Article type : Original Articles

Title: Increasing incidence of non-alcoholic steatohepatitis as an indication for liver transplantation in Australia and New Zealand.

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Keywords: Liver transplant, epidemiology, non-alcoholic fatty liver, hepatocellular carcinoma, trends.

List of abbreviations: Non-alcoholic steatohepatitis (NASH), orthotopic liver transplantation (OLT), hepatocellular carcinoma (HCC), hepatitis C virus (HCV), hepatitis B virus (HBV), primary sclerosing cholangitis (PSC), cryptogenic cirrhosis (CC), annual percentage change (APC), Body mass Index (BMI), Model for End-stage Liver Disease score (MELD), international normalized ratio (INR).

Grants and financial support:

Dr Luis Calzadilla Bertot has been awarded a scholarship from the Liver Foundation of Western Australia.

Conflicts of interest: None

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The world-wide increase in obesity and diabetes has led to predictions that non-alcoholic steatohepatitis (NASH) will become the leading indication for orthotopic liver transplantation (OLT). Data supporting this prediction from outside the United States is limited. Thus, we aimed to determine trends in the frequency of NASH among adults listed and undergoing OLT in Australia and New Zealand (ANZ) from 1994-2017. Data from the ANZ Liver Transplant Registry was analysed with patients listed for fulminant liver failure, re-transplantation or multi-visceral transplants excluded. Non-parametric trend, Spearman rank correlation and regression analysis were used to assess trends in aetiologies of liver disease over time. Of 5016 patient's wait-list registrants, a total of 3470 received an OLT. The percentage of patients with NASH activated for OLT increased significantly from 2.0% in 2003 to 10.9% in 2017 (trend analyses $p<0.001$). In 2017, NASH was the third leading cause of chronic liver disease among wait-list registrants behind chronic hepatitis C (29.5%) and alcohol (16.1%). Similarly, significant increases over time in the percentage of patients undergoing OLT were observed for HCV and NASH (all trend analyses $p<0.001$) but with significant reductions in primary sclerosing cholangitis (PSC) and cryptogenic cirrhosis (both $p<0.05$). By 2017, NASH was the third leading cause of liver disease among patients undergoing OLT (12.4%) and behind chronic hepatitis C (30.2%) and alcohol (18.2%). NASH also became third most frequent aetiology of chronic liver disease in patients transplanted (13.8%) with concomitant hepatocellular carcinoma by 2017. **In conclusion** NASH is increasing as a primary aetiology of liver disease requiring listing and liver transplantation in Australia and New Zealand.

Introduction

As the prevalence of obesity increases around the world (1), the liver-related manifestations of non-alcoholic fatty liver disease (NAFLD) and non-alcoholic steatohepatitis (NASH) are increasingly diagnosed.(2) The presence of NAFLD parallels the obesity epidemic with up to 84–96% of morbidly obese patients showing histological evidence of NAFLD.(3, 4) In developing countries up to one fifth of patients have evidence of NAFLD and data from develop countries indicates a prevalence up to 35%.(2)

Although NAFLD has a benign course in the majority of individuals, a proportion of patients develop NASH-related cirrhosis with risk of liver decompensation or hepatocellular carcinoma (HCC), both of which are indications for orthotopic liver transplantation (OLT).(5, 6) As NAFLD has a very high prevalence in the general population, even a relatively small proportion of patients developing end-stage liver disease will result in a significant population health burden. The United States (US) has had the highest prevalence of severe obesity for several decades.(7) Consequently, it is not surprising that recent data has demonstrated that NASH is becoming an increasingly common indication for liver transplantation overall and is already the second most common indication for liver transplantation in patients with HCC in the US. (8-11) In contrast, the demand for liver transplantation for hepatitis C has declined since 2015 following the introduction of safe and effective direct acting antivirals. Consequently, current trends suggest that NASH will surpass hepatitis C as the most common indication for liver transplantation in the United States within the next 10 years.(12, 13).

