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Original Article

Prevalence of clinically significant liver fibrosis in the general population: A systematic review and meta-analysis

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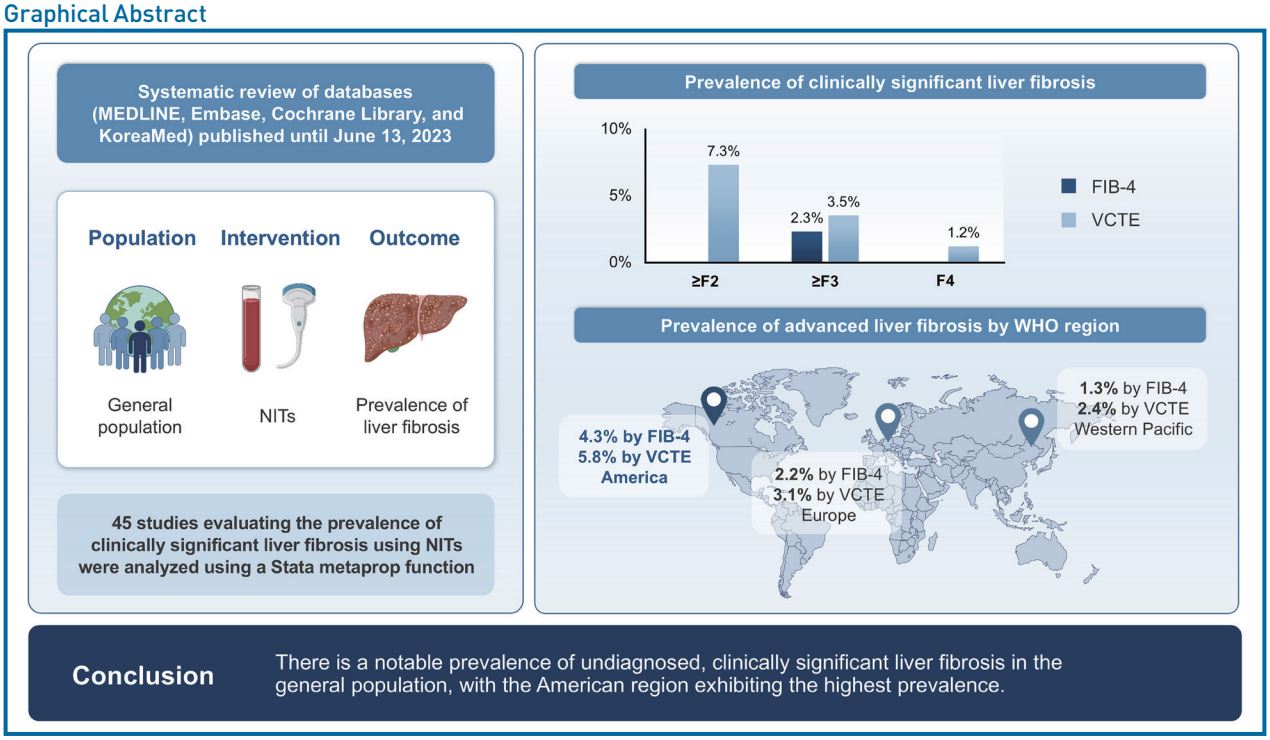
Graphical Abstract



Study Highlights

- The prevalence of advanced liver fibrosis, using the high probability cutoff of the fibrosis-4 index, was 2.3%. Based on the vibration-controlled transient elastography, the pooled prevalence of significant liver fibrosis, advanced liver fibrosis, and cirrhosis was 7.3%, 3.5%, and 1.2%, respectively. This study highlights the prevalence of clinically significant liver fibrosis in the general population. The population that should be screened for advanced liver fibrosis needs to be determined.

Background/Aims: Although important, clinically significant liver fibrosis is often overlooked in the general population. We aimed to examine the prevalence of clinically significant liver fibrosis using noninvasive tests (NITs) in the general population.

Methods: We collected data from four databases (MEDLINE, Embase, Cochrane Library, and KoreaMed) from inception to June 13, 2023. Original articles reporting the prevalence of clinically significant liver fibrosis in the general population were included. The Stata metaprop function was used to obtain the pooled prevalence of liver fibrosis with NITs in the general population.

Results: We screened 6,429 articles and included 45 eligible studies that reported the prevalence of clinically significant liver fibrosis in the general population. The prevalence of advanced liver fibrosis, using the high probability cutoff of the fibrosis-4 (FIB-4) index, was 2.3% (95% confidence interval [CI], 1.2–3.7%). The prevalence of significant liver fibrosis, advanced liver fibrosis, and liver cirrhosis, assessed using vibration-controlled transient elastography (VCTE) among the general population, was 7.3% (95% CI, 5.9–8.8%), 3.5% (95% CI, 2.7–4.5), and 1.2% (95% CI, 0.8–1.8%), respectively. Region-based subgroup analysis revealed that the highest prevalence of advanced fibrosis using the high probability cutoff of the FIB-4 index was observed in the American region. Furthermore, the American region exhibited the highest prevalence of significant liver fibrosis, advanced liver fibrosis, and liver cirrhosis, using VCTE.

Conclusions: Previously undiagnosed clinically significant liver fibrosis is found in the general population through NITs. Future research is necessary to stratify the risk in the general population. **(Clin Mol Hepatol 2024;30(Suppl):S199-S213)**

Keywords: Population Surveillance; Liver fibrosis; Meta-analysis; Systematic review

INTRODUCTION

Chronic liver diseases constitute a significant public health concern, contributing to considerable morbidity and mortality globally.[1] Implementing interventions to reduce the global burden of chronic liver diseases is urgent. Various factors, particularly chronic viral hepatitis, excessive alcohol consumption, and metabolic disorders contribute to chronic liver inflammation. Chronic liver diseases are typically characterized by sustained liver inflammation, which, if left untreated, can result in progressive liver fibrosis, potentially leading to the development of cirrhosis and/or he-

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Abbreviations:

CI, confidence interval; FIB-4, fibrosis-4; kPa, kilopascal; HCC, hepatocellular carcinoma; MRE, magnetic resonance elastography; NFS, non-alcoholic fatty liver disease fibrosis score; NIT, noninvasive test; VCTE, vibration-controlled transient elastography; WHO, World Health Organization

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patocellular carcinoma (HCC).[2] In most patients with chronic liver disease, typical symptoms do not manifest until the development of decompensation after many years.[2] The stage of liver fibrosis is a major prognostic factor for the development of liver-related events in chronic liver diseases.[3] Particularly, advanced fibrosis (fibrosis stage 3, F3) or cirrhosis (fibrosis stage 4, F4) stands out as the important histologic feature linked to liver-related mortality.[4-6] Moreover, significant fibrosis (fibrosis stage 2, F2) is important as a target for inclusion in clinical trials or for initiating therapy.[7,8] Therefore, identifying individuals at risk of clinically significant liver fibrosis (≥F2) early will facilitate specialist referral and enable timely medical interventions or lifestyle adjustments before they develop cirrhosis.[9,10]

Noninvasive tests (NITs) utilizing serum markers, vibration-controlled transient elastography (VCTE), and imaging method effectively assess liver fibrosis with relative accuracy.[11] Therefore, NITs can serve as screening tools for clinically significant liver fibrosis in asymptomatic populations. Several referral pathways using NITs have been suggested to diagnose clinically significant liver fibrosis early.[9,12] However, debate on the choice between mass screening of asymptomatic patients and targeted screening of patients at risk of clinically significant liver fibrosis persists.[9,13] When establishing a screening strategy among populations, the prevalence of clinically significant liver fibrosis is crucial for determining the screening population scale.

Recent cohort studies investigating the prevalence of liver fibrosis in asymptomatic individuals and individuals with various risk factors have yielded a broad range of estimates. This variation can be partly attributed to differences in diagnostic methods and the prevalence of risk factors. Hitherto, one systematic review, including 19 studies and several general reviews, has been conducted.[9,12-14] The prevalence of liver fibrosis varied from 0.7% to 25.7%. More specifically, the prevalence of advanced liver fibrosis or cirrhosis among the general population with a diverse setting was 0.9–2.0% or 0.1–1.7%, respectively.[14] Owing to the importance of understanding the burden of clinically significant liver fibrosis among the general population to develop effective screening strategies, we conducted a systematic review, incorporating subsequent publications after the previous systematic review, to evaluate the prevalence of clinically significant liver fibrosis in the general population.

MATERIALS AND METHODS

Data sources and search strategy

We performed a comprehensive search of electronic databases, including MEDLINE (OVID), EMBASE, the Cochrane Library, and KoreaMed, from their inception to June 13, 2023. Keywords: “liver fibrosis,” “cirrhosis,” “noninvasive tests,” “elastography,” “community,” “general population,” “prevalence.” The details of our comprehensive search strategy are presented in Supplementary Table 1. This systematic review and meta-analysis followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (Supplementary Table 2).[15]

Study selection

We included cohort studies that (1) enrolled individuals aged ≥18 years from asymptomatic populations or primary care settings and (2) reported the prevalence of liver fibrosis using NITs. We excluded secondary or tertiary hospital settings and specific patient population groups, such as those with diabetes, alcoholic liver disease, or chronic viral hepatitis. Reviews, editorials, commentaries, case reports, guidelines, conference abstracts, and studies conducted in pediatric populations were also excluded. We included studies that were originally written in or translated into English. Where data overlapped among several studies within the same cohort, we prioritized data from the largest, most comprehensive, and/or most recent studies.

Two independent reviewers (KHY and CYE) screened the titles and abstracts for eligibility and assessed the full text for inclusion. Any disagreements were resolved through consensus between the reviewers and/or with the involvement of a third author. Furthermore, we explored the bibliographies of relevant studies to identify potential additional studies.

Data extraction and quality assessment

Two authors (KHY and CYE) independently extracted pertinent data, including study details and participant char-

acteristics, in a structured format. The primary outcome of this study was the prevalence of liver fibrosis in the general population. The study details included the authors, publication year, study location, study design, NITs used, and total number of participants enrolled. Participant characteristics included age, sex, proportion of risk factors (such as fatty liver, metabolic syndrome, diabetes, obesity, dyslipidemia, history of alcohol consumption, or chronic liver disease), and prevalence of liver fibrosis or cirrhosis. The diagnostic threshold values of NITs for significant liver fibrosis (≥F2), advanced liver fibrosis (≥F3), or cirrhosis (F4) were also collected.

