Revista Española de Enfermedades Digestivas
The Spanish Journal of Gastroenterology

Title:
Prognostic value of liver stiffness in metabolic dysfunction-associated steatotic liver disease: a systematic review and meta-analysis

Authors:
Yijun Mu, Cheng Peng, Huijun Chang, Shaotong Wang, Xiuli Zuo

DOI: 10.17235/reed.2024.10353/2024
Link: PubMed (Epub ahead of print)

Please cite this article as:
Mu Yijun, Peng Cheng, Chang Huijun, Wang Shaotong, Zuo Xiuli. Prognostic value of liver stiffness in metabolic dysfunction-associated steatotic liver disease: a systematic review and meta-analysis. Rev Esp Enferm Dig 2024. doi: 10.17235/reed.2024.10353/2024.

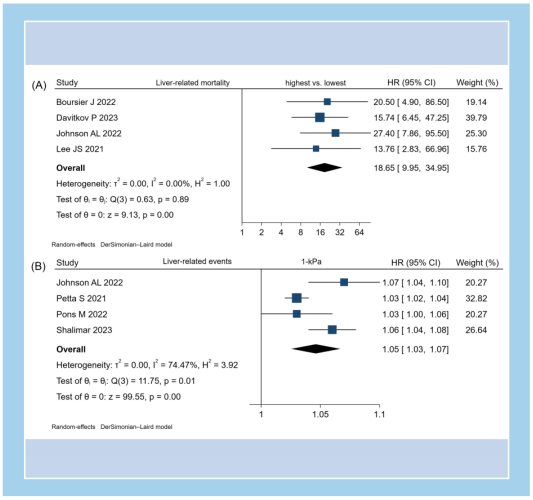
Revista Española de Enfermedades Digestivas
The Spanish Journal of Gastroenterology

Prognostic value of liver stiffness in metabolic dysfunction-associated steatotic liver disease: a systematic review and meta-analysis

Metabolic dysfunction–associated steatotic liver disease is a predominant cause of chronic liver disease. Patients with advanced fibrosis have a higher risk of overall mortality and liver-related events.

Vibration-controlled transient elastography is an internationally recognized noninvasive method for evaluating liver fibrosis through liver stiffness measurement. This technique has demonstrated significant potential in predicting clinical outcomes for patients with fatty liver disease.

A total of 20587 individuals from 7 studies were included. The pooled HRs were 18.65 (95% CI 9.95-34.95, *P* < 0.01, I^2 = 0%) in the stratification analysis of the highest versus lowest liver stiffness measurement categories. In 1-kPa analysis, the risk of liver-related events was increased with 1 kPa increment (HR 1.05, 95% CI 1.03-1.07, *P* < 0.01, I^2 = 74.47%).



Mu, et al.

Revista Española de Enfermedades Digestivas (REED)
The Spanish Journal of Gastroenterology

Revista Española de Enfermedades Digestivas
The Spanish Journal of Gastroenterology

Revista Española de Enfermedades Digestivas
The Spanish Journal of Gastroenterology

Prognostic value of liver stiffness in metabolic dysfunction-associated steatotic liver disease: a systematic review and meta-analysis

Yijun Mu[1,2], Cheng Peng[1,2], Huijun Chang[1,2], Shaotong Wang[1,2], Xiuli Zuo[1,2]

1 Department of Gastroenterology, Qilu Hospital of Shandong University, Jinan, China

2 Laboratory of Translational Gastroenterology, Qilu Hospital of Shandong University, Jinan, China

Corresponding author

Xiuli Zuo, No. 107, Wenhuaxi Road, Jinan, China; Postal code: 250012, E-Mail: zuoxiuli@sdu.edu.cn, , ORCID ID: 0000-0001-9556-8771.

Conflict of Interest

No declared.

Author contributions: Formal Analysis: C.P., S.W.; Methodology: H.C.; Writing – original draft: Y.M.; Writing – review & editing: X.Z.

Abbreviations

NAFLD, Non-alcoholic fatty liver disease. MASLD, Metabolic dysfunction-associated steatotic liver disease. LRE, Liver-related events. HCC, Hepatocellular carcinoma. VCTE, Vibration-controlled transient elastography. LSM, Liver stiffness measurement. HRs, Hazard ratios. PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses.

Visual abstract

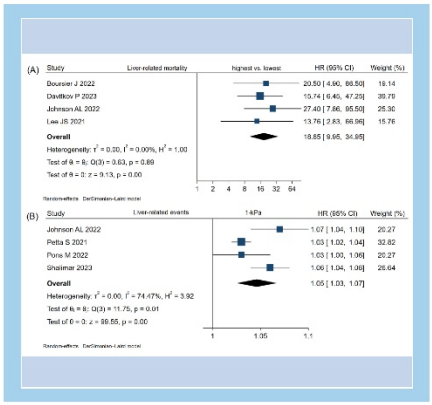
Revista Española de Enfermedades Digestivas
The Spanish Journal of Gastroenterology

Prognostic value of liver stiffness in metabolic dysfunction-associated steatotic liver disease: a systematic review and meta-analysis

Metabolic dysfunction–associated steatotic liver disease is a predominant cause of chronic liver disease. Patients with advanced fibrosis have a higher risk of overall mortality and liver-related events.

Vibration-controlled transient elastography is an internationally recognized noninvasive method for evaluating liver fibrosis through liver stiffness measurement. This technique has demonstrated significant potential in predicting clinical outcomes for patients with fatty liver disease.