The prevalence of obesity (14) and diabetes (15) in Australia and New Zealand are almost similar to the US and thus a similar trend in the setting of liver transplantation is anticipated in the next few years. An increasing health burden related to NASH would clearly have important implications for public health strategies and resource allocation as well as direct implications for patients competing on liver transplant waitlists. This current study evaluates the trends in transplantation for NASH in Australia and New Zealand (ANZ), where the prevalence of NAFLD is similar to US (16). Our specific aims were to determine the annual frequency and temporal trends in the diagnosis of NASH related cirrhosis, among patients with chronic liver disease with and without HCC, who were activated for transplantation and who underwent transplantation from 1994 to 2017.

Patients and methods

A retrospective database review of the ANZ liver transplant registry data was performed for all patients aged >18 years who were listed for liver transplantation between December 31, 1994 and December 31, 2017. The ANZ liver transplant registry is a prospectively collected database from the five liver transplant units in Australia and the single unit in New Zealand.

Only patients listed electively for primary isolated liver transplantation were included in this study. Recipient variables at time of transplantation included age; gender; ethnicity (Caucasian, Asian, other); weight; specific comorbidities (diabetes mellitus, hypertension, coronary artery disease); Model for End-stage Liver Disease score (MELD), specific laboratory variables [total bilirubin, international normalized ratio (INR), creatinine, albumin level), presence of HCC and aetiology of the underlying liver disease (primary and secondary transplant indication). For the purpose of the primary outcome analysis among patients with HCC, we considered the underlying liver disease based on the secondary diagnosis provided.

Follow up data was maintained by each unit with regular clinic review of transplant recipients.

The primary outcome was the trend in annual rates of listing and transplantation for NASH related chronic liver disease. Secondary outcomes includes the trend in annual rates of listing and transplantation for NASH related-HCC.

Statistical analysis

Clinical and demographic characteristic at time of transplantation were described as the mean and standard deviation when normally distributed and as the median (including minimum to maximum values) when not normally distributed. The Mann-Whitney test was used to compare means between cohorts and categorical variables were compared using the Pearson chi squared test.

For the trend analyses, the percentage of activated and transplanted patients according to the underlying aetiology of chronic liver disease were calculated for each calendar year. Subsequently, three types of different trend analyses were performed; 1) non-parametric test of trends, 2) Spearman rank correlation using percentage of patients within a specific aetiology and calendar year were used to analyse trends between 1994 to 2017 and 3) regression analysis using joint points to explore specific annual percentage changes (APC).

Additional trend analysis in both liver transplant registrants and recipients with NASH were conducted for age (median age for each year), gender (proportion of male/females each year) and ethnicity (proportion of Caucasians, Asian and other ethnicity each year). Trend analyses in activated patients were limited to between 2003 to 2017 because of missing data before 2003. The analysis was repeated in the sub-group of patients with HCC. Analysis in the cohort of patients with HCC was performed from 2004 to 2017 as no NASH patients with HCC underwent OLT prior to 2004. No missing data were found for transplanted patients. Analysis was performed using STATA, software release 14.1 and Joint Point regression, software release 4.3.1.0.

Results

Cohort overview

From 1994 to 2017, 5016 patients were activated for a liver transplant in ANZ liver transplant centres; 356 patients were excluded (fulminant liver failure, re-transplant or multi-organ transplant) and 3470 underwent OLT **(Figure 1).** Over study period, the commonest underlying aetiologies of liver disease in listed patients were hepatitis C virus (HCV) (35%), alcoholic liver disease (16%), primary sclerosing cholangitis (PSC) (9%), hepatitis B virus infection (HBV) (9%) NASH (6%) and cryptogenic cirrhosis (CC) (4%). Other aetiologies (including metabolic, non-PSC cholestatic disease and non-HCC tumours) represented the remaining 21% of the cohort. A similar distribution of aetiologies of liver disease was seen in patients undergoing OLT.

Trends in aetiology of liver disease in patients activated for liver transplantation.

The annual percentage of activated patients stratified by aetiology is show in **Figure 2**. HCV and alcohol related liver disease were the leading indications for listing for liver transplantation from 2003 to 2017 (39% and 16 % respectively). There was no significant change in the frequency of these aetiologies over the study period (Table 1). In contrast during the same time period, the proportion of patients listed for NASH-related liver failure increased and the proportion listed for HBV-related liver failure decreased. By 2017, NAFLD (10.9 %) had surpassed HBV (7.9%) and PSC (7.6%) and become the third most common indication for listing for liver transplantation. Specific trend periods analysis shows significant annual percentage changes (APC) for NASH between the period from 2003-2005 and 2014-2017. On the contrary the percentage of waitlist registrants with HBV and CC demonstrated a significant decrease in the whole period analysed according to trend analysis.