The quality of the studies included in this systematic review and meta-analysis was assessed using the Joanna Briggs Institute's (JBI) critical appraisal tool, specifically the Checklist for Prevalence Studies. Each study was independently reviewed by two authors (KHY and CYE). Any discrepancies between the reviewers were resolved by reaching a consensus via discussion (Supplementary Table 3). The overall score on the scale was 9.

Statistical analysis

Continuous variables are presented as either the median (interquartile range) or the mean±standard deviation. The pooled prevalence rate of clinically significant liver fibrosis within the general population is indicated as a proportion with a 95% confidence interval (95% CI) using a random effects model and expressed as a forest plot. Two-tailed statistical significance was set at *P*-value of <0.05. Analysis of proportions was performed using the Metaprop function to assess the prevalence of liver fibrosis in the general population. Statistical heterogeneity was evaluated using both I^2 and Cochran's Q test values, with I^2 values of 50% and 75% denoting moderate and high degrees of heterogeneity, respectively.[16] To identify potential sources of heterogeneity, subgroup analysis was conducted based on the NIT used, stage of fibrosis, and geographical regions defined by the World Health Organization (WHO) (Americas, European, Southeast Asian, African, Eastern Mediterranean, and Western Pacific regions). A sensitivity analysis was performed by excluding studies with a high or low prevalence of liver fibrosis. An additional sensitivity analysis was conducted using the leave-one-out method, which systematically excludes individual studies, to evaluate the robustness of our primary results. All statistical analyses were performed using Stata version 15.1 (StataCorp., College Station, TX, USA).

RESULTS

Search results

The process of selecting studies for analysis is illustrated in Figure 1. Among 6,429 studies identified in the initial search, 6,357 remained after duplicates were removed. Following the initial screening of titles and abstracts, 110 articles underwent a full text review, resulting in the inclusion of 44 studies. An additional article was identified through a manual literature search. Finally, 45 studies, comprising 566,160 participants, were included in the meta-analysis.

Study characteristics

Supplementary Table 4 presents the characteristics of the included studies. The NIT methods used were Fibrosis-4 (FIB-4) index, VCTE, FibroTest nonalcoholic fatty liver disease fibrosis score (NFS), and magnetic resonance elastography (MRE) in thirteen, twenty-seven, two, one, and two studies, respectively. Nineteen studies were from the European region (5, 12, and 2 studies used FIB-4, VCTE, and FibroTest respectively), nine studies from the American region (four, four, and one studies used FIB-4, VCTE, and NFS, respectively), thirteen studies from the Western Pacific region (four, seven, and two studies used FIB-4, VCTE, and MRE, respectively), two studies from the South-East Asian region (used VCTE), one study from the African region (used VCTE), and one study from mixed regions (used VCTE). The mean age and proportion of males were 45.7±13.3 years and 46.2%, respectively.

Variability was observed in the outcome parameters, including the staging of liver fibrosis, thresholds used to define liver fibrosis, and prevalence of risk factors for liver fibrosis, such as obesity, fatty liver disease, metabolic syndrome, type 2 diabetes, dyslipidemia, and alcohol consumption, among the general population. The outcome parameters included significant liver fibrosis (≥F2), advanced liver fibrosis (≥F3), liver cirrhosis (F4), and a combination of

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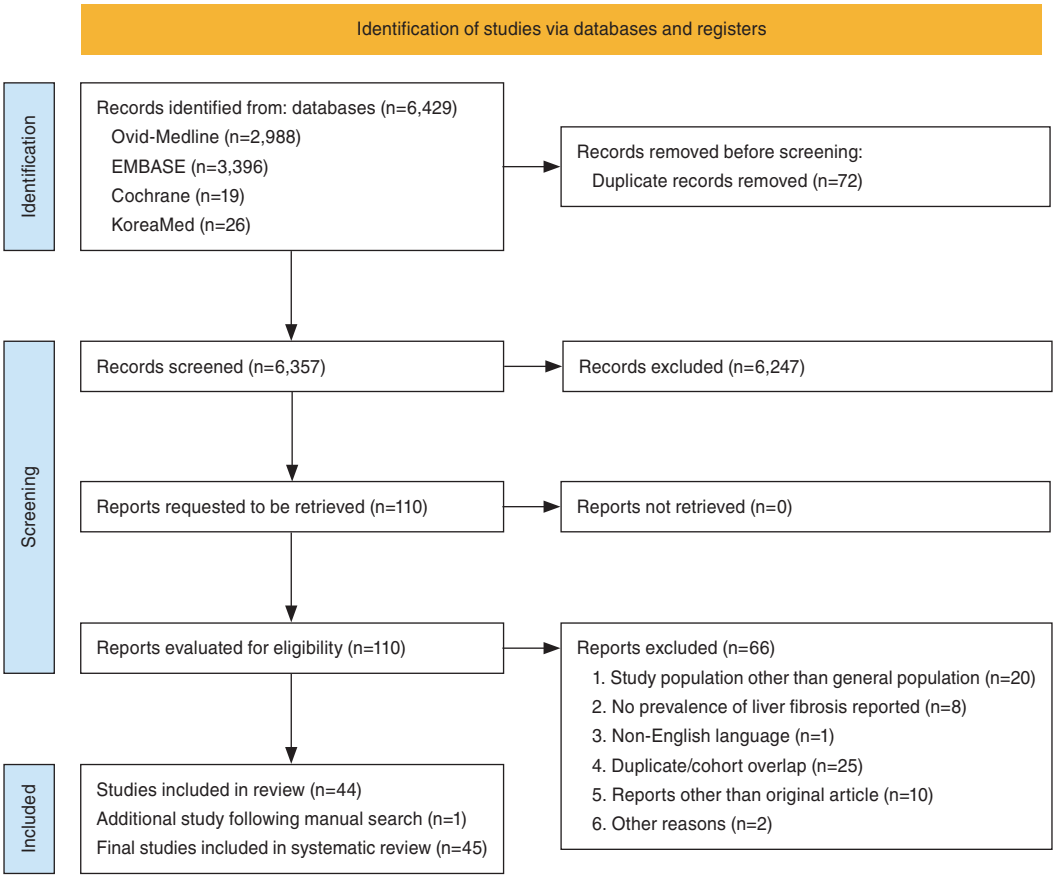

Figure 1. PRISMA flow diagram. PRISMA, Preferred Reporting Items for Systematic Review and Meta-Analysis.

these.

The prevalence of liver fibrosis was assessed based on a predetermined threshold set for the NITs. The FIB-4 threshold defining a high risk for advanced liver fibrosis was predominantly set at 2.67. However, one study[17] used 3.25, whereas another[18] did not specify the cutoffs. The VCTE cutoffs defining significant liver fibrosis, advanced liver fibrosis, and liver cirrhosis ranged 5.9–9.6, 8–10, and 10.3–15 kPa, respectively. In the two studies presenting the prevalence of liver fibrosis using FibroTest, the cutoffs for defining advanced fibrosis were 0.48 and 0.59, respectively.[19,20] One study reporting the prevalence of liver fibrosis using NFS defined advanced liver fibrosis as NFS >0.676.[21] In two studies, the thresholds for defining significant fibrosis using MRE were 2.9 and 3.0 kPa, respectively. Both studies identified advanced fibrosis as 3.6 kPa.[22,23] Conducting a meta-analysis using FibroTest, NFS, or MRE was impossible owing to insufficient data. To address the potential heterogeneity stemming from variations in diagnostic methods for assessing liver fibrosis, the analysis was stratified based on these diagnostic approaches.

Prevalence of advanced liver fibrosis determined using the FIB-4 index

The overall prevalence of advanced liver fibrosis determined using the high probability cutoff of the FIB-4 index within the general population was 2.3% (95% CI, 1.2–3.7%). The study conducted by Halfon yielded the highest estimate, recorded at 7.3%.[24] To account for heterogeneity potentially arising from differences in geographic region, the analysis was stratified by WHO region. The prevalence of advanced liver fibrosis was 4.3% (95% CI, 1.7–7.9%; three studies, 21,552 patients) in the American region, 2.2% (95% CI, 0.8–4.3%; six studies, 200,332 patients) in the European region, and 1.3% (95% CI, 0.2–3.2%; four studies, 287,307 patients) in the Western Pacific region (P<0.0001; Table 1, Fig. 2). In a sensitivity analysis exclud-

Table 1. Pooled prevalence of liver fibrosis among the general population stratified by noninvasive tests and geographical regions

Noninvasive fibrosis tests	Stage of liver fibrosis	Number of studies	Region	Number of patients	Pooled prevalence (95% confidence interval) (%)	I^2 (%) (*P*)
Fibrosis-4 index	Advanced liver fibrosis (≥F3)	13	Overall	509,191	2.3 (1.2–3.7)	99.8 (<0.001)
		3	Region of the Americas	21,552	4.3 (1.7–7.9)	N/A
		6	European Region	200,332	2.2 (0.8–4.3)	99.8 (<0.001)
		4	Western Pacific Region	287,307	1.3 (0.2–3.2)	99.9 (<0.001)
Vibration-controlled transient elastography	Significant liver fibrosis (≥F2)	22	Overall	56,969	7.3 (5.9–8.8)	97.4 (<0.001)
		3	Region of the Americas	8,587	10.7 (8.7–12.9)	N/A
		11	European Region	41,049	6.1 (4.5–7.9)	97.9 (<0.001)
		5	Western Pacific Region	2,381	7.1 (3.2–12.2)	94.4 (<0.001)
		1	South-East Asian Region	901	14.4 (12.2–16.9)	N/A
		1	African Region	72	11.1 (4.9–20.7)	N/A
		1	Mixed	3,979	5.6 (4.9–6.4)	N/A
	Advanced liver fibrosis (≥F3)	15	Overall	45,395	3.5 (2.7–4.5)	95.4 (<0.001)
		4	Region of the Americas	8,886	5.8 (4.7–7.0)	73.6 (0.01)
		6	European Region	31,411	3.1 (2.4–3.9)	92.0 (<0.001)
		4	Western Pacific Region	4,197	2.4 (1.1–4.2)	88.1 (<0.001)
		1	South-East Asian Region	901	2.2 (1.4–3.4)	N/A
	Liver cirrhosis (F4)	14	Overall	38,232	1.2 (0.8–1.8)	94.7 (<0.001)
		3	Region of the Americas	8,587	2.2 (1.4–3.1)	N/A
		6	European Region	20,216	1.1 (0.5–2.1)	95.7 (<0.001)
		2	Western Pacific Region	2,889	0.2 (0.1–0.5)	N/A
		2	South-East Asian Region	2,561	1.4 (0.9–1.9)	N/A
		1	Mixed	3,979	1.2 (0.9–1.6)	N/A

N/A, not available.

