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Frailty as a predictor of poor outcomes among patients awaiting liver transplant: a systematic review and meta-analysis

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ABSTRACT

Aim: This review sought to evaluate the significance of a functional assessment for liver transplant candidates, i.e., frailty, in the pre-transplant setting and its association with mortality and morbidities.

Background: Liver transplantation (LT) remains the treatment of choice for patients with end-stage liver disease. Due to the shortage of organs for LT, a careful selection of suitable recipients is essential. Frailty, a measure of physiologic reserve and increased vulnerability to stressors, was initially used in geriatrics and then introduced to the field of transplantation for better patient selection.

Methods: PubMed, Scopus, and Web of Science databases were reviewed up until January 2023. The search terms included: "frail*", "liver", and "transplant*". A Meta-analysis was conducted for the hazard ratios (HRs) obtained from the COX regression models. Fifty-five studies were included in this review; ten were included in the meta-analysis.

Results: The prevalence of frailty varied from 2.82% to 70.09% in the studies. Meta-analysis showed that overall frailty had a significant association with mortality (pooled adjusted HR [95%CI]: 2.66 [1.96−3.63]). Subgroup analyses revealed that both the Liver Frailty Index and Fried Frailty Index were significantly associated with mortality. Furthermore, these studies have demonstrated that this population's frailty is associated with ascites, hepatic encephalopathy, and esophageal varices.

Conclusion: According to emerging evidence, frailty is associated with increased morbidity and mortality of the patients on the LT waiting list. Further randomized trials are required to determine the efficacy and safety of variable interventions in the frail population.

Keywords: End-stage liver disease, Cirrhosis, Mortality, Hepatic encephalopathy, Ascites.

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Introduction

Liver transplantation (LT) remains the gold-standard treatment for patients with decompensated end-stage liver disease. While assessing patients during LT evaluation, the overall health status is an important step clinicians perform to identify patients who are "too sick" for LT (1). The Model for End-Stage Liver Disease (MELD) score does not account for the effects of muscle wasting, malnutrition, and functional decline, which are nearly universal in decompensated cirrhosis and contribute to excess mortality rates in this population. Patients on the LT waiting list tend to have low muscle mass and function, reflecting their poor general health, the MELD score alone might be inaccurate in determining their disease burden. Therefore, the MELD score can fail to determine the sickest patients for LT (2).

Frailty assessments have recently been investigated in LT recipients (3). Frailty, a measure of physiologic reserve and increased vulnerability to stressors, was initially described by gerontologists in community-dwelling older adults (4). It was subsequently examined

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in older general surgery patients (5), kidney transplant candidates and recipients (6-8), and recently, in LT candidates and recipients (9) and was found to be associated with adverse outcomes in these populations. This review sought to systematically review the literature to evaluate the significance of frailty assessment in patients on the LT waiting list and its role in predicting outcomes in this population.

Methods

Study design

The study was carried out according to the recommendations of Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) guidelines. The protocol was registered on PROSPERO (ID: CRD42021260256) in June 2021 after the initial literature search and was subsequently updated in January 2023. Eligible studies included observational studies or randomized controlled trials that reported the impact of frailty on the morbidity and mortality of patients with cirrhosis on the LT waitlist. To better evaluate the impact of frailty on mortality, studies comparing frail and non-frail populations or evaluating frailty based on increasing in measured frailty tools were included in the meta-analysis. Reviews, editorials, case reports, case series, animal studies, book chapters, conference abstracts, and duplicate publications were excluded. There were no language restrictions.

Search strategy

A systematic search of PubMed, Scopus, and Web of Science using the Cochrane guidelines was used to conduct the meta-analysis following THE PRISMA statement. All published studies that investigated the relationship between frailty and outcomes of patients on the LT waitlist, using the terms “frail*”, “liver” and “transplant*” were identified from the beginning of a given database through to January 18, 2023. We used asterisk to minimize the risk of missing any related search terms and have broader search results. Furthermore, the references of selected articles were manually reviewed for additional studies (Appendix 1).

Study selection

First, all records were identified from searches of the electronic databases, and duplicates were removed. Then, two investigators (SM and AM) independently evaluated all articles' retrieved titles and abstracts to identify potentially relevant studies. Lastly, full-text reviews were conducted when the reviewer(s) deemed the abstracts warranted further investigation according to our eligibility criteria. Any disagreement was resolved by discussion and consensus.

Data extraction

Data were independently extracted by SM and ET and subsequently verified by AM. Extracted data included the following: first author, study design, publication year, country of origin, tools used to assess the frailty, number of frail and non-frail patients, setting (outpatient vs. inpatient), age of the patients, proportions of women and men, duration of follow-up, primary endpoint (all-cause mortality and/or Hazard Ratio (HR)-related delisting), HR for the frailty effect, and numbers of frail and non-frail patients who achieved or did not achieve the primary endpoint.

Assessment of quality

The quality assessment of studies included in the meta-analysis part of our study was performed using the Newcastle-Ottawa Scale (NOS) for cohort studies, comprising eight items and nine scoring points. The point score system evaluated the categories of study participant selection, the results' comparability, and the outcomes' quality. A score less than or equal to 5 was rated as low quality, 6 or 7 as moderate quality, and 8 or 9 as high quality (Appendix 2). Besides, since no randomized controlled trial was included in the meta-analysis, and quality assessment for one RCT included in the systematic review was not done.