A total of 20587 individuals from 7 studies were included. The pooled HRs were 18.65 (95% CI 9.95-34.95, $P < 0.01$, $I^2 = 0\%$) in the stratification analysis of the highest versus lowest liver stiffness measurement categories. In 1-kPa analysis, the risk of liver-related events was increased with 1 kPa increment (HR 1.05, 95% CI 1.03-1.07, $P < 0.01$, $I^2 = 74.47\%$).



Mu, et al.

Revista Española de Enfermedades Digestivas (REED)
The Spanish Journal of Gastroenterology

Revista Española de Enfermedades Digestivas
The Spanish Journal of Gastroenterology

Lay summary

Metabolic dysfunction–associated steatotic liver disease is a widespread chronic liver disease. Liver stiffness measurement, assessed by vibration-controlled transient elastography, has been recognized as a powerful tool for liver fibrosis assessment. The potential of liver stiffness measurement to predict clinically relevant outcomes in fatty liver disease has received considerable attention. We conducted a systematic review and meta-analysis to investigate the value of liver stiffness measurement in predicting liver-related events in metabolic dysfunction–associated steatotic liver disease patients.

A total of 20587 individuals from 7 studies were included. The pooled HRs were 18.65 (95% CI 9.95-34.95, $P < 0.01$, $I^2 = 0\%$) in the stratification analysis of the highest versus lowest liver stiffness measurement categories. In 1-kPa analysis, the risk of liver-related events was increased with 1 kPa increment (HR 1.05, 95% CI 1.03-1.07, $P < 0.01$, $I^2 = 74.47\%$).

Our study demonstrated that high liver stiffness measurement values were associated with an increased risk of liver-related events in patients with metabolic dysfunction–associated steatotic liver disease.

Abstract

Background and aims: Liver stiffness measurement, assessed by vibration-controlled transient

Revista Española de Enfermedades Digestivas
The Spanish Journal of Gastroenterology

elastography, has been recognized as a powerful tool for liver fibrosis assessment. The potential of liver stiffness measurement to predict clinically relevant outcomes in fatty liver disease has received considerable attention. This study aimed to investigate the prediction of liver-related events in metabolic dysfunction–associated steatotic liver disease patients by liver stiffness measurement value on transient elastography.

Methods: We systematically searched the Electronic databases including PubMed, EMBASE, Cochrane Library, and ClinicalTrials.gov until 6 September 2023. The hazard ratios adjusted for confounders were extracted and pooled by random-effects model analysis.

Results: A total of 20587 individuals from 7 studies were included. The pooled HRs were 18.65 (95% CI 9.95-34.95, $P < 0.01$, $I^2 = 0\%$) in the stratification analysis of the highest versus lowest liver stiffness measurement categories. In 1-kPa analysis, the risk of liver-related events was increased with 1 kPa increment (HR 1.05, 95% CI 1.03-1.07, $P < 0.01$, $I^2 = 74.47\%$).

Conclusions: Metabolic dysfunction–associated steatotic liver disease patients with high liver stiffness measurement values were at an increased risk of liver-related events. Liver stiffness measurement can be used as a prognostic tool to achieve risk stratification in fatty liver patients.

Keywords: Metabolic dysfunction-associated steatosis liver disease. Vibration-controlled transient elastography. Liver stiffness measurement. Liver-related events. Meta-analysis.

Introduction

Non-alcoholic fatty liver disease (NAFLD) is the leading cause of chronic liver disease, which affects more than 25% of adults globally (1). In recent years, recognizing the significance of metabolic dysfunction in the onset and progression of NAFLD, metabolic dysfunction–associated steatotic liver disease (MASLD) has been proposed as a new nomenclature (2). Despite differences in the diagnostic criteria between MASLD and NAFLD, multiple studies have demonstrated that the populations identified by the two diagnostic criteria overlap almost entirely (3,4). MASLD patients with advanced fibrosis have a significantly increased risk of overall mortality and liver-related events (LRE) (5,6). LRE is considered to be an important factor affecting patients' survival and quality of life, including the occurrence of hepatic decompensation or the development of hepatocellular carcinoma (HCC) (7-9). Therefore, it is crucial to detect fibrosis early on, and those

who have advanced fibrosis deserve special attention (4). Liver biopsy has been applied as the gold standard for evaluating liver fibrosis degree (10). However, this is an invasive procedure with a potential risk of serious clinical complications and poor acceptance. In addition, due to the high prevalence of MASLD, it would be challenging to implement this strategy for screening and follow-up in clinical practice (11,12). Vibration-controlled transient elastography (VCTE) is an internationally recognized noninvasive technique. VCTE can be used to evaluate liver fibrosis by liver stiffness measurement (LSM) with excellent diagnostic accuracy and high reliability (13,14). Recently, several studies have shown the ability of LSM to predict the risk of LRE (15-17). This systematic review and meta-analysis pooled HRs of different values for LRE to elucidate the utility of LSM values by VCTE for predicting the incidence of LRE in MASLD patients.