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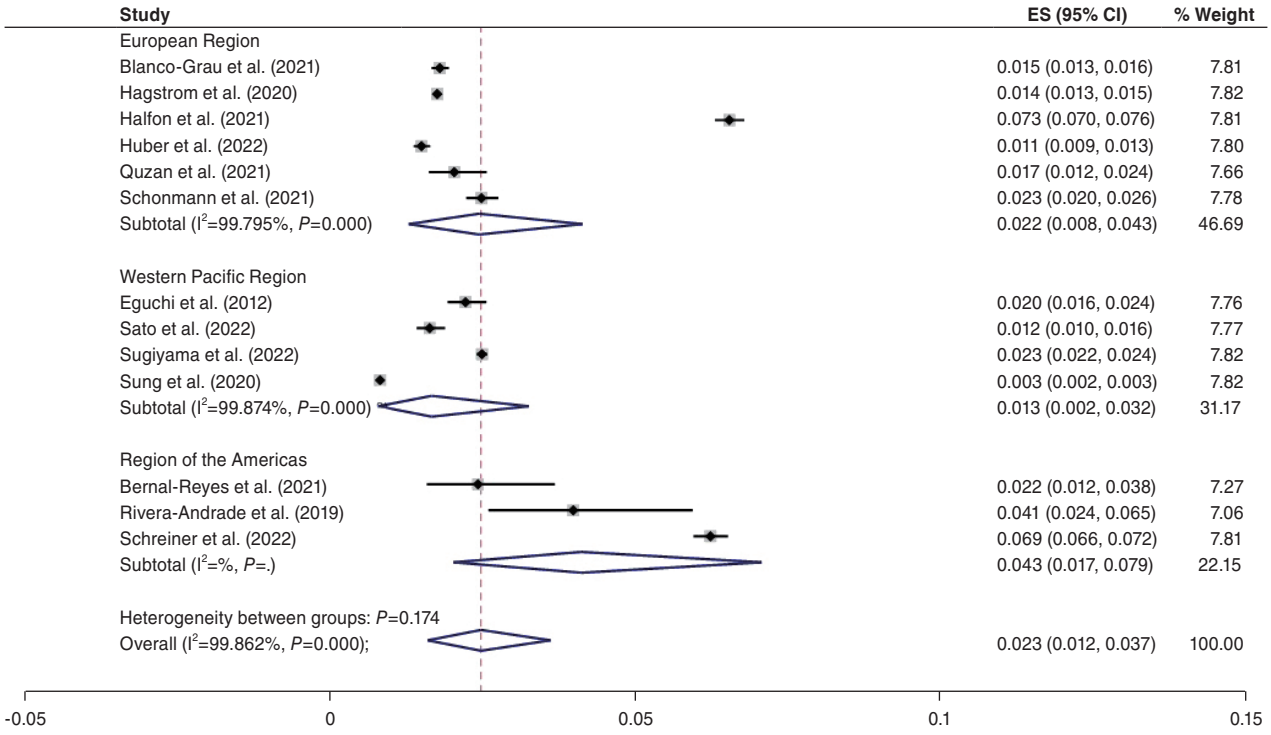

Figure 2. Forest plot referred to the prevalence of liver fibrosis determined by fibrosis-4 index in the general population, stratified by World Health Organization-defined regions. ES, effect size; CI, confidence interval.

ing studies with a high and low prevalence of liver fibrosis (two studies, 230,186 patients), the prevalence of advanced liver fibrosis defined by a high probability cutoff of FIB-4 index was 2.2% (95% CI, 1.5–3.1%). The overall effect size did not change significantly following the application of the leave-one-out method to assess the robustness of the meta-analysis. The *P*-value was <0.001 across all iterations of the leave-one-out analysis (Supplementary Fig. 1A).

Prevalence of significant liver fibrosis determined using VCTE

In 22 studies comprising 56,969 participants, the prevalence of significant liver fibrosis in the general population was 7.3% (95% CI, 5.9–8.8%). Studies reporting higher estimates utilized lower thresholds (5.9–7.5 kPa).[25-27] However, Trifan's study reported the highest estimates using a threshold of 8 kPa.[28] In addition to lower cutoffs defining significant liver fibrosis, studies reporting higher estimates had a higher prevalence of diabetes within their populations.[26-28] In region-based subgroup analysis, the prevalence of liver fibrosis was 10.7% (95% CI, 8.7–12.9%; 3 studies, 8,587 patients) in the American region, 6.1% (95% CI, 4.5–7.9%; 11 studies, 41,049 patients) in the European region, and 7.1% (95% CI, 3.2–12.2%; 5 studies, 2,381 patients) in the Western Pacific region. Only one study was obtained from the Southeast Asian, African, and mixed regions, respectively (Table 1, Fig. 3A). In a analysis excluding studies with a high and low prevalence of liver fibrosis (two studies, 2,013 patients), the prevalence of significant liver fibrosis determined using VCTE was 7.2% (95% CI, 5.9–8.6%). Another sensitivity analysis, excluding studies with high and low cutoff values, revealed a prevalence of significant liver fibrosis of 7.4% (95% CI, 6.0–8.9%). Sensitivity analysis performed using the leave-one-out method also demonstrated that the effects were consistent and replicable across the included studies (Supplementary Fig. 1B).

Prevalence of advanced liver fibrosis determined using VCTE

Fifteen studies involving 45,395 participants reported the prevalence of advanced liver fibrosis using VCTE. The pooled prevalence rate of advanced liver fibrosis assessed

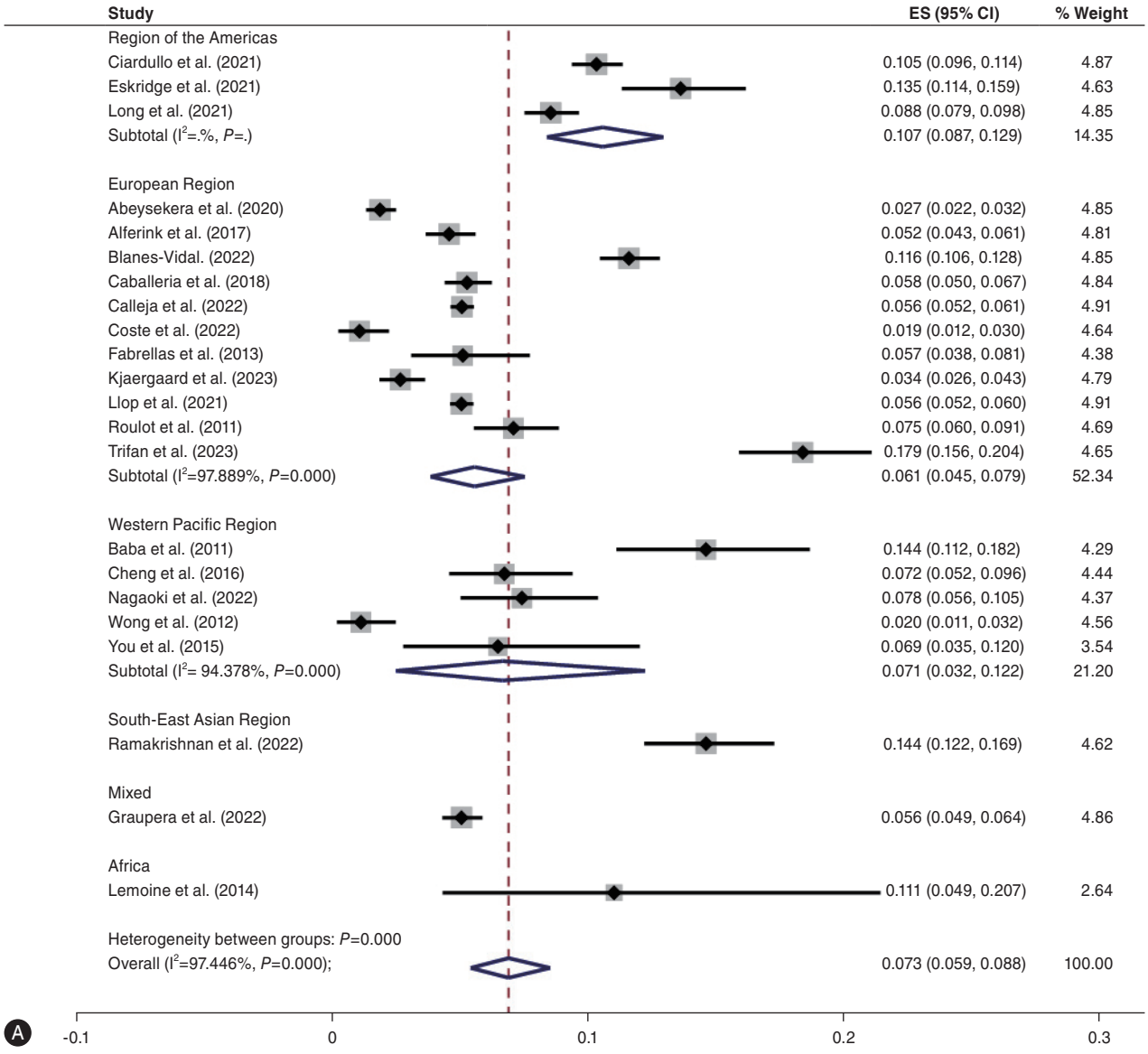

Figure 3. Forest plot referred to the prevalence of liver fibrosis using vibration-controlled transient elastography in the general population, stratified by fibrosis stage and World Health Organization-defined regions. (A) Significant liver fibrosis (≥F2). (B) Advanced liver fibrosis (≥F3). (C) Liver cirrhosis (F4). ES, effect size; CI, confidence interval.

using VCTE was 3.5% (95% CI, 2.7–4.5%). Region-based subgroup analysis indicated that the prevalence of advanced liver fibrosis was 5.8% (95% CI, 4.7–7.0%; four studies, 8,886 patients) in the American region, 3.1% (95% CI, 2.4–3.9%; six studies, 31,411 patients) in the European region, and 2.4% (95% CI, 1.1–4.2%; four studies, 4,197 patients) in the Western Pacific region (Table 1, Fig. 3B). In a sensitivity analysis excluding studies with a high and low prevalence of liver fibrosis (two studies, 2,700 patients), the prevalence of advanced liver fibrosis determined using VCTE was 3.6% (95% CI, 2.8–4.5%). Another sensitivity analysis, excluding studies employing high and low cutoff values, revealed a prevalence of advanced liver fibrosis at 3.5% (95% CI, 2.8–4.5%). Sensitivity analysis performed using the leave-one-out method did not reveal high levels of heterogeneity (Supplementary Fig. 1C).

