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# Short-term Outcomes of Pancreatoduodenectomy in Patients with Liver Cirrhosis

## *A Systematic Review and Meta-analysis*

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**Objectives:** The objective of this study was to compare short-term outcomes of pancreatoduodenectomy between patients with and without liver cirrhosis (LC).
**Background:** It is not uncommon to encounter a patient with LC and with an indication for pancreatoduodenectomy; however, the knowledge on the outcomes after pancreatoduodenectomy in patients with LC is poorly developed.
**Methods:** A systematic review and meta-analysis was conducted in line with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses statement standards. Short-term outcomes of pancreatoduodenectomy between patients with and without LC were compared using random effects modeling and the certainty of the evidence was assessed using the GRADE system.
**Results:** Analysis of 18,184 patients from 11 studies suggested LC increased the risk of postoperative mortality (odds ratio [OR]: 3.94, $P < 0.00001$), major complications (OR: 2.25, $P = 0.0002$), and pancreatic fistula (OR: 1.73, $P = 0.03$); it resulted in more blood loss (mean difference [MD]: 204.74 ml, $P = 0.0003$) and longer hospital stay (MD: 2.05 days, $P < 0.00001$). LC did not affect delayed gastric emptying (OR: 1.33, $P = 0.21$), postoperative bleeding (OR: 1.28, $P = 0.42$), and operative time (MD: 3.47 minutes, $P = 0.51$). Among the patients with LC, Child-Pugh B or C class increased blood loss (MD: 293.33 ml, $P < 0.00001$), and portal hypertension increased postoperative mortality (OR: 2.41, $P = 0.01$); the other outcomes were not affected.
**Conclusions:** Robust evidence with high certainty suggests LC of any severity with or without portal hypertension results in at least a fourfold increase in mortality and a twofold increase in morbidity after pancreatoduodenectomy. Whether such risks increase with the severity of the liver disease or decrease with optimization of underlying liver disease should be the focus of future research.

**Keywords:** liver cirrhosis, morbidity, mortality, pancreatoduodenectomy

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*This study is a systematic review with meta-analysis of outcomes which does not include research directly involving human or animal participation.*

*PROSPERO registration number: CRD42024531188.*

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## INTRODUCTION

Pancreatoduodenectomy (PD) is recognized as a technically complex operation with a conspicuous risk of morbidity; hence, there is an ongoing effort to predict and reduce the risk of morbidity after PD.[1–3] PD remains the only curative treatment for pancreatic and periampullary cancers which occur more frequently in patients with liver cirrhosis than those without cirrhosis.[4,5] Consequently, it is not uncommon to encounter a patient with liver cirrhosis and with an indication for PD. This means a high-risk operation in a high-risk patient as liver cirrhosis is a recognized risk factor for postoperative complications; the more severe the liver cirrhosis, the higher the risk of early postoperative morbidity and mortality.[6,7]

The knowledge base regarding postoperative morbidity and mortality outcomes after PD in patients with liver cirrhosis is poorly developed. Such knowledge is valuable to multidisciplinary teams when formulating the management plan for a patient with liver cirrhosis who requires PD. The outcomes of PD in patients with liver cirrhosis have been evaluated by several observational studies providing a robust rationale for conducting a comparative meta-analysis. Considering that cirrhosis is a prognostic factor rather than an intervention, performing a randomized controlled trial is not possible in this setting as cirrhosis cannot be randomized; hence, a meta-analysis of observational studies serves as the best evidence. In view of the above, we aimed to conduct a systematic review and meta-analysis to compare short-term outcomes of PD between patients with liver cirrhosis and those without cirrhosis.

## METHODS

This study was protocoled (PROSPERO registration number: CRD42024531188), conducted, and reported in compliance with Preferred Reporting Items for Systematic Reviews and Meta-Analyses statement standards.[8]

### Eligibility Criteria

#### *Study Design*

All prospective and retrospective comparative observational studies were considered for inclusion. As explained previously, a randomized controlled trial is not feasible in this setting because cirrhosis cannot be randomized.

#### *Population*

All patients aged 18 years or older who underwent open or minimally invasive PD due to either benign or malignant indications were considered eligible for inclusion.

#### *Prognostic Factor of Interest and Comparison*

Liver cirrhosis of any severity was considered as the prognostic factor of interest, and no liver cirrhosis was considered as the comparison.

#### *Outcomes*

Postoperative mortality and major complications (Clavien–Dindo ≥3) were considered as primary outcomes. The secondary outcomes included intraoperative blood loss, operative time, grade B-C postoperative pancreatic fistula, postoperative bleeding, delayed gastric emptying, and length of hospital stay.

### Search Methods

A comprehensive search strategy was created by 2 independent authors with experience in evidence synthesis using proper search limits, keywords, thesaurus headings, and operators (Appendix I, http://links.lww.com/AOSO/A363). The search strategy had no language restrictions and was last run on March 20, 2024. The reference lists of relevant systematic reviews and original studies were also evaluated to find more eligible studies.

