GLOBAL HEART

# The Effect of Liver Cirrhosis on Patients Undergoing Cardiac Surgery

ORIGINAL RESEARCH

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## ABSTRACT

The aim of this study was to investigate the impact of liver cirrhosis (LC) on postoperative complications and long-term outcomes in patients who underwent cardiac surgery. Three databases, including PubMed, Embase, and the Cochrane Library, were searched on July 24, 2022. A total of 1,535,129 patients were enrolled in the seven included studies for analysis. According to our analysis, LC was a risk factor for postoperative overall complications (OR = 1.48, 95% CI = 1.21 to 1.81, $I^2$ = 90.35%, P = 0.00 < 0.1). For various complications, more patients developed pulmonary (OR = 1.86, 95% CI = 1.21 to 2.87, $I^2$ = 90.79%, P = 0.00 < 0.1), gastrointestinal (OR = 2.03, 95% CI = 1.32 to 3.11, $I^2$ = 0.00%, P = 0.00 < 0.05), renal (OR = 2.20, 95% CI = 1.41 to 3.45, $I^2$ = 91.60%, P = 0.00 < 0.1), neurological (OR = 1.14, 95% CI = 1.03 to 1.26, $I^2$ = 7.35%, P = 0.01 < 0.05), and infectious (OR = 2.02, 95% CI = 1.17 to 3.50, $I^2$ = 92.37%, P = 0.01 < 0.1) complications after surgery in the LC group. As for cardiovascular (OR = 1.07, 95% CI = 0.85 to 1.35, $I^2$ = 75.23%, P = 0.58 > 0.1) complications, there was no statistical significance between the 2 groups. As for long-term outcomes, we found that in-hospital death (OR = 2.53, 95% CI = 1.86 to 3.20, $I^2$ = 44.58%, P = 0.00 < 0.05) and death (OR = 3.31, 95% CI = 1.54 to 5.07, $I^2$ = 93.81%, P = 0.00 < 0.1) in the LC group were higher than the non-LC group. LC was a risk factor for cardiac surgery. Patients with LC who would undergo cardiac surgery should be fully assessed for the risks of cardiac surgery. Similarly, the surgeon should assess the patient's liver function before surgery.

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## BACKGROUND

Liver cirrhosis (LC) is a common disease that kills about 1.03 million people each year [1–2]. Patients with LC often suffered from nutritional damage, immune system dysfunction, coagulation disorders, acute kidney injury, etc. [3–5]. These issues cause surgeons to be hesitant to operate on patients with LC. Surgery on patients with LC remains a challenge for surgeons and anaesthetists. This challenge depends on the type of liver disease and its severity, the surgical procedure, and the type of anaesthesia [6–7].

As for cardiothoracic surgery, especially cardiac surgery requiring cardiopulmonary bypass, LC remains a tricky problem [8–10]. Liver disease remains a major risk factor in the perioperative period of cardiac surgery [11]. Cardiac disease could be a fatal condition. Surgery was an excellent treatment. As for LC patients, the surgeon should assess the patient's liver function before surgery. The underlying physiological conditions caused by LC make these patients vulnerable to coagulation dysfunction and major organ dysfunction after direct cardiac surgery with extracorporeal circulation [12].

Figuring out the impact and mechanism of LC on cardiac surgery could help surgeons find preventive measures. However, according to our review of previous studies, the effects of LC on the postoperative outcomes of cardiac surgery continued to be controversial. Some studies suggest a poor effect of LC on postoperative outcomes in cardiac surgery [13–17]. Other studies demonstrated that there was no association between LC and postoperative cardiac surgery outcomes [18–19]. Therefore, this pooling-up analysis aimed to investigate the impact of LC on postoperative complications and long-term outcomes in patients who underwent cardiac surgery.

## METHODS

Our meta-analysis was produced in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement [20]. Three databases were searched, including PubMed, Embase, and the Cochrane Library, on July 24, 2022. The key words of the search strategy were LC and cardiac surgery. The search strategy for LC was as follows: "liver cirrhosis" OR "cirrhosis" OR "cirrhotic", and as for cardiac surgery, we searched "cardiac surgery" OR "cardiac operation" OR "heart surgery" OR "heart operation" OR "thoracic surgery" OR "cardiac surgical procedures" OR "cardiopulmonary bypass" OR "CPB" OR "congenital heart disease". Then, the two search strategies were combined by "AND". The search was limited to titles and abstracts, and the language was limited to English.

