DERLEME REVIEW

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Frailty Predicts Outcomes and Prognosis of Liver Cirrhosis Patients: A Meta-Analysis and Systematic Review

Kırılganlık Karaciğer Sirozu Hastalarının Sonuçlarını ve Prognozunu Öngördürüyor: Bir Metaanaliz ve Sistematik Derleme

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ABSTRACT Studies have assessed the role of frailty in estimating the prognosis of liver cirrhosis patients; however, conflicting findings were found across the reports. The focus of this study was to look into the relationship between frailty and the prognosis of patients with liver cirrhosis. We performed a meta-analysis between August 2020 and January 2021. Data were obtained from articles present in the Web of Science, Embase, and PubMed. The comparison between frailty and the outcomes [ascites, hepatic encephalopathy, mortality, and the model for end-stage liver disease (MELD) score] among liver cirrhosis patients was calculated using a Z test. We included 1,318 liver cirrhosis patients with frailty and 3,579 patients without frailty, retrieved from 9 papers. Frail patients used to have a 1.5-fold and 1.94-fold greater chance of developing ascites [relative risk (RR): 1.65; 95% confidence interval (CI): 1.29, 2.13] and hepatic encephalopathy (RR: 1.94; 95% CI: 1.39, 2.70), respectively, compared with patients without frailty among liver cirrhosis patients. We also revealed that liver cirrhosis patients with frailty had higher odds of mortality than patients without frailty (RR: 2.10; 95% CI: 1.33, 3.34). Furthermore, a higher MELD score was noted in liver cirrhosis patients with frailty than in patients without frailty (mean difference: 2.07; 95% CI: 1.08, 3.07). Frailty is an important predictor of ascites, hepatic encephalopathy, mortality, and a higher MELD score among liver cirrhosis patients.

Keywords: Liver cirrhosis; frailty; clinical outcome; prognosis

ÖZET Karaciğer sirozu hastalarının prognozunu tahmin etmede kırılganlığın rolü çeşitli çalışmalarda değerlendirilmiştir ancak bulgular arasında çelişkiler söz konusudur. Bu çalışmada, karaciğer sirozu olan hastalarda kırılganlık ile prognoz arasındaki ilişkiyi incelemek amaçlandı. Ağustos 2020-Ocak 2021 arasında bir metaanaliz gerçekleştirildi. Veriler, Web of Science, Embase ve PubMed'de bulunan makalelerden elde edildi. Karaciğer sirozu hastalarında kırılganlık ve sonuçlar [asit, hepatik ensefalopati, mortalite ve son dönem karaciğer hastalığı modeli (model for endstage liver disease "MELD") skoru] arasındaki karşılaştırma bir Z testi kullanılarak hesaplandı. Dokuz çalışmada yer alan, kırılganlığı olan 1.318 ve kırılganlığı olmayan 3.579 karaciğer sirozu hastası araştırmaya dâhil edildi. Kırılgan hastalarda, kırılgan olmayan hastalara kıyasla asit ve hepatik ensefalopati gelişme olasılığının sırasıyla 1,5 kat [rölatif risk (RR): 1,65; %95 güven aralığı (GA): 1,29, 2,13] ve 1,94 kat (RR: 1,94; %95 GA: 1,39, 2,70) daha fazla olduğu bulundu. Kırılgan karaciğer sirozu hastalarının, kırılgan olmayan hastalara göre daha yüksek mortalite olasılığına sahip olduğu da izlendi (RR: 2,10; %95 GA: 1,33, 3,34). Ayrıca kırılgan karaciğer sirozu hastalarında, kırılgan olmayanlara göre daha yüksek bir MELD skoru kaydedildi (ortalama fark: 2,07; %95 GA: 1,08, 3,07). Kırılganlık, karaciğer sirozu hastalarında asit, hepatik ensefalopati, mortalite ve daha yüksek MELD skoru için önemli bir öngördürücüdür.

