Elsevier Editorial System(tm) for
International Journal of Surgery
Manuscript Draft

Manuscript Number: IJS-D-17-00935R1

Title: Laparoscopic vs open hepatectomy for hepatocellular carcinoma in patients with cirrhosis: a meta-analysis of the long-term survival outcomes

Article Type: Systematic review and/or Meta-analysis

Keywords: hepatobiliary; hepatocellular carcinoma; cirrhosis, laparoscopic hepatectomy; open hepatectomy

Corresponding Author: Mr. En Lin Goh, B.Sc.

Corresponding Author's Institution: Imperial College London

First Author: En Lin Goh, B.Sc.

Order of Authors: En Lin Goh, B.Sc.; Swathikan Chidambaram, B.Sc.; Shaocheng Ma, Ph.D.

Manuscript Region of Origin: UNITED KINGDOM

Abstract: Background: In patients with hepatocellular carcinoma (HCC) and cirrhosis, laparoscopic hepatectomy (LH) confers short-term benefits over open hepatectomy (OH) but the long-term outcomes of this procedure are unclear. This systematic review aims to compare the long-term survival outcomes of LH and OH for patients with HCC and underlying cirrhosis.

Methods: EMBASE, MEDLINE and Scopus databases were searched from date of inception to 7th October 2016. Controlled clinical studies comparing LH to OH for HCC in cirrhotic patients, which reported long-term overall and disease-free survival were included. The studies were evaluated using the MOOSE guidelines and Newcastle-Ottawa Scale. Data were extracted and analysed using a fixed-effects model.

Results: Five non-randomised, retrospective observational studies representing 888 patients were included. LH was associated with significantly lower tumour recurrence [OR: 0.65, 95% CI: 0.48, 0.89]. LH conferred greater overall survival at 1- [HR: 0.41, 95% CI: 0.25, 0.68], 3- [HR: 0.63, 95% CI: 0.46, 0.87] and 5-years [HR: 0.60, 95% CI: 0.45, 0.80]. With LH, there was higher disease-free survival at 1-year [HR: 0.71, 95% CI: 0.53, 0.96], but not at 3- [HR: 0.89, 95% CI: 0.70, 1.14]; and 5-years [HR: 0.85, 95% CI: 0.70, 1.04].

Conclusions: Laparoscopic surgery is associated with comparable postoperative and survival outcomes in patients with HCC and underlying cirrhosis. With careful selection of patients, this approach is safe, feasible and advantageous.

International Journal of Surgery Author Disclosure Form

The following additional information is required for submission. Please note that failure to respond to these questions/statements will mean your submission will be returned. If you have nothing to declare in any of these categories then this should be stated.

Please state any conflicts of interest

The authors have no conflicts of interest to report.

Please state any sources of funding for your research

The authors have no sources of funding to report.

Please state whether Ethical Approval was given, by whom and the relevant Judgement's reference number

Patients were not involved in the conception, design, analysis, drafting, interpretation or revision of this research. All data used were publicly available.

Research Registration Unique Identifying Number (UIN)

Please enter the name of the registry and the unique identifying number of the study. You can register your research at http://www.researchregistry.com to obtain your UIN if you have not already registered your study. This is mandatory for human studies only.

N/A

Author contribution

Please specify the contribution of each author to the paper, e.g. study design, data collections, data analysis, writing. Others, who have contributed in other ways should be listed as contributors.

ELG was a major contributor in writing the manuscript and revising it critically for important intellectual content. SC was a major contributor in writing the manuscript and revising it critically for important intellectual content. SM supervised the writing of the manuscript and revising it critically for important intellectual content. All authors read and approved the final manuscript.

Guarantor

The Guarantor is the one or more people who accept full responsibility for the work and/or the conduct of the study, had access to the data, and controlled the decision to publish.

ELG, SC and SM had full access to all the data (including statistical reports and tables) in the study and can take responsibility for the integrity of the data and the accuracy of the data analysis.

***Cover Letter**

Imperial College London

Mr En Lin Goh, BSc
Faculty of Medicine
Imperial College London, South Kensington
London, SW7 2AZ
Tel: +44 (0) 7540282657
E-mail: elg12@imperial.ac.uk

13 October 2017

Dear Editor,

Thank you for offering us this opportunity to amend our work. We have carefully amended accordingly. All the changes that we have made are highlighted in yellow on the manuscript. The point to point response to the reviewers' comments is enclosed with this submission.

Kind regards,

En Lin Goh

***Potential Reviewers together with their specialty, institution and e-mail address**

Potential Reviewers

Mr Simon Erridge
Hepatobiliary and General Surgery, Imperial College London
Email: simon.erridge12@imperial.ac.uk

Ms Yan Mei Goh
General Surgery, Milton Keynes University Hospital
Email: yanmei.goh@doctors.org.uk

***Detailed Response to Reviewers (without Author Details)**

Reviewer #1: A one more step in understanding topic and improving clinical outcome
Thank you for your feedback on this.

Reviewer #2: Thank you for submitting your article. We feel it contributes to our growing medical knowledge on the subject and merits publication with minor revisions This article addresses the question of laparoscopic vs open partial hepatectomy for HCC in the background of cirrhosis. While it is applicable to a small patient population, we feel it is worth exploration. The study appears to be appropriately conducted and controlled with two independent reviewers. The sample size within the laparoscopic and open cohorts are disproportionate, however, this is an unfortunate limitation of the study. Again, there limitations inherent to the type of study. Being a retrospective observational study, there are inherent biases that con not be controlled for. Four of the five studies were case matched which helps. Furthermore, all patients were "candidates" for laparoscopic partial hepatectomy, however, it is difficult to remove selection bias in a non-randomized study.
Thank you for your comments regarding the manuscript. We agree that the limitations mentioned are inherent to the type of study and have done our best to ensure that these limitations are discussed.

Appropriate statistical analysis was used. However, unsure why odds ratios were used for tumor recurrence and hazard ratios were used for overall survival and disease survival. Consistency may be beneficial.
This is an excellent point. The reason why odds ratios were used for tumor recurrence and hazard ratios for overall survival and disease-free survival is due to the type of data reported. The data for tumor recurence are presented as incidence rates in all studies, thereby making odds ratio the most appropriate statistical comparison. Meanwhile, the data for overall survival and disease-free survival data were extracted from Kaplan-Meier survival curves over a continuous period of time, making hazard ratios the most appropriate statistical comparison.

May be worth noting and mentioning that the majority of the included studies showed no individual statistical differences in outcome parameters (recurrence, overall survival, and disease free survival). Only when the data is pooled for analysis, does marginal statistical significance emerge.
Thank you for this suggestion. This is a very important point and we have emphasised this on:
Page 9-10 – *"Finally, it is worth noting that most of the studies reported no individual statistical differences between the laparoscopic and open groups in terms of tumour recurrence, overall and disease-free survival. However, a marginal statistical difference does emerge following pooling of data for analysis. Thus, it can be reasonably concluded that the laparoscopic approach is at least as efficacious at the open approach and that further studies are necessary to determine superiority."*

Would caution the authors on avoiding statements that may be misinterpreted to represent broader overarching conclusions. E.g. "laparoscopic surgery is associated with improved postoperative and survival outcomes in patients with HCC and underlying cirrhosis". Bear in mind, this is for a highly selected group of patients, in a non- randomized study, that doesn't show any long term disease free survival.
This is a very good comment. This statement has been amended on:
Page 1 – *"Laparoscopic surgery is associated with comparable postoperative and survival outcomes in patients with HCC and underlying cirrhosis."*

I believe this report is most useful as a non-inferiority study to support the use of laparoscopic partial hepatectomy in a highly selected patient population. Overall, the manuscript is easy to read and flows well. Would recommend careful editing for grammar and typos. E.g. the first part of the results section, under "study characteristics" mentions "seven comparative cohort studies" when I believe only 5 were used.
Thank you for this comment. The appropriate changes have been made and highlighted on:

Page 2 – *"It is estimated that 80% of HCC cases can be attributed to such chronic liver diseases and the incidence of HCC in patients with liver cirrhosis ranges from 0.2% to 8.0%, depending on the aetiology [3, 4]."*
Page 2 – *"In developed countries, HCC is a major cause of mortality in patients with cirrhosis, yet the management of these patients remains problematic despite improvements in treatment modalities available [5, 6]."*
Page 2 – *"In these patients, there is a dysfunction in primary haemostatic mechanisms and an increased prevalence of oesophageal varices due to poor hepatic function and cirrhosis, which can lead to intraoperative haemorrhage and excessive blood loss [11, 12]."*
Page 6 – *"Five comparative cohort studies comprising a total of 888 patients were included in this meta-analysis (Figure 1)."*

Reviewer #3: Dear editor
Thank you for inviting me to analyse the manuscript untitled »laparoscopic vs open hepatectomy for hepatocellular carcinoma in patients with cirrhosis: a meta-analysis of the long-term survival outcomes". This is a hot topic and we need powerful meta-analysis about this subject because nowadays, the laparoscopic approach is very widespread in the world. That is why it is very difficult to design randomized clinical trials because we cannot propose open approach any more for patients with accessible lesion. But I have some comments about this paper.
1. This meta-analysis is statistical weak. There are only 5 retrospective studies.
This is a good point. This is a specific subset of patients undergoing hepatectomy and therefore there are limited studies available. However, this still remains a topic worth exploring and we have acknowledged this in the limitations section on:
Page 9 – *"Firstly, only patients with HCC and cirrhosis were assessed, with data pooled from five retrospective studies so the generalisability of these findings to the wider population of patients with HCC should be treated with caution."*
2. One study (TT Cheung et al 2016) represents more than half of overall population of the meta-analysis and his conclusion are very similar to the meta-analysis conclusion
Thank you for this excellent comment. Due to the population size, there is a greater weightage attached to this study. We have acknowledged this in the limitations section on:
Page 9 – *"Moreover, the authors would like to highlight that the most recent analysis performed by Cheung et al makes up approximately half of the total number of patients, which is worth noting when interpreting the findings."*
3. Two studies published in 2013 and 2016 have the same authors and are from the same department. We can suppose the studies included the same patients.
This is a good point. This highlights the paucity of data available regarding this topic. We have performed sensitivity analysis by excluding the earlier study (2013) to test the robustness of the results, which does not change the findings and conclusions of the study. Furthermore, both analyses do not fit the criteria of duplicate studies and the authors believe that the data and conclusions from both are equally important. For transparency, we have noted this in the limitations section on:
Page 9 – *"Furthermore, there appears to be a degree of overlap between the patients used in both analyses by Cheung et al [25, 27]."*
4. There is no data about the cirrhosis etiology in the series.
Thank you for this comment. We have included the data about cirrhosis aetiology from the included studies (Table 2) and commented on this on:
Page 6 – "*Hepatitis B was the predominant cause of cirrhosis in both analyses by Cheung et al, while Hepatitis C was the main cause of cirrhosis in the studies performed by Belli et al and Memeo at al (Table 2) [23, 25-27]. Truant et al reported alcohol to be the major cause of cirrhosis in their study population [24]."*

5. In the introduction, you explained that operating time is known shorter in laparoscopic approach in the literature. It was the TT Cheung conclusion in his large series published in 2016. But most authors do not agree with this result.

This is a good point. We have removed this statement due to the conflicting evidence. Change is highlighted on: Page 3 – "*Compared to the open approach, laparoscopic techniques have been shown to reduce intraoperative blood loss and the need for blood transfusions whilst enabling wider surgical resection margins [16, 17].*"

Reviewer #5: I would like to compliment the authors of this manuscript with a very eloquently written and well exercised meta-analysis on an important issue. Besides the methodology, especially the discussion deserves a compliment since there all the limitations of their findings are discussed. It would therefore be advisable to bring some of the limitations of the findings (like how was cirrhosis was diagnosed in most studies, the non-randomisation, the observational character of the studies used for this meta-analysis) back in the final conclusion.

This is a very good suggestion. We have linked the limitations to the Conclusion section on:

Page 10 – *"Future research on the generalisability and applicability of laparoscopic resection in this subgroup of patients with HCC and underlying cirrhosis will be necessary to overcome the inherent limitations of the currently available evidence."*

Highlights

- Long-term survival outcomes of laparoscopic compared to open hepatectomy in patients with hepatocellular carcinoma and underlying cirrhosis is unclear.
- In this meta-analysis of five retrospective studies, laparoscopic hepatectomy was associated with significantly greater overall survival at one, three and five years compared to open hepatectomy.
- Laparoscopic hepatectomy is safe, feasible and advantageous in the treatment of well-differentiated hepatocellular carcinoma in patients with cirrhosis.

Laparoscopic vs open hepatectomy for hepatocellular carcinoma in patients with cirrhosis: a meta-analysis of the long-term survival outcomes

En Lin Goh, BSc,[1], Swathikan Chidambaram, BSc,[1], Shaocheng Ma, PhD,[1,2]

[1]Faculty of Medicine, Imperial College London, South Kensington, London, SW7 2AZ, United Kingdom

[2]Department of Surgery and Cancer, Faculty of Medicine, Imperial College London, London, W6 8PR, United Kingdom

Correspondence:

Mr En Lin Goh, BSc

Imperial College London

South Kensington, London, SW7 2AZ, United Kingdom

Phone: +44 (0) 7540282657

Fax: N/A

E-mail: elg12@imperial.ac.uk

Sources of funding: No funding was received for this work.

Submission category: Review (meta-analysis)

There have been no previous publications or presentations of this work.

Abstract word count: 222 words

Manuscript word count: 2517 words

Abstract

Background: In patients with hepatocellular carcinoma (HCC) and cirrhosis, laparoscopic hepatectomy (LH) confers short-term benefits over open hepatectomy (OH) but the long-term outcomes of this procedure are unclear. This systematic review aims to compare the long-term survival outcomes of LH and OH for patients with HCC and underlying cirrhosis.

Methods: EMBASE, MEDLINE and Scopus databases were searched from date of inception to 7th October 2016. Controlled clinical studies comparing LH to OH for HCC in cirrhotic patients, which reported long-term overall and disease-free survival were included. The studies were evaluated using the MOOSE guidelines and Newcastle-Ottawa Scale. Data were extracted and analysed using a fixed-effects model.

Results: Five non-randomised, retrospective observational studies representing 888 patients were included. LH was associated with significantly lower tumour recurrence [OR: 0.65, 95% CI: 0.48, 0.89]. LH conferred greater overall survival at 1- [HR: 0.41, 95% CI: 0.25, 0.68], 3- [HR: 0.63, 95% CI: 0.46, 0.87] and 5-years [HR: 0.60, 95% CI: 0.45, 0.80]. With LH, there was higher disease-free survival at 1-year [HR: 0.71, 95% CI: 0.53, 0.96], but not at 3- [HR: 0.89, 95% CI: 0.70, 1.14]; and 5-years [HR: 0.85, 95% CI: 0.70, 1.04].

Conclusions: Laparoscopic surgery is associated with comparable postoperative and survival outcomes in patients with HCC and underlying cirrhosis. With careful selection of patients, this approach is safe, feasible and advantageous.

Introduction

Hepatocellular carcinoma (HCC) is the most common primary cancer of the liver, and is documented as the fifth and eighth most prevalent cancer worldwide in males and females respectively [1]. In recent years, there has been a rise in the incidence of HCC, which corresponds to the increase in the number of cases of liver cirrhosis associated with hepatitis B and C [2]. It is estimated that 80% of HCC cases can be attributed to such chronic liver diseases and the incidence of HCC in patients with liver cirrhosis ranges from 0.2% to 8.0%, depending on the aetiology [3, 4]. In developed countries, HCC is a major cause of mortality in patients with cirrhosis, yet the management of these patients remains problematic despite improvements in treatment modalities available [5, 6]. Liver transplantation is proven to be curative, but the inherent limitations of this approach, such as donor availability and patient age have restricted its application [7]. An alternative to transplantation is hepatectomy, which is now widely accepted as a potentially curative treatment for these subgroup of patients [8].

