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SYSTEMATIC REVIEWS

Impact of frailty on postoperative outcomes after hepatectomy: A systematic review and meta-analysis

Yao-Jia Lv, Guang-Xing Xu, Jia-Rong Lan

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Yao-Jia Lv, Day Surgery Ward, Huzhou Central Hospital, The Affiliated Central Hospital of Huzhou University, Huzhou 313000, Zhejiang Province, China

Guang-Xing Xu, School of Basic Medical Sciences, Zhejiang Chinese Medical University, Hangzhou 310053, Zhejiang Province, China

Jia-Rong Lan, Department of Medicine, Huzhou Traditional Chinese Medicine Hospital Affiliated to Zhejiang Chinese Medical University, Huzhou 313000, Zhejiang Province, China

Corresponding author: Jia-Rong Lan, MD, Doctor, Department of Medicine, Huzhou Traditional Chinese Medicine Hospital Affiliated to Zhejiang Chinese Medical University, No. 315 South Street, Huzhou 313000, Zhejiang Province, China. sdwaters@126.com

Abstract

BACKGROUND
The impact of frailty on postoperative outcomes in patients undergoing hepatectomy is still unclear.

AIM
To study the influence of frailty on postoperative outcomes, such as mortality, rate of complications, and length of hospitalization, following hepatectomy.

METHODS
PubMed, EMBASE, and Scopus databases were searched for observational studies with adult (≥ 18 years) patients after planned/elective hepatectomy. A random-effects model was used for all analyses, and the results are expressed as weighted mean difference (WMD), relative risk (RR), or hazards ratio (HR) with 95% confidence interval (CI).

RESULTS
Analysis of the 13 included studies showed a significant association of frailty with elevated risk of in-hospital mortality (RR = 2.76, 95%CI: 2.10-3.64), mortality at 30 d (RR = 4.60, 95%CI: 1.85-11.40), and mortality at 90 d (RR = 2.52, 95%CI: 1.70-3.75) in the postoperative period. Frail patients had a poorer long-term survival (HR = 2.89, 95%CI: 1.84-4.53) and higher incidence of "any" complications (RR = 1.69, 95%CI: 1.40-2.03) and major (grade III or higher on the Clavien-Dindo scale) complications (RR = 2.69, 95%CI: 1.85-3.92). Frailty was correlated with markedly lengthier hospital stay (WMD = 3.65, 95%CI: 1.45-5.85).

CONCLUSION
Frailty correlates with elevated risks of mortality, complications, and prolonged hospitalization, which need to be considered in surgical management. Further research is essential to formulate strategies for improved outcomes in this vulnerable cohort.

Key Words: Frailty; Frail adults; Hepatic resection; Hepatectomy; Complications; Mortality; Survival; Clinical outcomes; Meta-analysis

Core Tip: This meta-analysis examined how frailty affects people undergoing liver surgery (hepatectomy). Findings from published studies were utilized to compare frail individuals to non-frail ones in terms of outcomes after hepatectomy. The findings show that frail individuals had higher mortality rates while in the hospital and within 30 d and 90 d after surgery, compared to non-frail individuals. Frail people also had lower long-term survival rates, experienced more complications, and had to stay in the hospital longer. These findings suggest that it is important to consider frailty when planning hepatectomy.

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INTRODUCTION

Frailty, often characterized as a diminished physiological reserve and increased susceptibility to external stressors, is considered a significant determinant of postoperative outcomes[1-3]. Characteristic manifestations of frailty include diminished muscle mass, decreased physical activity, cognitive impairment, and nutritional deficits[4-6]. Frailty, therefore, was recognized as a significant risk factor for postoperative complications, prolonged hospitalization, increased readmission, and poorer functional outcomes following general surgical procedures[3,7,8]. With the gradual aging of the population, an increasing number of frail patients with comorbidities are being considered for major surgeries, including hepatectomy that emerged as a potentially curative treatment for primary and secondary hepatic malignancies[8-11].

The incidence of frailty among hepatectomy patients ranges from 15% to 30%[12,13]. However, a definitive connection between frailty and poorer postoperative outcomes in the context of hepatectomy is still not established.

This analysis aimed to investigate the relationship between frailty and postoperative outcomes following hepatectomy. The primary outcomes for the study included postoperative complications, length of hospital stay, and mortality/overall survival (OS) rates.