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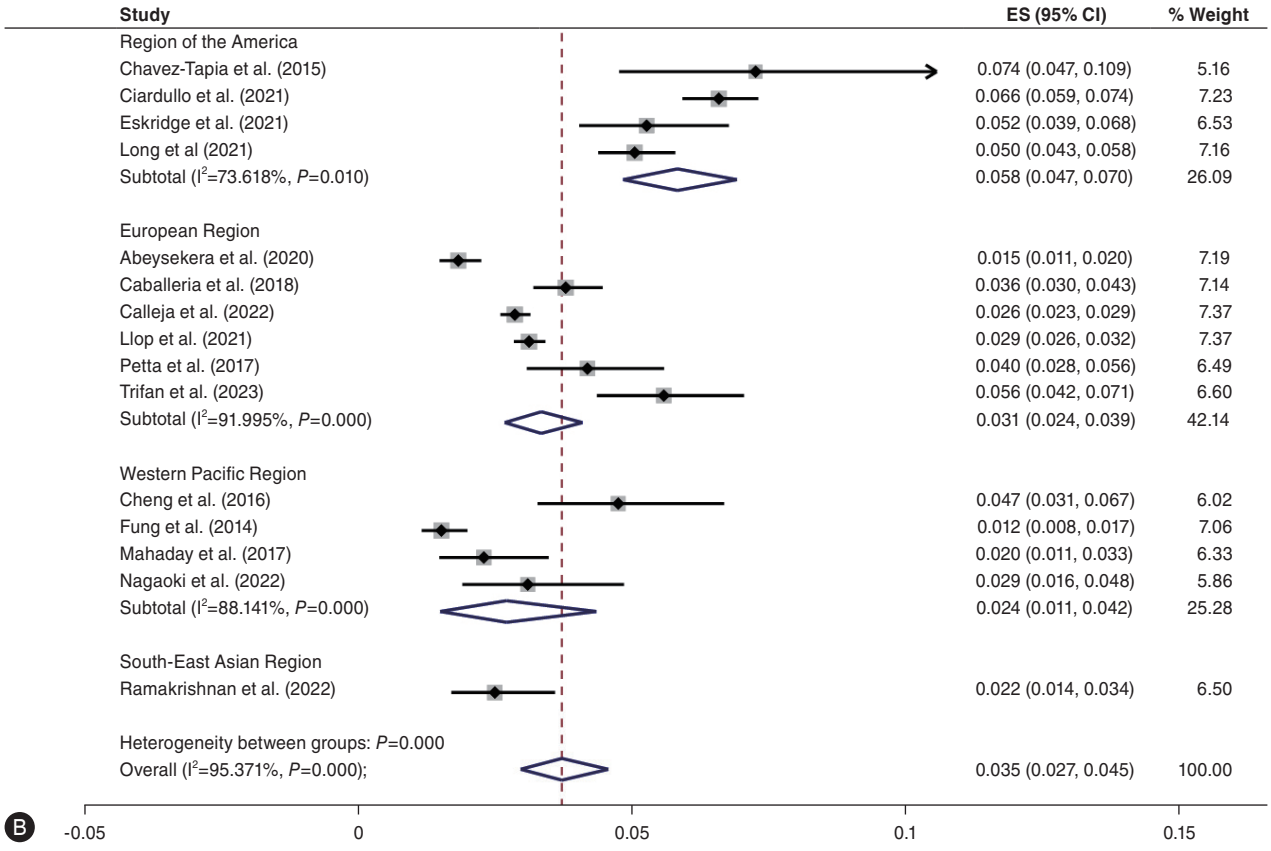

Figure 3. Continued.

Prevalence of liver cirrhosis determined using VCTE

We analyzed 14 studies with 38,232 subjects reporting the prevalence of liver cirrhosis using VCTE in the general population. The prevalence of liver cirrhosis was 1.2% (95% CI, 0.8–1.8%). The prevalence rates of liver cirrhosis by WHO regions were 2.2% (95% CI, 1.4–3.1%; 3 studies, 8,587 patients) in the Region of the Americas, 1.1% (95% CI, 0.5–2.1%; 6 studies, 20,216 patients) in the European Region, 0.2% (95% CI, 0.1–0.5%; 2 studies, 2,889 patients) in the Western Pacific Region, and 1.4% (95% CI, 0.9–1.9%; 2 studies, 2,561 patients) in the South-East Asian Region (Table 1, Fig. 3C). In a sensitivity analysis excluding studies with a high prevalence and a low prevalence of liver fibrosis (two studies, 3,428 patients), the prevalence of liver cirrhosis determined using VCTE was 1.2% (95% CI, 0.8–1.6%). Additional sensitivity analyses, which excluded studies utilizing both high and low cut-off values, uncovered a prevalence of liver cirrhosis of 1.2% (95% CI, 0.6–2.0%). The sensitivity analysis using the leave-one-out method did not reveal significant heterogeneity among the included studies (Supplementary Fig. 1D).

Prevalence of liver fibrosis determined using the FibroTest

Poynard et al.[19] reported that 2.8% (95% CI, 2.4–3.2%) of individuals had FibroTest results indicative of presumed advanced fibrosis (FibroTest >0.48), while Zelber-Sagi et al.[20] reported the prevalence of significant fibrosis (FibroTest >0.32) at 12.8% and advanced fibrosis (FibroTest >0.59) at 0.9%.

Prevalence of liver fibrosis determined using the NFS

One study reported the prevalence of liver fibrosis using NFS, where high probability of advanced fibrosis was defined as an NFS >0.676. This study demonstrated that the

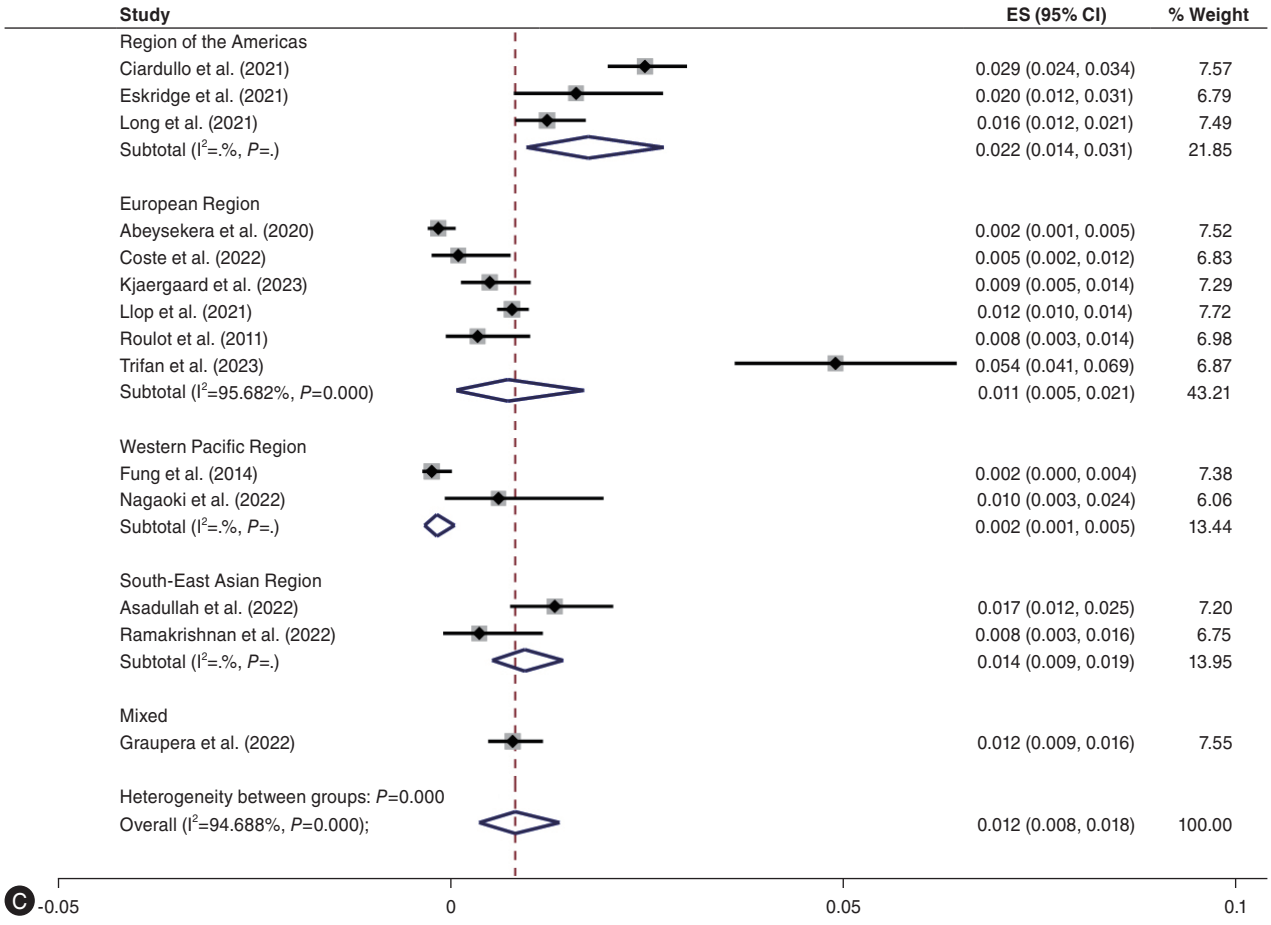

Figure 3. Continued.

prevalence of advanced liver fibrosis was 8.1% in the Mexican general population.[21]

Prevalence of liver fibrosis determined using MRE

Two South Korean studies using MRE in individuals who underwent health checkups reported the prevalence of significant liver fibrosis at 5.1% and 9.5%, respectively, and that of advanced liver fibrosis was 1.3% and 2.6%, respectively.