Anahtar Kelimeler: Karaciğer sirozu; kırılganlık; klinik sonuç; prognoz

Liver cirrhosis remains a primary health issue and is reported as the 23rd cause of death worldwide (31 million).[1] The incidence of this disease was 20.7 per 100,000 in 2015.[2] Moreover, liver cirrhosis is reported as the 12th primary cause of mortality and is considered the fifth primary cause of mortality in patients aged 45-54 years.[3] On the other hand, a United States report revealed that approximately 30,000 deaths occur because of liver cirrhosis annually.[4] The main problem with the unpredictable outcomes in liver cirrhosis patients is that this disease has a variety of clinical conditions

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related to worse outcomes, including ascites, bleeding, encephalopathy, and jaundice.[5] Therefore, liver cirrhosis management is challenging and may require a comprehensive approach, especially in some populations; one such population is patients with frailty.

The principal objectives of liver cirrhosis management are (1) management of etiology, (2) early identification of complications, and (3) avoidance of a critical condition. Liver cirrhosis management by early treatment of the etiology has been proven to improve the survival rate, result in better long-term prognosis, and cause recovery of the fibrosis.[6] However, predicting the prognosis of liver cirrhosis patients is challenging. Several prognostic tools have been developed in the last 2 decades to estimate the outcome and therapeutic options in patients with liver cirrhosis.[7] In the last three decades, the Child-Pugh score and modified Child-Pugh score are the prognostic tools that have been widely used for estimating the outcomes in liver cirrhosis patients.[8,9] On the other hand, the model for end-stage liver disease (MELD) score is considered to have better sensitivity and specificity and is more acceptable than the Child-Pugh score due to the subjective covariates are not included.[10-13] However, the MELD score is less able to reflect the actual situation because the nutritional and functional statuses are not assessed. Therefore, this score was expected to be a poor predictor of mortality.[14,15] Frailty is a syndrome of loss of energy, physical ability, and health, which causes vulnerability. The incidence of this syndrome generally increases in the elderly but is not an inevitable part of the aging process.[16,17] The MELD score excludes frailty, despite studies showing that frailty is related to greater lengths of stay, expanded hospitalizations, and risk of death.[14,18] In contrast, the addition of the frailty assessment to the MELD score has been proven to provide benefits in improving the prediction of mortality. However, the findings were inconsistent.[19] Therefore, a meta-analysis is required to elucidate the inconclusive evidence. In our study, the primary objective was to evaluate whether frailty is a significant predictor of mortality in liver cirrhosis patients using a meta-analysis approach.

MATERIAL AND METHODS

STUDY DESIGN

A meta-analysis was performed to examine the outcome and prognosis of liver cirrhosis patients either with or without frailty. The outcome and prognosis included ascites, hepatic encephalopathy, mortality, and the MELD score. Our study followed the preferred reporting items for systematic review and meta-analysis standards.[20]

ELIGIBILITY CRITERIA

If the study met the inclusion criteria, it was included in our review. The following were the target respondents: (1) assessed the incidence of ascites and hepatic encephalopathy, mortality, and MELD scores in liver cirrhosis patients with frailty and without frailty; (2) provided the required information to calculate the odds ratio and had a 95% confidence interval (CI); and (3) written in English. The exclusion criteria of our study were reviews, non-standard data presentation, low-quality papers, and double publications.

SEARCH STRATEGY AND DATA EXTRACTION

We started searching for the required data in the Web of Science, Embase, and PubMed on August 31, 2020. Potential outcomes were thoroughly identified, and a further search was conducted to obtain potential papers that might be included in our study. The keywords were [“Liver Cirrhosis” or “Hepatic Cirrhosis”] and [“frailty” or “frailness”] and [“prognosis” or “clinical outcome” or “ascites” or “hepatic encephalopathy” or “mortality” or “MELD scores”]. Only English-language studies were included. Articles with a large sample size were included if duplicate publications were found. We also identified potential studies from the reference list of related papers. The following information was extracted during the data extraction process: (1) author name and year, (2) study location, (3) number of samples between frailty and non-frailty groups, (4) ascites, (5) hepatic encephalopathy, (6) mortality, and (7) MELD scores. Two independent researchers (PIDA and AK) performed data extraction using a pilot form. We launched a discussion if there was disagreement.