### Study Selection and Data Extraction

The title and abstract of the identified articles were screened, and the full texts of relevant articles were retrieved by 2 independent authors who included the studies that met the eligibility criteria. An electronic data collection proforma was evaluated based on randomly selected studies and included information on the name of the first author, year of publication, name of journal, type of study design, description of the included population, sample size of each study, age, gender, Child-Pugh class, model for end-stage liver disease (MELD) score, portal hypertension, and the already mentioned outcomes. The 2 independent authors discussed and resolved disagreements during study data extraction, and a third independent author was consulted if required.

### Risk of Bias Assessment

Two independent authors evaluated the methodological quality of the included studies using the Quality In Prognosis Studies tool, which evaluates the risk of bias in studies of prognostic factors in terms of study participation, study attrition, prognostic factor measurement, outcome measurement, study confounding, and statistical analysis and reporting.[9]

### Data Analysis

Review Manager 5.4 software was used for meta-analysis. The odds ratio (OR) and mean difference (MD) were calculated as summary measures for dichotomous and continuous outcomes, respectively. The random effects modeling was used for analyses and forest plots with 95% confidence intervals (CIs) were constructed to present the results. Individual patients were considered as the unit of analysis. Meta-regression analysis was modeled to evaluate the effect of differences in Child-Pugh class, MELD score, and portal hypertension in cirrhotic patients among the included studies on the primary outcomes. The statistical heterogeneity was measured as $I^2$ using the Cochran Q test ($\chi^2$) and it was classified as low heterogeneity when $I^2$ was 0–25%, moderate heterogeneity when $I^2$ was 25–75%, and high heterogeneity when $I^2$ was 75–100%. The risk of publication bias was evaluated by constructing funnel plots for outcomes reported by at least 10 studies.

### Additional Analyses

The following comparisons were made among the patients with liver cirrhosis: (1) patients with Child-Pugh B or C disease *versus* patients with Child-Pugh A and (2) patients with portal hypertension *versus* patients without portal hypertension.

### Sensitivity Analyses

To evaluate the consistency and robustness of the results, a sensitivity analysis was performed for the outcomes reported by a minimum number of 4 studies: (1) leave-one-out analysis to investigate the effect of each study on the pooled outcomes; (2) Separate analysis of studies with low overall risk of bias.

### Certainty of Evidence

Certainty of evidence was judged based on the recommended standards and domains by the GRADE system.[10]

## RESULTS

### Literature Search Results

The search of electronic databases produced 278 articles, of which 266 articles were excluded directly because they were not relevant to the subject of this study. After reviewing the full text of the remaining 12 articles, 1 more article was excluded because it was a review article. Consequently, 11 comparative studies[11–21] including a total of 18,184 patients were included. Among the included population, 1001 patients had liver cirrhosis and 17,183 patients did not have liver cirrhosis. The study flow chart is shown in Figure 1. The baseline characteristics of the included studies and included populations are shown in Tables 1 and 2, respectively.

### Risk of Bias Assessment

Supplementary Figure 1, http://links.lww.com/AOSO/A363 highlights the outcomes of methodological quality assessment based on the Quality In Prognosis Studies tool. All the included studies were judged to be of low risk of bias in terms of study participation, study attrition, outcome measurement, and statistical analysis and reporting. The risk of bias due to prognostic factor measurement was judged to be low in 10 studies and unclear in 1 study. The risk of bias due to study confounding was judged to be low in 6 studies and unclear in 5 studies.