Data analysis

Meta-analyses were conducted for the HRs and Odds Ratio (OR)s obtained from the COX regression models. Adjusted data were prioritized because they account for confounding variables and are considered more reliable. Unadjusted HRs and ORs were not included in the meta-analysis. I-squared indicated statistical heterogeneity. The random-effect model was used where heterogeneity was significant at a 0.05 significant level. Also, the forest plot was provided for each study. We converted the median age to mean and standard deviation (10). Any potential publication bias was gauged statistically through the Egger linear regression test. All analyses were conducted via Stata SE, version 13.0 (Stata Corp, College Station, TX), with 2-sided $P<0.05$ considered statistically significant.

Results of the analyses are displayed as HRs and ORs with a 95% confidence interval (CI).

Results

We identified 788 titles and abstracts; after removing 294 duplicates, we reviewed 494 abstracts (Figure 1). We assessed 77 full-text articles and subsequently included 55 studies in the systematic review (2, 11-64). Of these, ten were included in the meta-analysis. All had an observational design except one article, a clinical trial (59). The included studies involved 367,423 participants and were published between 2014 and 2022. Countries of origin included the United States of America, Canada, India, Spain, Germany, England, Slovakia and Chile. Full details of included studies are provided in Appendix 3.

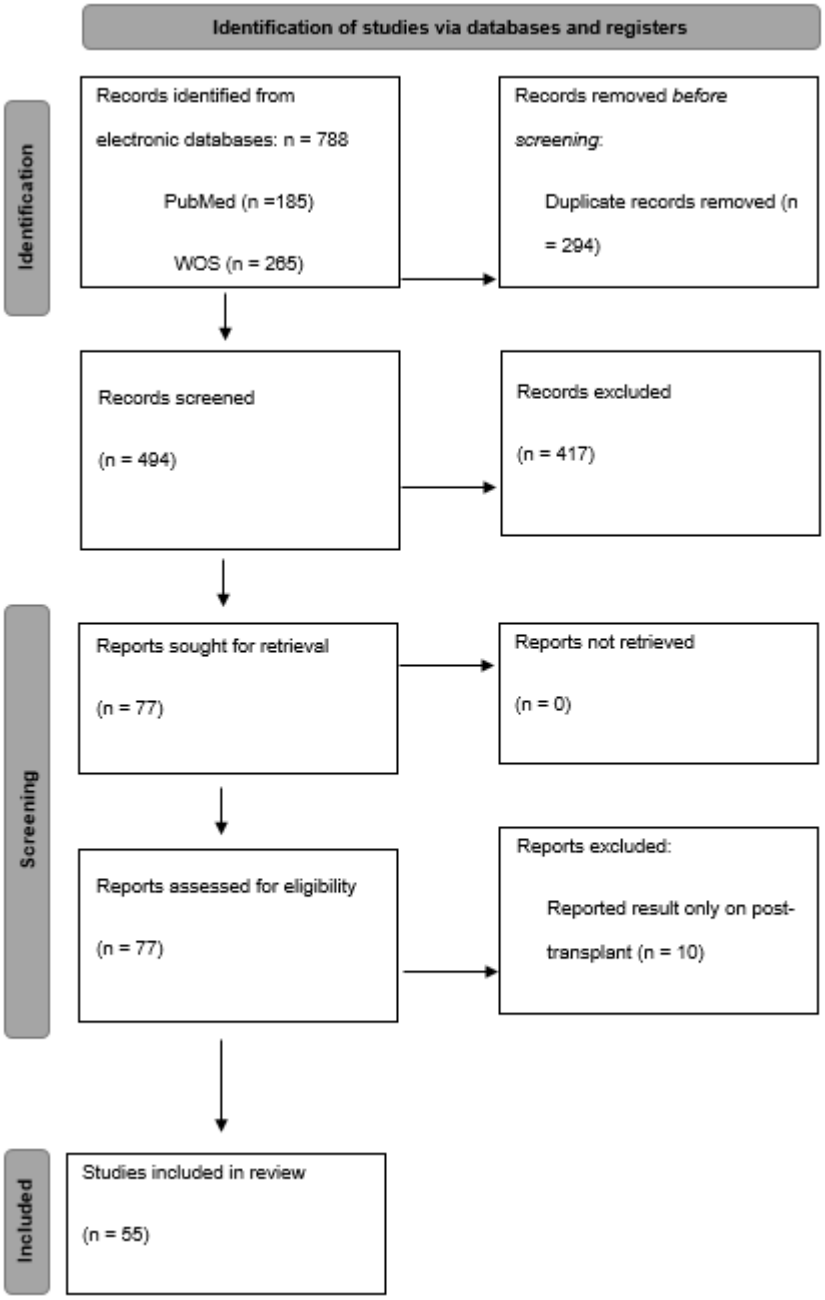

Figure 1. Preferred reporting items for systematic reviews and meta-analyses (PRISMA) flow diagram documenting the process of including and excluding studies.