DISCUSSION

Chronic liver disease is characterized by the progression of inflammation, liver damage, and regeneration, ultimately resulting in fibrosis and cirrhosis.[29] Owing to the prognostic importance of liver fibrosis in chronic liver diseases, early assessment of the stage of liver fibrosis will facilitate the implementation of preventive measures against its progression to cirrhosis, decompensation, or HCC.[9,10] NITs are attractive options for screening liver fibrosis and cirrhosis in the general population.[13] However, considering that no established strategy for screening liver fibrosis using NITs exists, assessing the prevalence of liver fibrosis to classify individuals at risk in the general population is crucial.

In this systematic review and meta-analysis, the overall prevalence estimate of advanced liver fibrosis using the high probability cutoff of the FIB-4 index within the general population was 2.3% (95% CI, 1.2–3.7%). The prevalence of significant liver fibrosis, advanced liver fibrosis, and liver cirrhosis using VCTE among the general population was 7.3% (95% CI, 5.9–8.8%), 3.5% (2.7–4.5%), and 1.2% (95% CI, 0.8–1.8%), respectively. Reviewing more recent data not included in the present study revealed that the preva-

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lence of liver fibrosis was 2.2% according to the high probability cut-off value of the FIB-4 index. A study conducted in China reported that the prevalence of advanced fibrosis (cut-off value of 10 kPa) and cirrhosis (cut-off value of 13.5 kPa) detected using VCTE was 2.85% and 0.8%, respectively, which is consistent with the findings of the present study.[30,31] Variations in the prevalence of liver fibrosis observed between FIB-4 and VCTE may arise from disparities in the diagnostic accuracies of these tests. Additionally, we adopted predefined cutoff values from individual studies because of the lack of established standard liver stiffness values in extensive cohorts of seemingly healthy individuals.[32,33] Therefore, the variability in the thresholds used to define the stage of liver fibrosis can also affect the prevalence of liver fibrosis.

Although chronic liver diseases are prevalent in the general population,[1] only small fractions of patients, 2.3% by FIB-4 and 3.5% by VCTE, were diagnosed with advanced fibrosis in this systematic review. The risk factors independently associated with advanced liver fibrosis include obesity, diabetes, metabolic syndrome, excessive alcohol consumption, fatty liver disease, elevated liver enzymes, and old age.[23,34-38] The lower prevalence of advanced liver fibrosis among the general population may be due to the reduced prevalence of risk factors compared to individuals with type 2 diabetes or alcohol use disorders, who exhibit elevated prevalence rates.[34,39] The current prevalence estimates of cirrhosis (1.2%, 95% CI [0.8–1.8%]) exceed those of previous reports (0.07–0.6%).[40-42] This could be attributed to undetected liver cirrhosis among the general population or overdiagnosis based on NITs; however, the true prevalence of liver fibrosis using a reference standard remains unknown from this systematic review, as not every participant underwent a liver biopsy.

VCTE and FIB-4 are the most commonly used tests in the general population. FIB-4 can be readily calculated using basic laboratory markers, whereas VCTE requires specialized equipment. Although the diagnostic performance of VCTE is superior to that of FIB-4,[43,44] the prevalence of advanced fibrosis was comparable between VCTE and FIB-4 in this systematic review. FIB-4 may serve as a viable alternative for assessing liver fibrosis in the general population when VCTE is unavailable. Implementing MRE for routine screening in the general population is challenging, although MRE is the most effective diagnostic method among several NITs for measuring hepatic fibrosis.[45] This systematic review included two studies conducted in South Korea utilizing MRE.[22,23] The prevalence of advanced fibrosis ranged 1.3–2.6%, indicating a lower prevalence compared to estimates obtained using VCTE. The limited number of studies utilizing MRE posed a challenge when comparing MRE with VCTE.

The burden of chronic liver disease differed across regions, correlating with the varying prevalence of risk factors in the different regions, including obesity, alcohol consumption, hepatitis B, and hepatitis C.[46] Although the data were limited to certain regions, we analyzed the prevalence of liver fibrosis based on geographic regions to minimize heterogeneity. After excluding small-scale studies, the highest prevalence of liver fibrosis was observed in the American Region. This could be attributed to the higher prevalence of obesity in the United States. The prevalence of cirrhosis is not the highest in the Region of the Americas according to the 2017 Global Burden of Disease of Cirrhosis.[47] The discrepancy between the findings of this study and those of previous studies may be attributed to the included population. This study primarily included individuals who were volunteers or underwent health examinations, which may not fully represent the true characteristics of the general population that have varying presences of risk factors.

Despite the considerable morbidity and mortality associated with liver disease,[1] prioritizing efforts for the early detection of clinically significant liver fibrosis in the general population has not received much attention in the public health agenda. Recent guidelines have suggested screening for advanced liver fibrosis in populations at risk for liver disease.[8,48,49] However, discrepancies exist between the persons at risk and specified cutoffs.[9] Future studies on the prevalence of clinically significant liver fibrosis and risk factors associated with a higher prevalence will contribute significantly to public health initiatives.

This study offers the most recently updated and comprehensive analysis of the prevalence of clinically significant liver fibrosis among the general population, surpassing the findings of the systematic review published in 2017.[14] Nonetheless, this study had some limitations. First, the performance of diagnostic tests varied depending on disease prevalence. In populations with less severe disease, the sensitivity and positive predictive value of the test de-

crease, reflecting the 'spectrum effect.' Therefore, the accuracy of NITs may decrease in the general population where the prevalence of significant fibrosis is lower than that in a sample population. Second, we adopted the definition of liver fibrosis based on NITs according to the criteria defined in individual studies. Conducting a meta-analysis cannot be justified in all cases owing to the different cut-off values used in different studies. To overcome this limitation, we conducted a leave-one-out sensitivity analysis used to evaluate the influence of each individual study on the overall meta-analysis results. Systematic exclusion of each study ensured that the conclusions were not influenced by a single study. The results from the sensitivity analysis supported the validity of combining the data in a meta-analysis and robustness of our overall conclusions. Currently, no established cutoff values for liver fibrosis using NITs exist in the general population. The derivation and validation of the majority of evidence-based cutoffs have primarily involved patients in secondary care; therefore, the emphasis of these tests on the general population may lack validity. Third, the definition of the general population varied among studies, and the study population may not accurately represent the entire population. Additionally, most studies included volunteers or individuals undergoing health checkups, leading to an underestimation of the prevalence of clinically significant liver fibrosis. Fourth, the prevalence of liver fibrosis may vary based on the proportion of known risk factors for liver fibrosis, including age, obesity, type 2 diabetes mellitus, chronic viral hepatitis, and alcohol consumption.[37,50-53] Lastly, we acknowledge the absence of pre-registration for our meta-analysis. This omission may introduce potential bias, as the protocol was not available for external scrutiny by other researchers.

In conclusion, this systematic review demonstrates the notable prevalence of undiagnosed, clinically significant liver fibrosis in the general population. Future studies are required to stratify the risk in the general population.

Authors' contributions

All authors have full access to all data used in this study and take responsibility for the integrity and accuracy of the data analyses. HY Kim, JH Yu, and DW Jun were responsible for the conception and design of the study; HY Kim, YE Chon, SU Kim, MN Kim, JW Han, JH Yu, HA Lee, YJ Jin, J An, M Choi and DW Jun were responsible for the acquisition, analysis, interpretation of data, and the drafting of the manuscript. M Choi performed statistical analyses. All the authors approved the final version of the manuscript.

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Conflicts of Interest

The authors have no conflicts to disclose.

SUPPLEMENTARY MATERIAL

Supplementary material is available at Clinical and Molecular Hepatology website (http://www.e-cmh.org).

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Supplementary Table 1. Electronic search strategy

Classification	Number	Search terms
Population	1	exp general practice/ OR exp primary health care/ OR exp community health services/ OR exp population/ OR (family practice or population* OR general practice* OR community health service* OR unselected OR community OR non-hospital OR non hospital OR outreach OR primary health care OR primary care* OR unknown liver disease* OR population stud*).tw,kw.
Intervention	2	exp Elasticity Imaging Techniques/ OR (noninvasive test* OR non-invasive test* OR non-invasive marker* OR noninvasive marker* OR transient elastography OR Fibrotest OR elastograph* OR TE OR NAFLD fibrosis score* OR NFS OR Elasticity Imag* OR Enhanced liver fibrosis score* OR ELF score* OR enhanced liver fibrosis test OR ELF test* OR vibration controlled transient elastograp* OR VCTE OR FibroMeter OR liver stiffness OR fibrosis test* OR fibroscan OR VCTE OR LSM OR TE OR shear wave elastograp* OR SWE OR fibrosis-4* OR FIB-4 OR FIB4 OR FibroMeter OR NIT OR NITs OR Acoustic Radiation Force Impuls* OR ARFI OR APRI OR aspartate aminotransferase to platelet ratio index OR AST to platelet ratio index).tw,kw.
P&I	3	1 AND 2
Outcome	4	exp Prevalence/ or exp Morbidity/ OR exp epidemiology/ OR (prevalence* or morbidity or incidence* or person time*).tw,kw.
Outcome	5	exp Liver Cirrhosis/ or (cirrhosis or liver fibros* or hepatic fibros* or fibros* or significant liver disease* OR severe liver disease* OR advanced chronic liver disease*).tw,kw.
P&I&O	6	3 AND (4 OR 5)

P, population; I, intervention; O, outcome; TE, transient elastography; NAFLD, non-alcoholic fatty liver disease; NFS, NAFLD fibrosis score; ELF, enhanced liver fibrosis; VCTE, vibration controlled transient elastography; LSM, liver stiffness measurement; SWE, shear wave elastography; FIB-4, fibrosis-4 index; NIT, noninvasive test; ARFI, acoustic radiation forse impulse; APRI, aspartate aminotransferase to platelet ratio index.

