates (date of admission rather than date of initial diagnosis), we matched these 67 cases with VCR registrations to March 4, 2015. There were 26 cases registered incorrectly, only 2 cases of late registration and 39 cases remained unaccounted for.

## DIFFERENCES BETWEEN HISTOLOGY DEFINED AND CLINICALLY DIAGNOSED HCC IN THE VCR COHORT

We examined the 205 matched VCR cases for which we had clinical information from our independent data collection and compared the 100 cases defined by histology with the 105 cases diagnosed clinically (see Supporting Table 1). The clinically diagnosed cases were significantly different in racial background (higher proportion of Caucasian [$P = 0.0315$], lower Asian [$P = 0.0387$]), and more likely to have advanced disease (presence of cirrhosis [$P = 0.0004$], higher Child-Pugh scores [$P = 0.0021$], and later BCLC staging [$P = 0.0001$]). They were also less likely to be undergoing surveillance despite fulfilling indications for screening ($P = 0.0254$).

## Discussion

The management of HCC is complex and costly, requiring involvement of tertiary health care and the use of advance diagnostic modalities and therapeutics, including liver transplantation. Accurate representation of HCC epidemiology is required to adequately address the increasing burden of disease on the health system. This is the first study in Australia to independently define the problem at the population-based level using current clinicoradiological diagnostic criteria, thus addressing the shortcomings of current epidemiological literature that is primarily dependent upon cancer registries.

We have shown that HCC incidence rates in Melbourne are 2-fold higher than those reported by the VCR using histology as a basis for classification. The data demonstrate the importance of using current diagnostic criteria for registry classification of HCC in cancer registries. HCC is no longer diagnosed histologically, but based on clinic-radiological criteria. These criteria have been validated and accepted by international liver societies; histology is reserved for indeterminate cases.

As a direct result of our study, the VCR have adopted a new methodology to classify HCC by both histological and/or clinicoradiological criteria as of January 1, 2014. Indeed, cancer registries across the world are starting to recognize the need for a change in classification of HCC to a broader diagnostic criteria consisting of both clinical and radiological bases of...
diagnosis. Comparing reports from the International Association of Cancer Registries in Cancer Incidence in Five Continents Vol. IX (2007)\(^{(7)}\) and Vol. X (2014),\(^{(15)}\) many registries from China, South East Asia, Italy, and other regions are gradually implementing clinical criteria, resulting in lower rates for unspecified PLC and higher rates for HCCs. As with Victoria from 2014 onward, incidence rates for HCC will be higher than previously reported.

We then tested whether a population-based incidence study, using multiple capture methods to diagnose cases identified through comprehensive clinical case collection, would identify a greater number of incident HCCs compared to our local cancer registry. For the comparator, we used the adjusted VCR incident data for the matching time period, after reclassification of cases that were originally classified as Liver Cancer Unspecified, but which, on review, had been given a clinical diagnosis of HCC at the point of notification. We still identified higher incidence rates than the adjusted registry incidence rates for clinically diagnosed HCC. This difference did not meet statistical significance, possibly owing to our conservative approach in presuming that all 23 cases notified to the VCR from nonstudy sources were indeed HCC.

Nevertheless, the fact remains that one quarter of the total HCC cases identified in our study were not notified to the VCR (including those notified incorrectly and thus not included in published incidence figures). In contrast, using this capture method, our missed rate was less than 2%. This highlights both the importance of identifying appropriate sources of case capture to optimize cancer registration completeness, as well as the need to be familiar with the methodology of the local registry, especially in light of newer clinical diagnostic criteria. Best practice management of HCC should involve multidisciplinary case review meetings involving hepatologists, radiologists, surgeons, and oncologists. On the basis of our findings, we propose that mandatory notification from multidisciplinary meetings to cancer registries should be required and supported.

In addition to correctly classifying HCC using current diagnostic criteria, it is also important for researchers to differentiate HCC epidemiology from that of ICC. Many studies\(^{(11,12,16,17)}\) have used HCC and PLC interchangeably, quoting total PLC rates from cancer registries for incidence and mortality when, in fact, the discussion relates to HCC. Greater emphasis needs to be made of the significant contribution ICC rates make to PLC figures in different populations. For example, ICCs make up between 5% and 25% of total PLC rates across United States registries and up to 45% in UK registries (International Association of Cancer Registries).\(^{(7)}\) ICC incidence and mortality rates have also risen in recent times,\(^{(18-20)}\) suggesting that trends in PLC incidence need to account for changes in both HCC and ICC rates independently, particularly given that the biological behavior, clinical management, prognosis, and survival rates differ significantly between HCC and ICC. Hence, more accurate representation will assist planning of education and preventative screening practices as well as allow appropriate utilization of health care resources.