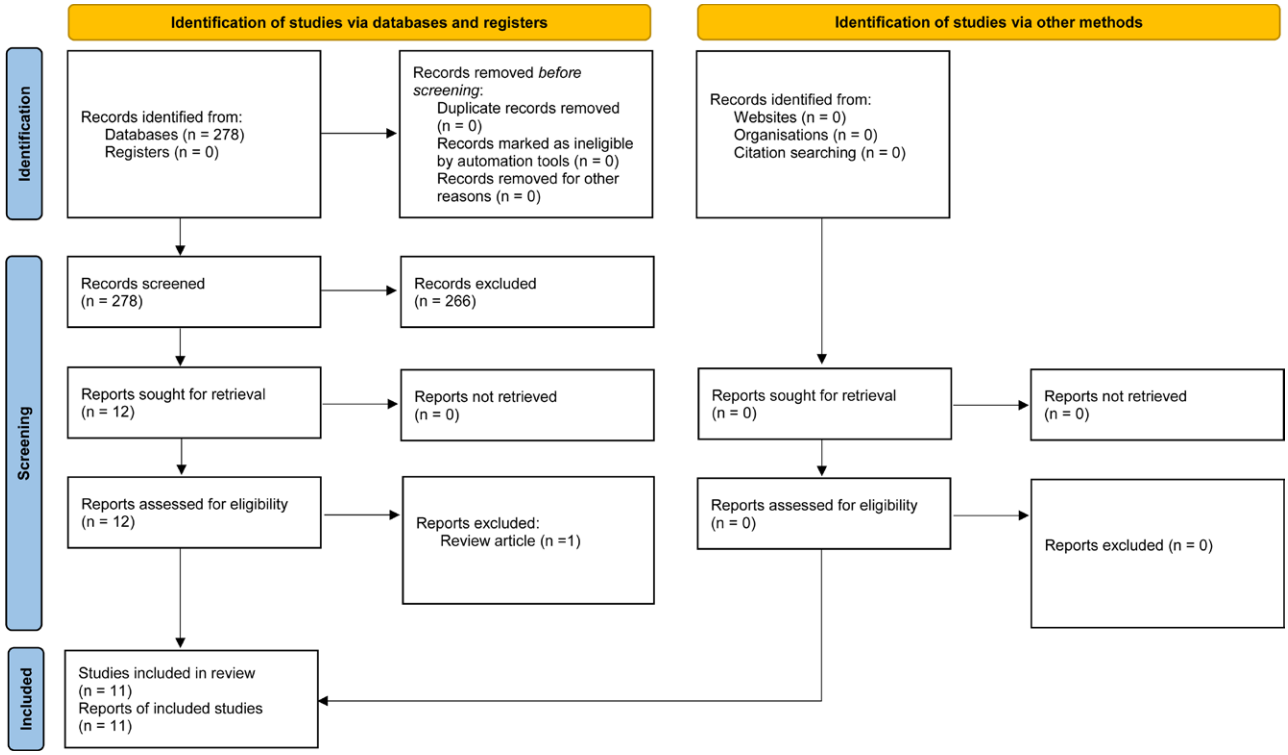



**FIGURE 1.** Study PRISMA flow diagram

**TABLE 1.**

**Baseline Characteristics of the Included Studies**

| Study | Country | Journal | Design | Population | Sample Size | | |
|---|---|---|---|---|---|---|---|
| | | | | | Total | No Cirrhosis | Cirrhosis |
| Nevarez et al (2023)[11] | USA | *HPB* | Retrospective observational | Patients undergoing elective pancreatoduodenectomy | 16,355 | 16,152 | 203 |
| Zamorano et al 2023[12] | USA | *Langenbecks Arch Surg* | Retrospective observational | Patients undergoing elective pancreatoduodenectomy | 48 | 32 | 16 |
| Kang et al 2023[13] | South Korea | *Acta Chir Belg* | Retrospective observational | Patients undergoing elective pancreatoduodenectomy | 221 | 196 | 25 |
| Cheng et al 2021[14] | China | *PLoS One* | Retrospective observational | Patients undergoing elective pancreatoduodenectomy | 84 | 56 | 28 |
| Enderes et al 2021[15] | Germany | *J Clin Med* | Retrospective observational | Patients undergoing elective pancreatoduodenectomy | 255 | 240 | 15 |
| Futagawa et al 2019[16] | Japan | *J Hepatobiliary Pancreat Sci* | Retrospective observational | Patients with cirrhosis undergoing elective pancreatoduodenectomy | 529 | 0 | 529 |
| Butler et al 2018[17] | USA | *HPB* | Retrospective observational | Patients with cirrhosis undergoing elective pancreatoduodenectomy | 36 | 0 | 36 |
| Busquets et al 2016[18] | Spain | *Cir Esp* | Prospective observational | Patients undergoing elective pancreatoduodenectomy | 45 | 30 | 15 |
| Regimbeau et al 2015[19] | France | *J Surg Oncol* | Retrospective observational | Patients undergoing elective pancreatoduodenectomy | 105 | 70 | 35 |
| Nakeeb et al 2013[20] | Egypt | *World J Gastroenterol* | Retrospective observational | Patients undergoing elective pancreatoduodenectomy | 442 | 375 | 67 |
| Warnick et al 2011[21] | Germany | *Pancreatology* | Retrospective observational | Patients undergoing elective pancreatoduodenectomy | 64 | 32 | 32 |

## Primary Outcomes

### *Postoperative Mortality*

Analysis of 17,619 patients from 9 studies showed that the risk of postoperative mortality was higher in patients with liver cirrhosis (OR: 3.94, 95% CI = 2.73–5.69, $P < 0.00001$) (Fig. 2A). The statistical between-study heterogeneity was low ($I^2 = 0\%$, $P = 0.75$) and the GRADE certainty of the evidence was high (Supplementary Table 1, http://links.lww.com/AOSO/A363). Meta-regression showed that the risk of postoperative mortality was not influenced by the differences in Child-Pugh class (coefficient: 0.01, $P = 0.685$), MELD score (coefficient: 0.037, $P = 0.933$) and portal hypertension (coefficient: 0.014, $P = 0.536$) in cirrhotic patients among the included studies (Table 3 and Supplementary Figure 2, http://links.lww.com/AOSO/A363).