EVALUATION OF THE ARTICLE QUALITY

Prior to the analysis, articles were graded upon that New Castle-Ottawa scale for quality. In this assessment, the evaluation of patient selection, group comparison, and exposure assessment was performed. A score of <4 indicated that the paper was of a low quality, a score of 5-6 indicated that the paper had moderate quality, and high quality was considered if the paper had a score of ≥7.[21] Articles included in our analysis were those of moderate-to-high quality. Two independent investigators (LNP and NFP) performed a study assessment using a pilot form. Other investigators (PIDA) were consulted if a disagreement was found.

STUDY MEASURES

The predictor variable in our study was frailty. Frailty is a syndrome of loss of energy, physical ability, and health with the evidence of increased susceptibility to stressors due to age-related impairment in physiologic function in the context of neuromuscular, metabolic, and immune systems.[16,17,22] The outcome covariates were ascites, hepatic encephalopathy, mortality, and MELD scores. Ascites was defined as pathological fluid accumulation in the cavity of the peritoneum.[23,24] Hepatic encephalopathy had been a classification proposed by the working group in 1998, i.e., Type A (the evidence of acute liver failure was found), Type B (the evidence of portosystemic bypass and no intrinsic hepatocellular disease was found), and Type C (the evidence of cirrhosis or portal-hypertension or portosystemic shunt was found).[25,26] The MELD score involved three assessments: serum bilirubin, creatininemia, and international normalized ratio.[27]

STATISTICAL ANALYSIS

The comparison of ascites, hepatic encephalopathy, mortality, and the MELD score between liver cirrhosis patients with and without frailty was analyzed using a Z test, and the odds ratio and 95% CI were used to calculate the effect estimates. Before assessing the correlation and effect estimates, we examined the data for the potential for publication bias and study heterogeneity. An Egger test was used to determine the strength of publication bias. The potential of publication bias was considered if the p-value was <0.05. Furthermore, heterogeneity among studies was assessed using a Q test. Data were interpreted as having heterogeneity if the p-value was <0.10. The Comprehensive Meta-Analysis software (CMA, Chicago, US) was used to calculate our meta-analysis.

RESULTS

THE ELIGIBLE STUDIES

There were 991 potential studies found in total, with 973 studies being excluded caused by inadequate titles and abstracts. Moreover, we conducted a further review of the full text of 18 potential studies. Furthermore, we excluded nine articles because of review (n=5), inadequate data for calculating the odds ratios and 95% CI (n=2), and poor study quality (n=2). Finally, nine studies (22-30) were included in our meta-analysis. Figure 1 depicts the case selection pathway for our study, and Table 1 summarizes the characteristics of the publications, and Table 2 summarize the association between frailty and the clinical outcomes.

THE OUTCOME COVARIATES OF LIVER CIRRHOSIS PREDICTED BY FRAILTY

From nine papers, we found that four outcomes were available for the meta-analysis. The evidence for ascites appeared significantly higher in liver cirrhosis patients with frailty than in those without frailty [relative risk (RR): 1.65; 95% CI: 1.29, 2.13]. We also showed that the risk of hepatic encephalopathy was increased in liver cirrhosis patients with frailty than in those without frailty (RR: 1.94; 95% CI: 1.39, 2.70). Moreover, our findings confirmed that liver cirrhosis patients with frailty had a higher risk of mortality than patients without frailty (RR: 2.10; 95% CI: 1.33, 3.34). Furthermore, a higher MELD score was found in liver cirrhosis patients with frailty than in those without frailty (mean difference: 2.07; 95% CI: 1.08, 3.07) (Figure 2, Figure 3, Figure 4, Figure 5).