The inclusion criteria for eligible studies were as follows: 1) all patients were diagnosed with cardiac disease and underwent cardiac surgery; 2) both the LC group and the non-LC group were reported; 3) at least 1 of the following complications (cardiovascular, pulmonary, gastrointestinal, renal, neurological, infectious) was reported; and 4) as for long-term outcomes, in-hospital death or death should be reported. The exclusion criteria were as follows: 1) case reports, case series, comments, letters to the editor, conference abstracts, and nonoriginal articles; 2) data was repeated or overlapped; and 3) incomplete information. Two authors searched the databases and identified eligible studies separately. First, duplicate studies were excluded. Then, the two authors scanned the titles and abstracts to find eligible studies. Finally, the full text would be read to identify studies that could be included. Any disagreements were settled by a third author.

Patients were divided into the LC group and the non-LC group according to whether they were diagnosed with LC. The cardiac surgery types included coronary artery bypass graft, surgery with cardiopulmonary bypass, cardiac surgery, and aortic valve replacement. The complication was defined as a cardiovascular, pulmonary, gastrointestinal, renal, neurological, or infectious disease that occurred after surgery. Overall complication was the sum of all complications reported in the included studies that were not directly reported. In-hospital death was defined as a patient's cause of death when they died in the hospital after surgery. Death was defined as a patient's cause of death after they left the hospital.

The information included characteristics of the studies, baseline information on patients, medical history, postoperative complications, and long-term outcomes. The characteristics of

the studies were as follows: the first author, published year, published country, study date, sample size of the LC group and the non-LC group, and Newcastle-Ottawa Scale (NOS) score. The baseline information for patients included age, gender, and race. For medical history, hypertension, diabetes, chronic obstructive pulmonary disease (COPD), heart failure, prior myocardial infarction (MI), and malignancy were collected. For complications, cardiovascular, pulmonary, gastrointestinal, renal, neurological, and infectious diseases were collected. As for long-term outcomes, in-hospital death and death were collected.

In-hospital death was defined as a death that occurred during hospitalization, regardless of cause. Death was defined as a death that occurred after discharge from the hospital due to cardiac failure or liver cirrhosis. If the cause of death during this period was unknown, it was also considered related.

The NOS was used to assess the quality of the included studies [21]. High-quality studies would be scored at nine points. Median quality had scores ranging from 7 to 8 points. Low-quality studies were indicated by a score of less than 7 points.

The mean difference (MD) and 95% confidence interval (CI) were calculated for age. The odds ratio (OR) and 95% CI were calculated for gender, medical history, complications, and long-term outcomes. $I^2$ values were used to assess the statistical heterogeneity of the included studies [22–23]. When $I^2 > 50\%$, which was considered to be high heterogeneity, the random effects model was used, and $P < 0.1$ was considered statistically significant. Otherwise, the fixed effects model would be used, and $p < 0.05$ meant statistically significant. We performed data analysis with Stata V16.0 software.

## RESULTS

A total of 1,158 studies were searched from the three databases (353 studies in PubMed, 778 studies in Embase, and 27 studies in the Cochrane Library). 359 duplicate studies were eliminated. After the remaining 799 studies were viewed for titles and abstracts, 21 studies were left for full-text screening. Then, there were 13 studies left for qualitative synthesis. Finally, seven eligible studies were included in this analysis [13–19]. (Figure 1)