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Supplementary Table 2. PRISMA 2020 checklist

Section and Topic	Item #	Checklist item	Location where item is reported
TITLE			
Title	1	Identify the report as a systematic review.	1
ABSTRACT			
Abstract	2	See the PRISMA 2020 for Abstracts checklist.	2
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of existing knowledge.	3
Objectives	4	Provide an explicit statement of the objective(s) or question(s) the review addresses.	3
METHODS			
Eligibility criteria	5	Specify the inclusion and exclusion criteria for the review and how studies were grouped for the syntheses.	3
Information sources	6	Specify all databases, registers, websites, organisations, reference lists and other sources searched or consulted to identify studies. Specify the date when each source was last searched or consulted.	3
Search strategy	7	Present the full search strategies for all databases, registers and websites, including any filters and limits used.	3
Selection process	8	Specify the methods used to decide whether a study met the inclusion criteria of the review, including how many reviewers screened each record and each report retrieved, whether they worked independently, and if applicable, details of automation tools used in the process.	3
Data collection process	9	Specify the methods used to collect data from reports, including how many reviewers collected data from each report, whether they worked independently, any processes for obtaining or confirming data from study investigators, and if applicable, details of automation tools used in the process.	3,4
Data items	10a	List and define all outcomes for which data were sought. Specify whether all results that were compatible with each outcome domain in each study were sought (e.g. for all measures, time points, analyses), and if not, the methods used to decide which results to collect.	4
	10b	List and define all other variables for which data were sought (e.g. participant and intervention characteristics, funding sources). Describe any assumptions made about any missing or unclear information.	4
Study risk of bias assessment	11	Specify the methods used to assess risk of bias in the included studies, including details of the tool(s) used, how many reviewers assessed each study and whether they worked independently, and if applicable, details of automation tools used in the process.	4
Effect measures	12	Specify for each outcome the effect measure(s) (e.g. risk ratio, mean difference) used in the synthesis or presentation of results.	4
Synthesis methods	13a	Describe the processes used to decide which studies were eligible for each synthesis (e.g. tabulating the study intervention characteristics and comparing against the planned groups for each synthesis (item #5)).	4
	13b	Describe any methods required to prepare the data for presentation or synthesis, such as handling of missing summary statistics, or data conversions.	4
	13c	Describe any methods used to tabulate or visually display results of individual studies and syntheses.	4
	13d	Describe any methods used to synthesize results and provide a rationale for the choice(s). If meta-analysis was performed, describe the model(s), method(s) to identify the presence and extent of statistical heterogeneity, and software package(s) used.	4

Supplementary Table 2. Continued.

Section and Topic	Item #	Checklist item	Location where item is reported
	13e	Describe any methods used to explore possible causes of heterogeneity among study results (e.g. subgroup analysis, meta-regression).	4
	13f	Describe any sensitivity analyses conducted to assess robustness of the synthesized results.	4
Reporting bias assessment	14	Describe any methods used to assess risk of bias due to missing results in a synthesis (arising from reporting biases).	N/A
Certainty assessment	15	Describe any methods used to assess certainty (or confidence) in the body of evidence for an outcome.	4
RESULTS			
Study selection	16a	Describe the results of the search and selection process, from the number of records identified in the search to the number of studies included in the review, ideally using a flow diagram.	4
	16b	Cite studies that might appear to meet the inclusion criteria, but which were excluded, and explain why they were excluded.	4
Study characteristics	17	Cite each included study and present its characteristics.	Suppl. Table 4
Risk of bias in studies	18	Present assessments of risk of bias for each included study.	Suppl. Table 3
Results of individual studies	19	For all outcomes, present, for each study: (a) summary statistics for each group (where appropriate) and (b) an effect estimate and its precision (e.g. confidence/credible interval), ideally using structured tables or plots.	6
Results of syntheses	20a	For each synthesis, briefly summarise the characteristics and risk of bias among contributing studies.	5,7,8,9
	20b	Present results of all statistical syntheses conducted. If meta-analysis was done, present for each the summary estimate and its precision (e.g. confidence/credible interval) and measures of statistical heterogeneity. If comparing groups, describe the direction of the effect.	5,7,8,9
	20c	Present results of all investigations of possible causes of heterogeneity among study results.	5,7,8,9
	20d	Present results of all sensitivity analyses conducted to assess the robustness of the synthesized results.	5,7,8,9
Reporting biases	21	Present assessments of risk of bias due to missing results (arising from reporting biases) for each synthesis assessed.	N/A
Certainty of evidence	22	Present assessments of certainty (or confidence) in the body of evidence for each outcome assessed.	5,7,8,9
DISCUSSION			
Discussion	23a	Provide a general interpretation of the results in the context of other evidence.	10
	23b	Discuss any limitations of the evidence included in the review.	11-12
	23c	Discuss any limitations of the review processes used.	11-12
	23d	Discuss implications of the results for practice, policy, and future research.	12
OTHER INFORMATION			
Registration and protocol	24a	Provide registration information for the review, including register name and registration number, or state that the review was not registered.	N/A
	24b	Indicate where the review protocol can be accessed, or state that a protocol was not prepared.	N/A
	24c	Describe and explain any amendments to information provided at registration or in the protocol.	N/A

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Supplementary Table 2. Continued.

Section and Topic	Item #	Checklist item	Location where item is reported
Support	25	Describe sources of financial or non-financial support for the review, and the role of the funders or sponsors in the review.	12
Competing interests	26	Declare any competing interests of review authors.	12
Availability of data, code and other materials	27	Report which of the following are publicly available and where they can be found: template data collection forms; data extracted from included studies; data used for all analyses; analytic code; any other materials used in the review.	Suppl. Table 1

From: Page MJ, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ 2021;372:n71.

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Supplementary Table 3. Quality assessment of included studies using the Joanna Briggs Institute (JBI) critical appraisal tool for prevalence studies

Study	1. Was the sample frame appropriate to address the target population?	2. Were study participants sampled in an appropriate way?	3. Was the sample size adequate?	4. Were the study subjects and the setting described in detail?	5. Was the data analysis conducted with sufficient coverage of the identified sample?	6. Were valid methods used for the identification of the condition?	7. Was the condition measured in a standard, reliable way for all participants?	8. Was there appropriate statistical analysis?	9. Was the response rate adequate, and if not, was the low response rate managed appropriately?	Score
Bernal-Reyes et al. (2023)[1]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	9
Blanco-Grau et al. (2021)[2]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	9
Eguchi et al. (2012)[3]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	9
Hagström et al. (2020)[4]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	9
Halfon et al. (2021)[5]	Yes	Unclear	Yes	Unclear	Yes	Yes	Yes	Yes	Yes	7
Huber et al. (2022)[6]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	9
Ouzan et al. (2021)[7]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	9
Rivera-Andrade et al. (2019)[8]	Yes	Yes	Unclear	Yes	Yes	Yes	Yes	Yes	Unclear	7
Sato et al. (2022)[9]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	8
Schonmann et al. (2021)[10]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	9
Schreiner et al. (2022)[11]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Unclear	8
Sugiyama et al. (2022)[12]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Unclear	8
Sung et al. (2020)[13]	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	8
Abeysekera et al. (2020)[14]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Unclear	8
Alferink et al. (2017)[15]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	9
Asadullah et al. (2022)[16]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Unclear	8
Baba et al. (2011)[17]	Yes	Unclear	Unclear	Yes	No	Yes	Yes	Yes	Unclear	5
Blanes-Vidal et al. (2022)[18]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Unclear	8
Caballería et al. (2018)[19]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Unclear	8
Calleja et al. (2022)[20]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	9
Chávez-Tapia et al. (2015)[21]	No	Yes	Unclear	Yes	Yes	Yes	Yes	Yes	Unclear	6
Cheng et al. (2016)[22]	Yes	Yes	Unclear	Yes	Yes	Yes	Yes	Yes	Unclear	7
Ciardullo et al (2021)[23]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	9
Coste et al. (2022)[24]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	8
Eskridge et al. (2021)[25]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	9
Fabrellas et al. (2013)[26]	Yes	Yes	Unclear	Yes	Yes	Yes	Yes	Yes	Unclear	7
Fung et al. (2015)[27]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	9

Supplementary Table 3. Continued

Study	1. Was the sample frame appropriate to address the target population?	2. Were study participants sampled in an appropriate way?	3. Was the sample size adequate?	4. Were the study subjects and the setting described in detail?	5. Was the data analysis conducted with sufficient coverage of the identified sample?	6. Were valid methods used for the identification of the condition?	7. Was the condition measured in a standard, reliable way for all participants?	8. Was there appropriate statistical analysis?	9. Was the response rate adequate, and if not, was the low response rate managed appropriately?	Score
Graupera et al. (2022)[28]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Unclear	8
Kjaergaard et al. (2023)[29]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Unclear	8
Lemoine et al. (2014)[30]	Yes	Yes	Unclear	Yes	Unclear	Yes	Yes	Yes	Unclear	6
Llop et al. (2021)[31]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Unclear	8
Long et al. (2021)[32]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	9
Mahady et al. (2017)[33]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Unclear	8
Nagaoki et al. (2022)[34]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	9
Petta et al. (2018)[35]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	9
Ramakrishnan et al. (2022)[36]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Unclear	8
Roulot et al. (2011)[37]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	9
Trifan et al. (2023)[38]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	9
Wong et al. (2012)[39]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	9
You et al. (2015)[40]	Yes	No	Unclear	Yes	Yes	Yes	Yes	Yes	Unclear	6
Poynard et al. (2010)[41]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	9
Zelber-Sagi et al. (2012)[42]	Yes	Yes	Unclear	Yes	Yes	Yes	Yes	Yes	Unclear	7
García-Compeán et al. (2020)[43]	Yes	Yes	Unclear	Yes	Yes	Yes	Yes	Yes	Unclear	7
Kang et al. (2020)[44]	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	8
Nah et al. (2021)[45]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	9

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Supplementary Table 4. Background characteristics of the included articles