SOURCE OF HETEROGENEITY

We detected heterogeneity in all data including ascites, hepatic encephalopathy, mortality, and

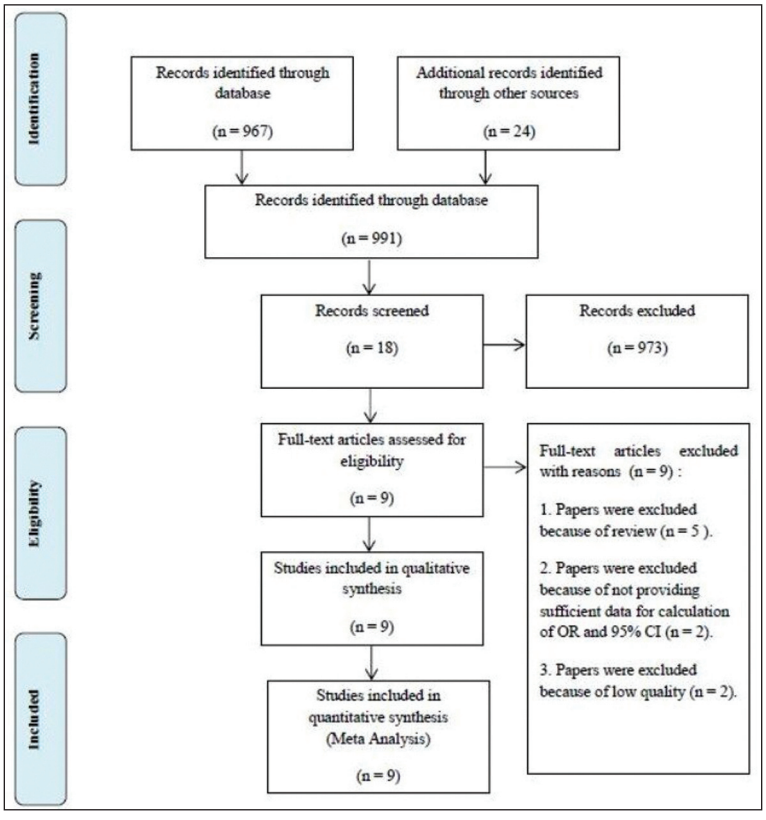

FIGURE 1: A flowchart of paper selection in our study.

TABLE 1: Baseline characteristics of studies included in our analysis.

				Sample size			
Author&year	**Country**	**City**	**Hospital**	**Frail**	**Non-frail**	**Study setting**	**NOS**
Lai et al.[28] 2020	USA	San Francisco	University of California San Francisco	151	932	Robust vs prerobust vs prefail vs fail	9
Fozouni et al.[29] 2019	USA	San Francisco	University of California San Francisco	30	163	Frail vs non-frail	9
Lai et al.[30] 2019	USA	Mixed	Multicenter	265	779	Frail vs non-frail	8
Tapper et al.[31] 2018	USA	Ann Arbor	University of Michigan Hospital	279	406	Frail vs non-frail	9
Bhanji et al.[32] 2018	USA	Rochester	Mayo Clinic, Rochester, Minnesota	88	127	Frail vs non-frail	7
Sinclair et al.[33] 2017	USA	San Francisco	University of California San Francisco	184	399	Frail vs non-frail	9
Tandon et al.[34] 2016	Canada	Alberta	Multicenter	54	246	Frail vs non-frail	8
Cron et al.[35] 2016	USA	Ann Arbor	University of Michigan Hospital	216	284	Frail vs non-frail	9
Lai et al.[36] 2014	USA	San Francisco	University of California San Francisco	51	243	Frail vs non-frail	8

HE: Hepatic encephalopathy; NOS: New-Castle Ottawa scale.

TABLE 2: Summary of the association between frailty and the clinical outcomes.