Methods

Search strategy

We searched all relevant literature from electronic databases including PubMed, EMBASE, Cochrane Library, and ClinicalTrials.gov up to 6 September 2023. The following keywords were used: liver stiffness measurement, LSM, FibroScan, transient elastography, VCTE, fatty liver, steatosis, LRE, liver-related event, liver-related outcome, decompensation, variceal bleeding, ascites, liver failure, hepatic failure, hepatic encephalopathy, liver neoplasm, liver cancer, liver carcinoma, hepatic neoplasm, hepatic cancer, hepatocellular cancer. Following the duplicates removed, two authors independently screened all titles and abstracts to eliminate irrelevant studies and then conducted full-text reviews for potentially eligible studies. Then a manual evaluation of the reference lists of all eligible studies was conducted. In addition, two investigators extracted relevant information and assessed the quality of the included studies. Disagreements of studies were resolved by discussion to achieve a consensus. This meta-analysis was reported based on the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement and registered on the PROSPERO (CRD42023461039) (18).

Inclusion/exclusion criteria

Studies published in English were considered as potentially eligible if they met the inclusion criteria: (1) MASLD patients > 18 years of age, (2) LSM values by VCTE were used for the degree of liver

fibrosis assessment, and (3) LREs were reported in different LSM values and the adjusted hazard ratio (aHR) with 95% confidence interval (CI) could be extracted. If the datasets overlapped in different studies, the one with the larger sample size was included. The exclusion criteria were as follows: (1) abstracts, letters, reviews, case reports, case-control studies, meta-analyses, and animal studies; (2) studies with unavailable statistical data.

Data extraction

Two authors completed data extraction independently, including the first author's name, publication year, population number, follow-up period, average age, sex ratio, study design, outcomes, aHR, and confounders of the clinical outcomes.

Data synthesis and analysis

In this study, the LRE was defined as a composite endpoint including the occurrence of hepatic decompensation (variceal bleeding, ascites, liver failure, hepatic encephalopathy) and/or the development of HCC. The pooled HRs and 95% CIs were calculated and the random effects model was performed for statistical analysis (19). To better characterize the relationship between LSM and LRE, we first pooled HRs in different stratification of LSM values. However, considering the different stratification categories used in different studies, we only conducted a preliminary assessment for the highest versus lowest LSM categories. Since the LSM was a continuous value, we then pooled HRs for 1-kPa analysis to further confirm the predictive capability of different LSM values. Heterogeneity was measured by I^2, and $I^2 \geq 50\%$ suggested significant heterogeneity between studies (20). When I^2 results were ≥ 50%, we then conducted subgroup analyses and sensitivity analyses to investigate the potential source of heterogeneity. The publication bias was estimated by Egger's test. Study quality assessment was conducted by the Newcastle-Ottawa Scale (21,22). Review Manager V.5.4 and STATA.17 were utilized for all statistical analyses.

Results

Search results

Our search yielded a potential 1705 studies through database search. After removing 216 duplicates and excluding 1464 non-relevant studies, we conducted a thorough full-text review of 25 studies. Ultimately, 7 studies were included (Figure 1).

Study characteristics

The relevant information of all included studies was collected and summarized in Table 1. This meta-analysis included 5 multi-center retrospective cohort studies and 2 single-center retrospective cohort studies (16,17,23-27). In the cohort studies, the follow-up period ranged from 1.1 to 5.1 years, and HRs adjusted for different confounders were all directly extracted. To evaluate the impact of LSM values on LRE, we could extract HR from 4 studies for stratification analysis and 4 studies for 1-kPa analysis.

Outcomes

Four studies with 17595 MASLD patients were included for stratification analysis, investigating the association between different categories of LSM and LRE. Compared with the lowest category groups, patients in the highest LSM category groups had a considerably increased incidence of LRE (HR 18.65, 95% CI 9.95-34.95, $P < 0.01$, Figure 2A). For 1-kPa analysis, two multi-center studies and two single-center studies were included to evaluate the predictive value of LSM for LRE. The finding suggested that the risk of LRE could be increased by 5% with a 1-kPa increment in LSM (HR 1.05, 95% CI 1.03-1.07, $I^2 = 74.47\%$, $P < 0.01$, Figure 2B). A subgroup analysis based on the number of study centers was performed (Figure 3). The risk of LRE was increased both in the single-center study subgroup (HR 1.05, 95% CI 1.02-1.08, $P = 0.10$) and multi-center study subgroup (HR 1.05, 95% CI 1.01-1.09, $P = 0.01$). Then the sensitivity analysis was conducted by removing each study in turn and the heterogeneity was reduced after excluding the study by Petta et al (i.e., I^2 reduced from 74.47% to 47.52%).

Publication bias and quality assessment

Funnel plots and Egger's test were conducted to assess the publication bias of 7 studies (Figure 4). There was no obvious asymmetry distribution among studies in the group contributing to the association between LSM and the risk of LRE. Similarly, Egger's test showed no significant publication bias, regardless of stratification analysis or 1-kPa analysis ($P = 0.6985, 0.4386$). The score of the quality assessment ranged from 7 to 8 on the Newcastle-Ottawa Scale, and the detailed results of the study quality assessment were shown in Table 1.

Revista Española de Enfermedades Digestivas
The Spanish Journal of Gastroenterology

Discussion

This meta-analysis included 7 studies to evaluate the relationship between LSM values and the risk of LRE. The HRs for the outcome in these studies were directly extracted, and adjusted for age, sex, or other confounders. The results showed that an increased risk of LRE was linked to higher LSM on VCTE for MASLD patients, in stratification analysis and 1-kPa analysis, indicating that a high LSM value on VCTE might be a critical prognostic marker for LRE in patients with MASLD.