**TABLE 2.**

**Baseline Characteristics of the Included Population**

| Study | Age* Mean (SD) | Female* No/Total (%) | Child–Pugh Class in Cirrhotic Patients No/Total (%) | | | MELD Score in Cirrhotic Patients mean (SD) | Portal Hypertension* No/Total (%) |
|---|---|---|---|---|---|---|---|
| | | | A | B | C | | |
| Nevarez et al 2023[11] | 65 (23) *vs* 65 (21) | 7757/16152 (48%) *vs* 80/203 (39%) | NR | NR | NR | NR | 37/16152 (0.2%) *vs* 16/203 (8%) |
| Zamorano et al 2023[12] | 68 (12) *vs* 63 (10) | 18/32 (56%) *vs* 8/16 (50%) | NR | NR | NR | NR | 0/32 (0%) *vs* 2/16 (13%) |
| Kang et al 2023[13] | 64 (12) *vs* 63 (10) | 90/196 (45%) *vs* 12/25 (48%) | NR | NR | NR | 8 (2.3) | 0/196 (0%) *vs* 13/25 (52%) |
| Cheng et al 2021[14] | 60 (5) *vs* 62 (5) | 14/56 (25%) *vs* 7/28 (25%) | 11/28 (39%) | 17/28 (61%) | 0/28 (0%) | 12 (2.3) | NR |
| Enderes et al 2021[15] | 68 (4) *vs* 63 (5) | 106/204 (51%) *vs* 5/15 (33%) | 13/15 (87%) | 3/15 (13%) | 0/15 (0%) | NR | NR |
| Futagawa et al 2019[16] | 70 (3) | 105/529 (19%) | 427/529 (81%) | 98/529 (18%) | 4/529 (1%) | NR | 63/529 (12%) |
| Butler et al 2018[17] | 60 (13) | 20/36 (55%) | 30/36 (83%) | 6/36 (17%) | 0/36 (0%) | 9 | 16/29 (55%) |
| Busquets et al 2016[18] | 62 (11) *vs* 64 (9) | 7/30 (23%) *vs* 4/15 (26%) | 15/15 (100%) | 0/15 (0%) | 0/15 (0%) | NR | NR |
| Regimbeau et al 2015[19] | 59 (11) *vs* 59 (10) | 18/70 (25%) *vs* 7/35 (20%) | 35/35 (100%) | 0/35 (0%) | 0/35 (0%) | 10 (8) | 0/70 (0%) *vs* 6/35 (17%) |
| Nakeeb et al 2013[20] | 53 (11) *vs* 54 (9) | 150/375 (40%) *vs* 15/67 (22%) | 63/67 (94%) | 4/67 (6%) | 0/67 (0%) | NR | 0/375 (0%) *vs* 16/67 (24%) |
| Warnick et al 2011[21] | 57 (12) *vs* 57 (12) | 7/32 (21%) *vs* 7/32 (21%) | 30/32 (94%) | 2/32 (6%) | 0/32 (0%) | 11 (5) | NR |

*No cirrhosis group versus cirrhosis group.

MELD indicates model for end-stage liver disease; NR: not reported; SD, standard deviation.



### *Major Complications (Clavien-Dindo ≥3)*

Analysis of 777 patients from 6 studies showed that the risk of major complications (Clavien-Dindo ≥3) was higher in patients with liver cirrhosis (OR: 2.25, 95% CI = 1.48–3.43, $P = 0.0002$) (Fig. 2B). The statistical between-study heterogeneity was low ($I^2 = 0\%$, $P = 0.50$) and the GRADE certainty of the evidence was high (Supplementary Table 1, http://links.lww.com/AOSO/A363). Meta-regression showed that the risk of major complications was not influenced by the differences in Child-Pugh class (coefficient: 0.017, $P = 0.195$), MELD score (coefficient: 0.016, $P = 0.927$), and portal hypertension (coefficient: –0.005, $P = 0.730$) in cirrhotic patients among the included studies (Table 3 and Supplementary Figure 2, http://links.lww.com/AOSO/A363).

## Secondary Outcomes

### *Intraoperative Blood Loss*

Analysis of 1107 patients from 5 studies showed that liver cirrhosis resulted in more intraoperative blood loss (MD: 204.74 ml, 95% CI = 92.76–316.72, $P = 0.0003$) (Fig. 2C). The statistical between-study heterogeneity was high ($I^2 = 92\%$, $P < 0.00001$) and the GRADE certainty of the evidence was moderate (Supplementary Table 1, http://links.lww.com/AOSO/A363).

### *Operative Time*

Analysis of 1354 patients from 7 studies showed no difference in operative time between patients with and without liver cirrhosis (MD: 3.47 minutes, 95% CI = –6.74 to 13.68, $P = 0.51$) (Fig. 2D). The statistical between-study heterogeneity was moderate ($I^2 = 40\%$, $P = 0.12$) and the GRADE certainty of the evidence was moderate (Supplementary Table 1, http://links.lww.com/AOSO/A363).