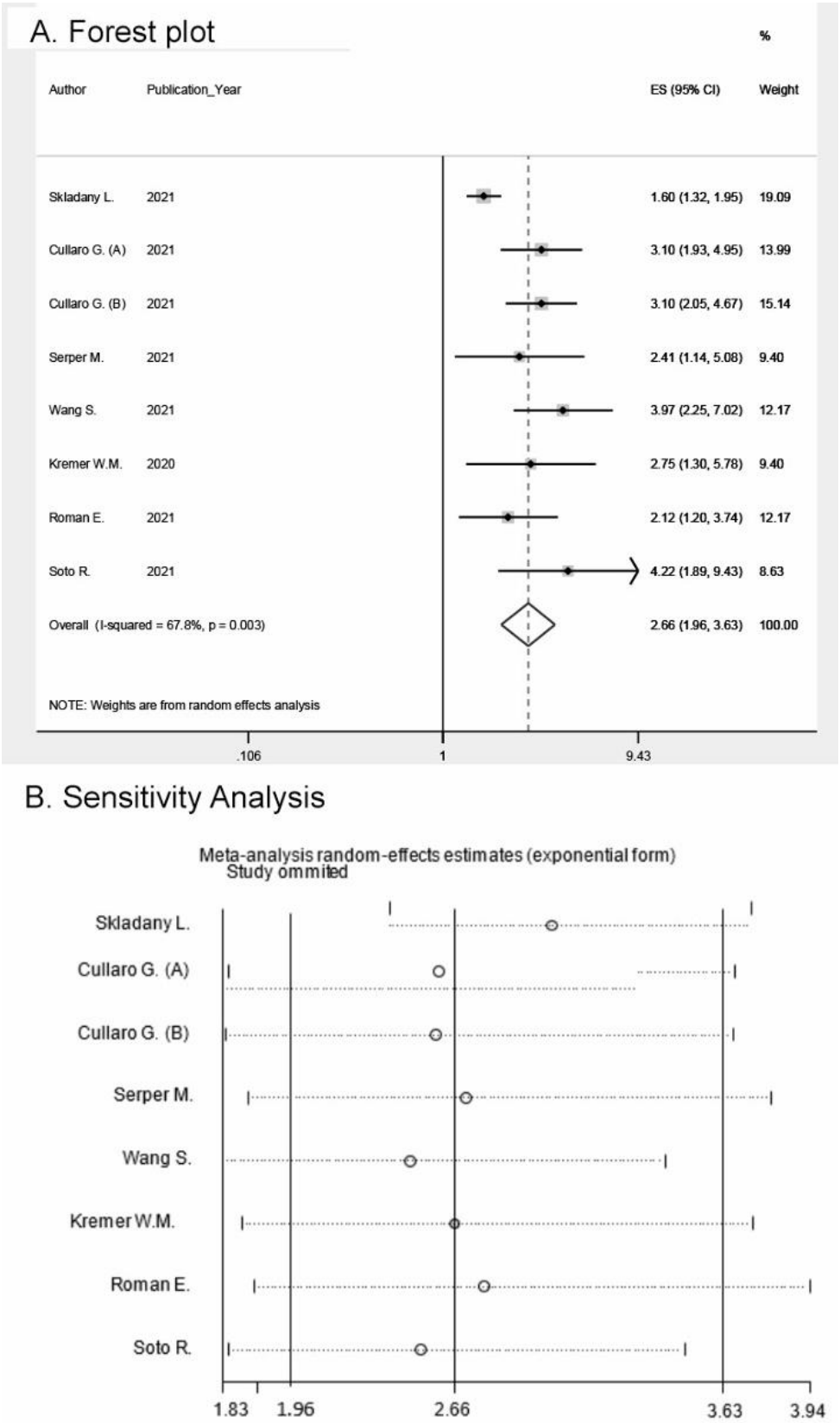

Figure 2. A and B. Forest plot of pooled adjusted Hazard Ratios and Sensitivity analysis of HRs (95% CI) for studies reporting association between frailty and mortality. Abbreviations: ES, Effect size.

Frailty tools

Frailty was assessed using different tools. These tools, their components, and other details are provided in Appendix 4. The most frequent tool in the included studies was the Liver Frailty index (LFI), which was used in 23 records (11, 15, 17, 22-24, 27-31, 33, 34, 36, 42, 45, 49, 50, 57, 58, 60, 61, 63). LFI is a performance-based tool comprising three separate tests, including grip strength, chair stands, and balance testing (28). The other most commonly used tools were fried phenotype and Fried Frailty Index (FFI) in 15 studies (2, 13, 14, 16, 18, 25, 35, 37, 43, 48, 49, 51, 53, 54, 62) followed by Karnofsky Performance Scale (KPS) in 7 studies (19, 20, 39, 40, 47, 52, 61) and Short Physical Performance Battery (SPPB) in 7 studies (2, 32, 41, 48, 49, 53, 59).

Prevalence and mortality

Based on the different tools, the number of frail population was reported in 43 studies (2, 11, 13-19, 22, 23, 25-27, 31, 34-45, 47-55, 57-63). These studies' calculated prevalence of frailty varied from 2.82% (39) to 70.09% (37).