No significant changes in the percentage of activated patients were observed for the other aetiologies **(Table 1).**

Trends in liver transplantation

Figure 3 and **Table 2** show the annual percentage and trend analyses of patients who underwent OLT stratified by aetiology from 1994-2017. HCV was the leading cause of liver transplantation during the study period, accounting of 30 % of liver transplants. The proportion of liver transplants performed for HCV-related liver failure increased over the study period. The most significant APC for HCV was observed between the periods from 2006 to 2012.

The proportion of liver transplants performed for NASH also increased significantly over the study period from 0% in 1994 to 12.4% in 2017 (table 2). In the period 1994 to 2004, the percentage of patients who underwent liver transplant for NASH increased marginally from 0% to 2.4%. In the subsequent 12 year period, the percentage of NASH patients increased from 6.8% in 2005 to 12.4% in 2017 where it was the third leading aetiology of chronic liver disease. There was a significant increase in the velocity of transplantation for NASH observed between 2004 and 2006 (APC=72.18 %, p< 0.005) and also from 2009 to 2017 (APC=11.82 %, p< 0.005)

The proportion of subjects transplanted for alcohol related liver disease remained constant whilst the proportion of patients transplanted for PSC and CC decreased during the study period.

Trends in waitlist and transplantation: 2013-2017

To explore specific changes within the last five years (2013-2017) during which direct-acting anti-viral therapy became available for chronic HCV infection, we conducted an additional trend analysis in both waitlist registrants and recipients. Over this period, a significant decrease was noted in the proportion of HCV activated patients (42% in 2013 to 29% in 2017, APC=-9.61 %, p= 0.05) and HCV transplanted patients (43% in 2013 to 29% in 2017, APC=-9.61 %, p= 0.20), shown in Supplemental Table 1, 2. On the contrary, the proportion of NASH liver transplant registrants increased from 8.5% in 2013 to 11% in 2017 (APC=9.40 %, p<0.05). Similarly, the percentage of NASH liver transplant recipients increased significantly from 9.2% to 12.4% (APC=8.20 %, p<0.05). No significant changes were observed for PSC, alcohol or HBV aetiologies. See Supplementary table 1 and 2.

Trends in age, gender and ethnicity of transplant registrants and recipients, 2003-2017

Between 2003 and 2017 the median age of liver transplants registrants significantly increased from 51 to 57 years (z = 3.41, p<0.001) (ρ= 0.91, p<0.001). Analysing the same period, the overall median age of NASH registrants was 57 years (range 26-73) but no significant change was observed. (z =0.34, p=0.73), (ρ= 0.23, p=0.74). Similarly, the median age of recipients increased significantly between 2003 (52 years) to 2017 (58 years) (z = 3.40, p<0.001) (ρ= 0.90, p<0.001*)* in the overall cohort, but not for NASH patients (z =1.44, p=0.14), (ρ= 0.38, p=0.15).

Overall, male waitlist registrants (78%) and liver transplant recipients (79%) were predominant in the cohort. No significant change in gender was observed within the whole cohort or within NASH patients over the period analysed (z =0.23, p=0.81), (ρ= 0.06, p=0.82).

Caucasian was the commonest ethnicity among activated (65%) and transplanted (70%) patients. Asian patients accounted for 8 and 9 percent of registrants and recipients respectively. Other ethnicities (Pacific Islander, Polynesian, Aboriginal, Hispanics, Africans) represented 27% of activated and 30% of transplanted patients respectively. No significant change over time occurred in ethnicity in both transplant registrants (z =1.21, p=0.22), (ρ= 0.32, p=0.24) and recipients (z=0.25, p=0.82), (ρ= 0.08, p=0.72). Similarly, there was no difference over time in ethnic groups when analysing only NAFLD patients..