Although tertiary referral bias may be a concern in terms of adequate population representation, the unique nature of HCC management reduces this limitation. HCC is a complex disease with a poor prognosis, mostly referred to specialists and generally requiring a tertiary hospital service for diagnosis or treatment at some point. In addition, as a cancer, HCC is mandatorily reportable in Australia; patients, including those with terminal disease and palliative needs, who present elsewhere (e.g., private hospitals, nursing homes, and death-certificate-only notifications) are captured by the population-based VCR. Our favorable comparison with the VCR data suggests that tertiary referral bias has not negatively influenced our reported incidence rates. Instead, the cases missed by the VCR did, in fact, present to a tertiary hospital as hypothesized and were captured by our methods. Moreover, any residual failure of capture on our part would serve to further strengthen our suggestion that incidence is currently under-reported.

We recognize that the 2-fold discrepancy between our HCC incidence and the local registry rates examined over a 1-year period in Melbourne may not be generalizable to other populations. Incidence rates in any population will depend upon the prevailing risk factors present; in the case of developed countries with historically low incidence, migrants from countries with high HCC incidence play an important role. Our data show that people born overseas are over-represented in HCC cases in Melbourne. We suggest that our methodology could be validated in other cities, such as those in Australia, the United States, Canada, and Europe, which have similarly high proportions of overseas-born residents. Furthermore, the degree of discrepancy between rates from an independent, population-based study, such as this and that of the local registry, will also depend upon individual cancer registry practices as well as local epidemiology.
Particularly important would be populations where the local registry is yet to adopt clinical criteria in cancer registrations and is still reporting disproportionately high rates of unspecified PLCs (Fig. 1). Although our results based on a capture period of only 1 year may not reflect longer term trends, and may not be reproducible in all populations, our methodology may nevertheless help other regions improve case ascertainment to better inform health policies.

This study is the first Australian study to describe HCC incidence at a population-based level using current accepted clinicoradiologic and pathological criteria, independent of cancer registry data. Our HCC incidence rates are 2-fold higher than that reported by the cancer registry, suggesting that the revision of cancer registration methodology in line with current diagnostic criteria was required. Furthermore, the inclusion of additional clinical sources of cases may improve data capture and estimates. Finally, we reiterate the importance of using HCC-specific data in publications and discussion of epidemiological data, which requires having a full understanding of registration methodologies of the local reporting cancer registry. Accurate epidemiological data will assist policy makers to implement public health interventions such as education, screening for viral hepatitis and cancer, and allow effective resource allocation.

REFERENCES


Supporting Information

Additional Supporting Information may be found at onlinelibrary.wiley.com/doi/10.1002/hep.28267_suppinfo.
Surveillance improves survival of patients with hepatocellular carcinoma: a prospective population-based study

Thai P Hong, Paul J Gow, Michael Fink, Anouk Dev, Stuart K Roberts, Amanda Nicoll, John S Lube, Ian Kronborg, Niranjan Arachchi, Marno Ryan, William W Kemp, Virginia Knight, Vijaya Sundararajan, Paul Desmond, Alexander JV Thompson, Sally J Bell

Abstract

Objectives: To determine the factors associated with survival of patients with hepatocellular carcinoma (HCC) and the effect of HCC surveillance on survival.

Design, setting and participants: Prospective population-based cohort study of patients newly diagnosed with HCC in seven tertiary hospitals in Melbourne, 1 July 2012 – 30 June 2013.

Main outcome measures: Overall survival (maximum follow-up, 24 months); factors associated with HCC surveillance participation and survival.