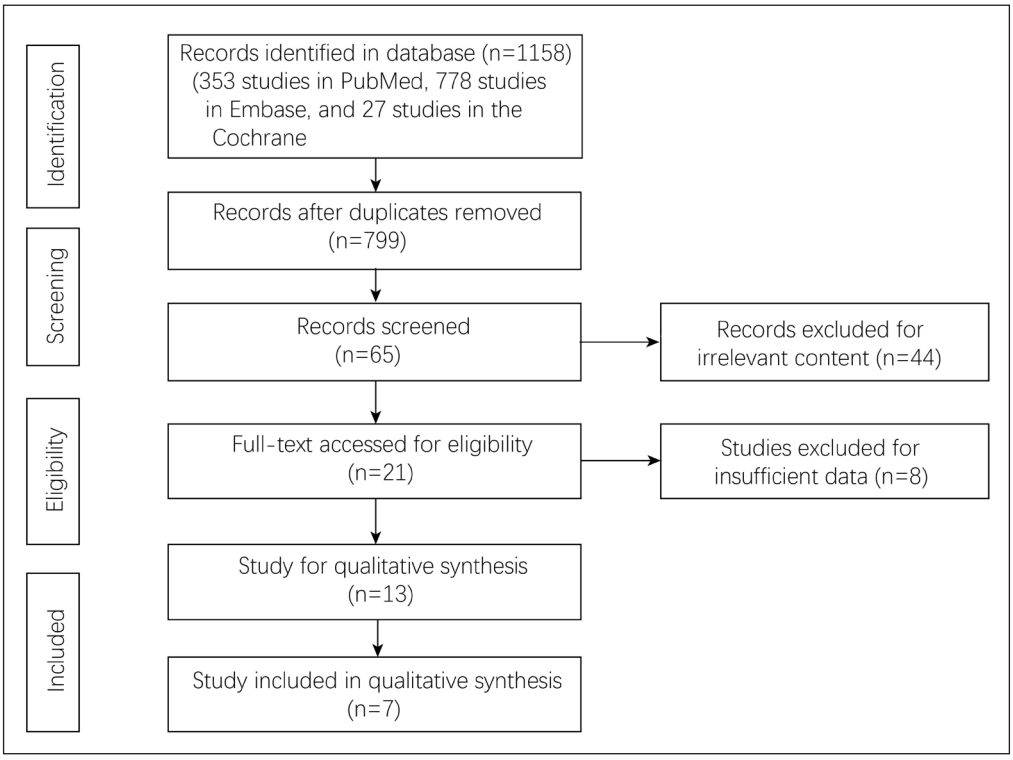


**Figure 1** Flowchart of study selection.

A total of 1,535,129 patients were included in this analysis using the seven included studies. All patients were divided into the LC group and the non-LC group (8,370 in the LC group and 1,526,759 in the non-LC group). The studies were published from 2009 to 2019. The study

period was from 1984 to 2014. More information (authors, published countries, surgery type, sample size, and NOS score) is shown in Table 1.

**Table 1** Characteristics of the studies included in the meta-analysis.

Abbreviations: LC, liver cirrhosis; CABG, coronary artery bypass graft; AVR, aortic valve replacement; NOS, Newcastle-Ottawa Scale.

| AUTHOR | YEAR | COUNTRY | STUDY DATE | SURGERY TYPE | SAMPLE SIZE | | FOLLOW-UP (MONTHS) | NOS |
|---|---|---|---|---|---|---|---|---|
| | | | | | LC | NON-LC | | |
| Shaheen AAM | 2009 | Canada | 1998–2004 | CABG | 711 | 402383 | 156 | 9 |
| MACARON C | 2012 | Florida | 1992–2009 | surgery with cardiopulmonary bypass | 54 | 216 | 3 | 7 |
| Ruiz-Morales J | 2015 | Spain | 1984–2008 | cardiac surgery | 308 | 2828 | 360 | 8 |
| Steffen RJ | 2017 | USA | 1998–2011 | AVR | 2769 | 421020 | 156 | 9 |
| Chou AH | 2017 | China | 1997–2011 | CABG | 1040 | 1040 | 32 | 8 |
| Singh V | 2018 | USA | 1998–2004 | CABG | 2231 | 696568 | 156 | 9 |
| Xavier S | 2019 | Canada | 2004–2014 | cardiac surgery | 60 | 310 | 120 | 8 |

After pooling up all the baseline information (including age, gender, and race), the outcomes showed a statistical difference in race (OR = 0.57, 95% CI = 0.50 to 0.65, $I^2$ = 69.69%, P = 0.00 < 0.1) between the 2 groups. However, there were no statistical differences in age (MD = –8.47, 95% CI = –22.71 to 5.78, $I^2$ = 100.00%, P = 0.24 > 0.1) or gender (OR = 1.10, 95% CI = 0.94 to 1.28, $I^2$ = 64.11%, P = 0.25 > 0.1) (Table 2).