			Value						
Outcomes	**NS**	**Model**	**Frail**	**Non-frail**	**pE**	**pHet**	**p value**	**RR**	**95% CI**
Ascites	9	Random	634 (48.10)	1002 (27.91)	0.345	<0.00001	<0.0001	1.65	1.29-2.13
Hepatic encephalopathy	7	Random	465 (43.05)	730 (24.88)	0.387	<0.00001	<0.0001	1.94	1.39-2.70
Death	5	Random	69 (14.22)	98 (6.35)	0.660	0.00006	0.009	2.39	1.24-4.58
MELD	6	Random	16.36±1.65	14.41±2.15	0.904	0.04	<0.0001	2.07	1.08-3.07

Value, data were presented in number (%); NS: Number of studies; pE: p Egger; pHet: p heterogeneity; RR: Relative risk; CI: Confidence interval; MELD: Model for end-stage liver disease.

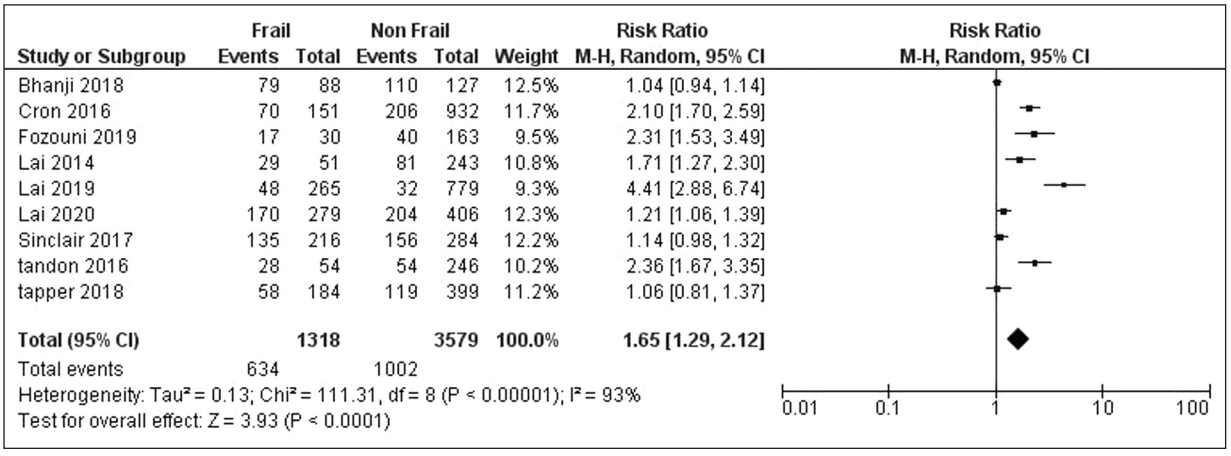

FIGURE 2: A forest plot of the association between frailty and ascites in end-stage liver disease patients.
CI: Confidence interval; df: Degrees of freedom.

