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Title:
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Date:
2019-12-01

Citation:
Cosic, L., Ma, R., Churilov, L., Nikfarjam, M., Christophi, C. & Weinberg, L. (2019). Health economic implications of postoperative complications following liver resection surgery: a systematic review. ANZ Journal of Surgery, 89 (12), pp.1561-1566. https://doi.org/10.1111/ans.15213.

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Title The health economic implications of postoperative complications following liver resection surgery: a systematic review

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This is the author manuscript accepted for publication and has undergone full peer review but has not been through the copyediting, typesetting, pagination and proofreading process, which may lead to differences between this version and the Version of Record. Please cite this article as doi: 10.1111/ans.15213

Short Title Costs of liver resection complications

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Systematic review registration number PROSPERO: ID=89178

Funding The authors declare that no funding was obtained for this review. The corresponding author is not a recipient of a research scholarship.

Word count 3808 words total (including abstract, headings, subheadings and in-text citations, and references). Abstract 197 words

Figures and tables Four figures are included. There are three tables and one figure as appendices.

Abstract

Background/Objectives: Limited data exists concerning the health economics of liver resection, with even less information on the costs emerging from complications, despite this remaining an important target from a health economic perspective. Our objective was to describe the financial burden of complications following liver resection.

Methods: We conducted a systematic search and included studies reporting resource use of in-hospital complications during the index liver resection admission. All indications for liver resection were considered. All techniques were considered. Data was collected using a data extraction table and a narrative synthesis was performed.

Results: We identified 12 eligible articles. There was considerable heterogeneity in study designs, patient populations and outcome definitions. We found weak evidence of increased costs associated with major liver resection compared to minor resections. We found robust evidence supporting the increasing economic burden arising from complications after liver resection. Acceptable evidence for increased cost due to the presence and grade of complication was found. Strong evidence concerning the association of length of stay with costs was demonstrated.

Conclusions: The presence and grade of complications increase hospital cost across diverse settings. The costing methodology should be transparent and complication grading systems should be consistent in future studies.

Key words: liver, hepatectomy, postoperative complications, hospital costs, costs and cost analysis

Introduction

Health economic data regarding liver resection remains limited, and there is an absolute dearth of evidence in an Australasian context. Less information exists on the costs emerging from complications occurring as sequelae to liver resection, despite this remaining an important target from a health economic perspective. Meaningful data regarding cost effectiveness of complex interventions, treatments, and techniques is often a necessity to make efficient use of limited resources[1, 2].

An estimated 9.9% of global GDP[3] was utilised on healthcare expenditure in 2014, a figure reflected by the 10% of GDP spent on healthcare in Australia in 2014-15[4]. With over 38% of annual health expenditure in Australia directed towards hospitals over the 2014-15 fiscal periods, hospital expenditure remains the single greatest economic target for reducing healthcare spending. Given the limited costing data regarding surgery for adult liver resection, we performed a review of the existing evidence with respect to costs and complications. Further, we identify the association between complication severity, operative technique (laparoscopic vs. open vs. robotic), length of stay and readmission, and hospital costs. Lastly, we establish an understanding of areas requiring further research and analysis.

Methodology

This review was completed according to the PRISMA statement for systematic reviews[5]. The study protocol can be found online (https://www.crd.york.ac.uk/prospero/display_record.php?RecordID=89178). Eligible studies included randomised controlled trials (RCTs), comparative observational studies, case series and abstracts containing full or partial economic evaluation of complications of liver resection. Additional eligibility criteria included adults (>18 years). All indications for liver resection were considered. Patients undergoing anatomical and non-anatomical segmental resection were included. Major resections were defined as resection of four or more liver segments[6]. Combined liver resection with other surgeries (i.e. cholecystectomy) were also included. All techniques including open, hand-assisted laparoscopy, laparoscopy and robotic were considered. Excluded procedures were liver transplantation, radio-frequency and microwave ablation, and other radiological procedures. Studies including other surgeries that specifically reported complications and costs of liver resection were included.

The primary outcome was in-hospital cost of complications following liver resection surgery. Secondary outcomes considered were costs of liver resection and complications by surgical technique (open vs. laparoscopic) and extent of resection (major vs. minor).

Searches and study selection

MEDLINE Ovid, Embase Ovid, The Cochrane Library and EconLit databases were searched, with articles in all languages being considered. Search terms are listed in *Appendix 1*. Two authors, LC and LW, screened the titles and abstracts to determine eligibility, completing the process independently and in a blinded manner. Studies were retrieved as full text and categorised as either included, excluded, unclear or duplicate. Disputes were referred to a third author (MN) for review. Bibliographies of included articles were screened to identify further studies.