**Table 2** Summary of characteristics between LC group and Non-LC group.

Abbreviations: LC, liver cirrhosis; COPD, chronic obstructive pulmonary disease; MI, myocardial infarction; CI, confidence interval; RE, random-effects; FE, fixed-effects.

| CHARACTERISTICS | STUDIES | PARTICIPANTS (LC/ NON-LC) | MEAN DIFFERENCE/ ODDS RATIO (95% CI) | MODEL | HETEROGENEITY |
|---|---|---|---|---|---|
| Baseline information | | | | | |
| Age, year | 4 | 4580/ 824753 | –8.47 [–22.71, 5.78]; P = 0.24 | RE | $I^2$ = 100.00%; P = 0.00 |
| Gender, male | 6 | 4404/ 1103345 | 1.10 [0.94, 1.28]; P = 0.25 | RE | $I^2$ = 64.11%; P = 0.02 |
| Race, white | 4 | 5765/ 1520187 | 0.57 [0.50, 0.65]; P = 0.00 | RE | $I^2$ = 69.69%; P = 0.02 |
| Medical history | | | | | |
| Hypertension | 4 | 6100/ 1118938 | 0.70 [0.47, 1.06]; P = 0.09 | RE | $I^2$ = 93.46%; P = 0.00 |
| Diabetes | 4 | 6100/ 1118938 | 1.37 [1.09, 1.71]; P = 0.01 | RE | $I^2$ = 90.59%; P = 0.00 |
| COPD | 3 | 6040/ 1118628 | 1.44 [1.22, 1.70]; P = 0.00 | RE | $I^2$ = 82.67%; P = 0.00 |
| Heart failure | 3 | 3869/ 422370 | 1.61 [0.63, 4.13]; P = 0.32 | RE | $I^2$ = 97.59%; P = 0.00 |
| Prior MI | 2 | 1100/ 1350 | 0.94 [0.75, 1.18]; P = 0.60 | FE | $I^2$ = 0.00%; P = 0.50 |
| Malignancy | 3 | 6040/ 1118628 | 1.22 [0.78, 1.91]; P = 0.37 | RE | $I^2$ = 88.47%; P = 0.00 |

The medical history included hypertension, diabetes, COPD, heart failure, prior MI, and malignancy. After pooling up the data, there were a higher proportion of diabetes (OR = 1.37, 95% CI = 1.09 to 1.71, $I^2$ = 90.59%, P = 0.01 < 0.1), COPD (OR = 1.44, 95% CI = 1.22 to 1.70, $I^2$ = 82.67%, P = 0.00 < 0.1) and a lower proportion of hypertension (OR = 0.70, 95% CI = 0.47 to 1.06, $I^2$ = 93.46%, P = 0.09 < 0.1) in the LC group. As for other medical history, heart failure (OR = 1.61, 95% CI = 0.63 to 4.13, $I^2$ = 97.59%, P = 0.32 > 0.1), prior MI (OR = 0.94, 95% CI = 0.75 to 1.18, $I^2$ = 0.00%, P = 0.60 > 0.05) and malignancy (OR = 1.22, 95% CI = 0.78 to 1.91, $I^2$ = 88.47%, P = 0.37 > 0.1) had no statistical differences between the two groups. (Table 2)

The complications included cardiovascular, pulmonary, gastrointestinal, renal, neurological, and infectious diseases. According to our analysis, LC was a risk factor for postoperative overall complications (OR = 1.48, 95% CI = 1.21 to 1.81, $I^2$ = 90.35%, P = 0.00 < 0.1). (Figure 2) Figure 3 shows the publication bias of the studies included. For various complications, more patients developed pulmonary (OR = 1.86, 95% CI = 1.21 to 2.87, $I^2$ = 90.79%, P = 0.00 < 0.1), gastrointestinal (OR = 2.03, 95% CI = 1.32 to 3.11, $I^2$ = 0.00%, P = 0.00 < 0.05), renal (OR = 2.20, 95% CI = 1.41 to 3.45, $I^2$ = 91.60%, P = 0.00 < 0.1), neurological (OR = 1.14, 95% CI = 1.03 to