However, liver resection in patients with HCC and underlying cirrhosis is associated with numerous complications [9, 10]. In these patients, there is a dysfunction in primary haemostatic mechanisms and an increased prevalence of oesophageal varices due to poor hepatic function and cirrhosis, which can lead to intraoperative haemorrhage and excessive blood loss [11, 12]. Moreover, these patients are highly susceptible to developing postoperative complications such as pleural effusion, lung infection, portal vein thrombosis, ascites, renal failure and transient encephalopathy [13, 14]. Thus, these factors have led surgeons to develop rigorous selection criteria in stratifying patients with HCC in combination with background cirrhosis for surgery. It is evident that the severity of cirrhosis has a significant influence on outcomes following hepatic resection, as patients with cirrhosis classified as Childs-Pugh A demonstrate a mortality rate of 10% whilst those with cirrhosis classified as Childs-Pugh C have a mortality rate of 63% [15].

Whilst OH remains the mainstay of liver resection in patients with HCC, the role of laparoscopy in the management of HCC has evolved from diagnostic staging to curative hepatectomy over the past few decades. This technique is now widely accepted to be a safe and feasible option for both benign and malignant tumours of the liver. Compared to the open approach, laparoscopic techniques have been shown to reduce intraoperative blood loss and the need for blood transfusions whilst enabling wider surgical resection margins [16, 17]. Furthermore, patients undergoing laparoscopic resection experience fewer postoperative complications and therefore, lower morbidity, leading to shorter hospital stays compared to those undergoing open resection [18]. Although the short-term benefits of laparoscopic hepatectomy (LH) in patients with HCC are well-established, there is yet to be a consensus regarding the long-term benefits of this procedure. Additionally, it is unclear how applicable these findings are to the more complex subgroup of patients suffering from liver cirrhosis [19]. It is hypothesised that laparoscopic resection would confer improved long-term outcomes over open resection. This systematic review and meta-analysis aims to elucidate and compare the long-term outcomes between LH and open hepatectomy (OH) for patients with HCC and underlying cirrhosis.

Methods

Literature search methods, inclusion and exclusion criteria, outcome measures and statistical analysis were defined according to the Meta-analysis of Observational Studies in Epidemiology (MOOSE) recommendations [20]. Patients were not involved in the conception, design, analysis, drafting, interpretation or revision of this research. Thus, ethics approval was not required.

Electronic search

The following databases were searched: a) MEDLINE (1946 till October week 1 2016) via OvidSP, last search on 7th October 2016; b) MEDLINE in-process and other non-indexed citations (latest issue) via OvidSP, last search on 7th October 2016; c) Ovid EMBASE (1974

to latest issue), last search 7th October 2016; d) Scopus (1996 till present), last search on 7th October 2016. Search terms used four strings, which were then linked by an AND modifier. The first string included: laparoscopy OR laparoscopic OR minimally invasive; the second string: liver resection OR hepatectomy; the third string: hepatocellular OR liver; and the fourth string: carcinoma OR cancer OR malignancy OR neoplasm. Truncated search terms utilising the wildcard character and the "related articles" function were used to broaden the search. Additionally, the references of included articles were hand-searched to identify any additional studies.

Study selection

All controlled clinical studies in which the laparoscopic approach for HCC was compared with open surgery in terms of postoperative and long-term outcomes of overall and disease-free survival were selected. In addition, all of the studies included in the meta-analysis met the following criteria: a) tumours were solitary, restricted to the left lateral lobe or the peripheral subcapsular right segments of the liver, accompanied by no documented non-hepatic disseminated disease in preoperative imaging and no major vascular invasion; and disease was treatable by limited resection (three or fewer segments); b) patients had no contraindication for the laparoscopic approach, did not require any other additional procedures, and had no history of upper major laparotomy, or of cardiac or respiratory impairments; c) reporting of at least postoperative outcomes, long-term overall survival and disease-free survival assessed as outcome measures of the effect of the treatment; d) article was published or accepted for publication as full-length articles, and at least 20 patients were included. No restrictions were made on language. Non-human studies, experimental trials, review articles, editorials, case reports, letters, conference abstracts and unpublished studies were excluded.

Outcome measures

Outcomes assessed were: long-term oncological parameters (tumour recurrence; 1-, 3-, and 5-year overall survival; and 1-, 3- and 5-year disease-free survival). Other additional outcomes reported were also reviewed.

Data extraction and quality assessment

Two independent reviewers (E.L.G and S.C.) screened all the titles and abstracts for inclusion, both of whom were blinded to authors, journals, institutional affiliations and dates of publication. Both reviewers evaluated each selected reference independently and summarised relevant study characteristics. In case of disagreement, a consensual decision between the two reviewers under involvement of a third independent reviewer (S.M.) was reached. The following data items were extracted: the year of publication, study design, sample size, country of study, type of patients, patient characteristics, outcome measures, and conclusions. Data were entered into Review Manager 5.3 (Cochrane Collaboration, Oxford, United Kingdom). The quality of observational studies was appraised for rigorousness using the Newcastle-Ottawa quality assessment tool.

Data synthesis and analysis

The reported odds ratio (OR) with 95% confidence interval (CI) was used in the analysis. The hazard ratio (HR) was used as a summary statistic for long-term outcomes (survival analysis) as described by Parmar et al [21]. A HR of less than one represented a survival benefit favouring the LH group. Medians were converted to means using the formula described by Hozo et al [22]. The fixed-effects model was used to pool the results. Authors of the original publications were contacted in the event of insufficient data, but this was not the case in this analysis. The standard heterogeneity test, the I^2 statistic, was used to assess the consistency of the effect sizes, which indicates the percentage of the variability in effect estimates because of true between-study variance rather than within-study variance. In all

cases, statistical heterogeneity was assessed by using I^2 statistic and was categorised as low, moderate and high for an I^2 statistic of above 25%, 50% and 75%, respectively. Results above 60% were considered as substantial heterogeneity.

Results

Study characteristics

Five comparative cohort studies comprising a total of 888 patients were included in this meta-analysis (Figure 1). There were 276 patients in the laparoscopic group and 612 patients in the open group [23-27]. No significant differences were present in patient demographics between both groups. All studies were single centre retrospective cohort studies, and four studies were case-matched in terms of demographic data, tumour characteristics, operative data, and/or postoperative outcomes. The total number of patients in each study ranged from 28 to 330. Following a diagnosis of HCC, patients underwent hepatectomy according to their clinical features, serum α-fetoprotein levels, liver function, results of transabdominal ultrasonography, and results of liver imaging, which included preoperative triple-phase multi-slice computed tomography and/or magnetic resonance imaging. Patients were confirmed to have HCC by postoperative pathological examination of samples. In the laparoscopic group, 97.8% of patients were classified as Childs-Pugh Class A. Meanwhile, 97.7% of patients in the open group were classified as Childs-Pugh Class A. The remaining patients in both groups were classified as Class B. The overall conversion rate was 8.3% (Table 1). Hepatitis B was the predominant cause of cirrhosis in both analyses by Cheung et al, while Hepatitis C was the main cause of cirrhosis in the studies performed by Belli et al and Memeo at al (Table 2) [23, 25-27]. Truant et al reported alcohol to be the major cause of cirrhosis in their study population [24].

Quality of included studies

The non-randomised studies were evaluated for sources of bias using a modified Newcastle-Ottawa Scale (Table 3). Four studies achieved a score of 7/8 while one study scored 8/8.

The four studies scoring 7/8 attained maximum points for the ‘‘selection’’ and “comparability” category, but lost a point under the “outcome” category, specifically for lack of adequate follow-up and missing data, both of which potentiate possible bias. Using a funnel plot, the risk of publication bias was examined (Figure 2). No asymmetry of the plot was noted. In all studies, resectability was defined as the absence of extrahepatic disease on radiographic imaging, anatomically suitable disease and no portal vein thrombosis. No limit on tumour size was present in the studies and although Belli et al limited laparoscopic surgery to lesions less than 5 cm, this was extended to lesions greater than 5 cm in the final year of their study [23]. Belli et al, Cheung et al and Memeo et al limited their cohort to patients with Childs-Pugh Class A and Class B cirrhosis while Truant et al and Cheung et al limited their cohort solely to patients with Childs-Pugh Class A cirrhosis [23-27].