The findings of this review may be used to inform clinical practice and decision-making, such as risk stratification, and development of targeted pre- and postoperative interventions for this vulnerable group of patients undergoing hepatectomy.

MATERIALS AND METHODS

Search strategy

A comprehensive systematic search was done in PubMed, EMBASE, and Scopus databases up to August 15, 2023 using the following combination of terms: (Frailty OR muscle weakness OR sarcopenia OR frail elderly OR impaired muscle function OR frail older adults) AND (hepatectomy OR liver resection OR liver surgery OR hepatic surgery OR hepatic segmental resection) AND (clinical outcomes OR postoperative outcomes OR mortality OR survival OR complications). To ensure transparency and accountability, our protocol was registered with PROSPERO under registration number CRD42023456351, and PRISMA guidelines were followed[14].

Selection of studies

The inclusion criteria were as follows: (1) Observational (prospective and retrospective cohort and case-control) studies; (2) Studies with adult participants (18 years or older) undergoing planned/elective hepatectomy (either partial or complete); (3) Recognized tools used for frailty assessment; (4) Definition and categorization of frailty according to established criteria; (5) Studies with a comparator group of non-frail participants undergoing elective hepatectomy; (6) Studies with at least one of the following outcomes: Mortality, OS, postoperative complications, and length of hospital stay; and (7) Data sufficient for effect size calculation.

The exclusion criteria were as follows: (1) Case reports, case series, editorials, reviews, and conference abstracts; (2) Studies with participants aged < 18 years; (3) Studies that involved patients undergoing emergency hepatectomy; (4) Studies focusing exclusively on patients undergoing liver transplantation, as opposed to hepatectomy; and (5) Studies without a comparison group.

In cases of studies that resulted in more than one publication, data were taken from the most complete and recent publication.

Screening and selection

After executing the search strategy across three databases and assembling the initial pool of studies, duplicate entries were eliminated. Subsequently, two researchers examined the titles and abstracts of studies for their relevance to the research question(s), followed by the full-text examination of the shortlisted studies for eligibility. All differences were resolved by consensus or a consultation with the third author.

Quality assessment, data extraction, and analysis

The Newcastle-Ottawa Scale (NOS) was employed for study quality assessment[15], and two independent reviewers used a standardized data extraction form to systematically extract relevant data such as author's name, publication year, study location, number and characteristics of the participants, duration of follow-up, the operational definition of "frailty" employed, and the outcomes of interest. All differences were resolved by consensus or a consultation with the third author.

All statistical analyses were performed with STATA version 15.0. Data are reported as relative risk (RR) when the outcome is categorical and as weighted mean difference (WMD) when it is continuous. Survival outcomes after a long-term follow-up are expressed as hazards ratio (HR). All estimates included 95% confidence interval (CI). A random-effects model was used for all analyses. To evaluate potential publication bias, we utilized both Egger's test and funnel plots[16]. $P < 0.05$ was considered significant.

RESULTS

Our search strategy yielded a total of 271 studies. Of them, 74 duplicate papers were removed. Title and abstract screening eliminated 171 studies as not meeting the predetermined criteria, leaving 26 studies. After full-text examination, 13 studies were included in the final analysis[17-29]. The selection process is summarized in Figure 1.

As shown in Table 1, all studies, except two, were retrospective cohort ones. The remaining two studies were prospective. The majority of the studies were performed in the United States (n = 6) and Japan (n = 5). One study each was done in Canada and the United Kingdom. Male gender was prevalent in all studies, and the average age of patients was between 58 and 80 years. The indication for hepatectomy in the included studies was either primary hepatic malignancy or liver metastasis. Laparoscopic resection was done in two studies and open resection in five (Table 1). Other studies did not report on the mode of surgical intervention. We detected a substantial variability in the criteria used for the assessment of frailty. Even when similar assessment tools were used, the cut-offs considered for frailty differed. The tools to assess frailty included the Modified Frailty Index (mFI), the Clinical Frailty Scale (CFS), the Johns Hopkins Adjusted Clinical Groups (JHACG) frailty assessment, and the Kihon Checklist (KCL) tool[30-36]. mFI was used in six studies, CFS was used in four studies, JHACG was used in two studies, and one study used the KCL tool.