1.26, $I^2$ = 7.35% P = 0.01 < 0.05), and infectious (OR = 2.02, 95% CI = 1.17 to 3.50, $I^2$ = 92.37%, P = 0.01 < 0.1) complications after surgery in the LC group. As for cardiovascular (OR = 1.07, 95% CI = 0.85 to 1.35, $I^2$ = 75.23%, P = 0.58 > 0.1) complication, no statistical significance was found between the 2 groups (Table 3).

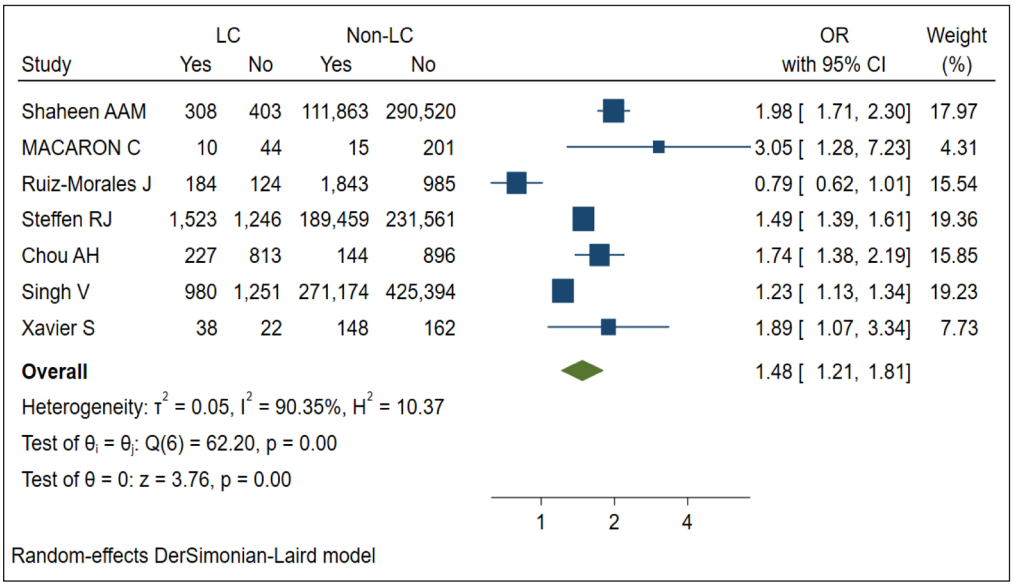


**Figure 2** Overall complications of the LC group and the non-LC group.

*Note*: LC, liver cirrhosis.