Listing and transplantation for NASH and Cryptogenic Cirrhosis

In contrast to NASH, there was a reduction in both the frequency of listing and transplantation for CC during the study period. To examine for the impact of possible misclassification of NASH as CC, the phenotypic profiles of patients with NASH and CC patients at the time of transplantation were compared (supplemental **Table 3)**. In contrast to CC patients, NASH recipients had significantly higher proportion of diabetes mellitus (50% vs. 16%, p<0.001), hypertension (18% vs. 7.5%, p=0.002) and coronary artery disease (11% vs. 3%, p<0.001) as well as a higher mean body weight at the time of transplantation (93.8 kg vs. 68.1 kg, p<0.001) suggesting a low misclassification rate. Furthermore, when NASH and CC were combined for trend analysis, there remained a strong and significant increase in both activated (2003-2017) and transplanted patients (1994-2017) (all trend analysis $p<0.05$). Supplementary Figures 1, 2

Hepatocellular carcinoma: Trends in underlying aetiology of chronic liver disease in listed and transplanted patients.

From 2004 to 2017, 894 patients with the diagnosis of HCC were listed for liver transplantation of whom 676 were transplanted. Of those patients transplanted for HCC, the underlying aetiology of chronic liver disease was HCV in 58%, HBV in 21% , alcoholic liver disease in 9%, NASH in 8% and cholestatic liver disease (including PSC and primary biliary cirrhosis) in 3%.

HCV was the most common underlying liver disease in patients listed for HCC throughout the study period and the proportion actually increased from 51% in 2004 to 64% in 2017 (see Figure 4). During the same period, the proportion of patients listed for HCC with underlying NASH increased from 4% in 2004 to **9% in 2016/17.** The proportion of HBV related HCC among waitlist registrants decreased significantly from 33.3% in 2004 to 20% in 2017 **(Figure 4).** No significant changes were observed for cholestatic and alcohol related HCC **(Table 3).**

Similar trends were seen for patients who were transplanted for HCC (see **Figure 5).** HCV was the most common underlying liver disease in patients transplanted for HCC and the proportion increased between 2004 and 2017. Most significant increased were noted in the period (2009-2012) (APC=10.70 %, $p< 0.005$). In contrast the proportion of HCC related HBV significantly decreased between 2004 and 2017.

During the same period, the percentage of patients listed for HCC with underlying NASH increased from 4% to 14%, becoming the third leading cause for HCC-related liver transplantation from 2015, and showing significant increase on trend analyses specifically in the period from 2013 to 2017 (APC=28.82 %, $p< 0.005$). **(Table 4)**. The other aetiologies of liver disease related HCC in liver transplant recipients did not change significantly during the period analysed.

Discussion

Analysis of trends in liver transplantation provides an important insight into the current and future disease burden associated with specific chronic liver diseases. Over the last 24 years to

2017, HCV has clearly remained the leading indication for liver transplantation in Australia and New Zealand, accounting for one third of all adult liver transplants and 60% of HCC related transplants. Alcohol related liver disease has remained the second leading cause for transplant, consistently accounting for approximately 16% of all transplants, but a less common cause of transplants related to HCC. Notably however, the disease burden associated with NAFLD has rapidly increased over the past 2 decades. NASH is now the third most common indication for both waitlist registration and for liver transplantation in Australia and New Zealand.

Several studies from the US have demonstrated increasing proportions of transplants being performed for underlying NASH. Analysis of the Scientific Registry of Transplant Recipients and (UNOS/OPTN) databases has shown significant increases in the number and proportion of NASH transplanted patients in the United States since 2001 (17-19). In 2008, NASH surpassed alcoholic liver disease to become the second leading aetiology for liver transplantation in the US, accounting for 17% of transplants by 2014 (19). Within Australia and New Zealand, NASH currently only represents approximately 12% of all transplants. Similarly, a recent analysis of the Nordic Liver Transplant Registry demonstrated that NAFLD as indication for liver transplant increased significantly between 1994 to 2015 but only represented six percent of adult liver transplants between 2011-2015.(20) It is notable that the velocity of obesity rates increased significantly in Australia after 1995 from an average increase of 3.1% per decade to 6.0% increase per decade.(1) Subsequently, there was a significant increase in NASH related transplantation one decade later (Table 2) demonstrating the long-term sequelae of obesity related liver disease. Additionally, the epidemic of obesity, which underpins the development of NAFLD, occurred in Australia a decade later than the US (1), suggesting that rates of end-stage liver disease and HCC related to NASH in Australia will continue to increase to mirror the experience in the US. Given the development of cirrhosis due to NASH typically occurs over several decades (21), it is also likely that the impact of NASH on demand for liver transplantation will be delayed in countries where the obesity epidemic is relatively recent. It is possible that different nation-wide strategies of tackling obesity may also impact on future transplant rates for NAFLD.