### *Grade B-C Postoperative Pancreatic Fistula*

Analysis of 1114 patients from 6 studies showed that the risk of grade B-C postoperative pancreatic fistula was higher in patients with liver cirrhosis (OR: 1.73, 95% CI = 1.05–2.84, $P = 0.39$) (Fig. 2E). The statistical between-study heterogeneity was low ($I^2 = 4\%$, $P = 0.50$) and the GRADE certainty of the evidence was moderate (Supplementary Table 1, http://links.lww.com/AOSO/A363).

### *Postoperative Bleeding*

Analysis of 1043 patients from 7 studies showed that liver cirrhosis did not affect the risk of postoperative bleeding (OR: 1.28, 95% CI = 0.70–2.36, $P = 0.42$) (Fig. 2F). The statistical between-study heterogeneity was low ($I^2 = 0\%$, $P = 0.73$) and the GRADE certainty of the evidence was high (Supplementary Table 1, http://links.lww.com/AOSO/A363).

### *Delayed Gastric Emptying*

Analysis of 980 patients from 6 studies showed that liver cirrhosis did not affect the risk of delayed gastric emptying (OR: 1.33, 95% CI = 0.86–2.07, $P = 0.21$) (Fig. 2G). The statistical between-study heterogeneity was low ($I^2 = 0\%$, $P = 0.73$) and the GRADE certainty of the evidence was high (Supplementary Table 1, http://links.lww.com/AOSO/A363).

### *Length of Hospital Stay*

Analysis of 1112 patients from 6 studies showed that liver cirrhosis resulted in longer length of hospital stay (MD: 2.05 days, 95% CI = 1.40–2.69, $P < 0.00001$) (Fig. 2H). The statistical between-study heterogeneity was low ($I^2 = 0\%$, $P = 0.70$) and the GRADE certainty of the evidence was high (Supplementary Table 1, http://links.lww.com/AOSO/A363).

## Child-Pugh B or C Disease Versus Child-Pugh A in Cirrhotic Patients

Child-Pugh B or C class was associated with more intraoperative blood loss compared with Child-Pugh A class (MD: 293.33 ml, 95% CI = 231.96–354.71, $P < 0.00001$). There was no difference between Child-Pugh B or C class and Child-Pugh A class in postoperative mortality (OR: 2.56, 95% CI =