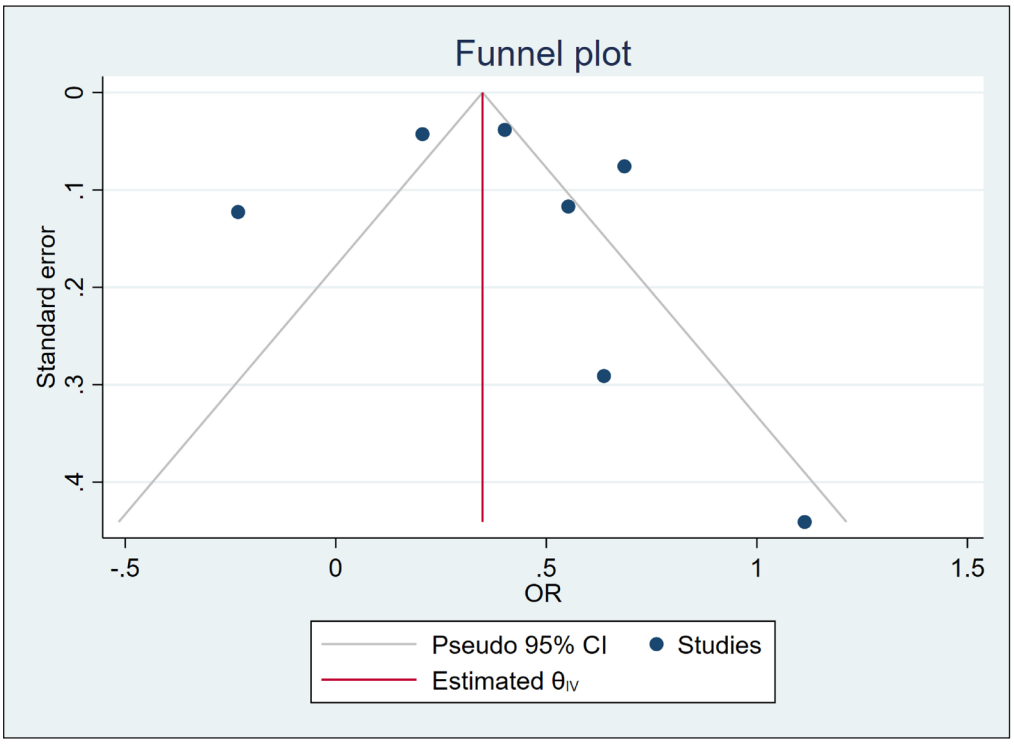


**Figure 3** Funnel plot of overall complications.

According to our data analysis, we found that in-hospital death (OR = 2.53, 95% CI = 1.86 to 3.20, $I^2$ = 44.58%, P = 0.00 < 0.05) and death (OR = 3.31, 95% CI = 1.54 to 5.07, $I^2$ = 93.81%, P = 0.00 < 0.1) in the LC group were higher than the non-LC group (Table 3).

Meta subgroup analysis was conducted to find out why there was a high heterogeneity among the included studies. The covariates included study period, published country, sample size, propensity-score matching, study type, cirrhosis definition, and surgery type. After performing data analysis, we found that heterogeneity derived from the published country and the study type (OR = 1.48, 95% CI = 1.21 to 1.81, $I^2$ = 90.35%, P = 0.00 < 0.1) (Figure 4).

Meta-analysis was repeated to analyze the sensitivity by excluding each study at a time. The results were not significantly different after every analysis.

| CHARACTERISTICS | STUDIES | PARTICIPANTS (LC/ NON-LC) | HAZARD RATIO/ODDS RATIO (95% CI) | MODEL | HETEROGENEITY |
|---|---|---|---|---|---|
| Complications | | | | | |
| Any | 7 | 7173/ 1524365 | 1.48 [1.21, 1.81]; P = 0.00 | RE | $I^2$ = 90.35%; P = 0.00 |
| Cardiovascular | 4 | 3310/ 1102089 | 1.07 [0.85, 1.35]; P = 0.58 | RE | $I^2$ = 75.23%; P = 0.01 |
| Pulmonary | 3 | 3002/ 1099261 | 1.86 [1.21, 2.87]; P = 0.00 | RE | $I^2$ = 90.79%; P = 0.00 |
| Gastrointestinal | 2 | 771/ 402693 | 2.03 [1.32, 3.11]; P = 0.00 | FE | $I^2$ = 0.00%; P = 0.59 |
| Renal | 5 | 3364/ 1102305 | 2.20 [1.41, 3.45]; P = 0.00 | RE | $I^2$ = 91.60%; P = 0.00 |
| Neurological | 3 | 2599/ 699706 | 1.14 [1.03, 1.26]; P = 0.01 | FE | $I^2$ = 7.35%; P = 0.34 |
| Infectious | 4 | 4042/ 1100301 | 2.02 [1.17, 3.50]; P = 0.01 | RE | $I^2$ = 92.37%; P = 0.00 |
| Long-term outcomes | | | | | |
| In-hospital death | 4 | NA | 2.53 [1.86, 3.20]; P = 0.00 | FE | $I^2$ = 44.58%; P = 0.16 |
| Death | 4 | NA | 3.31 [1.54, 5.07]; P = 0.00 | RE | $I^2$ = 93.81%; P = 0.00 |

**Table 3** Summary of outcomes between LC group and Non-LC group.

Abbreviations: LC, liver cirrhosis; ICU, intensive care unit; OS, overall survival; CI, confidence interval; RE, random-effects; FE, fixed-effects; NA, not apply.