It is worth noting that we did not pool any two studies in the meta-analysis that share the same population to minimize the risk of bias. Therefore, we only included the most comprehensive study from a center. As there are multiple studies published on the Functional Assessment in Liver Transplantation (FrAILT) cohort, a multi-center cohort of patients with cirrhosis awaiting LT lead by the University of California, San Fransisco (UCSF) (65), we only included two (2, 15) of these reports in our meta-analysis. Since studies from the FrAILT cohort share the same population, we analyzed these two studies separately in different parts of the analyses to avoid any bias.

In the first step of the meta-analysis, seven studies (15, 26, 43, 45, 50, 51, 58) were methodologically similar and reported adjusted HR for the association between frailty and mortality on LT waitlist and were included in the meta-analysis. The result of pooling these seven studies included 2,912 people, including 1,006 women and 1,906 men with a mean age of 57.78 ± 7.00. The HR index was combined as the effect size for them. The results, including the subgroup analysis, are presented in Table 1 and Figures 2 and 3. Meta-analysis showed that the overall frailty calculated by various instruments has a statistically significant association with mortality (pooled adjusted HR: 2.66 [1.96−3.63] p=<0.001, I^2 =67.8%). We did subgroup analyses for each tool separately to address the risk of bias in pooling different studies that have calculated frailty by different tools. Subgroup analysis for each instrument showed that LFI and FFI have a statistically significant association with mortality (pooled adjusted HR: 2.63 [1.75−3.97] p<0.001, I^2 =78.2% and HR: 2.81 [1.45−5.47] p=0.002, I^2 =47.0%, respectively. We also performed a sensitivity analysis, shown in Figure 2B. Overall, heterogeneity was significant (p=0.003); thus, a random model was used. Publication bias was also significant in these seven cohorts based on Egger's test (HR: 3.43 [0.79−4.74] p=0.014) (Table 1). It should be noted that the study by

Table 1. Combined indexes for studies reporting the association of frailty and mortality by different frailty tools.

Effect size		Combined				Heterogeneity			Egger's test	
		Index	95%CI	Z statistic	P value	I^2(%)[a]	Chi square	P value	Bias (95%CI)	P value
HR for mortality	Total	2.66	1.96 - 3.63	6.21	<0.001	67.8	21.75	0.003	3.43 (0.79 - 4.74)	0.014
	LFI	2.63	1.75 - 3.97	4.62	<0.001	78.2	18.34	0.001	3.57 (-0.31 - 7.46)	0.061
	CFS	2.75	1.30 – 5.78	2.66	0.008	-	-	-	-	-
	FFI	2.81	1.45- 5.47	3.05	0.002	47.0	1.89	0.169	-	-
Another effect size and other definition	OR	3.73	1.90 – 7.31	3.85	<0.001	0	0.05	0.827	-	-
	HR (continues definition of FFI)	1.37	1.23 - 1.52	4.14	<0.001	0	0.09	0.766	-	-

Abbreviations: CFS, Clinical Frailty Score; FFI, Fried Frailty Index; HR, Hazard ratio; LFI, Liver Frailty Index; OR, Odds ratio

Cullaro et al. (15) had two separate populations and results shown by A and B in Figures 2 and 3.

In the second step, two studies that reported the association of frailty and mortality in OR (26, 53) were also pooled separately, and the pooled adjusted OR was 3.73 [1.90−7.31] (p=<0.001, I^2 = 0%). From these two studies, the study by Kremer et al. (26) was also previously included in the first step of the analysis since it has reported results both in HR and OR. The results of this analysis are summarized in Table 1 and Figure 4.

In the third step, two studies that reported the association of frailty per one-point increase in FFI and mortality in HR (2, 37) were also pooled, and the pooled adjusted HR was 1.37 [1.23−1.52 (p=<0.001, I^2 =0%). The results of this analysis are summarized in Table 1 and Figure 5. All studies included in the mortality meta-analysis are summarized in Appendix 5.

Complications

Liver-related complications: ascites, hepatic encephalopathy, and/or esophageal varices

The association between frailty and liver-related complications was also considered in several studies.