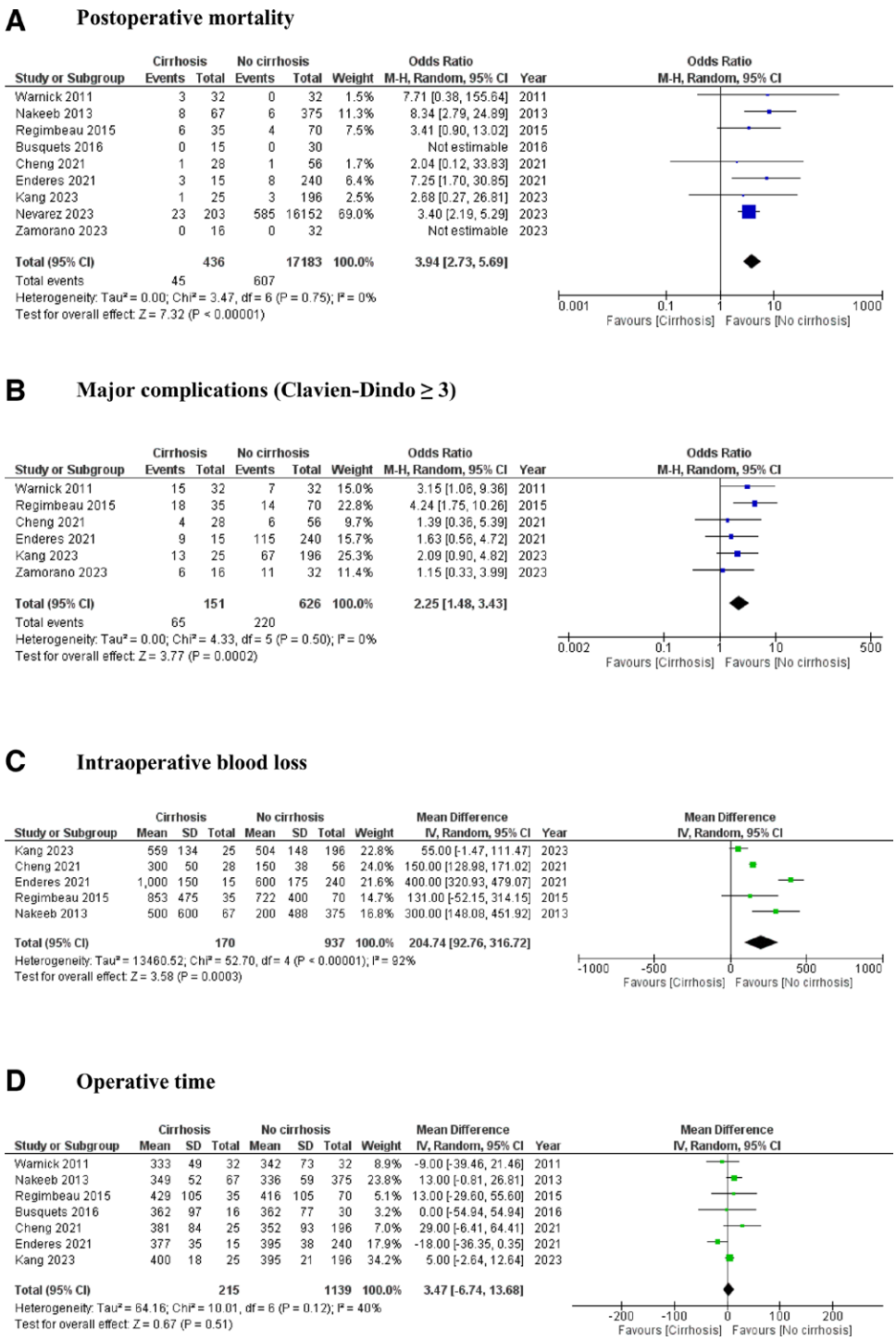


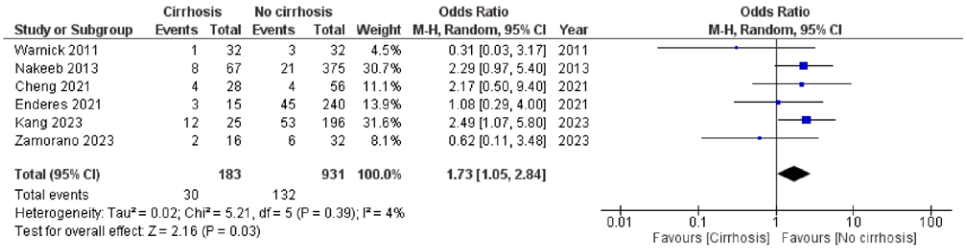

**FIGURE 2.** Forest plots for comparison between liver cirrhosis and no liver cirrhosis: (A) postoperative mortality. (B) Major complications (Clavien-Dindo ≥3). (C) Intraoperative blood loss. (D) Operative time. (E) Grade B-C postoperative pancreatic fistula. (F) postoperative bleeding. (G) Delayed gastric emptying. (H) Length of hospital stay.

0.55–11.81, $P$ = 0.23), major complications (Clavien-Dindo ≥3) (OR: 2.71, 95% CI = 0.32–23.13, $P$ = 0.36), operative time (MD: 121.18 minutes, 95% CI = −68.84 to 311.20, $P$ = 0.21), grade B-C postoperative pancreatic fistula (OR: 1.33, 95% CI = 0.24–7.35, $P$ = 0.74), postoperative bleeding (OR: 2.64, 95% CI = 0.45–15.66, $P$ = 0.28), delayed gastric emptying (OR: 0.72, 95% CI = 0.32–1.58, $P$ = 0.41), and length of hospital stay (MD: 2.03 days, 95% CI = 0.01–4.05, $P$ = 0.05) (Table 4 and Supplementary Figure 3, http://links.lww.com/AOSO/A363).

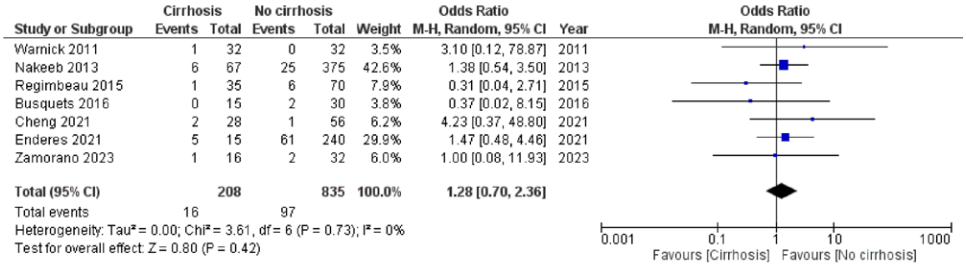
### Portal Hypertension Versus No Portal Hypertension in Cirrhotic Patients

Portal hypertension was associated with a higher risk of postoperative mortality (OR: 2.41, 95% CI = 1.20–4.86, $P$ = 0.01) and longer length of hospital stay (MD: 1.35 days, 95% CI = −6.38 to 9.09, $P$ = 0.73) compared with no portal hypertension. There was no difference between cirrhotic patients with or without portal hypertension in major complications (Clavien-Dindo ≥ 3) (OR: 1.49, 95% CI = 0.50–4.47, $P$ = 0.36), intraoperative blood loss (MD: 196.56 ml, 95% CI = −104.20 to 497.33, $P$ = 0.20),