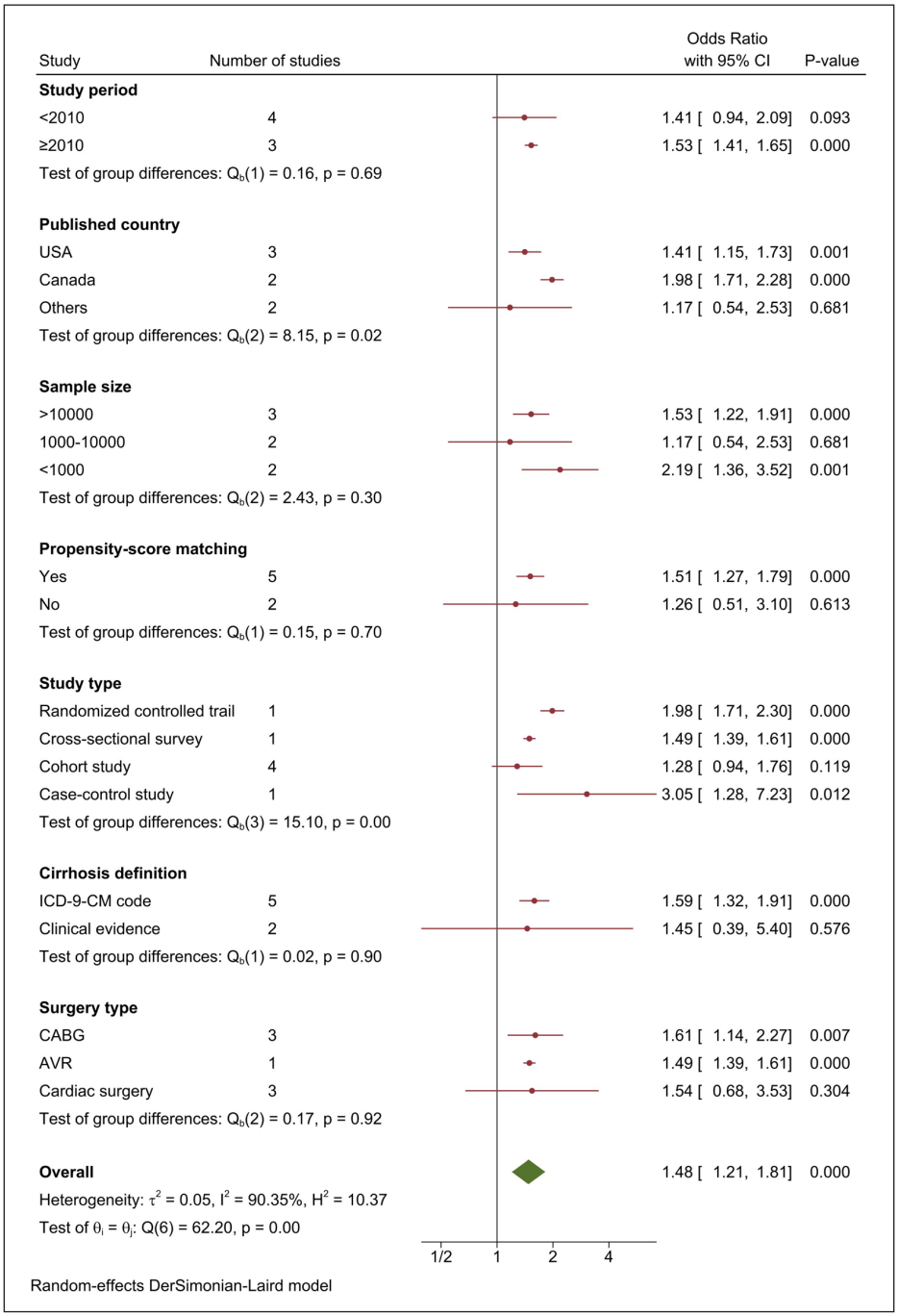


**Figure 4** Meta regression analysis of covariates.

## DISCUSSION

The aim of this pooling-up analysis was to figure out if there was an impact of LC on cardiac surgery. A total of seven studies containing 1,535,129 patients who underwent cardiac surgery were included [13–19]. All seven studies reported LC and non-LC groups. After analysis, we found that LC was a risk factor for cardiac surgery. In terms of overall complications, the LC group was higher than the non-LC group. However, we also found that both in-hospital death and death in the LC group were higher.