Long-term outcomes

Pooled analysis of the four studies reporting data on tumour recurrence displayed a lower incidence of tumour recurrence in the laparoscopic cohort compared to the open cohort (Figure 3). There was a statistically significant reduction in the risk of recurrence following laparoscopic resection of the tumour with an OR of 0.65 (95% CI: 0.48 to 0.89) and zero heterogeneity in the data obtained from the studies (I^2=0%, P=0.48).

Overall survival between the laparoscopic and open cohorts were compared at 1-, 3- and 5-years using the HR (Figure 4). Pooled analysis showed significantly improved overall survival in the laparoscopic group compared to the open group at 1-, 3- and 5-years. The HRs were as follows: 1-year, HR of 0.41 (95%CI: 0.25 to 0.68); 3-years, HR of 0.63 (95%CI: 0.46 to 0.87); and 5-years, HR of 0.60 (95%CI: 0.45 to 0.80). No heterogeneity was present in the data at all three time-points (I^2=0%, P=0.98).

Pooled analysis of the disease-free survival rates favoured LH over OH at 1-year (Figure 5). Disease-free survival following both procedures were comparable at 3- and 5-years although

there was a trend towards improved survival in the laparoscopic cohort. The HRs were as follows: 1-year, HR of 0.71 (95%CI: 0.53 to 0.96); 3-years, HR of 0.89 (95%CI: 0.70 to 1.14); and 5-years, HR of 0.85 (95%CI: 0.70 to 1.04). Overall, the data exhibited moderate heterogeneity at all three time-points (I^2=52%, P=0.01).

Discussion

The present review provides a summary and meta-analysis of the differences in long-term oncological outcomes of the laparoscopic approach compared to the open approach for patients undergoing hepatectomy for HCC with a background of cirrhosis. The analysis concludes significantly improved long-term outcomes in favour of the laparoscopic technique over the open technique. Patients undergoing laparoscopic resection had a lower risk of tumour recurrence and improved long-term overall and disease-free survival. These findings build on the previous meta-analysis, which was limited to intraoperative and postoperative measures, both of which are markers of short-term outcomes [19].

This review also suggests that the laparoscopic approach may confer oncological advantages over the open approach, given that patients in this cohort were at a significantly lower risk of tumour recurrence. This can be attributed to the higher rates of negative surgical margins (R_0 resection) achieved with laparoscopic resection [19]. Shi et al reported that a resection margin of 2 cm compared to the conventional 1 cm in patients undergoing liver resection for HCC correlated with improved long-term outcomes [28]. Laparoscopic surgery allows for magnification of affected tissue in high-definition, which can aid surgeons in the identification and assessment of the tumour and consequently, resection of a wider tumour-free margin. Furthermore, incorporating laparoscopic ultrasound into routine practice for liver resection may improve resection yield further [2, 29].

Previous meta-analyses have demonstrated comparable outcomes in terms of overall and disease-free survival between the laparoscopic and open techniques [19, 30]. The present

analysis demonstrates improved long-term overall survival in the laparoscopic cohort, at 1-, 3- and 5-years. Meanwhile, disease-free survival in the laparoscopic group was higher at 1-year but comparable at 3- and 5-years. These findings are likely to be due to the markedly lower amount of blood loss as well as the higher negative surgical margin rates, which lower the risk of tumour recurrence as noted earlier [31-33]. The haematogenous spread of malignant cells during surgical resection has been reported in pancreatic, colorectal and prostate cancer [34-36]. Furthermore, venous permeation and vascular penetration by malignant processes occur frequently in HCC, which may result in the pre-operative dissemination of these cells as well [37, 38]. The increased manipulation and mobilisation of the tumour that occurs in OH may promote the spread of these malignant cells into the systemic and intrahepatic portal venous system [39-42]. Thus, it is apparent that laparoscopic procedures are best suited for well-differentiated tumours with a survival benefit in patients with stage-II HCC compared to stage-I HCC [2, 25, 27, 43].

Limitations

There are several limitations that must be considered when interpreting the findings of this analysis. Firstly, only patients with HCC and cirrhosis were assessed, with data pooled from five retrospective studies so the generalisability of these findings to the wider population of patients with HCC should be treated with caution. Furthermore, there appears to be a degree of overlap between the patients used in both analyses by Cheung et al [25, 27]. There are also several inherent methodological limitations to the studies, which render them liable to selection bias; specifically, the non-randomised nature and small proportion of patients who are eligible for laparoscopic resection. However, the authors of these studies have attempted to address and minimise the effect of these factors with case-matching and propensity analysis. It must be emphasised that the diagnosis of cirrhosis in the patient population was made clinically and radiologically. As such, a small proportion of the diagnoses were refuted on postoperative histological examination. This is evident in both analyses by Cheung et al where the proportion of histologically confirmed cirrhosis cases were 82.3% and 74.5%

respectively [25, 27]. Only Memeo et al included patients with histologically-confirmed cirrhosis and this discrepancy highlights the difficulty and reality of retrospective trials [26]. No histological data were reported by Belli et al and Truant et al [23, 24]. Moreover, the authors would like to highlight that the most recent analysis performed by Cheung et al makes up approximately half of the total number of patients, which is worth noting when interpreting the findings [27]. Finally, it is worth noting that most of the studies reported no individual statistical differences between the laparoscopic and open groups in terms of tumour recurrence, overall and disease-free survival. However, a marginal statistical difference does emerge following pooling of data for analysis. Thus, it can be reasonably concluded that the laparoscopic approach is at least as efficacious at the open approach and that further studies are necessary to determine superiority.

Conclusion

The present meta-analysis concludes significantly improved long-term outcomes including tumour recurrence, 1-, 3- and 5-year overall survival and 1-year disease-free survival following LH for patients with HCC and underlying cirrhosis. These findings suggest that the laparoscopic approach as safe and efficacious as the open approach with careful selection of patients. A rigorous assessment of the suitability of patients for LH therefore allows the optimisation of long-term outcomes. Future research on the generalisability and applicability of laparoscopic resection in this subgroup of patients with HCC and underlying cirrhosis will be necessary to overcome the inherent limitations of the currently available evidence.

Acknowledgements

None.

Declarations

None.

References

[1] F.X. Bosch, J. Ribes, M. Díaz, R. Cléries, Primary liver cancer: Worldwide incidence and trends, Gastroenterology 127(5) S5-S16.

[2] D. Cherqui, A. Laurent, C. Tayar, S. Chang, J.T. Van Nhieu, J. Loriau, M. Karoui, C. Duvoux, D. Dhumeaux, P.-L. Fagniez, Laparoscopic liver resection for peripheral hepatocellular carcinoma in patients with chronic liver disease: midterm results and perspectives, Annals of Surgery 243(4) (2006) 499-506.

[3] J.M. Llovet, A. Burroughs, J. Bruix, Hepatocellular carcinoma, The Lancet 362(9399) 1907-1917.

[4] J. Bruix, M. Sherman, J.M. Llovet, M. Beaugrand, R. Lencioni, A.K. Burroughs, E. Christensen, L. Pagliaro, M. Colombo, J. Rodés, Clinical management of hepatocellular carcinoma. Conclusions of the Barcelona-2000 EASL conference, Journal of Hepatology 35(3) (2001) 421-430.

[5] G. Fattovich, T. Stroffolini, I. Zagni, F. Donato, Hepatocellular carcinoma in cirrhosis: incidence and risk factors, Gastroenterology 127(5) (2004) S35-S50.

[6] A. Sangiovanni, E. Del Ninno, P. Fasani, C. De Fazio, G. Ronchi, R. Romeo, A. Morabito, R. De Franchis, M. Colombo, Increased survival of cirrhotic patients with a hepatocellular carcinoma detected during surveillance, Gastroenterology 126(4) (2004) 1005-1014.