Since heterogeneity was present in the assessment of LRE for 1-kPa analysis, we conducted a subgroup analysis based on the number of clinical centers of the study. The results suggested that the number of study centers might not be the potential source of heterogeneity. Subsequently, a sensitivity analysis was conducted, revealing that the heterogeneity of the research would be significantly reduced following the exclusion of the study by Petta (17). This study retrospectively included 1039 MASLD patients from multiple research centers. All patients were tracked for at least 6 months and LREs were recorded during the follow-up period, including the occurrence of hepatic decompensation or HCC. In this study, Petta found that patients with higher LSM values on VCTE were more likely to have an occurrence of hepatic decompensation (aHR 1.03, 95% CI 1.02-1.04) and HCC (aHR 1.03, 95% CI 1.00-1.04) by Cox multifactorial analysis. The results demonstrated the potential of LSM values in predicting the development of LRE.

A previous meta-analysis reported a correlation between LSM values and the risk of different clinical outcomes in chronic liver disease patients. The results suggested that one kPa rise in LSM was linked with an 11% increased risk of LRE development (RR 1.11, 95% CI 1.05-1.17), and the pooled RR (95% CI) for all-cause mortality was 1.08 (1.06-1.11) (28). However, patients included in the study suffered from various liver diseases and there was no subgroup analysis of the etiology of chronic liver diseases. Therefore, it is challenging to definitively suggest the prognostic value of LSM for chronic liver diseases of different etiologies. Another meta-analysis explored the relationship between LSM and all-cause mortality by pooling HRs in MASLD patients without investigating the association between LSM and LRE (29). When exploring the clinical outcomes of MASLD, all-cause mortality was considered a significant indicator. However, LRE should also be taken seriously because it significantly affects the quality of life of patients. Therefore, different from previous studies, our meta-analysis focused on LRE with MASLD patients and explored the relationship

between LSM values and LRE. The results confirmed that there was a positive correlation between LSM value and risk of LRE.

In recent years, some studies have suggested that the cutoff point of 8 kPa was associated with advanced liver fibrosis in MASLD and with the potential to indicate the risk of future decompensation (30-32). Baveno VII has proposed criteria for identifying patients with compensated advanced chronic liver disease (33). LSM values below 10 kPa indicate a low risk of disease progression and liver decompensation. Patients with LSM values equal to or above 15 kPa are considered at increased risk of LRE or other complications. In addition, Baveno VII has pointed out that LSM values at different thresholds (10-15-20-25 kPa) were of great value in predicting decompensation and liver-related death in patients with MASLD or other chronic liver diseases. There are some limitations in this study. In our meta-analysis, the included studies stratified the LSM value of MASLD patients in different categories and we were unable to obtain consistent stratification subgroups to assess the outcomes of patients with different LSM values directly. Therefore, to measure the relationship between LSM values and LRE of MASLD patients, we extracted and pooled the aHR of LRE in the highest versus lowest categories from different studies for stratification analysis preliminarily. At the same time, 1-kPa analysis was conducted to further clarify the prognostic value of LSM on VCTE in MASLD patients, but many factors could affect the results such as age, sex, BMI, and platelet count. So we directly extracted the data after adjusting for confounders from the included studies. The differences in confounders adjusted between the included studies may account for the heterogeneity in the results of our meta-analysis. In addition, the increase of LRE risk may be more pronounced for each 1-kPa increment in the central stratification of LSM values. However, we did not perform further analysis on the central values due to stratification differences across studies, which is one of the limitations of our study. In the future, with the development of more relevant studies, we would perform dose-response analysis to further explore the relationship between LSM and LRE.

In conclusion, our meta-analysis verified the prognostic efficacy of LSM in predicting LRE of MASLD patients and quantified the increased risk of LRE with each 1-kPa increment in LSM value. LSM can be used as a tool to help physicians identify high-risk patients and develop more rational management strategies for patients. In the future, the potential of LSM in predicting the LRE of MASLD patients could be further explored by the change in LSM values during the follow-up period.

Revista Española de Enfermedades Digestivas
The Spanish Journal of Gastroenterology

Data availability

All data used for the analysis of this study are included in this article.

Funding

There was no funding source for this paper.

References

1. Riazi K, Azhari H, Charette JH, et al. The prevalence and incidence of NAFLD worldwide: a systematic review and meta-analysis. Lancet Gastroenterol Hepatol 2022;7:851-861.
2. Rinella ME, Lazarus JV, Ratziu V, et al. NAFLD Nomenclature consensus group. A multi-society Delphi consensus statement on new fatty liver disease nomenclature. Hepatology. 2023;78:1966–1986.
3. Ratziu V, Boursier J. Confirmatory biomarker diagnostic studies are not needed when transitioning from NAFLD to MASLD. J Hepatol 2024;80:e51-e52.
4. Song SJ, Lai JC, Wong GL, et al. Can we use old NAFLD data under the new MASLD definition? J Hepatol 2024;80:e54-e56.
5. Ong JP, Pitts A, Younossi ZM. Increased overall mortality and liver-related mortality in non-alcoholic fatty liver disease. J Hepatol 2008;49:608-12.
6. Ekstedt M, Hagström H, Nasr P, et al. Fibrosis stage is the strongest predictor for disease-specific mortality in NAFLD after up to 33 years of follow-up. Hepatology 2015;61:1547-54.
7. Angulo P, Kleiner DE, Dam-Larsen S, et al. Liver Fibrosis, but No Other Histologic Features, Is Associated With Long-term Outcomes of Patients With Nonalcoholic Fatty Liver Disease. Gastroenterology 2015;149:389-397.e310.
8. Hagström H, Kechagias S, Ekstedt M. Risk for hepatic and extra-hepatic outcomes in nonalcoholic fatty liver disease. J Intern Med 2022;292:177-189.
9. Taylor RS, Taylor RJ, Bayliss S, et al. Association Between Fibrosis Stage and Outcomes of Patients With Nonalcoholic Fatty Liver Disease: A Systematic Review and Meta-Analysis. Gastroenterology 2020;158:1611-1625.e12.
10. Bruzzi JF, O'Connell M, Murray JG. Liver biopsy. N Engl J Med 2001;344:2030.