LC was divided into three classes (Child-Pugh (CP) A, CP-B, and CP-C) according to the impairment of liver function. As previous studies suggested, mortality rates after cardiac surgery in patients with CP-A, CP-B, and CP-C cirrhosis were 0%–11%, 18%–50%, and 67%–100%, respectively [24–27]. One review of 19 studies reported that the mortality rates in patients with CP-A, CP-B, and CP-C cirrhosis were 9.6%, 33.9%, and 61.3% after cardiac surgery, respectively. Moreover, the total mortality rate was 20% after cardiac surgery in patients with LC [11]. In this pooling-up analysis, more patients developed pulmonary, gastrointestinal, renal, or infectious complications after surgery in the LC group. As for cardiovascular and neurological complications, there was no statistical significance between the two groups. One study suggested that the CP-A class was not associated with a poor prognosis [18]. Perhaps positive liver function was a condition for patient recovery.

Controversy remained over the relationship between LC and cardiac surgery. Among the included studies, some reported that patients with LC had a poor prognosis after cardiac surgery [13–17]. One of these studies divided the LC patients into two groups, which were bound by the CP score [19]. Another study discussed the impact of LC on cardiac surgery by dividing it into CP-A, CP-B, and CP-C groups [18]. Both concluded that the group with positive liver function (CP-A or CP-B, CP score less than eight) could safely perform cardiac surgery, while the group with poor liver function (CP-B or CP-C, CP score more than or equal to eight) was responsible for the poor prognosis of cardiac surgery. Based on this controversy, we carried out this pooling up-analysis.

The potential mechanism was that patients with LC often suffered from nutritional damage, immune system dysfunction, coagulation disorders, acute kidney injury, etc. [1–3]. These concomitant symptoms might be the cause of a poor prognosis for the patients. Meanwhile, many confounding factors exist, including but not limited to the type of surgery, the emergency nature of the surgery, potential co-morbidities, and the year of the surgery, as surgical techniques have changed over the past decade [28–30]. The impact of non-LC factors on cardiac surgery can also be significant. Therefore, additional risk factors needed to be discussed and analyzed.

To our knowledge, this study was the first to utilize pooling-up analysis. However, there were some limitations to this analysis. First, we did not discuss in depth the impact of individual liver function classes (CP-A, CP-B, CP-C, or other classification methods) on cardiac surgery. Therefore, the data on CP-A was insufficient. Second, the heterogeneity of the included studies was high. After subgroup analysis, we found that the sources of heterogeneity were the publication of nation and study type. Although there was a high heterogeneity among the included studies, the sensitivity analysis of these studies did not affect our results. Third, we lacked information about the severity of liver disease, which could strengthen the analysis significantly. Fourth, the earliest and most recent publication dates for the included studies were 2009 and 2020, respectively. In modern conditions, the results of operations could differ due to the improvement of anesthetic and surgical techniques. However, there were no relevant studies in the last three years.

In conclusion, LC was a risk factor of cardiac surgery. More attention should be paid to LC patients after cardiac surgery. Similarly, the surgeon should assess the patient's liver function before surgery.

## DATA AVAILABILITY STATEMENT

The data was accessed in the database.

## ABBREVIATIONS

LC, liver cirrhosis; OR, odds ratio; MD, mean difference; CI, confidence interval; NOS, Newcastle-Ottawa Scale; COPD, chronic obstructive pulmonary disease; MI, myocardial infarction; CP, Child-Pugh.

## ETHICS AND CONSENT

Informed consent forms were signed by all patients. In accordance with the World Medical Association Declaration of Helsinki, this study obtained ethical approval from the institutional review.

All authors agree to publish.

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## COMPETING INTERESTS

The authors have no competing interests to declare.

## AUTHOR CONTRIBUTIONS

All authors contributed to the study.

Fei Liu, Zi-Wei Li, Xu-Rui Liu These authors are co-first authors.

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