A pre-determined data extraction table was used to collate the relevant data from included studies. The extracted data included characteristics of the study, type of intervention (technique and procedure), complication incidence and severity, total hospital cost per patient, cost year and currency, total hospital costs/charges, measures of uncertainty, length of stay, cost of complication, and 30-day readmission.

Risk of bias and quality assessment

Two authors, LC and LW, independently assessed risk of bias. The Cochrane Collaboration's tool for assessing risk of bias was used for RCTs. Cohort studies were assessed using the SIGN Checklist for Cohort Studies, and similarly Economic Evaluations were assessed using the SIGN Checklist for Economic Studies. Disputes were resolved by two authors, MN and CC. Selective reporting bias was evaluated via comparison of reported results and outcomes of included studies. A funnel plot for formal assessment of publication bias was not included given that homogenous effect size across studies were not available.

Strategy for data synthesis

Findings have been presented as a narrative synthesis with focus on the in-hospital cost of complications, their severity and incidence, and the association of in-hospital costs with differences in technique, extent of resection, and length of stay. A meta-analysis was not able to be undertaken due to the significant heterogeneity of the reported studies. To provide an in-depth narrative synthesis, subgroup analyses were undertaken for complication severity. Additional subgrouping by surgical technique and major/minor resection were also included.

Results

In total, 762 records were identified, 120 of which were duplicates. After initial screening 57 studies were retrieved as full texts. Following reapplication of the eligibility criteria, 45 full-text records were excluded, leaving 12 publications to be included in the final review[9-20]. Details of the search and screening can be found in *Table S1* and *Figure S1*.

All included studies were published in English with publication dates between 2009 and 2017. All but one[7] were full reports. Seven[8-14] were cohort studies, three[15-17] were economic evaluations and one[18] was a RCT. The remaining study[7] was a conference abstract. Only Fretland et al[18] was completed prospectively. Study characteristics along with the extracted outcome measures and results are included in *Table S2* and *Table S3*.

All but two studies reported financial information using United States Dollar (USD). One[7] study used the British Pound (GBP) and one[13] used the Euro. Only five[10, 11, 14, 16, 18] studies reported the year of currency. For the remaining studies, the currency year was taken to be the year of publication, or in the case of the included conference abstract, the year of abstract presentation. For accurate comparison, currencies were converted based on the average currency price against the USD for the currency year[19]. Base currency was then inflated from the currency year to the 26th Feb 2018 using an online inflation calculator.[20]

There was significant variability in the definition of hospital resource utilisation across studies. Hospital cost, a measure of the expenditure for the provision of a service, was used by ten[8-14, 16-18] studies, with two[11, 16] of these studies deriving cost from hospital charges using previously specified cost to charge

ratios. Hospital charge, which represents the value invoiced to payers for provision of service was used by two[12, 15] studies. One[12] study reported using both hospital costs and charges. There was significant variability in the parameters included for hospital cost amongst the studies. Definitions for each study are presented in *Table S2*.

Risk of bias

Individual risk of bias within studies was assessed using the Cochrane Collaboration's tool for assessing risk of bias, alongside the Scottish Intercollegiate Guidelines Network (SIGN) Cohort Study Checklist and SIGN Economic Evaluations Checklist. The majority of studies included were completed retrospectively, and accordingly the quality of evidence is compromised.

The included RCT by Fretland et al[18] was considered to have 'low risk' of bias. Six[8-13] retrospective cohort studies were considered to have an 'acceptable' risk of bias, whilst one[14] was thought to be of 'low quality'. Three[15-17] economic evaluations were deemed to be of 'high quality'. However, as the primary outcome data required for this review were not primary outcomes for the economic evaluations, these studies were also assessed against the SIGN Cohort Study Checklist and found to be of 'acceptable' quality. One included conference abstract[7] was not able to be appropriately assessed for quality given the limited information available.

There is a risk that publication bias may affect this review as grey literature sources were not included. A study protocol[21] for Fretland et al was available[18], and no reporting bias was identified. For the remaining

retrospective studies, protocols were not available. Each study was reviewed by comparison of stated and reported outcomes, and no reporting bias was identified.

Synthesis of results

The complication incidence across all studies was between 7.6%[14] to 73.2%.[15] The wide disparity is attributable to multiple factors, most notably the variability in definitions of complications across studies. Despite variability in complication incidence, increasing costs with the occurrence of complications was a common finding across all studies (*Figure 1)*.