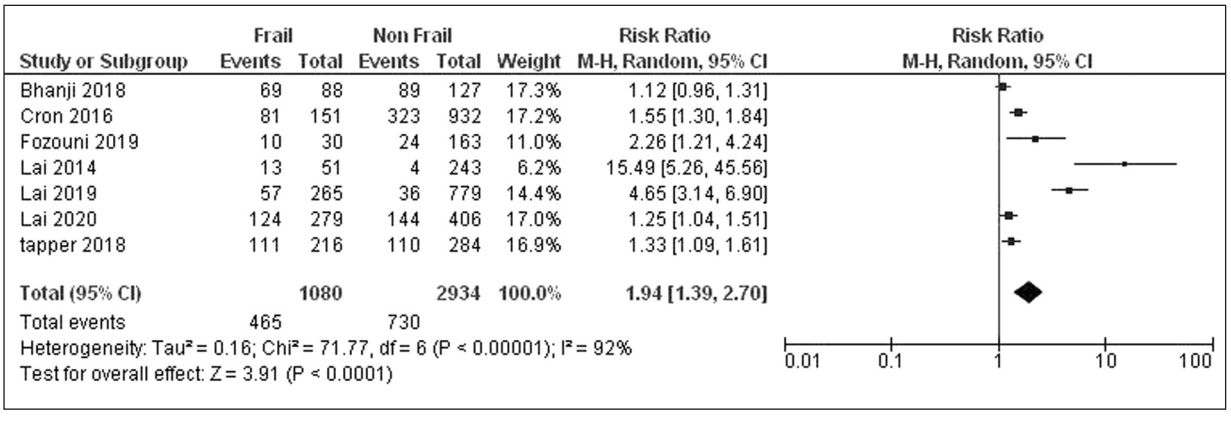

FIGURE 3: A forest plot of the association between frailty and hepatic encephalopathy in end-stage liver disease patients.
CI: Confidence interval; df: Degrees of freedom.

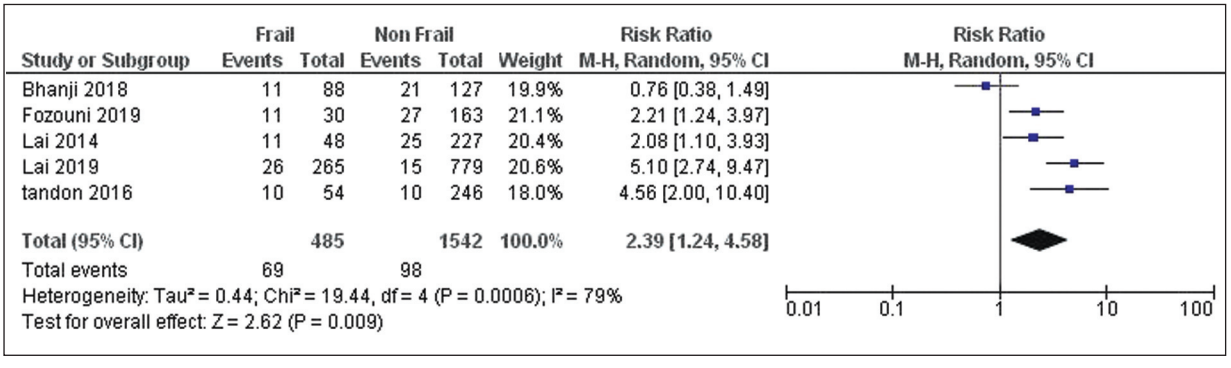

FIGURE 4: A forest plot of the association between frailty and mortality in end-stage liver disease patients.
CI: Confidence interval; df: Degrees of freedom.

MELD scores among the analyzed covariates. As a result, a random effect model was used to evaluate the data.

POTENTIAL PUBLICATION BIAS

The potential of publication bias was analyzed using an Egger test. Our analysis revealed that the potency