11. Mueller M, Kratzer W, Oeztuerk S, et al. Percutaneous ultrasonographically guided liver punctures: an analysis of 1961 patients over a period of ten years. BMC Gastroenterol 2012;12:173.
12. Ratziu V, Charlotte F, Heurtier A, et al. Sampling variability of liver biopsy in nonalcoholic fatty liver disease. Gastroenterology 2005;128:1898-906.
13. Vuppalanchi R, Siddiqui MS, Van Natta ML, et al. Performance characteristics of vibration-controlled transient elastography for evaluation of nonalcoholic fatty liver disease. Hepatology 2018;67:134-144.
14. Boursier J, Vergniol J, Guillet A, et al. Diagnostic accuracy and prognostic significance of blood fibrosis tests and liver stiffness measurement by FibroScan in non-alcoholic fatty liver disease. J Hepatol 2016;65:570-8.
15. Shili-Masmoudi S, Wong GL, Hiriart JB, et al. Liver stiffness measurement predicts long-term survival and complications in non-alcoholic fatty liver disease. Liver Int 2020;40:581-589.
16. Johnson AL, Hayward KL, Patel P, et al. Predicting Liver-Related Outcomes in People With Nonalcoholic Fatty Liver Disease: The Prognostic Value of Noninvasive Fibrosis Tests. Hepatol Commun 2022;6:728-739.
17. Petta S, Sebastiani G, Viganò M, et al. Monitoring Occurrence of Liver-Related Events and Survival by Transient Elastography in Patients With Nonalcoholic Fatty Liver Disease and Compensated Advanced Chronic Liver Disease. Clin Gastroenterol Hepatol 2021;19:806-815.e5.
18. Page MJ, McKenzie JE, Bossuyt PM, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. Bmj 2021;372:n71.
19. Borenstein M, Hedges LV, Higgins JP, et al. A basic introduction to fixed-effect and random-effects models for meta-analysis. Res Synth Methods 2010;1:97-111.
20. Higgins JP, Thompson SG, Deeks JJ, et al. Measuring inconsistency in meta-analyses. Bmj 2003;327:557-60.
21. Wells GA, Shea B, O'Connell D, et al. The Newcastle-Ottawa Scale (NOS) for assessing the quality of nonrandomised studies in meta analyses. Ottawa Hospital Research Institute, Ottawa (2011).
22. Egger M, Davey Smith G, Schneider M, et al. Bias in meta-analysis detected by a simple, graphical test. Bmj 1997;315:629-34.
23. Lee JS, Sinn DH, Park SY, et al. Liver Stiffness-Based Risk Prediction Model for Hepatocellular

Carcinoma in Patients with Nonalcoholic Fatty Liver Disease. Cancers 2021;13:4567.

24. Boursier J, Hagström H, Ekstedt M, et al.Non-invasive tests accurately stratify patients with NAFLD based on their risk of liver-related events. J Hepatol 2022;76:1013-1020.
25. Davitkov P, Hoffman K, Falck-Ytter Y, et al. Increasing liver stiffness is associated with higher incidence of hepatocellular carcinoma in hepatitis C infection and non-alcoholic fatty liver disease-A population-based study. PLoS One 2023;18(1):e0280647.
26. Pons M, Rivera-Esteban J, Manzano R, et al. Non-Invasive Tests of Liver Fibrosis Help in Predicting the Development of Hepatocellular Carcinoma among Patients with NAFLD. J Clin Med 2022;11(1):2466.
27. Shalimar, Sheikh SS, Biswas S, et al. Incidence and Predictors of Liver-Related Events in Patients With Nonalcoholic Fatty Liver Disease. J Clin Exp Hepatol 2023;13:37-47.
28. Shen Y, Wu SD, Wu L, et al. The prognostic role of liver stiffness in patients with chronic liver disease: a systematic review and dose-response meta-analysis. Hepatol Int 2019;13:560-572.
29. Ciardullo S, Muraca E, Zerbini F, et al. Liver stiffness is associated with all-cause mortality in patients with NAFLD: A systematic review and meta-analysis. Liver Int 2023;43:2604-2610
30. Roulot D, Costes JL, Buyck JF, et al. Transient elastography as a screening tool for liver fibrosis and cirrhosis in a community-based population aged over 45 years. Gut 2011;60:977-84.
31. EASL Clinical Practice Guidelines on non-invasive tests for evaluation of liver disease severity and prognosis - 2021 update. J Hepatol 2021;75:659-689.
32. Castera L, Friedrich-Rust M, Loomba R. Noninvasive Assessment of Liver Disease in Patients With Nonalcoholic Fatty Liver Disease. Gastroenterology 2019;156:1264-1281.e4.
33. de Franchis R, Bosch J, Garcia-Tsao G, Reiberger T, Ripoll C; Baveno VII Faculty. Baveno VII - Renewing consensus in portal hypertension. J Hepatol. 2022;76:959-974.