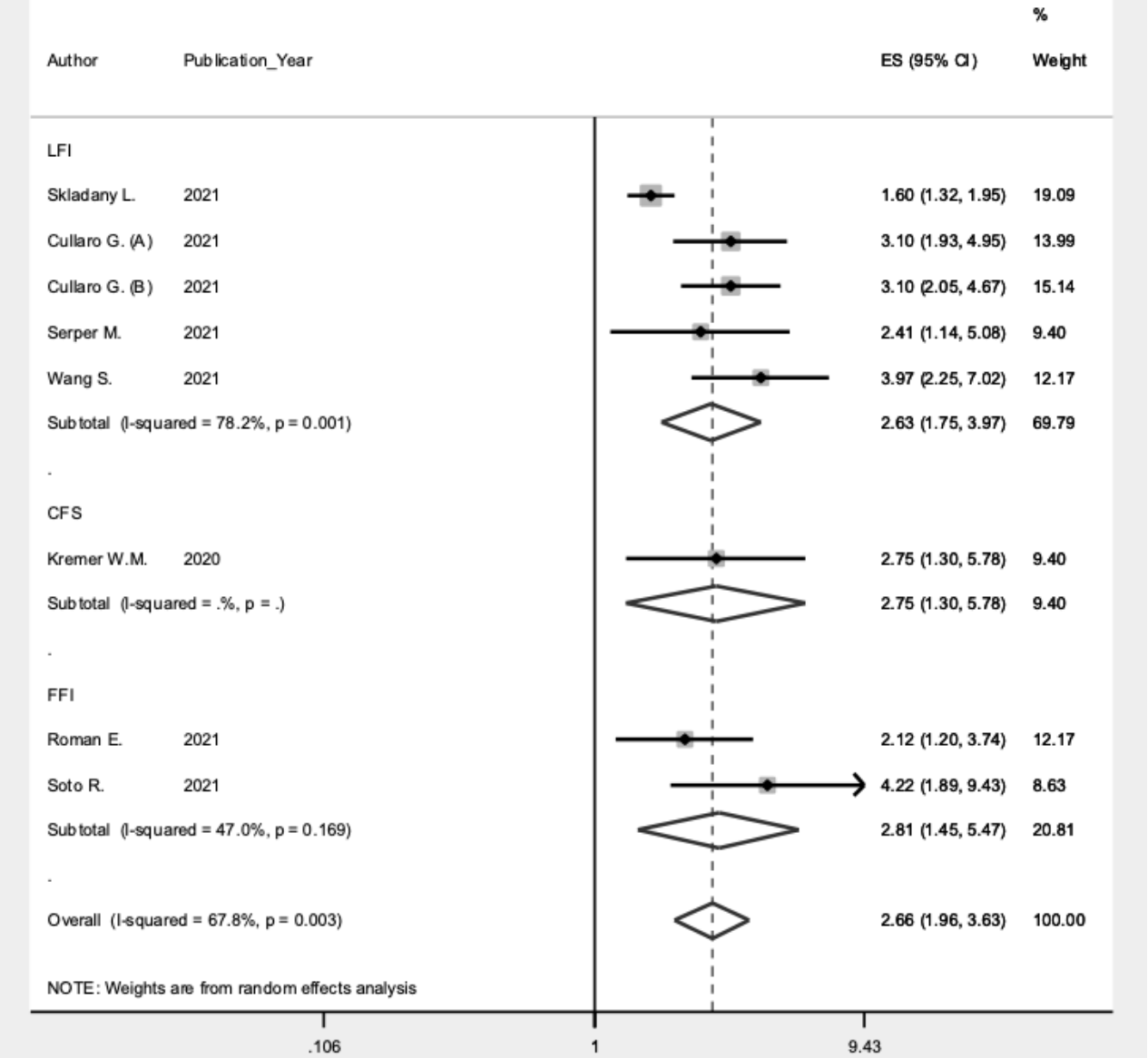

Figure 3. Subgroup analysis of HR and its 95 % CI of each study that reported an association between frailty and mortality.
Abbreviations: ES, Effect Size; CFS, Clinical Frailty Score; FFI, Fried Frailty Index; HR, Hazard ratio; LFI, Liver Frailty Index; OR