In most studies, the tumour characteristics and the extent of resection were similar in the two groups (frail and non-frail). However, frail patients had a higher baseline American Society of Anaesthesiology score, were older, and had a higher burden of comorbidities. The total number of patients included was 84096. Of them, 23964 were frail and 60132 were non-frail. Average NOS score of the studies was 7.2, with a maximal score of 9, indicating good quality (Table 1).

Mortality and OS

Frailty correlated with an increased incidence of in-hospital mortality (RR = 2.76, 95%CI: 2.10-3.64; n = 3, I^2 = 0.0%), with some evidence of publication bias on Egger’s test (P = 0.036). Frail patients had a higher mortality at 30 d (RR = 4.60, 95%CI: 1.85-11.40; n = 5, I^2 = 87.1%) and 90 d (RR = 2.52, 95%CI: 1.70-3.75; n = 2, I^2 = 0.0%) in the postoperative period (Figure 2A). No evidence of bias was detected for mortality at 30 d (P = 0.164). Since only a small number of studies reported the risk of mortality at 90 d, Egger’s test could not be done. The funnel plots for mortality outcomes (in-hospital and 30-d) are shown in Supplementary Figures 1 and 2.

Frailty was associated with worse long-term survival (5-year OS) (HR = 2.89, 95%CI: 1.84-4.53; n = 4, I^2 = 0.0%) in patients undergoing hepatectomy (Figure 2B), with no evidence of publication bias (P = 0.08; Supplementary Figure 3).

Complications and length of hospital stay

Frailty correlated with a higher rate of “any” complications (RR = 1.69, 95%CI: 1.40-2.03; n = 7, I^2 = 90.5%) as well as major complications (as indicated by the Clavien-Dindo scale classification of grade III or higher) (RR = 2.69, 95%CI: 1.85-3.92; n = 11, I^2 = 87.0%) (Figure 2C), with no publication bias detected for both outcomes (Supplementary Figures 4 and 5). Most common complications reported in the included studies were organ/space surgical site infection, post-hepatectomy hepatic failure, pneumonia, shock/sepsis, respiratory and renal complications, cardiac and cerebrovascular complications, bleeding requiring transfusion, and bile leak. Frail patients had significantly higher length (in days) of hospital stay (WMD = 3.65, 95%CI: 1.45-5.85; n = 11, I^2 = 99.9%; Figure 2D).