[7] F.Y. Yao, N.M. Bass, B. Nikolai, T.J. Davern, R. Kerlan, V. Wu, N.L. Ascher, J.P. Roberts, Liver transplantation for hepatocellular carcinoma: analysis of survival according to the intention-to-treat principle and dropout from the waiting list, Liver Transplantation 8(10) (2002) 873-883.

[8] P. Mathurin, B. Raynard, S. Dharancy, S. Kirzin, D. Fallik, F.R. Pruvot, D. Roumilhac, V. Canva, J.C. Paris, J.C. Chaput, Meta-analysis: evaluation of adjuvant therapy after curative

liver resection for hepatocellular carcinoma, Alimentary Pharmacology & Therapeutics 17(10) (2003) 1247-1261.

[9] H.H. Thompson, R.K. Tompkins, W.P. Longmire Jr, Major hepatic resection. A 25-year experience, Annals of Surgery 197(4) (1983) 375.

[10] G. Tanabe, M. Sakamoto, K. Akazawa, K. Kurita, M. Hamanoue, S. Ueno, Y. Kobayashi, S. Mitue, Y. Ogura, N. Yoshidome, Intraoperative risk factors associated with hepatic resection, British Journal of Surgery 82(9) (1995) 1262-1265.

[11] F. Violi, R. Leo, E. Vezza, S. Basili, C. Cordova, F. Balsano, C. Group, Bleeding time in patients with cirrhosis: relation with degree of liver failure and clotting abnormalities, Journal of Hepatology 20(4) (1994) 531-536.

[12] G. Garcia-Tsao, A.J. Sanyal, N.D. Grace, W. Carey, Prevention and management of gastroesophageal varices and variceal hemorrhage in cirrhosis, Hepatology 46(3) (2007) 922-938.

[13] O. Farges, B. Malassagne, J.F. Flejou, S. Balzan, A. Sauvanet, J. Belghiti, Risk of major liver resection in patients with underlying chronic liver disease: a reappraisal, Annals of Surgery 229(2) (1999) 210.

[14] A. Kanazawa, T. Tsukamoto, S. Shimizu, S. Kodai, S. Yamazoe, S. Yamamoto, S. Kubo, Impact of laparoscopic liver resection for hepatocellular carcinoma with F4-liver cirrhosis, Surgical Endoscopy 27(7) (2013) 2592-7.

[15] H. Neeff, D. Mariaskin, H.-C. Spangenberg, U.T. Hopt, F. Makowiec, Perioperative mortality after non-hepatic general surgery in patients with liver cirrhosis: an analysis of 138 operations in the 2000s using Child and MELD scores, Journal of Gastrointestinal Surgery 15(1) (2011) 1-11.

[16] L. Aldrighetti, E. Guzzetti, C. Pulitanò, F. Cipriani, M. Catena, M. Paganelli, G. Ferla, Case-matched analysis of totally laparoscopic versus open liver resection for HCC: Short and middle term results, Journal of Surgical Oncology 102(1) (2010) 82-86.

[17] C. Ker, J. Chen, K. Kuo, S. Chuang, S. Wang, W. Chang, K. Lee, H. Chen, C. Juan, Liver surgery for hepatocellular carcinoma: laparoscopic versus open approach, International Journal of Hepatology 2011 (2011).

[18] M. Shimada, M. Hashizume, S. Maehara, E. Tsujita, T. Rikimaru, Y. Yamashita, S. Tanaka, E. Adachi, K. Sugimachi, Laparoscopic hepatectomy for hepatocellular carcinoma, Surgical Endoscopy 15(6) (2001) 541-544.

[19] A. Twaij, P.H. Pucher, M.H. Sodergren, T. Gall, A. Darzi, L.R. Jiao, Laparoscopic vs open approach to resection of hepatocellular carcinoma in patients with known cirrhosis: systematic review and meta-analysis, World Journal of Gastroenterology 20(25) (2014) 8274-8281.

[20] D.F. Stroup, J.A. Berlin, S.C. Morton, I. Olkin, G.D. Williamson, D. Rennie, D. Moher, B.J. Becker, T.A. Sipe, S.B. Thacker, Meta-analysis of observational studies in epidemiology: a proposal for reporting, JAMA 283(15) (2000) 2008-2012.

[21] M.K. Parmar, V. Torri, L. Stewart, Extracting summary statistics to perform meta-analyses of the published literature for survival endpoints, Statistics in Medicine 17(24) (1998) 2815-2834.

[22] S.P. Hozo, B. Djulbegovic, I. Hozo, Estimating the mean and variance from the median, range, and the size of a sample, BMC Medical Research Methodology 5(1) (2005) 1.

[23] G. Belli, P. Limongelli, C. Fantini, A. D'Agostino, L. Cioffi, A. Belli, G. Russo, Laparoscopic and open treatment of hepatocellular carcinoma in patients with cirrhosis, British Journal of Surgery 96(9) (2009) 1041-8.

[24] S. Truant, A.F. Bouras, M. Hebbar, E. Boleslawski, G. Fromont, S. Dharancy, E. Leteurtre, P. Zerbib, F.R. Pruvot, Laparoscopic resection vs. open liver resection for peripheral hepatocellular carcinoma in patients with chronic liver disease: a case-matched study, Surgical Endoscopy 25(11) (2011) 3668-77.

[25] T.T. Cheung, R.T. Poon, W.K. Yuen, K.S. Chok, C.R. Jenkins, S.C. Chan, S.T. Fan, C.M. Lo, Long-term survival analysis of pure laparoscopic versus open hepatectomy for

hepatocellular carcinoma in patients with cirrhosis: a single-center experience, Annals of Surgery 257(3) (2013) 506-11.

[26] R. Memeo, N. de'Angelis, P. Compagnon, C. Salloum, D. Cherqui, A. Laurent, D. Azoulay, Laparoscopic vs. open liver resection for hepatocellular carcinoma of cirrhotic liver: a case-control study, World Journal of Surgery 38(11) (2014) 2919-26.

[27] T.T. Cheung, W.C. Dai, S.H. Tsang, A.C. Chan, K.S. Chok, S.C. Chan, C.M. Lo, Pure Laparoscopic Hepatectomy Versus Open Hepatectomy for Hepatocellular Carcinoma in 110 Patients With Liver Cirrhosis: A Propensity Analysis at a Single Center, Annals of Surgery 264(4) (2016) 612-20.

[28] M. Shi, R.-P. Guo, X.-J. Lin, Y.-Q. Zhang, M.-S. Chen, C.-Q. Zhang, W.Y. Lau, J.-Q. Li, Partial hepatectomy with wide versus narrow resection margin for solitary hepatocellular carcinoma: a prospective randomized trial, Annals of Surgery 245(1) (2007) 36-43.

[29] M. Kleemann, P. Hildebrand, M. Birth, H.P. Bruch, Laparoscopic ultrasound navigation in liver surgery: technical aspects and accuracy, Surgical Endoscopy And Other Interventional Techniques 20(5) (2006) 726-729.

[30] Z. Yin, X. Fan, H. Ye, D. Yin, J. Wang, Short-and long-term outcomes after laparoscopic and open hepatectomy for hepatocellular carcinoma: a global systematic review and meta-analysis, Annals of Surgical Oncology 20(4) (2013) 1203-1215.

[31] K.R. Stephenson, S.M. Steinberg, K.S. Hughes, J.T. Vetto, P.H. Sugarbaker, A.E. Chang, Perioperative blood transfusions are associated with decreased time to recurrence and decreased survival after resection of colorectal liver metastases, Annals of Surgery 208(6) (1988) 679.

[32] D.A. Kooby, J. Stockman, L. Ben-Porat, M. Gonen, W.R. Jarnagin, R.P. Dematteo, S. Tuorto, D. Wuest, L.H. Blumgart, Y. Fong, Influence of transfusions on perioperative and long-term outcome in patients following hepatic resection for colorectal metastases, Annals of Surgery 237(6) (2003) 860.

[33] R.T.-P. Poon, S.-T. Fan, I.O.-L. Ng, J. Wong, Significance of resection margin in hepatectomy for hepatocellular carcinoma: a critical reappraisal, Annals of Surgery 231(4) (2000) 544-551.