In contrast to the increase in transplantation for NASH, other aetiologies of cirrhosis are reducing in frequency. The introduction of safe and effective direct acting antiviral therapy for HCV has reduced the number of patients listed for liver transplantation by more than one third since 2015 in North America,(10, 22) and Europe,(23-28) and the same reduction its likely to occurred in Australia and New Zealand within the next few years. Meanwhile, the number of liver transplants for HBV have decreased steadily thanks to universal neonatal vaccination and widespread access to safe and effective oral antiviral therapy for patients with chronic hepatitis B (29, 30) A similar reduction in HBV related activation and transplants was observed in Australia and New Zealand.

A recent trend analysis of the most common causes of chronic liver disease among liver transplant candidates with HCC in the US showed a significant increase in the proportion of NAFLD patients from 2002-2016 with NAFLD representing the fastest growing indication for OLT.(11) Our analysis showed that between 2015 and 2017, NASH became the third aetiology among HCC waitlist registrants. Additional contributing factors were the significant decrease in the prevalence of HBV related HCC in the waiting list and the stable trend of alcohol related HCC.

It is possible that the lack of recognition of NASH as aetiology in the first decade of the study lead to a potential misclassification of NASH cirrhosis as CC. Contrasting trends in liver transplantation for NASH and CC have also been found in the UNOS database where the percentage of NASH cirrhosis as an indication for OLT increased from 1% to 16% between 1994 to 2016 whereas cryptogenic cirrhosis fell from 15% to 4%.(31, 32) In this cohort, NASH subjects were more likely to have diabetes and be obese than CC patients. Similarly in the ANZ cohort, the metabolic characteristics of NASH patients were different compared to those with CC, being older with a significantly greater body weight and prevalence of cardio-metabolic comorbidities (diabetes, hypertension and coronary artery disease) suggesting that misclassification was minimal. In addition, when cryptogenic and NASH patients were combined, the increase in trend for transplantation remained strong suggesting a true increase in transplantation requirements for NASH.

Our findings have important implications for the ongoing and future policy in liver transplant settings. With NASH likely to continue to increase as an aetiology of liver disease requiring transplantation, early recognition of NASH in primary care clinics and identification of high risk patients with subsequent tailored management are mandatory in order to decrease the proportion of patients progressing to end stage liver disease and HCC. Currently, NASH related cirrhosis is frequently missed as a diagnosis with the consequence of presenting with more advanced liver disease and HCC thereby limiting potential curative options including transplantation.(33) In addition, with the increasing prevalence of metabolic factors (diabetes, overweight or obesity) which have a negative impact on waitlist drop-out rates (34) and survival post-liver transplant (35),strategies to optimize weight and diabetes control and avoid sarcopenia should be prioritized in these patients within liver transplant programs.

In conclusion this study demonstrates that NASH is a rapidly growing indication for liver transplantation in Australia and New Zealand. These data confirm the trends seen in the US, however suggests that further significant increases in NASH cirrhosis in association with reduction in HCV related cirrhosis is required before NASH will become the leading cause for transplantation. With the ongoing epidemics of diabetes and obesity, increased awareness of NASH coupled with effective lifestyle and pharmacotherapeutics are required to reverse the significantly increasing requirements for liver transplantation.

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Figure legends

Figure 1. Patients activated and transplanted in Australia and New Zealand (1994-2015) according to aetiology of liver disease

Figure 2. Annual frequency of liver disease aetiology, among patients activated for liver transplant

Figure 3. Annual frequency by aetiology of liver disease, among patients undergoing liver transplant

Figure 4. Annual frequency of liver disease by aetiology, among patients with hepatocellular carcinoma activated for liver transplant

Figure 5. Annual frequency by aetiology of liver disease among patients undergoing liver transplant with hepatocellular carcinoma

Supplemental Figure 1. Annual frequency of liver disease activated for liver transplant NASH, Cryptogenic cirrhosis and NASH plus cryptogenic cirrhosis. 2003-2017

Foot note: Trend analysis for the combination of NASH and CC.