Table 1 Summary of included studies

Ref.	Study design	Country	Subject characteristics	Definitions used for frailty	Sample size	Newcastle Ottawa quality score
Okada *et al* [17], 2024	Prospective cohort	Japan	Median age of 73 years; males (74%); indication for surgery - HCC; the majority with laparoscopic surgery (60.0%; proportion with laparoscopic surgery higher in non-frail subjects); extent of resection similar in two groups; no differences in age, sex, underlying hepatic diseases, or proportion of patients with comorbidities in two groups	Assessed using KCL tool (phenotypic frailty index; self-administered questionnaire comprising 25 items); score of ≥ 8 points - frail; score of < 7 points - non-frail	Frailty: 25; no frailty: 56	7
Shahrestani *et al*[18], 2023	Retrospective cohort	United States	Mean age of 62 years; males (51%); indication for surgery - liver metastasis; type of surgery not specified	JHACG frailty-defining diagnosis indicator was used. It uses 10 categories of ICD-10 codes to predict a patient's frailty status	Frailty: 766; no frailty: 749	7
Osei-Bordom *et al* [19], 2022	Retrospective cohort	United Kingdom	Median age of 65.3 years; males (57%); most common indication for surgery - colorectal liver metastases followed by HCC; the majority undergoing open surgery (86.0%; proportion similar in two groups); extent of resection similar in two groups (P = 0.20); those classified as frail had increased BMI and prevalence of hypertension, diabetes, and COPD	MFI used: Patients stratified based on an mFI cut-off - frail (mFI ≥ 1) and robust (mFI = 0)	Frailty: 634; no frailty: 1192	8
Hosoda *et al* [20], 2022	Prospective cohort	Japan	Median age of 71 years; males (65%); indication for surgery - perihilar cholangiocarcinoma; type of surgery not specified; extent of resection similar in two groups; those with frailty had higher ASA classification; no differences in proportion of patients with comorbidities (hypertension and DM) in two groups	Assessed using CFS. Score of 3 to 9 points - frail; score of 1 to 2 points - non-frail	Frailty: 44; no frailty: 35	7
Madrigal *et al*[21], 2022	Retrospective cohort	United States	Mean age of 72 years; males (52%); most frail patients were male and had malignant liver disease as the indication for resection; compared with their non-frail counterparts, frail patients were older and had higher burden of comorbidities	JHACG frailty-defining diagnosis indicator	Frailty: 3655; no frailty: 37080	7
Maegawa *et al*[22], 2022	Retrospective cohort	United States	Patients underwent hepatectomy due to primary hepatobiliary cancer or secondary liver metastasis; open surgery in the majority (> 80%); mean age of 59 years; males (51%)	mFI-5: MFI = 0 indicated no frailty; mFI ≥ 1 indicated frailty	Frailty: 11687; no frailty: 12463	8
Dauch *et al* [23], 2022	Retrospective cohort	United States	Patients underwent minor hepatectomy; open surgery (82%); mean age of 58 years; males (58%); patients with frailty had higher ASA classification	mFI-5: MFI = 0 indicated no frailty; mFI ≥ 2 indicated frailty	Frailty: 654; no frailty: 2737	8
Yamada *et al* [24], 2021	Retrospective cohort	Japan	Mean age of 80 years; males (62%); similar burden of comorbidities (diabetes and hypertension) in two groups; primary indication for surgery - HCC; similar tumour characteristics in two groups; mean follow-up of 2.6 years	Assessed using CFS; score of ≥ 4 points - frail	Frailty: 21; no frailty: 71	7
McKechnie *et al*[25], 2021	Retrospective cohort	Canada	Patients with liver resection mainly due to HCC and colorectal cancer liver metastasis; median age of 64 years; females (45%); mean BMI of 28 kg/m^2; laparoscopic resection (57%); median number of liver segments resected similar in two groups; patients with low mFI were younger, had lower ASA class, and were more likely to have > 4 METS on exercise tolerance testing, and less likely to be smokers	MFI used: Patients stratified based on an mFI cut-off - frail (mFI ≥ 0.27) and robust (mFI < 0.27)	Frailty: 58; no frailty: 351	7
Tokuda *et al* [26], 2021	Retrospective cohort	Japan	Mean age of 70 years; males (63%); burden of comorbidities (diabetes and hypertension) higher in frail group; primary indication for surgery - colorectal liver metastasis; mean follow-up of 46 mo	Assessed using CFS. Score of ≥ 4 points - frail	Frailty: 29; no frailty: 58	7
Okabe *et al* [27], 2019	Retrospective cohort	Japan	Mean age of 75 years; males (74%); indication for surgery - liver metastasis from colorectal cancer; mean BMI of subjects 23 kg/m^2; type of surgery not specified; extent of resection similar in two groups	Assessed using CFS; score of ≥ 4 points - frail	Frailty: 16; no frailty: 127	6
Chen *et al* [28], 2018	Retrospective cohort	United States	Patients underwent liver and colorectal resection (for colorectal cancer with liver metastasis); open surgery (86%); mean age of 59 years; males (55%); patients with frailty were older, and had higher ASA classi-	5-item mFI; mFI = 0 indicated no frailty; mFI ≥ 2 indicated frailty	Frailty: 225; no frailty: 1063	8

			fication, higher BMI, and greater number of comorbidities (hypertension, COPD, and DM)			
Louwers *et al*[29], 2016	Retrospective cohort	United States	Mean age of 58 years; males (49%); indication for surgery - primary hepatic malignancy and liver metastasis; open hepatectomy in the majority	MFI used: Patients stratified based on an mFI cut-off- frail (mFI ≥ 1) and robust (mFI = 0)	Frailty: 6150; no frailty: 4150	6

mFI: Modified frailty index; COPD: Chronic obstructive pulmonary disease; DM: Diabetes mellitus; ASA: American Society of Anaesthesia; BMI: Body mass index; CFS: Clinical Frailty Scale; METS: Metabolic equivalents; HCC: Hepatocellular cancer; mFI-5: 5-point Modified Frailty Index; JHACG: Johns Hopkins Adjusted Clinical Groups; ICD-10: International Classification of diseases-10; KCL: Kihon Checklist.