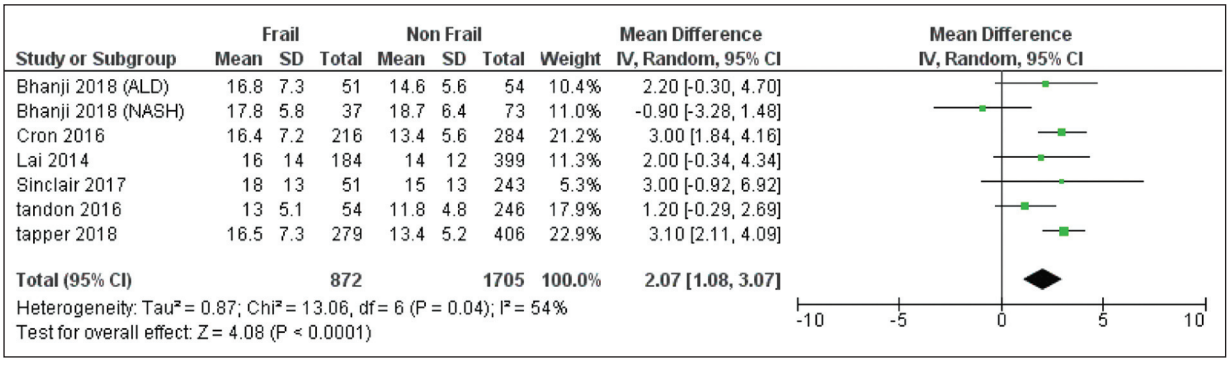

FIGURE 5: A forest plot of the association between frailty and the model for end-stage liver disease score in end-stage liver disease patients.
CI: Confidence interval; df: Degrees of freedom; SD: Standard deviation; ALD: Alcoholic liver disease; NASH: Nonalcoholic steatohepatitis.

of publication bias ($p<0.05$) was not found regarding ascites, hepatic encephalopathy, mortality, and MELD scores.

DISCUSSION

Our findings confirmed that patients with frailty had a 1.94-fold increased risk of developing hepatic encephalopathy compared with those without frailty among liver cirrhosis patients. Meta-analyses in this context have not been performed previously; therefore, we could not compare our findings. The metabolic function of skeletal muscle, which can transform ammonia into glutamine, which could then be eliminated from the body by the kidneys, is the most plausible reason for this elevated risk.[37] When liver function is impaired, this is an excellent alternative path that leads for ammonia homeostasis. Due to the obvious lack of muscle mass in sarcopenic patients, this compensatory process is reduced or excluded, increasing the risk of hyperammonemia and hepatic encephalopathy.[38] Nonetheless, because the investigations were cross-sectional, it is entirely feasible that the observed association used to have an opposite cause-and-effect orientation. Hyperammonemia, the primary underlying cause of hepatic encephalopathy, may predispose cirrhotic patients to sarcopenia by enhancing physical autophagy and decreasing muscle mass and strength.[39-41] A study in cirrhotic patients found that before hyperammonemia was corrected, there would be a substantial increment of protein synthesis.[42-44]

It can be concluded that among patients with hepatic cirrhosis, frail patients have a higher risk of developing ascites. Nowadays, the lack of evidence in meta-analysis approaches assessing the correlation between frailty and ascites among liver cirrhosis patients has made holistic comparison impossible. Moreover, the theories elucidating this topic are also not defined clearly. However, several related conditions, such as malnutrition and sarcopenia, in liver cirrhosis patients may bridge this correlation. The restriction of sodium may contribute to the change in nutritional status, leading to a lack of consumption of protein and calories, which may cause malnutrition.[45] Moreover, increased intra-abdominal pressure caused by ascites may also be considered a potential cause of reduced dietary intake in cirrhosis patients, which leads to malnutrition.[46] Malnutrition is thought to play a significant role in sarcopenia throughout patients with liver cirrhosis. Reduction of total energy consumption has already been linked to an increased risk of sarcopenia in patients with liver cirrhosis. A study reported that the median caloric consumption of sarcopenic and non-sarcopenic patients was 1,544 and 1,783 kcal, respectively.[47] Furthermore, severe factors such as repeated falls, traumas, disability, functional decline, repeated visits to the emergency room and hospitalization, cross-infection, loss of independence, admission to nursing homes, and poor quality of life are caused by sarcopenia through frailty.

Our findings also revealed that liver cirrhosis patients with frailty had a 2.10-fold increased risk of mortality and 2.07-fold increased MELD scores. Some proposed mechanism might be the reason for our findings. First, the elevated risk of mortality in liver cirrhosis patients with frailty may be associated