Results: 272 people were diagnosed with incident HCC during the study period; the most common risk factors were hepatitis C virus infection (41%), alcohol-related liver disease (39%), and hepatitis B virus infection (22%). Only 40% of patients participated in HCC surveillance at the time of diagnosis; participation was significantly higher among patients with smaller median tumour size (participants, 2.8 cm; non-participants, 6.0 cm; \( P < 0.001 \)) and earlier Barcelona Clinic Liver Cancer (BCLC) stage disease (A/B, 59%; C/D, 25%; \( P < 0.001 \)). Participation was higher among patients with compensated cirrhosis or hepatitis C infections; it was lower among those with alcohol-related liver disease or decompensated liver disease. Median overall survival time was 20.8 months; mean survival time was 18.1 months (95% CI, 16.6–19.6 months). Participation in HCC surveillance was associated with significantly lower mortality (adjusted hazard ratio [aHR], 0.60; 95% CI, 0.38–0.93; \( P = 0.021 \)), as were curative therapies (aHR, 0.33; 95% CI, 0.19–0.58). Conversely, higher Child–Pugh class, alpha-fetoprotein levels over 400 kU/L, and later BCLC disease stages were each associated with higher mortality.

Conclusions: Survival for patients with HCC is poor, but may be improved by surveillance, associated with the identification of earlier stage tumours, enabling curative therapies to be initiated.

Methods

Study cohort

Data for the prospective clinical cohort of patients in the Melbourne statistical division newly diagnosed with HCC during 1 July 2012...
— 30 June 2013, identified in our earlier study, were analysed. The Melbourne statistical division has an estimated population of 4,300,207 (projected population for 2012–13) that is ethnically diverse; 35% of residents were born outside Australia. Patients residing outside the division (defined by residential postcodes) were excluded.

The population-based Victorian Cancer Registry collects data for all patients with cancer in the Melbourne statistical division. The region includes seven tertiary referral public health services, all of which were participating study sites. Each health service includes a tertiary university teaching hospital, with associated secondary hospitals and radiology and pathology services.

Data collection
Our case ascertainment methodology was reported previously. Data for patients at all study sites were captured (with the informed consent of the patients) and cross-referenced with Victorian Cancer Registry data. Data were de-identified and stored on a secure database.

Data collated from patient records included demographic information (including ethnic background and place of birth), residential postcode, aetiology of chronic liver disease, the presence of cirrhosis, Child–Pugh scores, alpha-fetoprotein levels, mode of presentation, participation in a surveillance program, Barcelona Clinic Liver Cancer (BCLC) stage, and treatment modality. The aetiology of chronic liver disease was defined by the consulting physician, and verified by pathology or radiology results if the cause was not documented. Cirrhosis status was determined after a review of histology, transient electrograph, radiology, and biochemistry findings. Treatment modality was defined as the first treatment given, except for patients who were downstaged when more curative therapy was later assigned.

Three ethnic groups were defined for the purposes of our analysis: white (including Egypt, Middle East), African (sub-Saharan Africa), and Asian (mainly East and South-East Asia, with three patients from India or Sri Lanka). Indigenous status was not recorded.

Participation in a surveillance program was defined as patients with risk factors defined in international guidelines — cirrhosis of any cause; chronic HBV infection in Asian men over 40, Asian women over 50, African patients over 20 years of age, and people with a family history of HCC — undergoing 6-monthly ultrasound assessment with or without alpha-fetoprotein assessment.

The primary study outcome was overall survival. Survival time was calculated from the date of diagnosis until the date of notified death, as retrieved from hospital records, the Victorian Cancer Registry, and the Registry of Births, Deaths and Marriages Victoria. Patients were censored at last known medical attendance (consultation, radiology, pathology, other records), with a maximum follow-up period of 24 months.

Statistical analysis
Descriptive statistics are presented for continuous factors (medians with interquartile ranges [IQRs]) and categorical variables (numbers, proportions). Standardised HCC incidence ratios were calculated, comparing rates by country of birth with those for Australian-born patients (projected population for 2012–13). Correlations of clinically relevant variables were assessed as Spearman rank correlation coefficients (not reported); if the correlation of two variables was statistically significant, for the purposes of regression analysis they were either combined (eg, cirrhosis and Child–Pugh class combined as the new variable, “liver function”) or one variable was omitted (eg, BCLC stage but not tumour size retained).

To assess factors associated with surveillance participation, crude and adjusted odds ratios (ORs, aORs) were respectively estimated in logistic regression and multiple logistic regression models.