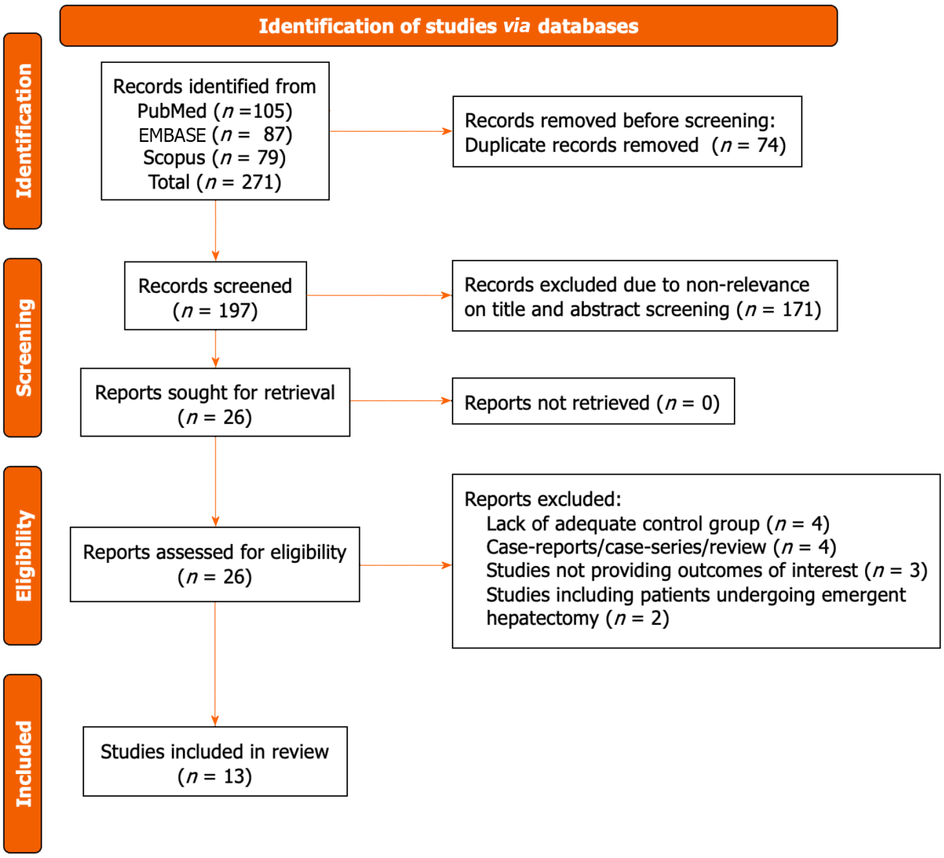
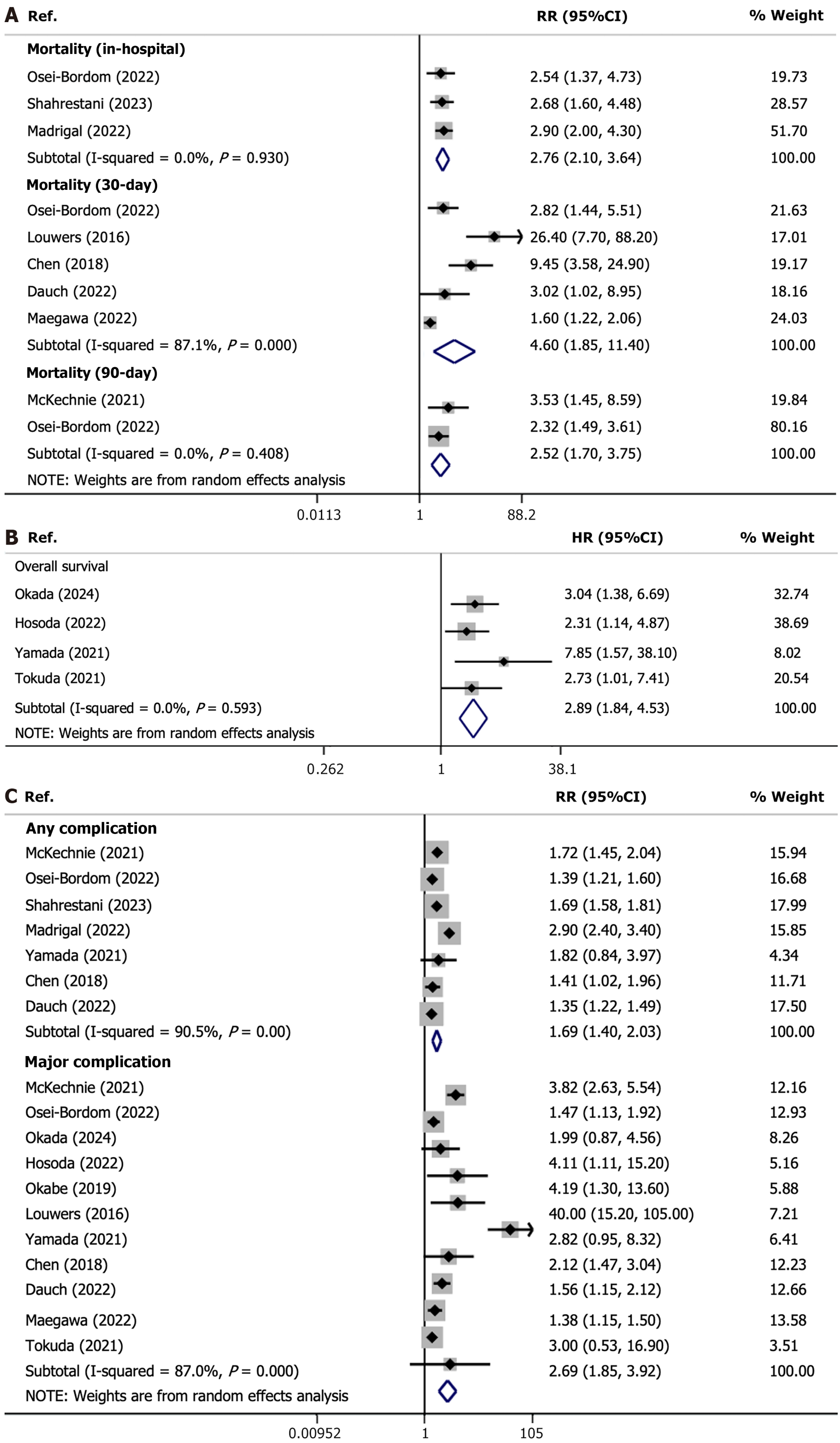