Table 1. The detailed characteristics of the studies included in the meta-analysis

Author	Population	Follow-up (years)	Age (year)	Male (%)	Design	Outcomes reported	aHR	Adjustment	Quality*
Johnson AL 2022[16]	243	4.2	59	53.1	Cohort	Hepatic decompensation with ascites, primary liver cancer, mortality, portal hypertension	LSM < 13.0 kPa vs. LSM > 13.0 kPa aHR 27.4（7.86-95.50) LSM by 1-kPa aHR 1.07（1.04-1.10）	Age, baseline cirrhosis	S3 C2 O3
Petta S 2021[17]	1039	2.9	60.3	56.3	Cohort	Hepatic decompensation with ascites, bleeding varices, jaundice, encephalopathy	LSM by 1-kPa aHR 1.03（1.02-1.04）	N/A	S3 C2 O3

Lee JS 2021[23]	2666	5.1	52	57.2	Cohort	Development of HCC	LSM < 9.3 kPa vs. LSM ≥ 9.3 kPa aHR 13.76（2.83-66.96）	N/A	S3 C2 O3
Boursier J 2022[24]	1057	3.1	55.4	62.3	Cohort	Cirrhosis complications (ascites, spontaneous bacterial peritonitis, hepatorenal syndrome, varices, liver failure), HCC	LSM < 8.0 kPa vs. LSM > 12.0 kPa aHR 20.50（4.90-86.50）	Age, sex, antidiabetic treatment, antihypertensive treatment, lipid-lowering treatment	S3 C2 O3
Davitkov P 2023[25]	13629	1.1	56.2	89.9	Cohort	Development of HCC	LSM < 9.5 kPa vs. LSM ≥ 14.5 kPa aHR 15.74 (6.45-47.25)	Age, smoking, alcohol, BMI, DM	S3 C2 O2

Pons M 2022[26]	996	2.5	60	49.1	Cohort	Development of HCC	LSM by 1-kPa aHR 1.03（1.00-1.06）	N/A	S3 C2 O3
Shalimar 2023[27]	957	3.9	40	67.8	Cohort	Liver-related death, ascites, hepatic encephalopathy, gastrointestinal bleeding, HCC, fibrosis progression	LSM by 1-kPa aHR 1.06（1.04-1.08）	Age, DM, ALT, hypertension, haemoglobin, platelet, albumin, serum creatinine	S3 C2 O3

aHR, adjusted hazard ratio; LSM, liver stiffness measurement; HCC, hepatocellular carcinoma; BMI, body mass index; DM, diabetes mellitus; ALT, alanine aminotransferase