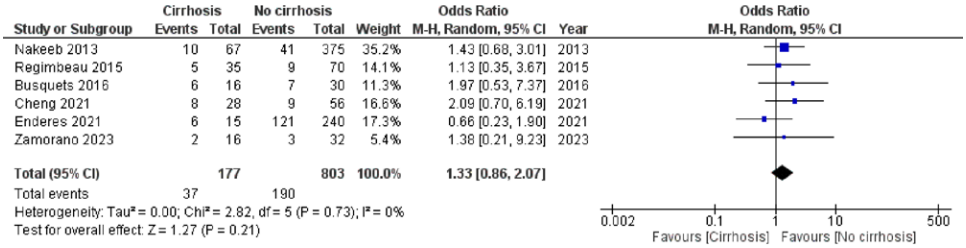
**E** **Grade B-C Postoperative pancreatic fistula**




**F** **Postoperative bleeding**




**G** **Delayed gastric emptying**




**H** **Length of hospital stay**

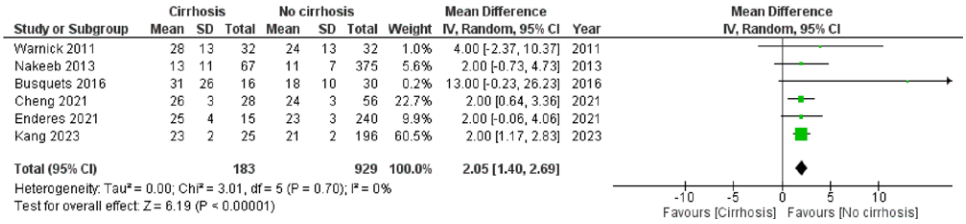



**FIGURE 2.** Continued

**TABLE 3.**

**Results of Meta-regression Analyses for the Primary Outcomes**

| | Postoperative Mortality | | Major Complications (Clavien-Dindo ≥3) | |
|---|---|---|---|---|
| | **Coefficient** | ***P* value** | **Coefficient** | ***P* value** |
| Child–Pugh class* | 0.01 | 0.685 | 0.017 | 0.195 |
| MELD score | 0.037 | 0.933 | 0.016 | 0.927 |
| Portal hypertension | 0.014 | 0.536 | -0.005 | 0.73 |

*Percentage of Child-Pugh A in each study was used for analyses.
MELD indicates model for end-stage liver disease.

**TABLE 4.**

**Comparison of the Outcomes in Cirrhotic Patients Based on Child–Pugh Class and Portal Hypertension Status**

| | | Number of Studies | Number of Patients | Summary Measure OR (95% CI) | *P*-value | Heterogeneity, $I^2$ |
|---|---|---|---|---|---|---|
| Child-Pugh B or C *vs* Child–Pugh A | Postoperative mortality | 3 | 600 | OR: 2.56 (0.55–11.81) | 0.23 | 55% |
| | Major complications (Clavien-Dindo ≥3) | 3 | 99 | OR: 2.71 (0.32–23.13) | 0.36 | 67% |
| | Intraoperative blood loss | 2 | 565 | MD: 293.33 ml (231.96–354.71) | <0.00001 | 0% |
| | Operative time | 2 | 565 | MD: 121.18 minutes (–68.84 to 311.20) | 0.21 | 89% |
| | Grade B-C postoperative pancreatic fistula | 1 | 26 | OR: 1.33 (0.24–7.35) | 0.74 | NA |
| | Postoperative bleeding | 3 | 600 | OR: 2.64 (0.45–15.66) | 0.28 | 44% |
| | Delayed gastric emptying | 3 | 592 | OR: 0.72 (0.32–1.58) | 0.41 | 0% |
| | Length of hospital stay | 2 | 565 | MD: 2.03 days (0.01–4.05) | 0.05 | 0% |
| Portal hypertension *vs* No portal hypertension | Postoperative mortality | 4 | 630 | OR: 2.41 (1.20–4.86) | 0.01 | 0% |
| | Major complications (Clavien-Dindo ≥3) | 2 | 54 | OR: 1.49 (0.50–4.47) | 0.47 | 0% |
| | Intraoperative blood loss | 2 | 54 | MD: 196.56 ml (–104.20 to 497.33) | 0.20 | 0% |
| | Operative time | 3 | 121 | MD: 23.06 minutes (–10.70, 56.82) | 0.18 | 58% |
| | Grade B-C postoperative pancreatic fistula | 2 | 92 | OR: 2.57 (0.86–7.71) | 0.09 | 0% |
| | Postoperative bleeding | 2 | 96 | OR: 3.90 (0.87–17.50) | 0.08 | 0% |
| | Delayed gastric emptying | 1 | 67 | OR: 2.50 (0.61–10.31) | 0.20 | NA |
| | Length of hospital stay | 2 | 96 | MD: 1.35 days (–6.38 to 9.09) | 0.73 | 50% |

CI indicates confidence interval; MD, mean difference; OR, odds ratio.

operative time (MD: 23.06 minutes, 95% CI –10.70 to 56.82, $P = 0.18$), grade B-C postoperative pancreatic fistula (OR: 2.57, 95% CI = 0.86–7.71, $P = 0.09$), postoperative bleeding (OR: 3.90, 95% CI = 0.87–17.50, $P = 0.08$), and delayed gastric emptying (OR: 2.50, 95% CI = 0.61–10.31, $P = 0.20$) (Table 4 and Supplementary Figure 4, http://links.lww.com/AOSO/A363).