Survival was estimated with the Kaplan–Meier method. As the upper confidence bound for median survival time could not be calculated (the point 95% CI never dropped below 0.5 during the 24-month maximum follow-up period), mean survival time — calculated as the area under the Kaplan–Meier survivor function with the Stata option rmean — is also presented. Cox proportional hazards models were fitted for individual factors associated with survival nominated by specialist hepatologists (crude hazard ratio [HR]); factors for which P < 0.1 in the univariate analysis were included in the multiple regression Cox proportional hazards model (adjusted HR [aHR]). Violations of the proportional hazards assumption were assessed by visual inspection of Kaplan–Meier curves and in Schoenfeld residuals tests. P < 0.05 was deemed statistically significant. All analyses were performed in Stata Statistical Software 12 (StataCorp).

Ethics approval
Human research ethics committees for each health network granted approval for the study: St Vincent’s Heath (reference, HREC-A 056.12), Melbourne Health (including Western Health; reference, 2012.150), Eastern Health (reference, E66-1112), Austin Health (reference, H2012/04713), Southern Health (reference, 12201A), and Alfred Health (reference, 357/12).

Results
A total of 272 people in the Melbourne statistical division were diagnosed with incident HCC during 1 July 2012 – 30 June 2013, including 216 men (79%). The most frequent risk factors for liver disease were HCV infection (112, 41%), alcohol (107, 39%), HBV infection (60, 22%), and non-alcoholic fatty liver disease (39, 14%); 73 patients (27%) had more than one risk factor (Box 1). Of 225 patients (83%) with cirrhosis, 72 (32%) were first diagnosed with cirrhosis at the time of HCC diagnosis.

Most patients (166, 61%) were born overseas (Box 1). The standardised incidence of HCC was higher for overseas-born than for Australian-born patients, and particularly high for those born in sub-Saharan Africa, Italy, Vietnam, or Egypt (Box 2). Significantly more overseas-born patients had viral hepatitis-related HCC (108 of 166, 65%) than Australian-born patients (55 of 106, 52%; P = 0.031); significantly more Australian-born patients had alcohol-related HCC (65 of 106, 61% vs 42 of 166, 25%, P < 0.001).

Treatment with curative intent was provided to 87 patients (32%) — liver transplantation (3%), resection (13%), and ablative therapies (radio-frequency, microwave, percutaneous alcohol; 16%) — and 180 patients (66%) were offered treatment with palliative intent — trans-arterial chemo-embolisation (24%), selective internal radiation radiotherapy (1.8%), systemic targeted therapy (sorafenib, 13%), and best supportive care (28%) (Box 1). Follow-up treatment for five patients with late stage disease was not recorded because they were overseas or otherwise lost to follow-up.

Surveillance at the time of hepatocellular carcinoma diagnosis
One hundred and ten patients (40%) were participating in surveillance at the time of HCC diagnosis; surveillance data were...
1 Baseline characteristics of the 272 people in Melbourne diagnosed with incident hepatocellular carcinoma, July 2012 – June 2013 (continued)