All four[8, 15, 17, 18] studies which graded complications demonstrated that costs increased along with severity of complications. The increase in cost due to major complications varied between $3282[18] and $64,677[8]. The only exception was the group of patients experiencing minor complications following open resection in Vanounou et al[17], who cost $1185 less than those without complications. Hospital costs based on complication severity can be seen in *Figure 2.* Two studies[12, 16] reported increasing costs with increasing number of complications, seen in *Figure 3*, which supported the evidence across all studies of increasing costs with increasing complication incidence, as well as severity.

Three[11, 13, 16] studies reported the costs of mortality in addition to complications, with a consistent finding of greatly increased costs associated with mortality. In high-volume hospitals, Gani et al [11] reported a $30,102 increase in costs due to mortality, compared with patients having complications, and an increase of $70,633 against patients with an uncomplicated course. A similar finding was reported for low and intermediate-volume hospitals. Lock et al[13] found patients dying following liver resection cost $88,379

more than patients who recovered, corresponding to findings by Idrees et al[16] which found an increased cost of $88,337 for mortality compared to those without complications.

Lock et al[13] reported a $89,450 increase in costs as a result postoperative liver failure, which was the most expensive complication across the included studies. Additionally, 87.5% patients with postoperative liver failure died, highlighting the clinical cost of postoperative liver failure.

There was disagreement amongst the three studies reporting financial information by surgical technique, represented in *Figure 4*. Cannon et al[15] reported mixed results, finding the laparoscopic and open techniques were equivocal for all patients aside those experiencing major complications. As only the open resection group experienced major complications, which carried a higher cost, the overall cost was $11,902 less for the laparoscopic group. Vanounou et al[17] supported this finding, reporting the overall cost for the laparoscopic group was $3,198 less than the open group, and additionally laparoscopy without a hand-port was $3,068 cheaper the hand-assisted technique. However, Fretland et al[18] found the overall costs of laparoscopic and open resection to be equivocal.

The cause of the disagreement is likely attributable to the heterogeneity amongst studies. Vanounou et al[17] and Fretland et al[18] included only minor resections, whilst Cannon et al[15] included both major and minor resections.. Additionally, all three studies had varying selection criteria, and study design varied greatly between Fretland et al[18], a RCT, against the two[15, 17] retrospective studies.

Increased length of stay following the occurrence of complications was a consensus finding amongst the six[8, 9, 12-14, 16] studies reporting the outcome. Additionally, Knechtle et al[12] demonstrated that length of stay increased as the number of complications increased. Only Idrees et al[16] described the financial impact associated with length of stay, reporting a mean incremental cost of $8929 (95% CI $3321-14536, p<0.001) for patients exceeding a length of stay beyond eight days.

Fretland et al[18] was the only study to report the cost of readmission and did so in the context of laparoscopic versus open resection, reporting that the two techniques were equivocal ($1886 (4869) vs $2027 (7490) respectively, p = 0.914) in terms of readmission cost (p=0.91). Knechtle et al[12] was the only study to report readmissions in terms of complications: rate of readmission increased from 5% for patients with no complications, to 14.3% for patients with four or more complications.

Both[15, 16] studies comparing the cost between major and minor resection showed an increased cost associated with major liver resection. Only Idrees et al[16] drew a direct comparison, reporting a mean incremental cost of $15,291 (95%CI: $5,272 to $25,310, p<0.001) for hemi-hepatectomy compared to a partial resection. Cannon et al[15] reported an increased cost of $11,709 for the laparoscopic right hepatectomy subgroup, in comparison to the entire cohort, although found that open resection was $1,536 cheaper for the right hepatectomy subgroup. No statistical analysis was included for this comparison. The two[17, 18] studies including only minor resection both had lower total cost than the major resection groups of Idrees et al[16] and Cannon et al[15]. However, given the heterogeneity of different hospital and economic environments, comparison across studies was difficult.

Discussion

We performed a systematic review of the health economic implications of postoperative complications following liver resection surgery. We found robust evidence supporting the increasing economic burden arising from complications after liver resection. Whilst there was considerable heterogeneity in study designs, patient populations, and outcome definitions, we found weak evidence of increased costs associated with major liver resection compared to minor resections, but robust evidence that costs increased with the development of complications; the more severe the complication, the greater the costs. The development of postoperative liver failure was associated with the highest costs. Our review found strong evidence concerning the association of length of stay with costs, a finding supported by others[23].

Large variations in the inclusiveness of hospital cost existed across the studies, with some studies opting to report charges as opposed to hospital cost. This proved problematic for comparison between studies, as charges are a poor substitution for hospital cost, given the considerable variation seen between healthcare systems and even hospitals in the same healthcare system[26]. Further contributing to uncertainties in quantifying the health economic burden of complications was the variability in reporting of mean and median costs, which also can lead to misinterpretation of the collective dataset. To establish a clearer picture of resource use and allow for informed decision making, it is recommended both mean and median be reported[24].