[34] F. Miyazono, S. Takao, S. Natsugoe, K. Uchikura, F. Kijima, K. Aridome, H. Shinchi, T. Aikou, Molecular detection of circulating cancer cells during surgery in patients with biliary-pancreatic cancer, The American Journal of Surgery 177(6) (1999) 475-479.

[35] J. Weitz, P. Kienle, J. Lacroix, F. Willeke, A. Benner, T. Lehnert, C. Herfarth, M. von Knebel Doeberitz, Dissemination of tumor cells in patients undergoing surgery for colorectal cancer, Clinical Cancer Research 4(2) (1998) 343-348.

[36] M.G. Oefelein, K. Kaul, B. Herz, M.D. Blum, J.M. Holland, T.C. Keeler, W.A. Cook, J.M. Ignatoff, Molecular detection of prostate epithelial cells from the surgical field and peripheral circulation during radical prostatectomy, The Journal of Urology 155(1) (1996) 238-242.

[37] I.O. Ng, E. Lai, S.T. Fan, M.M. Ng, Tumor encapsulation in hepatocellular carcinoma. A pathologic study of 189 cases, Cancer 70(1) (1992) 45-49.

[38] J.-N. Vauthey, D. Klimstra, D. Franceschi, Y. Tao, J. Fortner, L. Blumgart, M. Brennan, Factors affecting long-term outcome after hepatic resection for hepatocellular carcinoma, The American Journal of Surgery 169(1) (1995) 28-35.

[39] N. Hayashi, H. Egami, M. Kai, Y. Kurusu, S. Takano, M. Ogawa, No-touch isolation technique reduces intraoperative shedding of tumor cells into the portal vein during resection of colorectal cancer, Surgery 125(4) (1999) 369-374.

[40] J. Koo, K. Fung, K. Siu, N. Lee, Z. Lett, J. Ho, J. Wong, G. Ong, Recovery of malignant tumor cells from the right atrium during hepatic resection for hepatocellular carcinoma, Cancer 52(10) (1983) 1952-1956.

[41] M. Louha, J. Nicolet, H. Zylberberg, A. Sabile, C. Vons, G. Vona, K. Poussin, M. Tournebize, F. Capron, S. Pol, Liver resection and needle liver biopsy cause hematogenous dissemination of liver cells, Hepatology 29(3) (1999) 879-882.

[42] T. Matsumata, T. Kanematsu, K. Takenaka, K. Sugimachi, Lack of intrahepatic recurrence of hepatocellular carcinoma by temporary portal venous embolization with starch microspheres, Surgery 105(2 Pt 1) (1989) 188-191.

[43] C. Kawamoto, K. Ido, N. Isoda, M. Hozumi, N. Nagamine, K. Ono, Y. Sato, Y. Kobayashi, G. Nagae, K. Sugano, Long-term outcomes for patients with solitary hepatocellular carcinoma treated by laparoscopic microwave coagulation, Cancer 103(5) (2005) 985-993.

Tables

Study	Study Type	Number of patients		Age		Sex ratio (M:F)		Childs-Pugh A:B ratio		Conversion to open (%)
		LH	OH	LH	OH	LH	OH	LH	OH	
Belli et al. (2009)	Retrospective	54	125	63.30 ± 6.10	61.50 ± 7.80	31:23	78:47	49:5	117:8	4 (7.4)
Truant et al. (2011)	Retrospective matched	36	53	60.60 ± 10.20	63.30 ± 7.60	31:5	47:6	36:0	53:0	7 (19.4)
Cheung et al. (2013)	Retrospective matched	32	64	59.25 ± 11.55	58.25 ± 15.38	22:10	50:14	32:0	62:4	6 (18.8)
Memeo et al. (2014)	Retrospective matched	45	45	58.25 ± 12.03	60.75 ± 10.72	35:10	37:8	44:1	43:2	0 (0.0)
Cheung et al. (2016)	Retrospective matched	110	330	59.00 ± 15.02	59.00 ± 18.51	80:30	258:72	110:0	330:0	6 (5.5)

Table 1. Characteristics of included studies

Study	Aetiology (%)							
	Hepatitis B		Hepatitis C		Alcohol		Haemochromatosis	
	LH	OH	LH	OH	LH	OH	LH	OH
Belli et al. (2009)	3.7	12.8	92.6	81.6	–	–	–	–
Truant et al. (2011)	8.3	7.6	11.1	11.3	63.9	60.4	11.1	15.1
Cheung et al. (2013)	81.3	76.6	6.3	10.9	–	–	–	–
Memeo et al. (2014)	35.6	28.9	40.0	37.8	24.4	33.3	–	–
Cheung et al. (2016)	80.0	86.4	6.4	7.0	–	–	–	–

Table 2. Cirrhosis aetiology in included studies

Study	Selection				Comparability	Outcome			Score
	Representativeness of exposed cohort	Selection of non-exposed cohort	Exposure	Outcome of interest not present at start	Comparability of laparoscopic vs open	Assessment of outcome	Follow-up	Adequacy of follow-up/missing data	
Belli et al. (2009)	Truly representative	Same	Surgical records	Yes	Restricted in exophytic or subscapular tumours, no matching	Record linkage	3 years	Unclear	7
Truant et al. (2011)	Truly representative	Same	Surgical records	Yes	Restricted to subcapsular tumours located in the anterior or lateral segments II-VI, matched	Record linkage	5 years	Unclear	7
Cheung et al. (2013)	Truly representative	Same	Surgical records	Yes	No restrictions, matched	Record linkage	5 years	Complete	8
Memeo et al. (2014)	Truly representative	Same	Surgical records	Yes	No restrictions, matched	Record linkage	10 years	Complete	8
Cheung et al. (2016)	Truly representative	Same	Surgical records	Yes	No restrictions, matched	Record linkage	5 years	Unclear	7

Table 3. Newcastle-Ottawa Scale for included studies

Figures

Figure 1. Flow diagram illustrating screening and selection process

Figure 2. Funnel plot for publication bias

Figure 3. Tumour recurrence

Figure 4. A. 1-year overall survival B. 3-year overall survival C. 5-year overall survival

Figure 5. A. 1-year disease-free survival B. 3-year disease free survival C. 5-year disease-free survival