with a higher risk of sepsis, which may lead to an increased risk of mortality.[48-50] Sarcopenia is the loss of function and mass of muscle, and frailty is defined as functional impairment that may be associated with increased vulnerability to stressors.[51] Sarcopenia has been associated with an increased risk of severe infections in some populations, such as in elderly patients, causing impaired immunity. This suggested that the impairment of defense mechanisms might be unable to prevent microorganisms from reaching the systemic circulation.[52] Infections, particularly sepsis, are usually followed by cytokine storming, resulting in an excess of interleukin-6 and tumor necrosis factor, which have been known as the primary hepatic triggers for something like the production of acute-phase proteins.[53] Furthermore, infection in patients with liver cirrhosis may be compensated by higher production of acute-phase response proteins, which might also cause an exacerbation of hepatocyte function.[54] Second, the original MELD score has been simplified, and nowadays, it has been widely used to estimate the short-term prognosis in liver cirrhosis patients.[55-58] Patients with low MELD scores and high frailty may also provide the benefit to predict of death after hospital discharge.

To the best of the knowledge, our study was the first one to look into the outcome and prognosis of patients with liver cirrhosis who were frail. These findings have important implications for the monitoring and management of patients with liver cirrhosis. Physical frailty was more common among patients with ascites or hepatic encephalopathy, and it has been linked with mortality. We offered the hepatology community frailty as an independent predictor of outcome and prognosis throughout this study. However, future research combining frailty and standard scores may allow for considerably better prediction of outcomes and prognosis in patients with liver cirrhosis.[58]

The study had several limitations. First, several confounding factors that might affect the final findings, such as age, gender, ethnicity, nutritional status, underlying disease, family history, and environmental factors, were not included in the study. Second, seeing as included with the studies in our analysis were not randomized controlled trials, the scientific proof may be frail. Third, false-positive findings could have occurred because of the small sample size, even when combined. Thus, further studies with a larger sample size are required to investigate the association.

CONCLUSION

Our findings reveal that frailty is associated with ascites, hepatic encephalopathy, mortality, and the MELD score among liver cirrhosis patients, suggesting that frailty is a prominent predictor of the prognosis of liver cirrhosis patients. We suggest that the management of liver cirrhosis patients with frailty needs a special approach to prevent a poor prognosis.

Source of Finance

During this study, no financial or spiritual support was received neither from any pharmaceutical company that has a direct connection with the research subject, nor from a company that provides or produces medical instruments and materials which may negatively affect the evaluation process of this study.

Conflict of Interest

No conflicts of interest between the authors and / or family members of the scientific and medical committee members or members of the potential conflicts of interest, counseling, expertise, working conditions, share holding and similar situations in any firm.

Authorship Contributions

Idea/Concept: *Putu Ijiya Danta Awatara, Jonny Karunia Fajar, Syifa Mustika;* ***Design:*** *Putu Ijiya Danta Awatara, Jonny Karunia Fajar, Syifa Mustika;* ***Control/Supervision:*** *Putu Ijiya Danta Awatara, Jonny Karunia Fajar, Syifa Mustika;* ***Data Collection and/or Processing:*** *Putu Ijiya Danta Awatara, Adi Kuncoro, Nuansa Firgie Paramita, Levrita Nindya Poetri;* ***Analysis and/or Interpretation:*** *Putu Ijiya Danta Awatara, Adi Kuncoro, Nuansa Firgie Paramita, Levrita Nindya Poetri;* ***Literature Review:*** *Putu Ijiya Danta Awatara, Adi Kuncoro, Nuansa Firgie Paramita, Levrita Nindya Poetri;* ***Writing the Article:*** *Putu Ijiya Danta Awatara, Adi Kuncoro, Nuansa Firgie Paramita, Levrita Nindya Poetri,Jonny Karunia Fajar;* ***Critical Review:*** *Putu Ijiya Danta Awatara, Jonny Karunia Fajar, Syifa Mustika;* ***References and Fundings:*** *Putu Ijiya Danta Awatara, Adi Kuncoro, Levrita Nindya Poetri, Nuansa Firgie Paramita, Jonny Karunia Fajar, Syifa Mustika;* ***Materials:*** *Putu Ijiya Danta Awatara, Jonny Karunia Fajar, Syifa Mustika.*

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