*Quality assessment by the Newcastle-Ottawa Scale

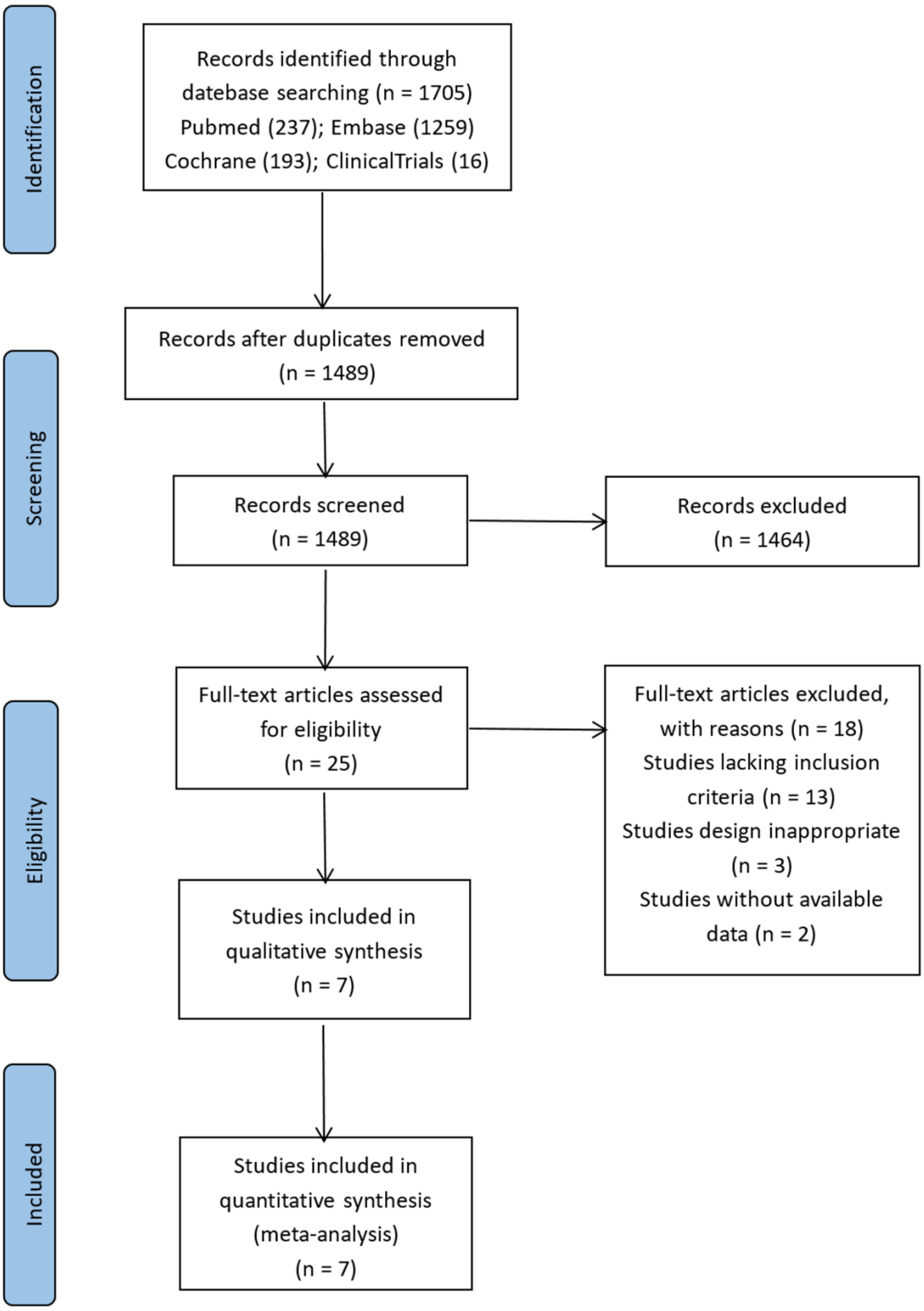

Identification
Records identified through datebase searching (n = 1705)
Pubmed (237); Embase (1259)
Cochrane (193); ClinicalTrials (16)
Screening
Records after duplicates removed (n = 1489)
Records screened (n = 1489)
Records excluded (n = 1464)
Eligibility
Full-text articles assessed for eligibility (n = 25)
Full-text articles excluded, with reasons (n = 18)
Studies lacking inclusion criteria (n = 13)
Studies design inappropriate (n = 3)
Studies without available data (n = 2)
Studies included in qualitative synthesis (n = 7)
Included
Studies included in quantitative synthesis (meta-analysis) (n = 7)

Figure 1 Flow of the literature search.

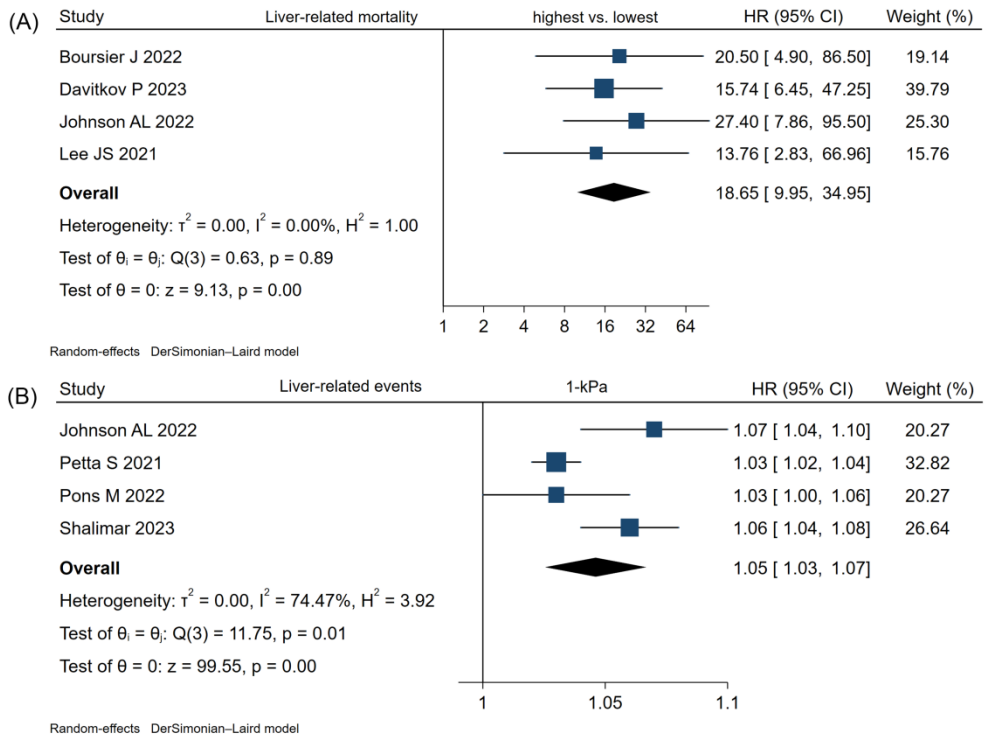


Figure 2 Forest plots for the pooled HRs of LRE. (A) Pooled HR of LRE for stratification analysis. (B) Pooled HR of LRE for 1-kPa analysis.