Study	Country	Noninvasive tests	Total number of subjects	Age (years)	Prevalence of risk factors (% in studied population)	Significant fibrosis (≥F2)		Advanced fibrosis (≥F3)		Liver cirrhosis (F4)	
						Cut-off	Prevalence	Cut-off	Prevalence	Cut-off	Prevalence
Bernal-Reyes et al. (2023)[1]	Mexico	FIB-4	585	48.2±14.1	BMI ≥25 kg/m^2 82.4%, NAFLD 41.3%, MetS 41.8%			N/A	2.2%		
Blanco-Grau et al. (2021)[2]	Spain	FIB-4	18,102	N/A	N/A			≥3.25	1.5%		
Eguchi et al. (2012)[3]	Japan	FIB-4	5,075	50.0±9.5	NAFLD 29.7%, obesity 8.2%			≥2.67	1.9%		
Hagström et al. (2020)[4]	Sweden	FIB-4	126,941	52.0 (43.9-62.9)[a]	T2DM 4.01%			≥2.67	1.4%		
Halfon et al. (2021)[5]	France	FIB-4	29,707	54±21	N/A			>2.67	7.3%		
Huber et al. (2022)[6]	Germany	FIB-4	14,950	55.0 (25-74)[a]	obesity 25.2%, T2DM 9.3%, dyslipidemia 34.6%, MetS 30.5%, alcohol 2.9%			>2.67	1.1%		
Ouzan et al. (2021)[7]	France	FIB-4	2,121	62±10	obesity 13%, T2DM 10%, alcohol 13%			>2.67	1.7%		
Rivera-Andrade et al. (2019)[8]	Guaetemala	FIB-4	411	55.4±1.06	obesity 30.9%, T2DM 21.6%, MetS 64.2%, alcohol 20.2%			>2.67	4.1%		
Sato et al. (2022)[9]	Japan	FIB-4	6,087	47 (11-89)[b]	obesity 25.5%, T2DM 5.2%, dyslipidemia 45.2%			>2.67	1.2%		
Schonmann et al. (2021)[10]	Israel	FIB-4	8,511	61.8±10.4	obesity 33.4%, statin use 19.2%			≥2.67	2.3%		
Schreiner et al. (2022)[11]	USA	FIB-4	20,556	51.0±16.6	NAFLD 2.3%, T2DM 29.5%, chronic liver disease 8.2%			>2.67	7%		
Sugiyama et al. (2022)[12]	Japan	FIB-4	75,666	N/A	NAFLD 23.7%, alcohol 13.8%			≥2.67	2.3%		
Sung et al. (2020)[13]	South Korea	FIB-4	200,479	36.4±7.7	BMI ≥25 kg/m^2 15.8%, T2DM 1.2%,			≥2.67	0.25%		

Supplementary Table 4. Continued

Study	Country	Noninvasive tests	Total number of subjects	Age (years)	Prevalence of risk factors (% in studied population)	Significant fibrosis (≥F2)		Advanced fibrosis (≥F3)		Liver cirrhosis (F4)	
						Cut-off	Prevalence	Cut-off	Prevalence	Cut-off	Prevalence
Abeysekera et al. (2020)[14]	England	VCTE	3,600	24 (23-25)[a]	obestiy 13.4%, alcohol 12.7%	≥7.9 kPa	2.7%	≥8.8 kPa	1.5%	≥11.7 kPa	0.3%
Alferink et al. (2017)[15]	Netherland	VCTE	2,424	66.5±7.4	NAFLD 34.6%, obesity 21.2%, T2DM 10.5%, MetS44.5%, alcohol 15.9%	≥8 kPa	5.2%				
Asadullah et al. (2022)[16]	India	VCTE	1,660	45.5±8.0 (urban) 45.1±7.9 (rural)	Obesity 65.2% (urban)/49.9% (rural), T2DM 30.1% (urban)/14.8%(rural)	≥7.9 kPa		≥8.6 kPa		≥14.2 kPa	2.8% (urban)/0.6% (rural)
Baba et al. (2011)[17]	Japan	VCTE	416	47.4±13.6	NAFLD 28.1%, BMI ≥25 16.6%, alcohol 36.3%	≥5.9 kPa	14.3%				
Blanes-Vidal et al. (2022)[18]	Denmark	VCTE	3,460	57±13	mean BMI 27.3±7 kg/m^2, T2DM 9.8%	>8 kPa	11.6%				
Caballería et al. (2018)[19]	Spain	VCTE	3,014	54±12	obesity 31%, T2DM 10%, MetS 28%, alcohol 9%, hepatitis B 1%, hepatitis C 0.3%	≥8 kPa	5.8%	≥9 kPa	3.6%		
Calleja et al. (2022)[20]	Spain	VCTE	11,440	51 (42-60)[a]	obesity 21.8%, T2DM 13.5%, dyslipidemia 64.8%, MetS 15.4%, alcohol 3.9%, hepatitis B 0.8%, hepatitis C 1.3%	≥8 kPa	5.61%	≥10 kPa	2.6%		
Chávez-Tapia et al. (2015)[21]	Mexico	VCTE	299	44.6±17.1	obesity 21.1%, T2DM 15.1%, dyslipidemia 17.1%, alcohol 11.7%			≥9 kPa	7.35%		
Cheng et al. (2016)[22]	Taiwan	VCTE	559	56.2±16.4	BMI ≥27 kg/m^2 21%, T2DM 11.1%, dyslipidemia 26.8%	≥7 kPa	7.2%	≥8 kPa	4.0%		

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Supplementary Table 4. Continued

Study	Country	Noninvasive tests	Total number of subjects	Age (years)	Prevalence of risk factors (% in studied population)	Significant fibrosis (≥F2)		Advanced fibrosis (≥F3)		Liver cirrhosis (F4)	
						Cut-off	Prevalence	Cut-off	Prevalence	Cut-off	Prevalence
Ciardullo et al (2021)[23]	USA	VCTE	4,371	47.9±0.57	Mean BMI 29.5±0.3 kg/m^2, T2DM 12.8%, hepatitis B 0.2%, hepatitis C 1%	≥8 kPa	10.5%	≥9.6 kPa	6.6%	≥13 kPa	2.9%
Coste et al. (2022)[24]	Spain	VCTE	986	56.2±8.9	Obesity 22.5%, T2DM 8.5%, dyslipidemia 63.1%, MetS 24.4%, alcohol 9.6%	≥9.2 kPa	1.9%			≥12.5 kPa	0.5%
Eskridge et al. (2021)[25]	USA	VCTE	940	47.6	obesity 44.8%, T2DM 26.3%	>7.5 kPa	13.5%	>10 kPa	5.21%	>14 kPa	2.02%
Fabrellas et al. (2013)[26]	Spain	VCTE	495	47.2±13.3	mean BMI 27.6±5.1, alcohol 9%	≥6.8 kPa	5.7%				
Fung et al. (2015)[27]	Hong Kong	VCTE	2,401	44 (17-80)[b]	NAFLD 42.3%, mean BMI 23.3			≥8.7 kPa	1.2%	≥10.3 kPa	0.17%
Graupera et al. (2022)[28]	Multinational	VCTE	3,979	55±12.2	N/A	≥8 kPa	5.6%			≥12 kPa	1.2%
Kjaergaard et al. (2023)[29]	Denmark	VCTE	1,973	57 (52-62)[a]	obesity 23%, T2DM 4%, MetS 43%, alcohol 10%	≥8 kPa	3.4%			≥12 kPa	0.9%
Lemoine et al. (2014)[30]	Gambia	VCTE	72	49.5 (39-57)[a]	median BMI 21.9 kg/m^2	>7.2 kPa	11%				
Llop et al. (2021)[31]	Spain	VCTE	11,440	50.3±12.5	obesity 21.8%, MetS 15.4%, alcohol 9.1%, hepatitis B 0.8%, hepatitis C 1.3%	>8 kPa	5.6%	≥10 kPa	2.9%	>15 kPa	1.2%
Long et al. (2021)[32]	USA	VCTE	3,276	54.3±9.1	NAFLD 28.8%, obesity 32.3%, T2DM 8.7%, MetS 26.4%, alcohol 7%	≥8.2 kPa	8.8%	≥9.7 kPa	5%	>13.6 kPa	1.6%
Mahady et al. (2017)[33]	Hong Kong	VCTE	749	47.8±10.5	mean BMI 22.6 kg/m^2, T2DM 4.5%			>9.6 kPa	2%		

Supplementary Table 4. Continued

Study	Country	Noninvasive tests	Total number of subjects	Age (years)	Prevalence of risk factors (% in studied population)	Significant fibrosis (≥F2)		Advanced fibrosis (≥F3)		Liver cirrhosis (F4)	
						Cut-off	Prevalence	Cut-off	Prevalence	Cut-off	Prevalence
Nagaoki et al. (2022)[34]	Japan	VCTE	488	56 (45-68)[a]	T2DM 15.4%, dyslipidemia 17.6%, alcohol 15.8%, hepatitis B 1.6%, hepatitis C 0.8%	≥6.6 kPa	7.8%	≥8 kPa	2.8%	≥10 kPa	1.0%
Petta et al. (2018)[35]	Italy	VCTE	890	53±14	obesity 29.1%, IFG or T2DM 19.8%			≥9.6 kPa	4%		
Ramakrishnan et al. (2022)[36]	India	VCTE	901	N/A	BMI≥25 kg/m^2 40%, T2DM 18.3%, MetS 23.6%, alcohol 22.6% (male)	≥6.5 kPa	14.4%	≥9.5 kPa	2.2%	≥12 kPa	0.8%
Roulot et al. (2011)[37]	France	VCTE	1,190	57.7±8.8	obesity 17.1%, MetS 20.3%	≥8 kPa	7.5%			>13.6 kPa	0.76%
Trifan et al. (2023)[38]	Romania	VCTE	1,027	53.1±13.6	obesity 28.4%, T2DM 22.3%	≥8 kPa	17.9%	≥9.6 kPa	5.6%	≥13 kPa	5.4%
Wong et al. (2012)[39]	Hong Kong	VCTE	759	48±11	T2DM 5.2%, MetS 20.3%, alcohol 22%	≥9.6 kPa	2.0%				
You et al. (2015)[40]	South Korea	VCTE	159	56.0±10.6	BMI>25 kg/m^2 41.5%, T2DM 11.9%	>7 kPa	6.9%				
Poynard et al. (2010)[41]	France	FibroTest	7,463	N/A	BMI≥27 kg/m^2 32.5%, MetS 53.5%, alcohol 22.6%, hepatitis B 0.1%			>0.48	2.8%		
Zelber-Sagi et al. (2012)[42]	Israel	FibroTest	338	50.8±10.4	mean BMI 27.1 kg/m^2, T2DM 6.8%, MetS 18.6%	≥0.32	12.8%	≥0.59	0.9%		
García-Compeán et al. (2020)[43]	Mexico	NFS	695	47.8±16.4	obesity 35.5%, T2DM 15.8%			>0.676	8.1%		
Kang et al. (2020)[44]	South Korea	MRE	2,170	50.6±8.5	NAFLD 19.0%, obesity 15.8%, T2DM 12.9%, MetS 22.4%, alcohol 21.9%, hepatitis B or C 9.9%	≥3 kPa	5.1%	≥3.6 kPa	1.3%		