Similarly, we found considerable variability in the reporting of complications, with only a minority of studies recognising the importance of using validated grading systems. Use varying grading systems made quantitative comparison by severity impracticable. Despite these differences, all uniformly reached the conclusion that costs increase with the incidence of complications, and where applicable, with the severity of the complications.

An important issue raised by our review is the lack of high-quality evidence available. Aside from the sole included RCT, the remaining included studies were all retrospective in nature. None of the included retrospective studies included a sensitivity analysis, and many failed to clearly state assumptions. Interestingly, this limitation is not isolated to liver resection, with systematic reviews by Wang et al[25] and Patel et al[23] failing to find RCT's reporting the costs of complications amongst hepatopancreaticobiliary, urology, gynaecology, and thoracic studies. Of note, both of these systematic reviews corroborated the findings of our paper, highlighting the large financial impact of complications, particularly following pancreaticoduodenectomy. Following these findings, we recommend future studies, particularly RCT's, include cost as an additional outcome. The reporting of the cost of complications through scientific journals may also be key to raising hospital performance, in addition to improving how health professionals and consumers access information to support better choices regarding healthcare.

Given that the heterogeneity between studies often precluded direct comparisons between studies and made meta-analysis redundant, it was considered more appropriate to include all studies, thus providing a detailed overview of available evidence as it pertains to health care policy. Given the general absence of high-quality data on the topic, our review stresses the need for further studies to provide accurate and reliable data on complications, including severity, to identify areas where interventions would provide the greatest benefit to both costs and clinical outcomes.

Notably, nearly all of the included studies failed to address readmissions, despite readmissions being a pertinent marker for clinical and economic outcomes. These limitations translate into an underestimation of both the financial and clinical impact of complications. Given that readmissions occur more frequently

amongst patients with increasing severity of complications we recommend future studies assessing financial outcomes include the cost of readmissions as an outcome.

This review has some limitations. The heterogeneity of the included studies precluded direct comparison of many of the outcomes and made quantitative analysis unfeasible. The lack of high-quality data from RCTs subjected our review to the inherent biases of the retrospective nature of most of the studies that were included. Although our search strategy was robust, grey literature was not included - this may have led to publication bias. Lastly, as not all studies reported a currency year, we assumed the currency year to be the year of publication, and this may have impacted the outcomes. However, this variability was accepted as a quantitative synthesis was not undertaken, and any such impact to outcomes was deemed to be minimal.

Conclusion

Postoperative complications following hepatectomy have a major impact on the clinical and economic burden facing health care providers, at both the systemic and individual level. This burden is worsened as the severity of complications increases. Future cost studies addressing postoperative complications should utilise a validated complication grading system as a minimum. Additionally, costs as opposed to charges are the preferred reporting metric, and both mean and median costs should be reported across all studies, allowing for more accurate interpretation of data. Any study reporting costs should include the currency year to improve interpretability of data. Given the large contribution of readmissions to the overall resource use following complications, future studies evaluating the economic burden of postoperative complications should strive to include both readmission incidence and costs within their analysis. To allow effective implementation of strategies to reduce economic burden, future studies assessing the

economic impact of complications require improvements in quality, reliability, and consistency of methodology. Finally, we stress the importance of high-quality surgical care to improve surgical outcomes and thereby reduce the incidence of complications contributing significantly to the increased financial burden on our health institutions.

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Figure legends

Figure 1: Cost of complications for liver resection surgery (data presented as mean unless otherwise stated).

^ cost reported as median, *only assessed major bleeding, # only assessed postoperative liver failure, **no complications group includes Clavien-Dindo grade I/II, complications group includes Clavien-Dindo grade III/IV. To allow for comparison, the charges reported in Cannon et al[15] were multiplied by a hospital specific cost-charge ratio[22] to obtain an estimate of costs.

Figure 2: Costs of complications by severity based on deviation-based cost modelling. (Costs reported by Cannon et al. were multiplied by a hospital specific cost-charge ratio to obtain an estimate cost).

Figure 3: Cost by number of complications

Figure 4: Costs of liver resection by surgical technique. (Costs reported by Cannon et al. were multiplied by a hospital specific cost-charge ratio to obtain an estimate cost).

Supporting information

Table S1 (Appendix 1): Search Strategy

Table S2 (Appendix 2): Study characteristics

Table S3 (Appendix 3): Summary of results calculated on 2018 USD value

Figure S1: PRISMA flow diagram