Figure 1 Selection process of studies included in the review.

DISCUSSION

This meta-analysis systematically evaluated the influence of frailty on postoperative outcomes following hepatectomy and showed that it was significantly associated with elevated risks of mortality, overall higher incidence of complications, and prolonged hospitalization. Our results further emphasize the significance of frailty assessment for optimizing patient care. A consistent association between frailty and adverse postoperative outcomes, elevated risks of short-term mortality, and poor long-term survival along with increased risk of complications underscore the consequences of reduced physiological reserves and increased susceptibility to operative stress.

Frail individuals often present with compromised cardiovascular, respiratory, and immune functions, which lowers their ability to endure the physiological strain of surgery and its aftermath[1,37,38]. This vulnerability might translate into increased susceptibility to postoperative complications, such as adverse cardiac events, respiratory failure, and infections, which may contribute to elevated mortality rates. The additional impact of frailty is linked to the disruption of the stress response that could lead to changed inflammatory status, impaired wound healing, and compromised tissue repair[39,40], which would may make frail subjects more prone to complications. Furthermore, the altered pharmacokinetics and drug metabolism, commonly associated with frailty due to changes in liver and kidney function, as well as changes in body composition, can compromise the effectiveness and safety of medications that are used during and after the surgery [41-43]. Subsequently, it may lead to adverse drug reactions, organ dysfunction, and ultimately poorer postoperative outcomes. Frail patients are also highly susceptible to infections that are associated with surgical procedures[40,44]. Compromised immune response in these patients predisposes them to developing postoperative infections, and increases the risk of mortality and long-term complications.