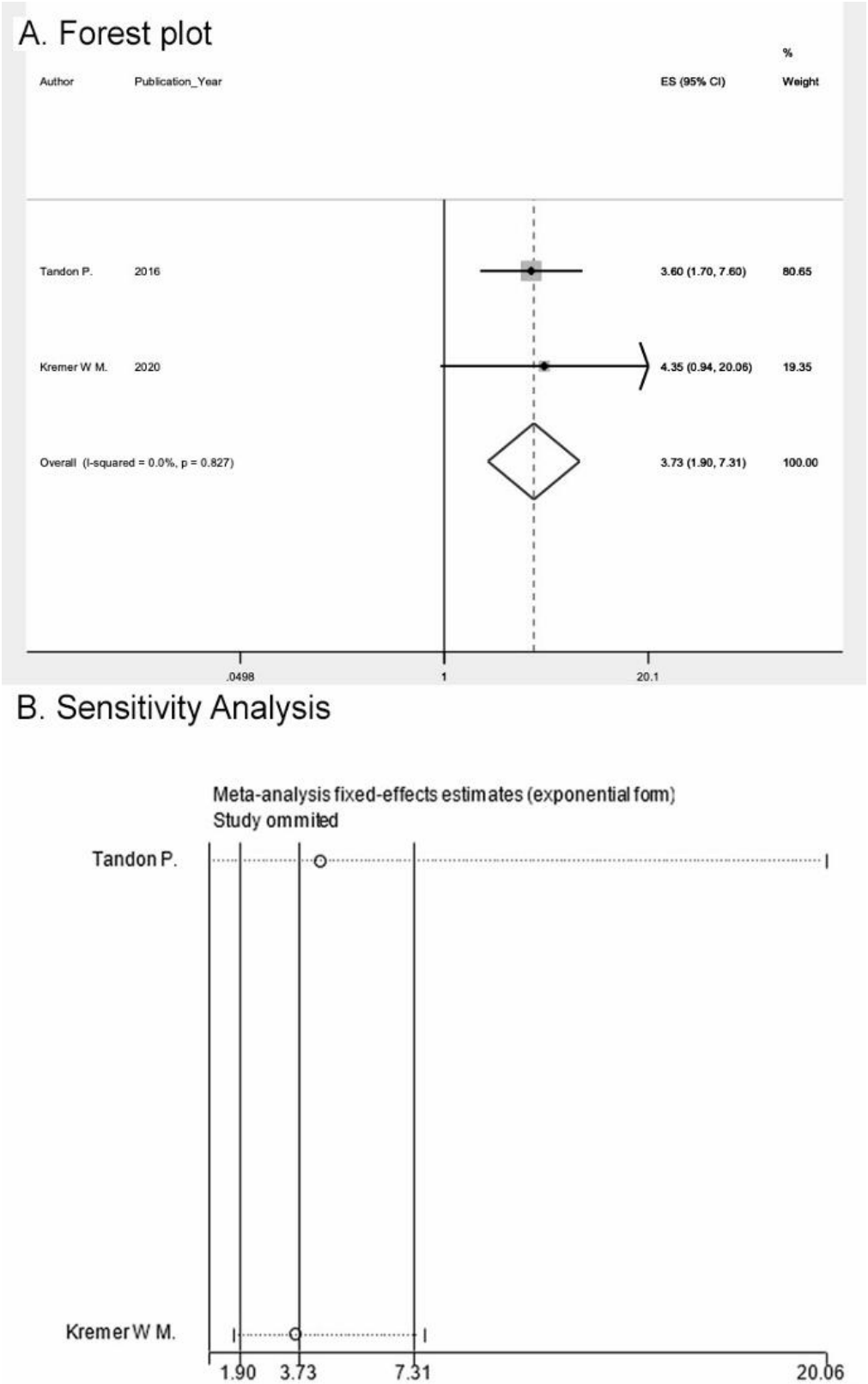

Figure 4. A and B. Forest plot of pooled Odd Ratios and Sensitivity analysis of Odds ratios (95% CI) of studies on association of frailty and mortality. Abbreviations: ES, Effect size.