### Sensitivity Analyses

Sensitivity analyses confirmed the consistency of the results for the primary outcomes and most of the secondary outcomes except postoperative pancreatic fistula and operative time. Leave-one-out analysis changes the direction of the effect size toward no difference in postoperative pancreatic fistula and in favor of no cirrhosis in operative time. However, separate analysis of studies with low overall risk of bias did not affect the pooled risk of any of the outcomes.

## DISCUSSION

A systematic review and meta-analysis was conducted to compare short-term outcomes of PD between patients with liver cirrhosis and those without cirrhosis. Analysis of 18,184 patients from 11 studies showed that liver cirrhosis increased the risks of postoperative mortality (high certainty), major complications (high certainty), and grade B-C postoperative pancreatic fistula (moderate certainty); it resulted in more intraoperative blood loss (moderate certainty) and longer length of hospital stay (high certainty). Liver cirrhosis did not affect delayed gastric emptying (high certainty), postoperative bleeding (high certainty), and operative time (moderate certainty). Meta-regression analyses suggested that postoperative morbidity and morbidity existed irrespective of Child-Pugh class, MELD score, and portal hypertension. Among the patients with liver cirrhosis, Child-Pugh B or C class increased intraoperative blood loss, and portal hypertension increased the risk of postoperative mortality; however, the other outcomes were not affected.

This study is the first comprehensive comparative meta-analysis in the literature with a reasonable sample size and methodology evaluating the effect of liver cirrhosis on short-term outcomes after PD; however, the risks of complications following pancreatic surgery in cirrhotic patients have been quantified previously by Schizas et al[22] who conducted a systematic review of 5 observational studies and 8 reported cases. The study by Schizas et al[22] concluded that pancreatic surgery in patients with liver cirrhosis is associated with increased risks of postoperative morbidity and mortality. Although the statistical methods used in the study by Schizas et al[22] for comparing the outcomes between patients with and without cirrhosis are subject to bias, their findings support the findings of the current study. Artinyan et al[6] retrospectively analyzed 106,729 patients who underwent resection for gastrointestinal malignancy and concluded that liver cirrhosis is associated with poor early postoperative and transitional outcomes. Ng et al[23] and Deng et al[24] reported similar findings in colorectal surgery and oesophagectomies, respectively. All of the above support the external validity of the findings of the current study.

The results of the current study suggest that liver cirrhosis of any severity with or without portal hypertension increases the risk of morbidity and mortality after PD. While we did not robustly demonstrate the actual relationship between the severity of the liver disease and increased risks of morbidity and mortality, this could be a type 2 error due to the small sample size for separate analyses of cirrhotic patients based on Child-Pugh class and portal hypertension status. This may be reflected by some of the reported *P* values in Table 4 which are approaching 0.05 value. Nevertheless, others have demonstrated that the more severe the liver cirrhosis, the higher the risk of early postoperative morbidity and mortality.[6,7]

The findings of the current study may be useful to multidisciplinary teams when formulating management plans for patients with liver cirrhosis and with indications for PD and when discussing the risks of surgery with such patients. Based on the available data, we can confidently with high certainty say that liver cirrhosis results in at least a fourfold increase in postoperative mortality and a twofold increase in postoperative morbidity in patients undergoing PD. Whether such risks increase with the severity of the liver disease or decrease with optimization of undergoing liver disease should be the focus of future research.

The study has inherent limitations. The retrospective nature of the included studies introduces the inevitable risk of selection and confounding bias. As mentioned earlier, considering that cirrhosis is a prognostic factor rather than an intervention, performing a randomized controlled trial is not feasible in this setting as cirrhosis cannot be randomized; hence, a meta-analysis of observational studies serves the best evidence. We could not formally assess the risk of publication bias because none of the outcomes were reported by more than 10 studies; hence, selective reporting cannot be excluded. Sensitivity analyses suggested that our findings regarding postoperative pancreatic fistula and operative time were not robust; nevertheless, we downgraded the certainty of evidence for these outcomes accordingly. Finally, as mentioned earlier our findings regarding the relationship between the severity of the liver disease and increased risks of morbidity and mortality may be subject to type 2 error. In contrast, the study has strengths. An objective and systematic approach was used in evidence synthesis, consistent with the appropriate and required standards. A GRADE system was used to evaluate the certainty of evidence for each outcome, considering the risk of bias, directness of evidence, heterogeneity, precision of effects estimates, and risk of publication bias. The adequate sample size, low between-study heterogeneity, high-GRADE certainty, and appropriate meta-regression analyses would make our conclusions about the primary outcomes robust.

## CONCLUSIONS

Robust evidence with high certainty suggests that liver cirrhosis of any severity with or without portal hypertension results in at least a fourfold increase in mortality and a twofold increase in morbidity after pancreatoduodenectomy. Whether such risks increase with the severity of the liver disease or decrease with optimization of underlying liver disease should be the focus of future research.

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