A Ref.
RR (95%CI)
% Weight
Mortality (in-hospital)
Osei-Bordom (2022) 2.54 (1.37, 4.73) 19.73
Shahrestani (2023) 2.68 (1.60, 4.48) 28.57
Madrigal (2022) 2.90 (2.00, 4.30) 51.70
Subtotal (I-squared = 0.0%, P = 0.930) 2.76 (2.10, 3.64) 100.00
Mortality (30-day)
Osei-Bordom (2022) 2.82 (1.44, 5.51) 21.63
Louwers (2016) 26.40 (7.70, 88.20) 17.01
Chen (2018) 9.45 (3.58, 24.90) 19.17
Dauch (2022) 3.02 (1.02, 8.95) 18.16
Maegawa (2022) 1.60 (1.22, 2.06) 24.03
Subtotal (I-squared = 87.1%, P = 0.000) 4.60 (1.85, 11.40) 100.00
Mortality (90-day)
McKechnie (2021) 3.53 (1.45, 8.59) 19.84
Osei-Bordom (2022) 2.32 (1.49, 3.61) 80.16
Subtotal (I-squared = 0.0%, P = 0.408) 2.52 (1.70, 3.75) 100.00
NOTE: Weights are from random effects analysis
0.0113
1
88.2
B Ref.
HR (95%CI)
% Weight
Overall survival
Okada (2024) 3.04 (1.38, 6.69) 32.74
Hosoda (2022) 2.31 (1.14, 4.87) 38.69
Yamada (2021) 7.85 (1.57, 38.10) 8.02
Tokuda (2021) 2.73 (1.01, 7.41) 20.54
Subtotal (I-squared = 0.0%, P = 0.593) 2.89 (1.84, 4.53) 100.00
NOTE: Weights are from random effects analysis
0.262
1
38.1
C Ref.
RR (95%CI)
% Weight
Any complication
McKechnie (2021) 1.72 (1.45, 2.04) 15.94
Osei-Bordom (2022) 1.39 (1.21, 1.60) 16.68
Shahrestani (2023) 1.69 (1.58, 1.81) 17.99
Madrigal (2022) 2.90 (2.40, 3.40) 15.85
Yamada (2021) 1.82 (0.84, 3.97) 4.34
Chen (2018) 1.41 (1.02, 1.96) 11.71
Dauch (2022) 1.35 (1.22, 1.49) 17.50
Subtotal (I-squared = 90.5%, P = 0.00) 1.69 (1.40, 2.03) 100.00
Major complication
McKechnie (2021) 3.82 (2.63, 5.54) 12.16
Osei-Bordom (2022) 1.47 (1.13, 1.92) 12.93
Okada (2024) 1.99 (0.87, 4.56) 8.26
Hosoda (2022) 4.11 (1.11, 15.20) 5.16
Okabe (2019) 4.19 (1.30, 13.60) 5.88
Louwers (2016) 40.00 (15.20, 105.00) 7.21
Yamada (2021) 2.82 (0.95, 8.32) 6.41
Chen (2018) 2.12 (1.47, 3.04) 12.23
Dauch (2022) 1.56 (1.15, 2.12) 12.66
Maegawa (2022) 1.38 (1.15, 1.50) 13.58
Tokuda (2021) 3.00 (0.53, 16.90) 3.51
Subtotal (I-squared = 87.0%, P = 0.000) 2.69 (1.85, 3.92) 100.00
NOTE: Weights are from random effects analysis
0.00952
1
105