Supplemental Figure 2. Annual frequency of liver disease among patients undergoing transplant for NASH, Cryptogenic cirrhosis and NASH plus cryptogenic cirrhosis. 1994-2017.

Foot note: Trend analysis for the combination of NASH and CC.

Table 1. Trend analyses for aetiology of chronic liver disease among patients activated for liver transplant in Australia and New Zealand 2003-2017.

Type of analysis	Aetiology					
	HCV	HBV	Alcohol	PSC	NASH	CC
Non parametric test of trends	*z = 0.16 p=0.87*	*z = -2.45 p= 0.01*	*z= 0.98 p= 0.32*	*z= 0.05 p= 0.95*	*z= 3.03 p<0.001*	*z= -2.34 p=0.01*
Spearman rank correlation	*ρ= 0.04 p=0.87*	*ρ= -0.65 p=0.00*	*ρ=0.26 p=0.26*	*ρ= 0.21 p=0.95*	*ρ=0.81 p<0.001*	*ρ= - 0.69 p=0.00*
Joint point Regression	*NS*	*NS*	*NS*	*NS*	*P<0.05 2003-2005 ^APC=83.29 2014-2017 ^APC=9.35*	*NS*

^ The Annual Percent change (APC) is significantly different from zero at alpha=0.05

All trend analysis are based in the percentage of transplanted patients for each aetiology in a calendar year.

Table 2. Trend analyses for aetiology of chronic liver disease among liver transplant recipients in Australia and New Zealand 1994-2017.

Type of analysis	Aetiology					
	HCV	**HBV**	**Alcohol**	**PSC**	**NASH**	**CC**
Non parametric test of trends	*z = 3.27 p<0.001*	*z = -1.39 p= 0.16*	*z= 2.16 p= 0.03*	*z= -2.37 p= 0.01*	*z= 4.38 p<0.001*	*z= -3.69 p<0.001*
Spearman rank correlation	*ρ= 0.68 p<0.001*	*ρ= -0.37 p=0.07*	*ρ=0.44 p=0.02*	*ρ= - 0.49 p=0.01*	*ρ=0.91 p<0.001*	*ρ= - 0.76 p<0.001*
Joint point Regression	*P<0.05 2006-2012 ^APC=4.97*	*NS*	*NS*	*NS*	*P<0.05 2004-2006 ^APC=72.18 P<0.05 2009-2017 ^APC=11.82*	*NS*

^ The Annual Percent change (APC) is significantly different from zero at alpha=0.05

All trend analysis are based in the percentage of transplanted patients for each aetiology in a calendar year.

Table 3. Trend analyses for aetiology of chronic liver disease among patients with hepatocellular carcinoma activated for liver transplant in Australia-New Zealand 2004-2017.

Type of analysis	Aetiology					
	HCV	**HBV**	**Alcohol**	**Cholestatic disease**	**NASH**	**CC**
Non parametric test of trends	*z = 2.90 p=0.00*	*z = -2.59 p= 0.01*	*z= 0.46 p= 0.64*	*z= -1.34 p= 0.18*	*z= 1.53 p=0.12*	*z= -2.15 p=0.03*
Spearman rank correlation	*ρ= 0.80 p>0.001*	*ρ= -0.71 p=0.00*	*ρ=0.12 p=0.66*	*ρ= -0.37 p=0.19*	*ρ=0.42 p=0.13*	*ρ= - 0.59 p=0.02*
Joint point Regression	*NS*	NS	*NS*	*NS*	*NS*	*NS*