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Total number of people</th>
<th>Treatment modality</th>
</tr>
</thead>
<tbody>
<tr>
<td>Place of birth</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Australia</td>
<td>106 (39%)</td>
<td></td>
</tr>
<tr>
<td>Overseas</td>
<td>166 (61%)</td>
<td></td>
</tr>
<tr>
<td>Ethnic background</td>
<td></td>
<td></td>
</tr>
<tr>
<td>White (Australian-born)</td>
<td>105 (39%)</td>
<td></td>
</tr>
<tr>
<td>White (overseas-born)</td>
<td>96 (36%)</td>
<td></td>
</tr>
<tr>
<td>Asian</td>
<td>59 (22%)</td>
<td></td>
</tr>
<tr>
<td>African</td>
<td>10 (4%)</td>
<td></td>
</tr>
<tr>
<td>Missing data</td>
<td>2 (1%)</td>
<td></td>
</tr>
<tr>
<td>Age (years), median (IQR)</td>
<td>65 (56–76)</td>
<td></td>
</tr>
<tr>
<td>Men</td>
<td>64 (56–74)</td>
<td></td>
</tr>
<tr>
<td>Women</td>
<td>74 (64–80)</td>
<td></td>
</tr>
<tr>
<td>White (Australian-born)</td>
<td>60 (56–71)</td>
<td></td>
</tr>
<tr>
<td>White (overseas-born)</td>
<td>70 (61–78)</td>
<td></td>
</tr>
<tr>
<td>Asian</td>
<td>63 (54–75)</td>
<td></td>
</tr>
<tr>
<td>African</td>
<td>56 (53–74)</td>
<td></td>
</tr>
<tr>
<td>Missing data</td>
<td>65 (55–75)</td>
<td></td>
</tr>
<tr>
<td>Risk factors for chronic liver disease present</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chronic hepatitis C virus infection</td>
<td>112 (41%)</td>
<td></td>
</tr>
<tr>
<td>Alcohol-related liver disease</td>
<td>107 (39%)</td>
<td></td>
</tr>
<tr>
<td>Chronic hepatitis B virus infection</td>
<td>60 (22%)</td>
<td></td>
</tr>
<tr>
<td>Non-alcohol fatty liver disease</td>
<td>39 (14%)</td>
<td></td>
</tr>
<tr>
<td>Haemochromatosis</td>
<td>6 (2%)</td>
<td></td>
</tr>
<tr>
<td>Primary biliary cirrhosis</td>
<td>5 (2%)</td>
<td></td>
</tr>
<tr>
<td>Autoimmune hepatitis</td>
<td>3 (1%)</td>
<td></td>
</tr>
<tr>
<td>Other/missing data</td>
<td>17 (6%)</td>
<td></td>
</tr>
<tr>
<td>More than one risk factor</td>
<td>73 (27%)</td>
<td></td>
</tr>
<tr>
<td>Mode of presentation</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Surveillance program (6–12-monthly ultrasound)</td>
<td>110 (40%)</td>
<td></td>
</tr>
<tr>
<td>Known indication but not screened</td>
<td>53 (19%)</td>
<td></td>
</tr>
<tr>
<td>First presentation of cirrhosis/other risk factor</td>
<td>32 (12%)</td>
<td></td>
</tr>
<tr>
<td>Incidental hepatocellular carcinoma finding</td>
<td>73 (27%)</td>
<td></td>
</tr>
<tr>
<td>Missing data</td>
<td>4 (2%)</td>
<td></td>
</tr>
<tr>
<td>Liver function status</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cirrhosis</td>
<td>225 (83%)</td>
<td></td>
</tr>
<tr>
<td>Child–Pugh A</td>
<td>125 (56%)</td>
<td></td>
</tr>
<tr>
<td>Child–Pugh B</td>
<td>67 (30%)</td>
<td></td>
</tr>
<tr>
<td>Child–Pugh C</td>
<td>33 (15%)</td>
<td></td>
</tr>
<tr>
<td>Barcelona Clinic Liver Cancer staging</td>
<td></td>
<td></td>
</tr>
<tr>
<td>BCLC A</td>
<td>70 (26%)</td>
<td></td>
</tr>
<tr>
<td>BCLC B</td>
<td>59 (22%)</td>
<td></td>
</tr>
<tr>
<td>BCLC C</td>
<td>98 (37%)</td>
<td></td>
</tr>
<tr>
<td>BCLC D</td>
<td>41 (15%)</td>
<td></td>
</tr>
<tr>
<td>Missing data</td>
<td>4 (1.5%)</td>
<td></td>
</tr>
</tbody>
</table>

The multivariable analysis indicated that Australia-born (aOR, 0.45; 95% CI, 0.24–0.85; P = 0.014) and Asian patients (aOR, 0.42; 95% CI, 0.20–0.91; P = 0.029) were less likely to participate in surveillance than white patients born overseas. Participation in incomplete for four patients. Most non-participating patients had guideline indications for surveillance: cirrhosis (120 of 158, 76%) or chronic HBV infection without cirrhosis (17, 11%); 120 of 225 patients with cirrhosis (53%) were not participating in surveillance, including 72 (60%) who were diagnosed with cirrhosis at the time of HCC diagnosis. Non-participation was most marked among those with chronic HBV infections but not cirrhosis (17 of 21, 81%), including 12 patients in whom the infection was first detected at the time of HCC diagnosis. Overall, 242 of 272 patients (89%) would have qualified for surveillance (225 with cirrhosis, 17 without cirrhosis but with chronic HBV infections).