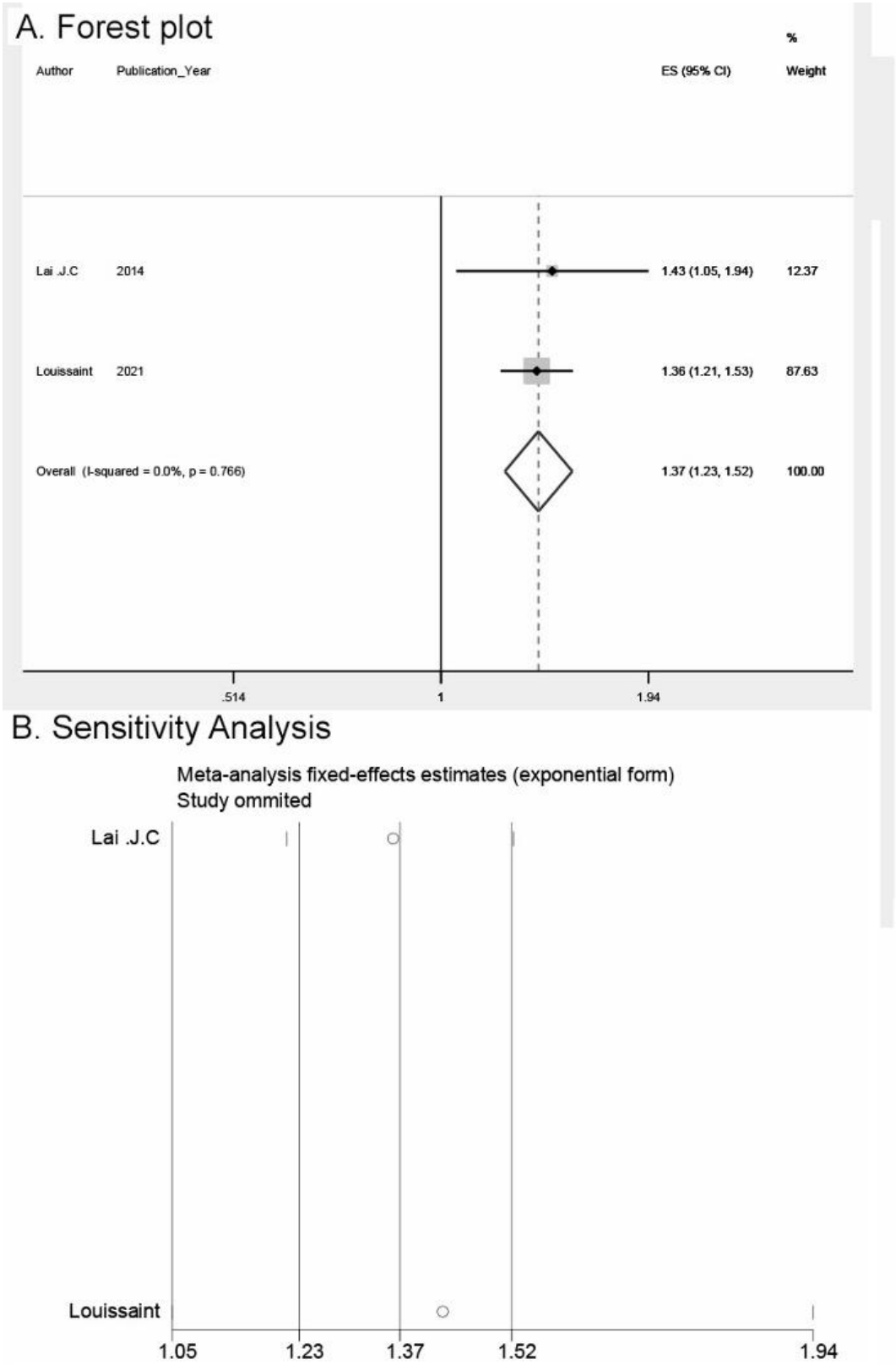

Figure 5. A and B. Forest plot of pooled adjusted HRs and Sensitivity analysis of HR (95% CI) for studies reporting the association between FFI per one-point increase and mortality. Abbreviations: ES, Effect Size; FFI, Fried Frailty Index

These complications include hepatic encephalopathy, clinical ascites and/or esophageal varices. These studies mainly assessed the association of frailty and these liver-related complications at the time of inclusion, with only one report assessing the risk of developing hepatic encephalopathy development in frail populations (41). In this study, adults with cirrhosis were observed as outpatients for six months or until their death or LT. They used a Montreal Cognitive Assessment and Clinical Frailty Scale composite to predict hepatic encephalopathy-related admissions within the follow-up period. The composite score ranged from 0 to 2, with 1 score per each abnormal value. The study showed that the composite score was associated with an increased risk of hospitalization due to hepatic encephalopathy [HR: 3.3 (1.5–7.7) and 5.7 (1.9–17.3) for the composite score of 1 and 2, respectively]. Besides, abnormal Montreal Cognitive Assessment and SPPB <10 were also associated with increased HR of hospitalization (10.34, 2.52–42.48).

Twenty-seven, 24, and five articles have respectively addressed the association between frailty and ascites (2, 11, 12, 14, 15, 18, 22, 26, 29, 31, 33, 34, 36, 40, 42-45, 47, 48, 51, 53, 54, 58, 60-62), hepatic encephalopathy (2, 12-14, 18, 26, 29, 31, 33, 34, 36, 40-42, 44-48, 51, 54, 58, 61, 62) and esophageal varices (12, 36, 51, 58, 62). Most reports assessing the association between frailty and ascites demonstrated that frailty was significantly associated with ascites, with only 3 articles showing no significant difference in ascites between frail and non-frail participants (12, 14, 45). Similarly, most of the studies reported a statistically significant association between frailty and hepatic encephalopathy with the absence of this association in only six reports (2, 12, 45, 51, 58, 62). However, the study by Soto et al. was the only one confirming the association of frailty with esophageal varices (51). Furthermore, one study reported a statistically significant association between the presence of variceal bleeding and frailty, based on the definition by LFI and the 6-minute walk test (36).

Hospitalization indices

The included studies contain information regarding factors related to hospitalization, including unplanned hospitalization, length of stay in the hospital, intensive care unit length of stay, time to re-admission, and total days of hospitalization per year. The hospitalization rate was higher among frailty patients compared to non-frail patients in five studies (43, 46, 48, 53, 58). Besides, four articles reported that frail participants had a longer hospital length of stay in comparison to non-frail participants (12, 16, 21, 45). However, there was no significant difference in length of stay in the intensive care unit between the frail and non-frail population (16). Furthermore, Serper et al. demonstrated that frailty had a statistically significant association with time to re-admission (HR: 1.53, 1.06–2.22) (45).

Psychological complications

Frailty was associated with some disorders of psychological health and wellness. Two studies reported that the prevalence of depression was significantly higher among those with frailty compared to participants without frailty (14, 51). Besides, two studies revealed that frail individuals had significantly higher rates of experiencing poor quality of life, sleep disturbance, and psychological distress (18, 37). Additionally, Deng et al. showed an increased incidence rate for psychological symptom subscale among those with frailty (RR: 1.3, 1.0–1.7, P<0.03) (17). Also, Berry, K. A. et al.'s study concluded that frailty is associated with higher odds of loneliness (OR=2.24, 1.23-4.08) (63).

Other complications

Five studies assessed the association between frailty and infections (16, 43, 45, 46, 48). Among these studies, two assessed infection rates at the baseline (43, 46), and both showed a statistically significant higher infection rate among the frail patients compared to the non-frail ones. The other 3 studies provided information regarding the incidence of infection in patients with cirrhosis (16, 45, 48). Only the study by Serper et al. showed a significantly higher incidence of infection in the frail population (8% among frail vs. 1% among non-frail, P=0.02) (45). Besides, the following complications were shown to be significantly higher among patients with frailty: the presence of comorbidities at the time of participation, including chronic kidney disease (40% vs. 20%, P=0.002) and coronary artery disease (17% vs. 7%, P=0.03) (43, 45), the occurrence of acute kidney injury (HR: 1.55, 1.05–2.30) (15), post-operative mortality in patients with cirrhosis undergoing non-transplant major surgery (HR: 1.74, 1.05–2.88) (38), incidence of falls (43, 55), progression of cirrhosis to the next clinical stage or

death (HR: 2.47, 1.63–3.76) (58) and non-home discharge (OR: 1.81, 1.14–2.86) (45).