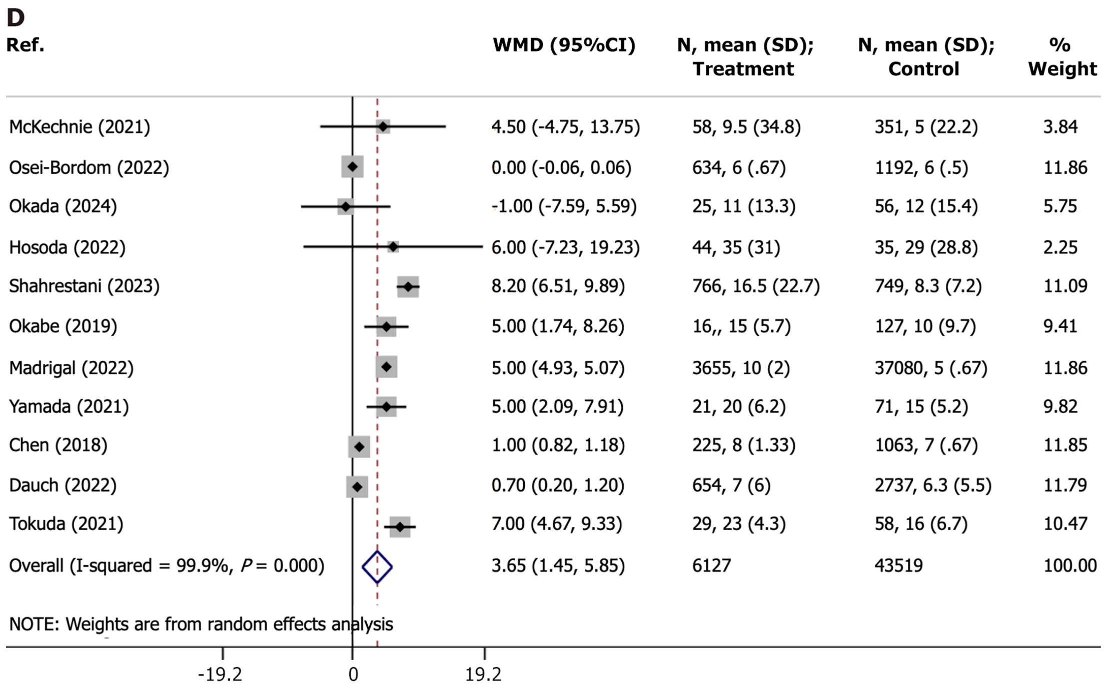


Figure 2 Frail patients compared with non-frail subjects for mortality, survival, complications, and length of hospital stay. A: Risk of mortality; B: Overall survival (5-year); C: Risk of complications; D: Length of hospital stay (in days).

Notably, malnutrition and muscle wasting that accompanies frailty can impede wound healing, compromise immune function, and delay recovery[45,46]. Moreover, the diminished functional capacity, a characteristic of frailty, often results in a slower recuperation following surgical stress: Effective postoperative rehabilitation requires physical and functional recovery which is challenging for frail patients[47,48]. The resulting prolonged immobility ultimately leads to more complications and increased mortality rates observed in this vulnerable population. Lastly, underlying chronic comorbidities such as cardiovascular disease, diabetes, and respiratory disorders can further complicate surgical procedures and lead to more postoperative complications in frail patients[49-51].

Our study demonstrated that frail patients undergoing hepatectomy require longer hospital stays. Longer hospitalization puts a substantial burden on the healthcare system and the well being of patients and their families. Our results further underscore the importance of the integration of frailty assessment into the preoperative evaluation process for these patients. Collaborative approach and timely identification of frail patients will allow to develop tailored interventions that may optimize care, minimize associated adverse effects, and improve survival of frail patients undergoing hepatectomy.

Our study has limitations. First, the included studies had some variability in patient populations, operational techniques, and classifications of outcomes, which may have led to variability in the reported data. Variations in frailty assessment methods may have contributed to variability in the classification of frailty, which may have in turn influenced the strength of our analysis. Additionally, most included studies were retrospective, which increases the risk of selection bias in including frail patients for hepatectomy. Moreover, we could not account for such confounding factors as accompanying diseases of socioeconomic variables that might have certain impact on the outcomes. Only a few studies reported long-term follow-up data for survival outcomes, which prevented us from the comprehensive assessment of the interplay between frailty and long-term survival. Nevertheless, our study provided an important synthesis of the existing literature and highlights the need for standardized approaches to frailty assessment and further investigation into interventions aimed at improving outcomes for frail individuals undergoing hepatectomy.

CONCLUSION

Our results further underscore the predictive value of frailty in assessing the risk of poor postoperative outcomes following hepatectomy. We show that frailty is linked to increased risks of mortality, complications, and prolonged hospital stays. Our results further emphasize the need for comprehensive strategies for the unique needs of such patients. Assessment of frailty needs to be incorporated into clinical practice to enhance the quality of care, guide clinical decision-making, and improve overall surgical outcomes in frail patients undergoing hepatectomy.

FOOTNOTES

Author contributions: Lv YJ, Xu GX, and Lan JR conceived and designed the study, collected the data, and performed the analysis; Lv YJ and Xu GX wrote the paper; Lan JR edited the paper; all authors have read and approved the final manuscript.

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ORCID number: Jia-Rong Lan 0009-0005-4939-9715.

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