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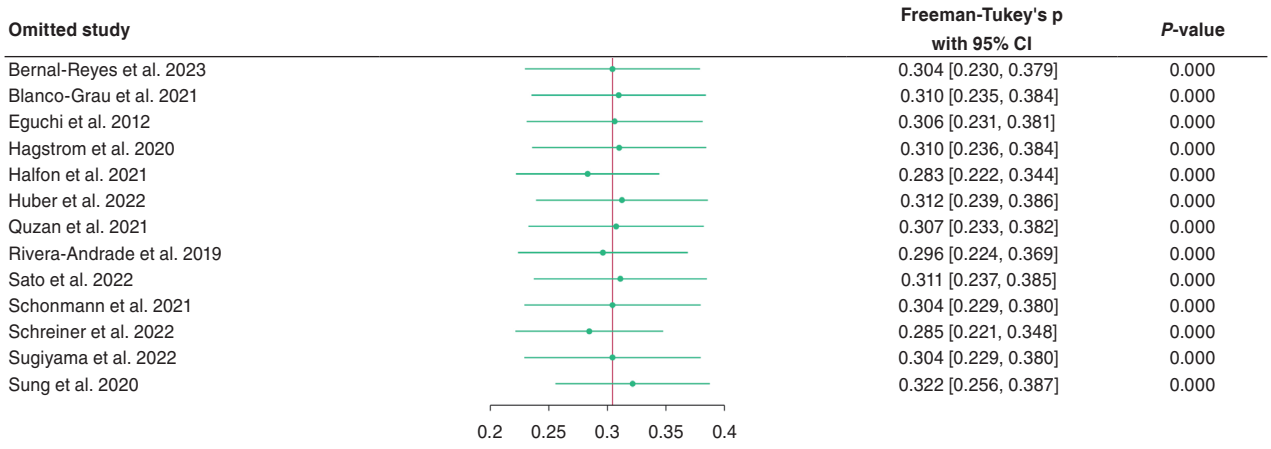
Supplementary Table 4. Continued

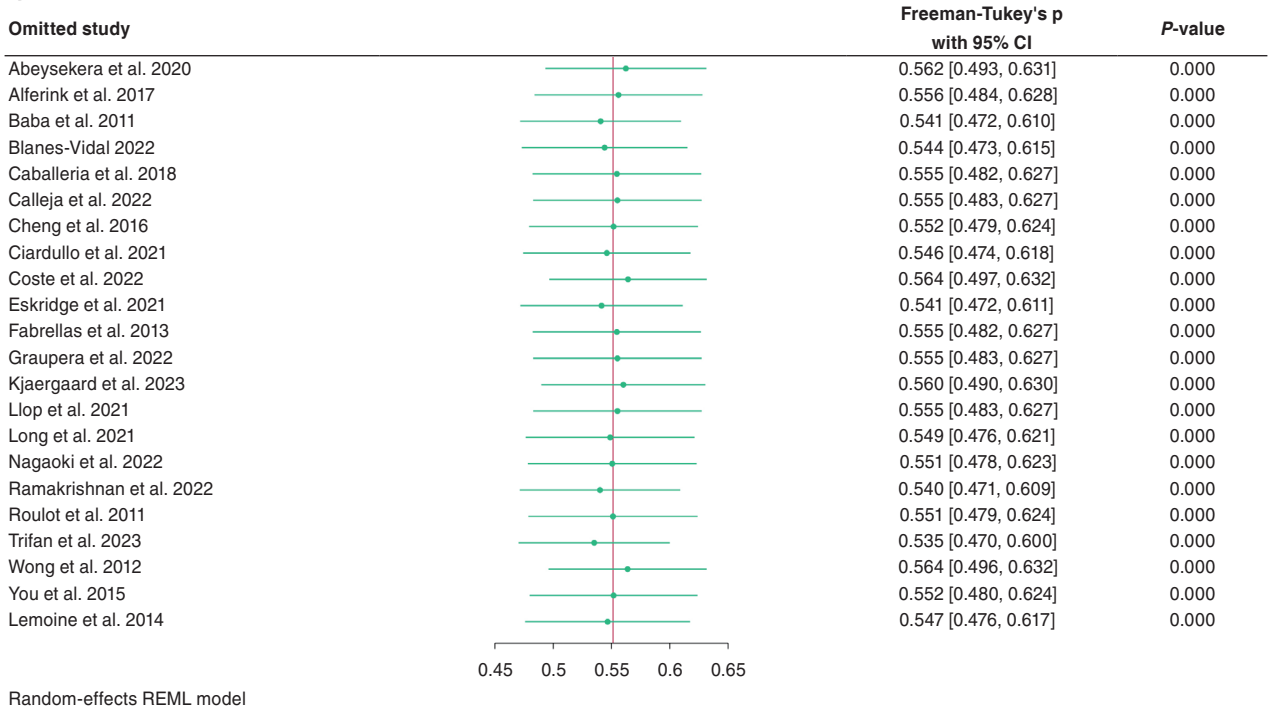
Study	Country	Noninvasive tests	Total number of subjects	Age (years)	Prevalence of risk factors (% in studied population)	Significant fibrosis (≥F2)		Advanced fibrosis (≥F3)		Liver cirrhosis (F4)	
						Cut-off	Prevalence	Cut-off	Prevalence	Cut-off	Prevalence
Nah et al. (2021)[45]	South Korea	MRE	8,183	47.2±10.8	BMI ≥25 kg/m^2 45.6%, T2DM 11.2%, MetS 21.9%, alcohol 36.9%, hepatitis B 8.6%, hepatitis C 0.3%	≥2.9 kPa	9.5%	≥3.6 kPa	2.6%		

[a]Median (interquartile range). [b]Median (ranges).

FIB-4, fibrosis index-4; VCTE, vibration-controlled transient elastography; NAFLD, nonalcoholic fatty liver disease; MetS, metabolic syndrome; T2DM, type 2 diabetes mellitus; BMI, body mass index; N/A, not available; IFG, impaired fasting glucose; NFS, NAFLD (nonalcoholic fatty liver disease) fibrosis score; kPa, kilopascal MRE, magnetic resonance elastography.

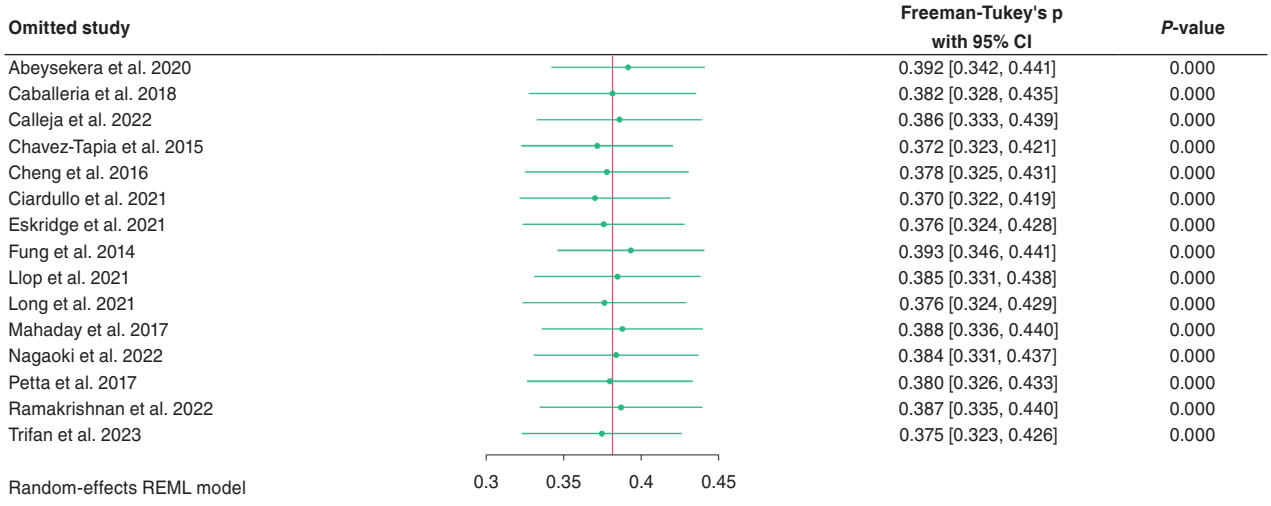


A

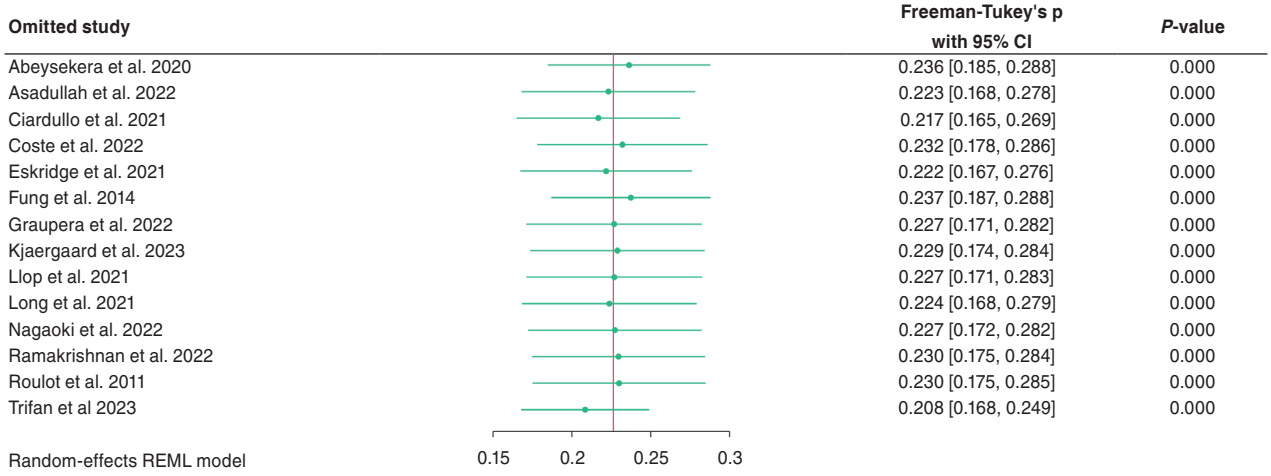


B

Supplementary Figure 1. Sensitivity analysis using the leave-one-out method. (A) Advanced liver fibrosis (≥F3) determined by fibrosis-4 index. (B) Significant liver fibrosis (≥F2) determined by vibration-controlled transient elastography (VCTE). (C) Advanced liver fibrosis (≥F3) determined by VCTE. (D) Liver cirrhosis (F4) determined by VCTE.



C



D

Supplementary Figure 1. Continued.

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