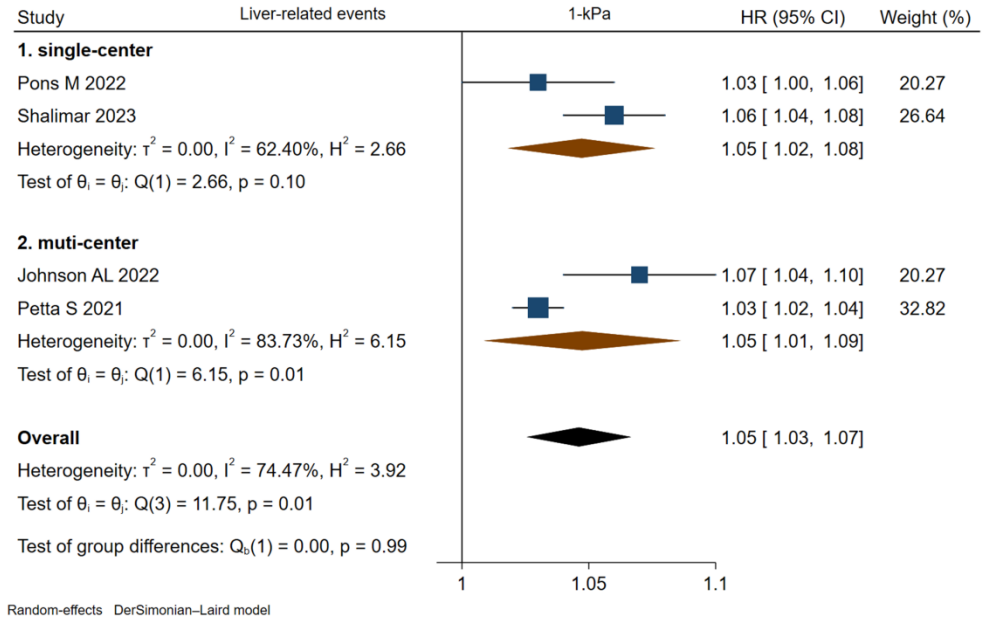


Figure 3 Subgroup analysis for pooled HR of LRE for 1-kPa analysis.

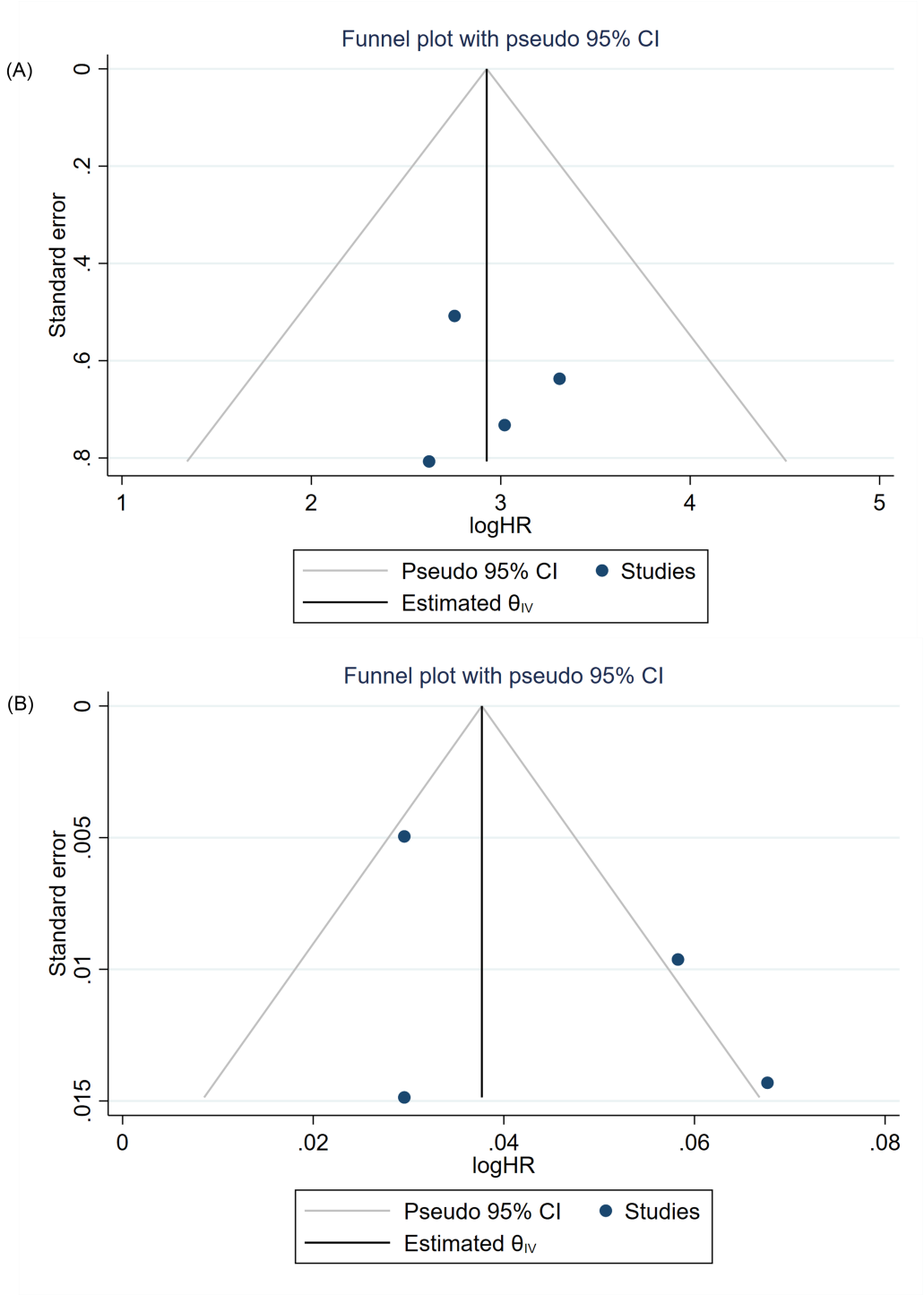


Figure 4 Funnel plots for the pooled logHR of LRE. (A) Funnel plots for the pooled logHR of LRE for stratification analysis. (B) Funnel plots for the pooled logHR of LRE for 1-kPa analysis.