Interventions

Among the included studies, only one was a clinical trial. In this study, a home-based exercise program was instructed to randomly select participants on the waiting list for LT (59). This program included functional strength and endurance training exercises for 12 weeks. The frailty was assessed using SPPB before and after this training program. The study showed that the SPPB score improved significantly in these patients.

Discussion

This systematic review included 55 research articles published between 2014 and 2022 that focused on aspects of frailty assessment in the pre-LT setting. Ten studies were included in a meta-analysis of the association between frailty status and mortality in patients with cirrhosis awaiting LT. The meta-analysis demonstrated that the overall frailty calculated by various instruments has a statistically significant association with mortality. Also, the subgroup analysis showed that LFI and FFI were associated with mortality.

Aside from the LT waiting list, the link between frailty and morbidity and/or mortality has been reported in other solid-organ transplant groups. Frailty has previously been associated with higher one-year mortality following referral for heart transplant assessment (66, 67). Frailty has also been linked to lower rates of preemptive transplantation, older recipient age, higher rates of delayed graft function, and longer length of stay in kidney transplant recipients (68).

The most frequent tool in the included studies was LFI, followed by FFI, KPS, and SPPB. Instruments such as the FFI (4) and SPPB (69) have been used to measure physical frailty in geriatrics and were initially developed using studies on the elderly population without known liver disease. Therefore, LFI was developed to be used in settings of chronic liver disease and consists of three tests: grip strength, chair stands, and balance testing (28). Lai et al. demonstrated that these direct physical function measures objectively measure physical frailty in patients with cirrhosis and have significant advantages over other frailty measures (2, 28, 32). Besides, the LFI improves the prognostic accuracy of the subjective clinician assessment in predicting waitlist mortality (29). So far, LFI has been primarily used in the studies on the FrAILT cohort led by the UCSF (15), and further studies from other centers can be beneficial to assess the applicability of this tool in different clinical settings.

Frailty assessments have already been routinely performed in geriatric clinics and certain medical specialties. They have shown promising potential in identifying patients who might have unfavorable outcomes following treatment or may require prehabilitation before a procedure (70). Identifying reversible components of frailty could aid in developing interventions to improve frailty in LT candidates and recipients. Exercise, nutritional support such as L-carnitine, and vitamin D have all been highlighted as possible treatment options for frailty (71, 72). Vitamin D insufficiency has been associated with falls, muscular dysfunction, and mortality in elderly adults, with supplementary vitamin D enhancing muscle function (73). Vitamin D level regulation could be a promising subject for future research in frailty optimization. Also, in the study by Williams et al., the only randomized control trial included in this meta-analysis (n= 18 patients), a 12-week home-based exercise program was used in patients awaiting LT. This study demonstrated that after 12 weeks, improvements were seen in both average daily steps and the SPPB test. They concluded that measures of aerobic and functional capacity demonstrated trends toward improvement; however, further investigations in larger randomized controlled trials were needed (59). The benefits and ongoing challenges of frailty assessment and interventions will become a priority for more healthcare providers as the world's population of older adults living with chronic conditions grows rapidly.

This study should be evaluated in terms of its strengths and limitations. Preregistration of protocols and adherence to best-practice recommendations for systematic reviews contribute to a comprehensive and low-risk bias review. We applied a robust search strategy, assessed the possibility of bias, and followed methods outlined in a published protocol. Pooled adjusted HR of the association between waitlist mortality and frailty were presented in this study. To ensure that our findings can positively impact clinical practice, we also considered several outcomes practically significant to patients, physicians, and the healthcare systems.

Limitations of this study should be pointed out before drawing any conclusions. First, different frailty tools were used in different studies, influencing the percentage of frail population among studies. Therefore, pooling all adjusted hazard ratios could not be done due to substantial heterogeneity in the meta-analysis. Second, the adjustment of the multivariable analysis varied among studies, which might affect our result. Third, as with any other meta-analysis on observational studies, there is a possibility of confounding factors and other systemic biases that are not fully controlled. Since frailty is a relatively new in the transplant setting, most studies were observational. It is now well-established that frailty is associated with various morbidities in pre-transplant and even post-transplant settings (74); therefore, further randomized trials are needed to help establish the efficacy and safety of variable intervention in frail populations.

Conclusion

The prevalence of frailty among liver transplant candidates varies remarkably in different studies. A refined measure tailored to the population with liver diseases, such as LFI, could improve risk stratification and guide frailty-specific interventions. According to emerging evidence, frailty is associated with increased morbidity and mortality of the patients on the LT waiting list. Further randomized trials are required to determine the efficacy and safety of variable interventions in frail populations.

Conflict of interests

The authors declare that there is no conflict of interest.

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