Figure 1

Click here to download high resolution image

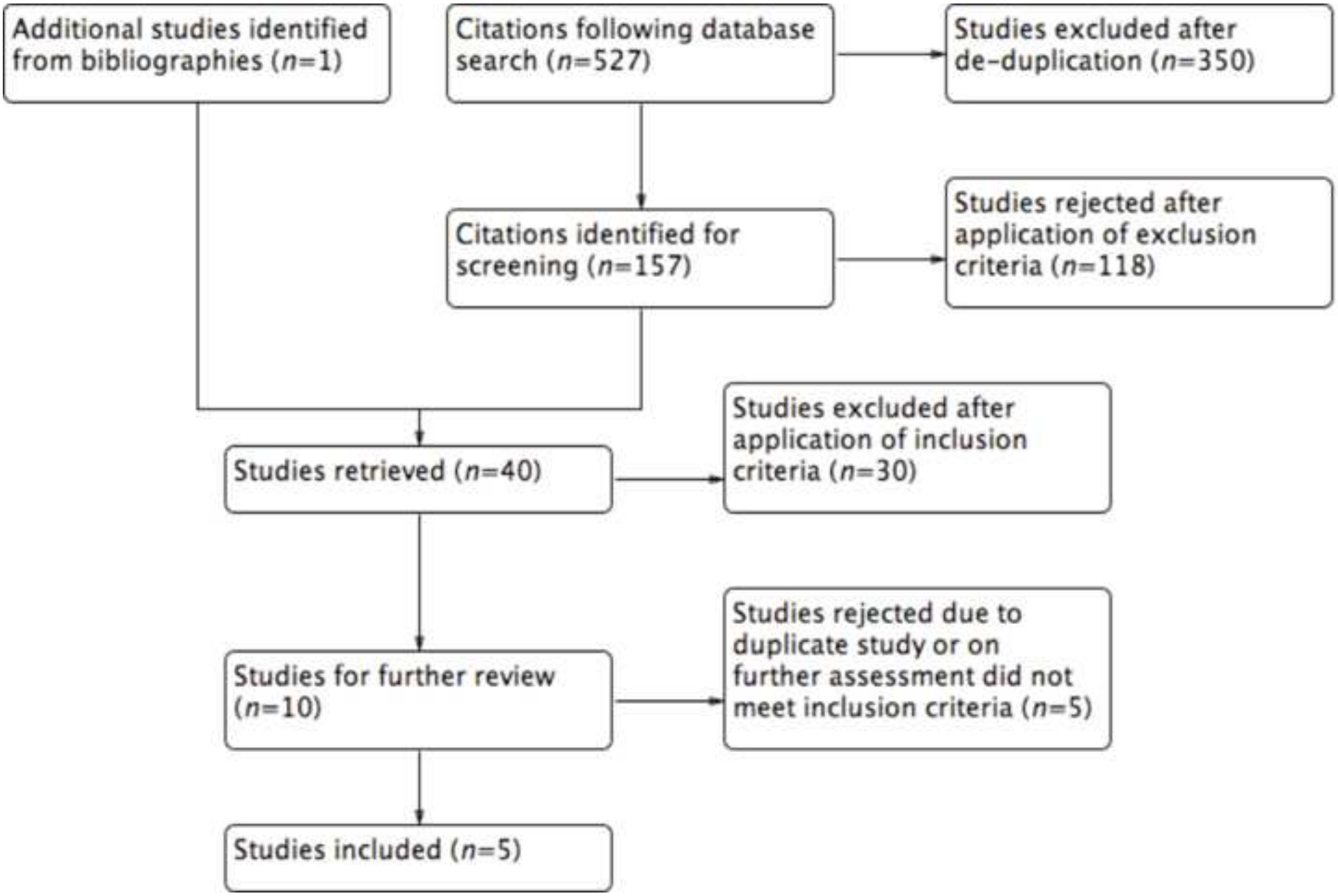


Figure 2

Click here to download high resolution image

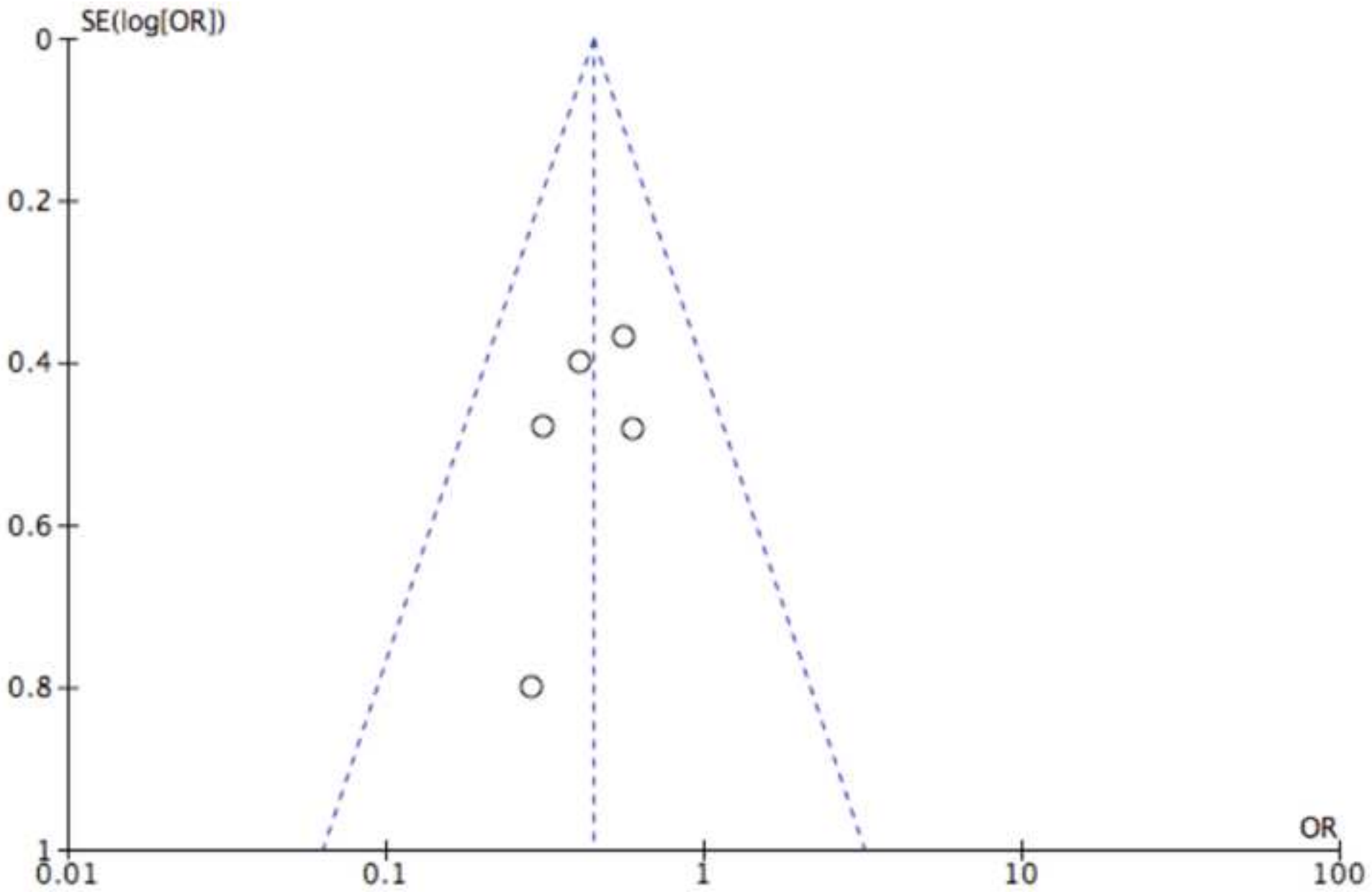


Figure 3

Click here to download high resolution image

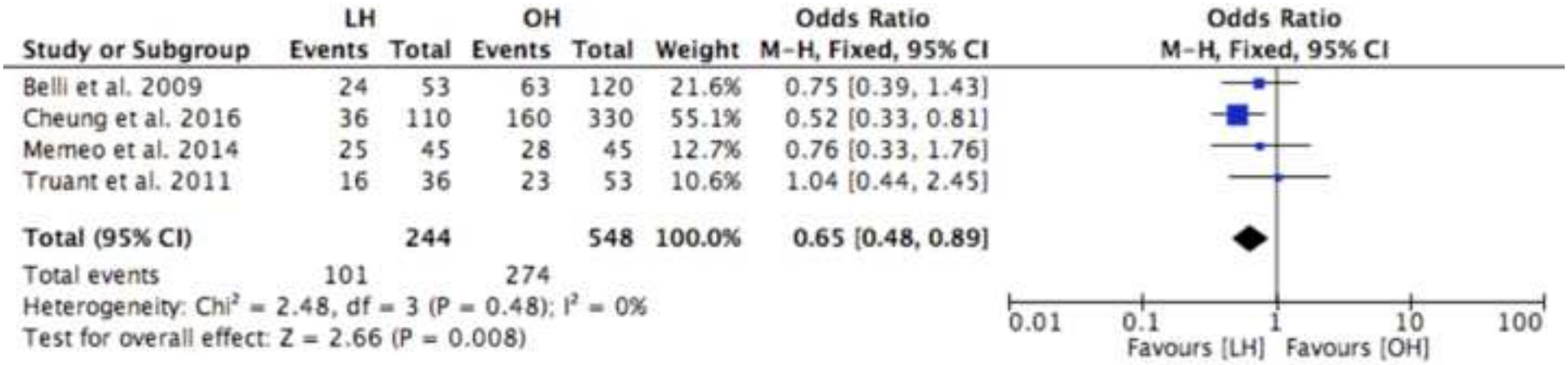


Figure 4

Click here to download high resolution image

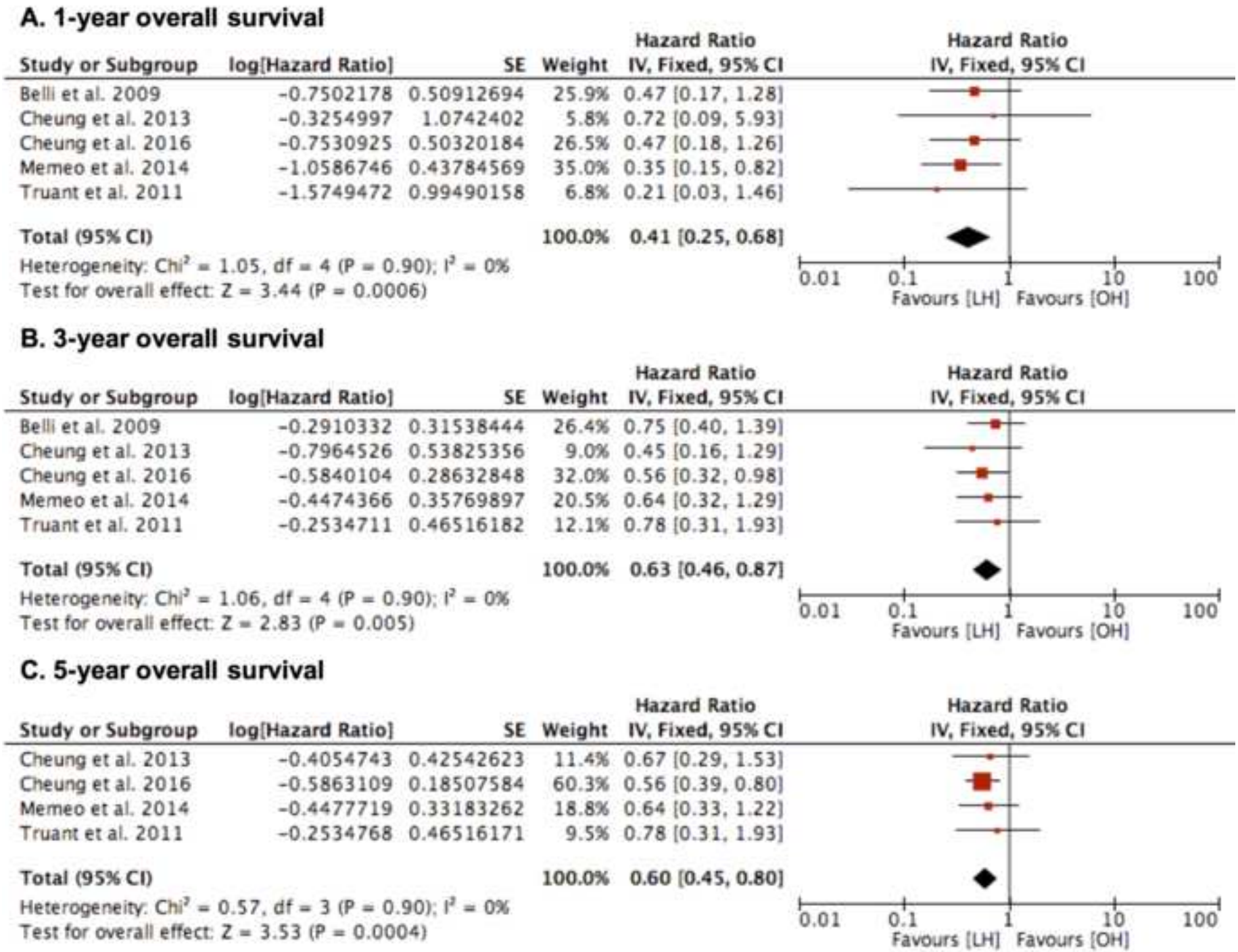
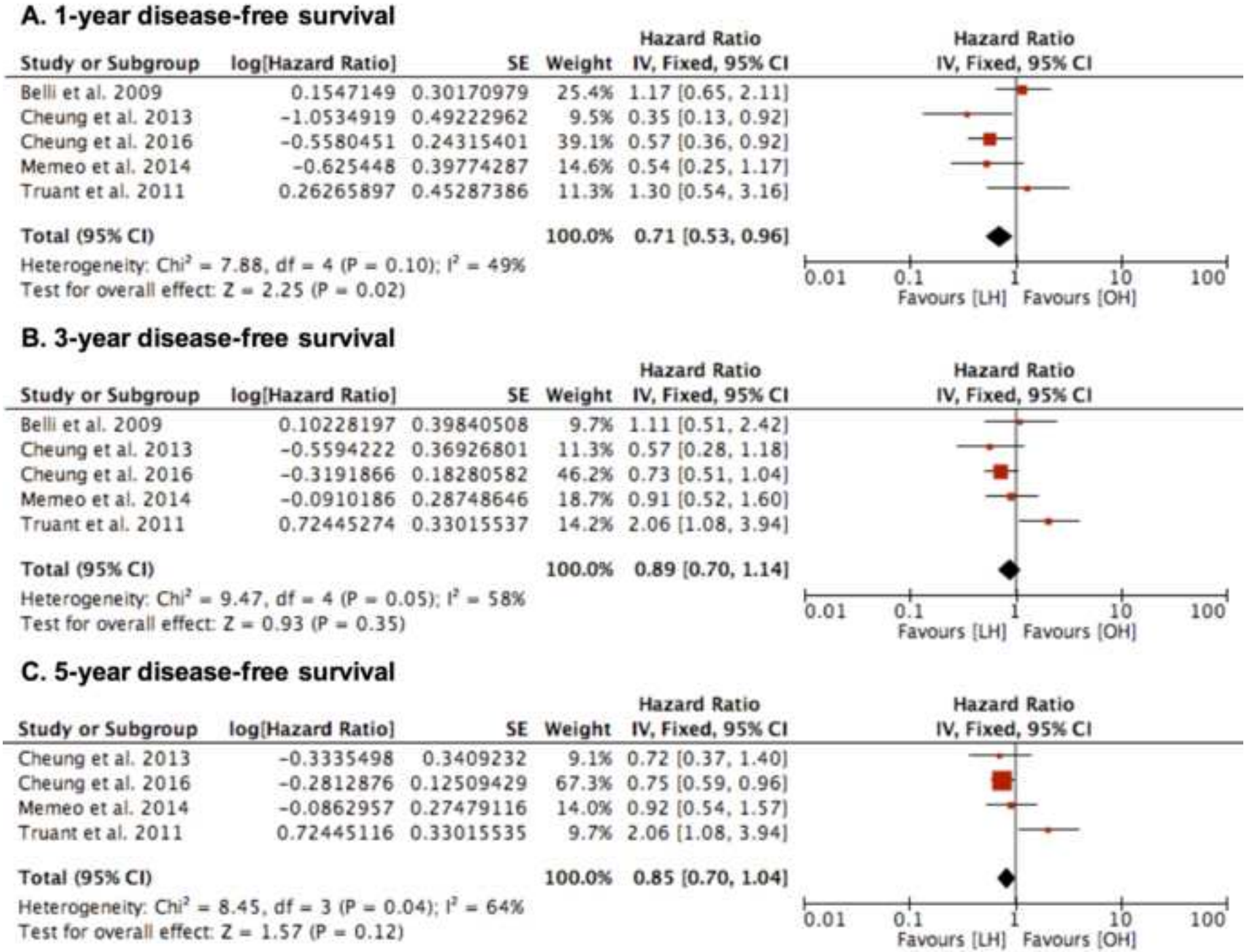


Figure 5

Click here to download high resolution image



PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	Title Page
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	1
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	2-4
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	4-6
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	5
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	4-5
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	4-5
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	3-5
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	4-5
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	4-5
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	4-5
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	5-6
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	5-6
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	5-6

PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	5-6
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	3-5
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	6
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	15
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	6-7
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	7
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	7
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	Figure 2
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	7
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	8-9
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	9
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	10
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	Title Page

From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(7): e1000097. doi:10.1371/journal.pmed1000097

For more information, visit: **www.prisma-statement.org**.