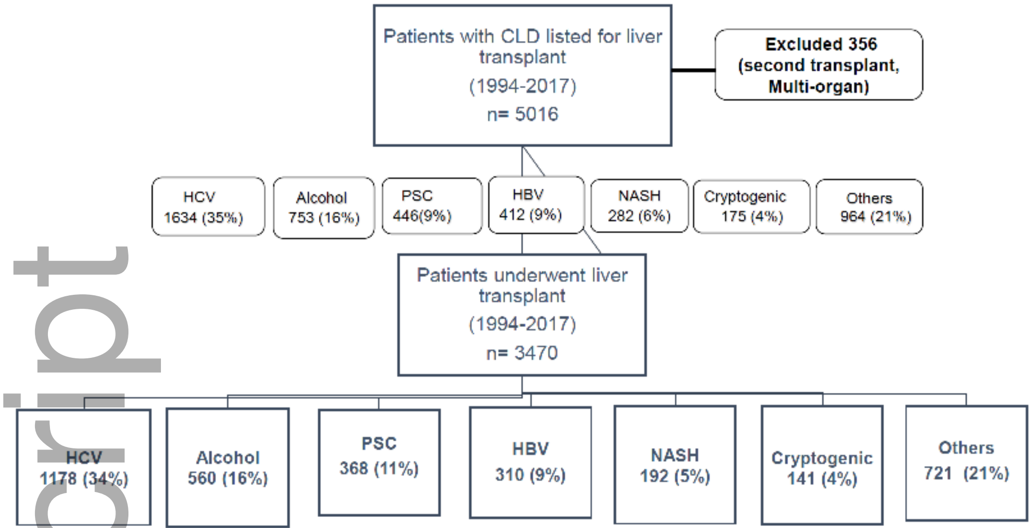
All trend analysis are based in the percentage of activated patients for each aetiology in a calendar year.

Table 4. Trend analyses for aetiology of chronic liver disease among patients with hepatocellular carcinoma who underwent liver transplant Australia-New Zealand 2004-2017

Type of analysis	Aetiology					
	HCV	HBV	Alcohol	Cholestatic disease	NASH	CC
Non parametric test of trends	*z =2.45 p=0.01*	*z = -2.79 p= 0.00*	*z= 1.02 p= 0.30*	*z= -2.15 p= 0.03*	*z =2.03 p=0.04*	*z=-1.82 p=0.06*
Spearman rank correlation	*ρ= 0.68 p<0.001*	*ρ= -0.77 p=0.00*	*ρ= 0.28 p=0.44*	*ρ= -0.59 p=0.02*	*ρ=0.56 p=0.03*	*ρ= -0.50 p=0.06*
Joint point Regression	*P<0.05 2009-2012 ^APC=10.70*	*P<0.05 2009-2012 ^APC=-17.63*	*NS*	*NS*	*P<0.05 2013-2017 ^APC=28.82*	*NS*

^ The Annual Percent change (APC) is significantly different from zero at alpha=0.05

All trend analysis are based in the percentage of transplanted patients for each aetiology in a calendar year.



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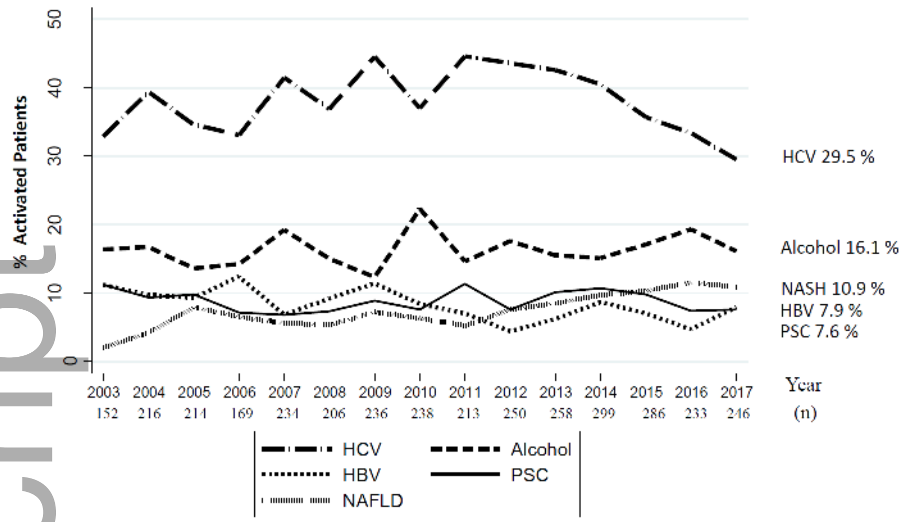