2 Standardised incidence ratios for hepatocellular carcinoma (compared with incidence among Australian-born people), by country/region of birth*

<table>
<thead>
<tr>
<th>Country (cases)</th>
<th>Sub-Saharan Africa (8)</th>
<th>Italy (32)</th>
<th>Vietnam (30)</th>
<th>Egypt (6)</th>
<th>Greece (10)</th>
<th>Malaysia (4)</th>
<th>China (8)</th>
<th>New Zealand (3)</th>
<th>India (3)</th>
<th>United Kingdom (5)</th>
<th>Australia (106)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Women</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Men</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* Countries of birth providing fewer than three patients not shown.
surveillance by patients with compensated cirrhosis (Childs–Pugh A) was higher than for those without cirrhosis (aOR, 5.70; 95% CI, 2.10–15.5; \( P = 0.001 \)), but decompensated cirrhosis (Childs–Pugh B or C) was associated with a lower surveillance rate than for patients with compensated cirrhosis or without cirrhosis (aOR, 0.53; 95% CI, 0.30–0.95; \( P = 0.033 \)). Surveillance was higher among patients with HCV-related HCC (aOR, 1.95; 95% CI, 1.11–3.42; \( P = 0.020 \)) and lower among those with alcohol-related HCC (aOR, 0.53; 95% CI, 0.29–0.95; \( P = 0.034 \)) (Box 3).

Participation in surveillance was higher for patients with earlier than later stage disease (BCLC A/B, 75 of 127, 59%; BCLC C/D, 35 of 139, 25%; \( P < 0.001 \)), with smaller tumour size (participants: median, 2.8 cm; IQR, 2.0–4.0 cm; non-participants: median, 6.0 cm; IQR, 3.6–10 cm; \( P < 0.001 \)), or receiving curative treatment (59 of 99, 60%; not receiving curative treatment, 51 of 169, 30%; \( P < 0.001 \)).

Survival analysis
Median overall survival time was 20.8 months (lower end of 95% CI, 16.6 months; upper limit not calculable because point 95% CI did not fall below 0.5 during 24-month follow-up), with 12-month and 24-month survival rates of 62% and 47% respectively (Box 4,A). Mean survival time was 18.1 months (95% CI, 16.6–19.6 months).

In the multivariable analysis, poor survival was predicted by higher Childs–Pugh class, alpha-fetoprotein level exceeding 400 kU/L (aHR, 2.06; 95% CI, 1.38–3.08; \( P < 0.001 \)), and later BCLC stage at HCC diagnosis (BCLC C/D vs BCLC A/B: aHR, 2.59; 95% CI, 1.57–4.27; \( P < 0.001 \)) (Box 4,B; Box 5); increased survival was associated with participation in surveillance programs (aHR, 0.60; 95% CI, 0.38–0.93; \( P = 0.021 \)) and curative treatment (aHR, 0.33; 95% CI, 0.19–0.58; \( P < 0.001 \)) (Box 5). Survival rates for surveillance participants were 79% at 12 months and 66% at 24 months, compared with 49% and 33% respectively for non-participants (Box 4,C).

### 3 Logistic regression analysis of factors influencing surveillance participation

<table>
<thead>
<tr>
<th>Risk factor</th>
<th>Surveillance participation</th>
<th>Odds ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Number of participants</td>
<td>110 (40%)</td>
<td>158 (58%)</td>
</tr>
<tr>
<td>Age (years), median (IQR)</td>
<td>64 (56–74)</td>
<td>66 (56–77)</td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Women</td>
<td>27</td>
<td>28</td>
</tr>
<tr>
<td>Men</td>
<td>83</td>
<td>130</td>
</tr>
<tr>
<td>Ethnic background/place of birth</td>
<td></td>
<td></td>
</tr>
<tr>
<td>White/overseas-born</td>
<td>52</td>
<td>45</td>
</tr>
<tr>
<td>White/Australian-born</td>
<td>36</td>
<td>67</td>
</tr>
<tr>
<td>African</td>
<td>3</td>
<td>7</td>
</tr>
<tr>
<td>Asian</td>
<td>19</td>
<td>39</td>
</tr>
<tr>
<td>Liver function</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Non-cirrhotic</td>
<td>6</td>
<td>32</td>
</tr>
<tr>
<td>Child–Pugh A</td>
<td>66</td>
<td>57</td>
</tr>
<tr>
<td>Child–Pugh B</td>
<td>26</td>
<td>41</td>
</tr>
<tr>
<td>Child–Pugh C</td>
<td>11</td>
<td>22</td>
</tr>
<tr>
<td>Decompensated cirrhosis (Childs–Pugh B/C)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>73</td>
<td>85</td>
</tr>
<tr>
<td>Yes</td>
<td>37</td>
<td>73</td>
</tr>
<tr>
<td>Chronic hepatitis B</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>88</td>
<td>120</td>
</tr>
<tr>
<td>Yes</td>
<td>22</td>
<td>38</td>
</tr>
<tr>
<td>Chronic hepatitis C</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>52</td>
<td>105</td>
</tr>
<tr>
<td>Yes</td>
<td>58</td>
<td>53</td>
</tr>
<tr>
<td>Alcohol-related liver disease</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>74</td>
<td>88</td>
</tr>
<tr>
<td>Yes</td>
<td>36</td>
<td>70</td>
</tr>
<tr>
<td>Non-alcohol fatty liver disease</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>97</td>
<td>132</td>
</tr>
<tr>
<td>Yes</td>
<td>13</td>
<td>6</td>
</tr>
</tbody>
</table>

CI = confidence interval; IQR = interquartile range. * Includes factors for which \( P < 0.1 \) in univariate analysis. † Based on an alternative model not including the variable “liver function”. ☞
The incidence of HCC in Australia is increasing. The parallel rises in incidence and population-attributable mortality rates suggest that the rise in incidence is not driven by detection of earlier tumours during surveillance alone, but may be related to demographic changes and the increased prevalence of underlying risk factors. Survival remains poor; our 12-month survival rate of 62% is similar to recent estimates for other developed countries.

Survveillance was associated with improved survival. Despite the acknowledged role of HCC surveillance in managing cirrhosis, only 40% of patients were participating in surveillance when diagnosed with HCC, a proportion similar to the 38% reported for one Melbourne tertiary centre more than a decade ago. Surveillance is particularly infrequent among patients of Asian or Australian-born backgrounds and those with alcohol-related liver disease. The emergence of non-alcoholic fatty liver disease-related HCC, linked with the rise of the metabolic syndrome in developed countries, is particularly challenging for surveillance because of the large population at risk.

We identified two major barriers to increased uptake of surveillance: adherence to surveillance was poor for patients with certain recognised risk factors (decompensated cirrhosis, alcohol misuse) and, perhaps more importantly, a considerable number of patients diagnosed with HCC had hitherto undiagnosed cirrhosis or viral hepatitis. These findings indicate that a two-tiered approach may be needed to improve outcomes.

Firstly, clinicians should be alert to risk factors for chronic liver disease, such as excessive alcohol use, chronic HCV and HBV infections, and non-alcoholic fatty liver disease in certain social groups (eg, patients of low socio-economic status or with mental health problems, injecting drug users, migrants, patients with diabetes or metabolic syndrome). Patients with these risks factors should be screened for cirrhosis, and those with active liver disease should be screened longitudinally. An aspartate transaminase to platelet ratio index (APRI) value greater than 1.0 predicts cirrhosis with 76% sensitivity and 72% specificity, and the test is simple to undertake. Community-based screening based on blood pathology and transient elastography identifies significant fibrosis in 16% of patients with hepatitis C.

HCC surveillance comprising 6-monthly liver ultrasound and alpha-fetoprotein assessment should be offered to all patients with cirrhosis, as well as to Asian men over 40, women over 50, Africans over 20 years of age, and patients with a family history of HCC without cirrhosis but with chronic HBV infections. This recommendation should be communicated during medical training and included in specialist society and jurisdictional guidelines.

Secondly, effective surveillance might be best achieved with a national HCC surveillance program. HCC fulfils many of the criteria for such programs: its incidence is high, a non-invasive and inexpensive screening method is available, and early detection is associated with improved survival when combined with effective therapy.

Preventive responses to known causes of chronic liver disease may also be beneficial as public health measures. Improving the diagnosis of viral hepatitis in at-risk populations, together with viral suppression (HBV) and eradication (HCV), could be cost-effective strategies for preventing HCC. As antiviral drugs for treating HBV and HCV infections are readily available in Australia, increased education and use of these drugs in community practice are important. Non-alcoholic fatty liver disease, a major indication for liver transplantation in many countries, may also be under-recognised as a risk factor by the general medical community.
5 Logistic regression analysis of factors influencing survival