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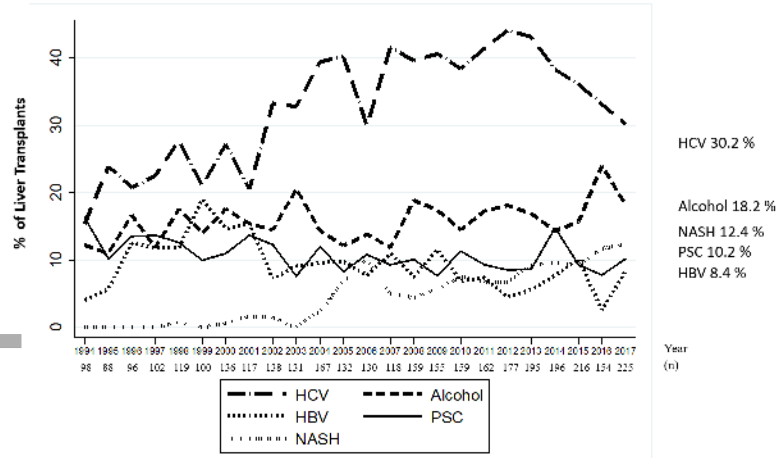

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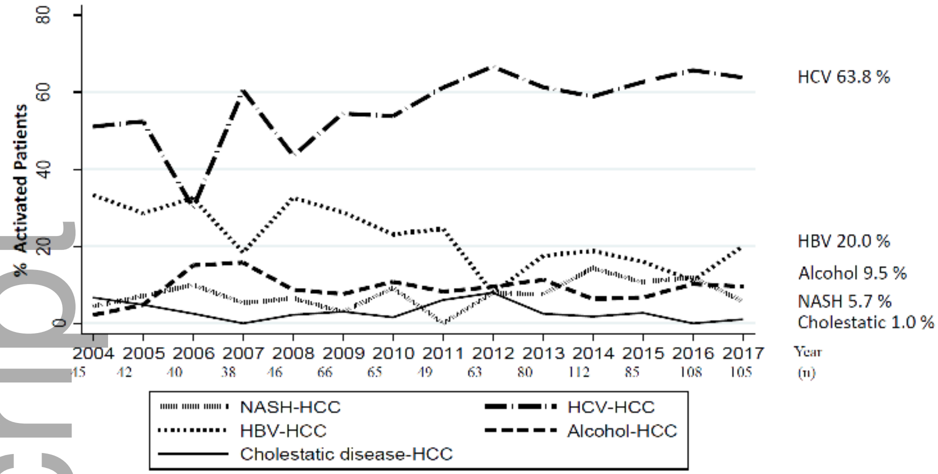

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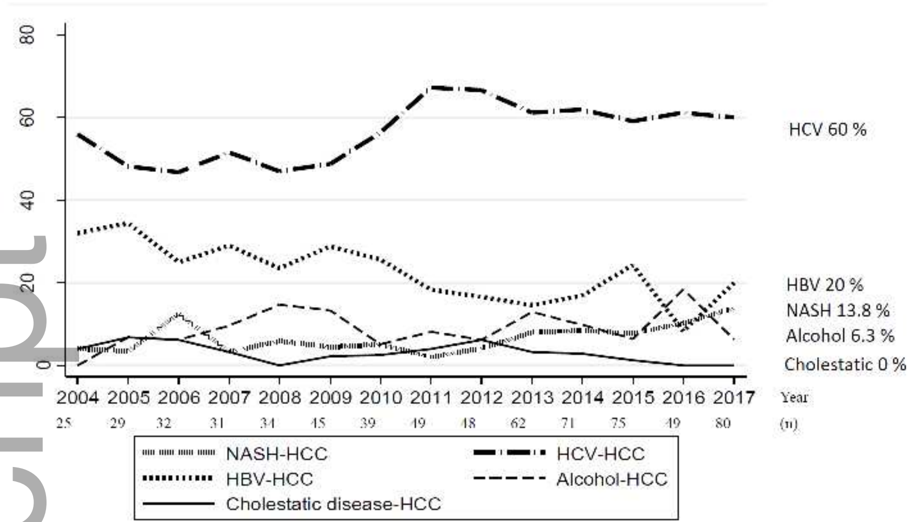

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