<table>
<thead>
<tr>
<th>Factor</th>
<th>Value</th>
<th>Hazard ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(univariate)</td>
<td>(multivariable)</td>
</tr>
<tr>
<td></td>
<td>$P$</td>
<td>$P$</td>
</tr>
<tr>
<td><strong>Age (years), median (IQR)</strong></td>
<td>65 (56–76)</td>
<td>1.02 (1.00–1.03)</td>
</tr>
<tr>
<td><strong>Sex (men)</strong></td>
<td>216 (79%)</td>
<td>0.77 (0.51–1.17)</td>
</tr>
<tr>
<td><strong>Ethnic background</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>White</strong></td>
<td>201 (74%)</td>
<td>1.00</td>
</tr>
<tr>
<td><strong>Afro</strong></td>
<td>10 (3.7%)</td>
<td>0.70 (0.26–1.90)</td>
</tr>
<tr>
<td><strong>Asian</strong></td>
<td>59 (22%)</td>
<td>0.56 (0.34–0.92)</td>
</tr>
<tr>
<td><strong>Liver function</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Non-cirrhotic</strong></td>
<td>38 (14%)</td>
<td>1.00</td>
</tr>
<tr>
<td><strong>Child–Pugh A</strong></td>
<td>125 (48%)</td>
<td>1.22 (0.59–2.52)</td>
</tr>
<tr>
<td><strong>Child–Pugh B</strong></td>
<td>67 (27%)</td>
<td>3.82 (1.87–7.81)</td>
</tr>
<tr>
<td><strong>Child–Pugh C</strong></td>
<td>33 (13%)</td>
<td>6.36 (2.96–13.7)</td>
</tr>
<tr>
<td><strong>Risk factor for cirrhosis</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Chronic hepatitis C</strong></td>
<td>112 (41%)</td>
<td>0.68 (0.47–0.99)</td>
</tr>
<tr>
<td><strong>Chronic hepatitis B</strong></td>
<td>60 (22%)</td>
<td>0.86 (0.55–1.32)</td>
</tr>
<tr>
<td><strong>Alcohol</strong></td>
<td>107 (39%)</td>
<td>1.29 (0.91–1.83)</td>
</tr>
<tr>
<td><strong>Non-alcoholic fatty liver disease</strong></td>
<td>39 (14%)</td>
<td>0.77 (0.45–1.29)</td>
</tr>
<tr>
<td><strong>Alpha-fetoprotein (&gt; 400 kU/L)</strong></td>
<td>81 (30%)</td>
<td>3.13 (2.20–4.46)</td>
</tr>
<tr>
<td><strong>BCLC staging (stages C/D vs A/B)</strong></td>
<td>139 (52%)</td>
<td>6.53 (4.24–10.1)</td>
</tr>
<tr>
<td><strong>Curative treatment (provided)</strong></td>
<td>85 (31%)</td>
<td>0.18 (0.11–0.30)</td>
</tr>
<tr>
<td><strong>Surveillance (participated)</strong></td>
<td>110 (40%)</td>
<td>0.33 (0.22–0.50)</td>
</tr>
</tbody>
</table>

BCLC = Barcelona Clinic Liver Cancer; CI = confidence interval; IQR = interquartile range. * Includes factors for which $P < 0.1$ in univariate analysis. ◆

Limitations

Our study was limited by inherent biases that affect interpretation of survival outcomes in cancer screening. As cirrhosis, the major trigger for surveillance, is itself asymptomatic and underdiagnosed, lead time in HCC diagnosis varies widely; as the growth rate for HCC is quite variable, length time bias is also important. Randomised controlled trials could circumvent these biases. Two older trials found that HCC surveillance improved survival,8,23 but their methodological flaws limit the generalisability of their findings. Randomised controlled trials are now impracticable, as informed patients usually decline randomisation in preference of direct access to surveillance.24 A number of studies have attempted to reduce lead time bias in HCC surveillance by adjusting for tumour growth during the asymptomatic phase; one such study found that the short term survival benefit of surveillance was markedly reduced after taking lead time into account, but not the long term survival benefits.25

Conclusion

Survival for patients with HCC in Australia is poor. While surveillance allows the detection of smaller, early stage tumours, enabling curative therapies associated with significantly better survival to be initiated, the rate of participation in HCC surveillance programs is relatively low. Cirrhosis had not previously been detected in one-third of patients newly diagnosed with HCC. Improving the identification of cirrhosis in primary care and by other physicians and enrolling patients in surveillance programs may improve their outcomes. A national surveillance program for patients at increased risk of HCC, in accordance with the relevant international guidelines, should also be considered.

Competing interests: No relevant disclosures.

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Author/s: Hong, Thai Phuoc

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Persistent Link: http://hdl.handle.net/11343/225659

File Description: An Australian population-based study of the incidence and outcomes of hepatocellular carcinoma: the Hepatomas of Melbourne Epidemiological Research (HoMER) study

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