Iran J Public Health, Vol. 51, No.9, Sep 2022, pp.1925-1935

Review Article

Spleen Stiffness on Magnetic Resonance Elastography for the Detection of Portal Hypertension: A Systematic Review and Meta-Analysis

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(Received 10 Apr 2022; accepted 18 Jun 2022)

Abstract

Background: Chronic liver disease, complicated by portal hypertension (PH), may alter the extra-hepatic hemodynamic condition and spleen stiffness (SS). We aimed to evaluate the diagnostic accuracy of MRI-based elastographic methods (MRE) for detecting PH.

Methods: Seven studies were included with reference to SS with regard to the prediction of PH patients. Major outcomes considered for data extraction were diagnostic parameters for MRI for concluding mild PH, clinically significant PH and severe PH. PubMed, Scopus, Google Scholar, Cochrane and Science Direct databases were used to extract the published literature through to May, 2021Using the Rayyan Zotero and R softwares

Results: Out of 587 studies extracted, 7 were selected based on inclusion and exclusion criteria. A QUADAS-2 assessment showed that all studies were clear in terms of patient selection and reference standard. A funnel plot showed that all the selected studies were outliers, indicating a low level of accuracy for the studies included. Subgroup analysis, with reference to SS as a predictor of PH, revealed raw mean difference (RMD) of 7.78% (95% CI 5.23-10.34, $P<0.01$). The corresponding RMD observed for <60 years and >60 yr were 34.26% (95% CI 9.33- 59.20, $I^2=100\%$, $\tau^2=646.7688$, $P=0$), and 46.92% (95% CI 20-59.33, $I^2=97\%$, $\tau^2=1003.023$, $P=0$) respectively. The specificity and sensitivity noted for MRI in determining SS were 0.721 and 0.747, respectively with an area-under the curve of 0.788. The estimated random effect models for specificity and sensitivity were 0.938 and 0.842, respectively.

Conclusion: The real-time MRE has acceptable specificity and sensitivity for diagnosing SS.

Keywords: Spleen stiffness; Portal hypertension; Elastography; Chronic liver disease

Introduction

The health and economic burden association with chronic liver disease is substantial and it accounts for 2 million deaths per year worldwide. Cirrhosis has been identified as the 11th leading cause of mortality globally and one of the top 20 causes of disability-adjusted life years and years of life lost (1). Paik et al. evaluated data from 2012-2017 and reported a substantial increase in the global burden due to liver cancer and cirrhosis, and 11.4% increase in liver-related deaths (2.14 million) since 2012 (2). Global prevalence of cirrhosis reported in the general population from

autopsy studies ranges between 4.5% and 9.5% (3).

Chronic liver disease, complicated by portal hypertension (PH), may alter the extra-hepatic hemodynamic condition and spleen stiffness through a remodeling process involving passive congestion, enhanced angiogenesis, and fibrogenesis. Early and accurate diagnosis of clinically significant portal hypertension (CSPH) is paramount for effective management of complications and evaluating the prognosis in chronic liver disease (4). CSPH is defined as hepatic venous pressure gradient (HVPG) ≥10mmHg, which could result in clinical complications such as esophageal varices, ascites, hepatic encephalopathy, and hepatorenal syndrome. Furthermore, severe portal hypertension (SPH), defined as HVPG≥12 mmHg, is a risk factor for variceal bleeding (5).

In recent years, spleen elastography has been proposed as an alternative method to liver stiffness to predict the severity and prognosis of liver disease, detecting PH and predicting esophageal variances (6). Ultrasonographic (US) and magnetic resonance imaging (MRI) are the most common elastographic methods for the assessment of spleen stiffness (7). The results from several single studies have suggested the potential usefulness of spleen elastography in evaluating the risk of esophageal varices in subjects with PH or liver cirrhosis (8). Similarly, several studies have agreed upon the accuracy of Magnetic Resonance Elastography (MRE) in predicting the liver fibrosis stages, and it comes with advantages such as excellent inter-scan reproducibility, inter-reader agreement, and large organ coverage (9). For detecting the fibrosis, the MRE utilizes the proliferation of acoustic shear waves in the spleen. A mathematical algorithm will be applied to work out the cross-sectional images, which displays the magnitude of the complex shear modulus (μ) of tissue (10).

The present meta-analysis was intended to evaluate the diagnostic accuracy of spleen stiffness on MRI-based elastographic methods for detecting PH.

Methods

The review was planned and conducted in accordance with Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (11). Relevant studies were retrieved from various electronic databases, included and screened on the basis criteria and eligibility.

A systematic review was performed to extract the published studies through to May 2021, from the PubMed, Scopus, Google Scholar, Cochrane and Science Direct databases. The keywords considered for the search were 'portal hypertension', 'spleen stiffness', and 'magnetic resonance elastography'. The Medical Subject Headings searching terms considered for search were 'portal hypertension', 'spleen', 'elastography imaging techniques', and 'MRE'.

The inclusion criteria considered were as follows: Studies that measured portal pressure using the hepatic venous pressure gradient; PH defined as ≥5 mmHg, CSPH ≥10 mmHg and SPH ≥12 mmHg. Studies that reported the data necessary to calculate the diagnostic results of MR elastography for the diagnosis of mild PH, CSPH and SPH. Studies that evaluated esophageal varices, splenomegaly, radiologic portal hypertension, and thrombocytopenia along with HVPG are considered as a reference standard for PH. The Child-Pugh score was calculated based on the severity of cirrhosis: 5-6 points (Child-Pugh A); 7-9 points (Child-Pugh B) and 10 -15 points for Child-Pugh C (12).

This study excluded abstracts, reviews, editorial articles, in-vitro/animal studies, randomised control trials, case reports, non-English language articles and those dealing with other elastography techniques.

Data extraction

The reviewers investigated and extracted data from selected and eligible studies. Major outcomes considered for data extraction were diagnostic parameters of MRI for concluding mild PH, CSPH and SPH. Fig. 1 shows the flow diagram of the study selection.

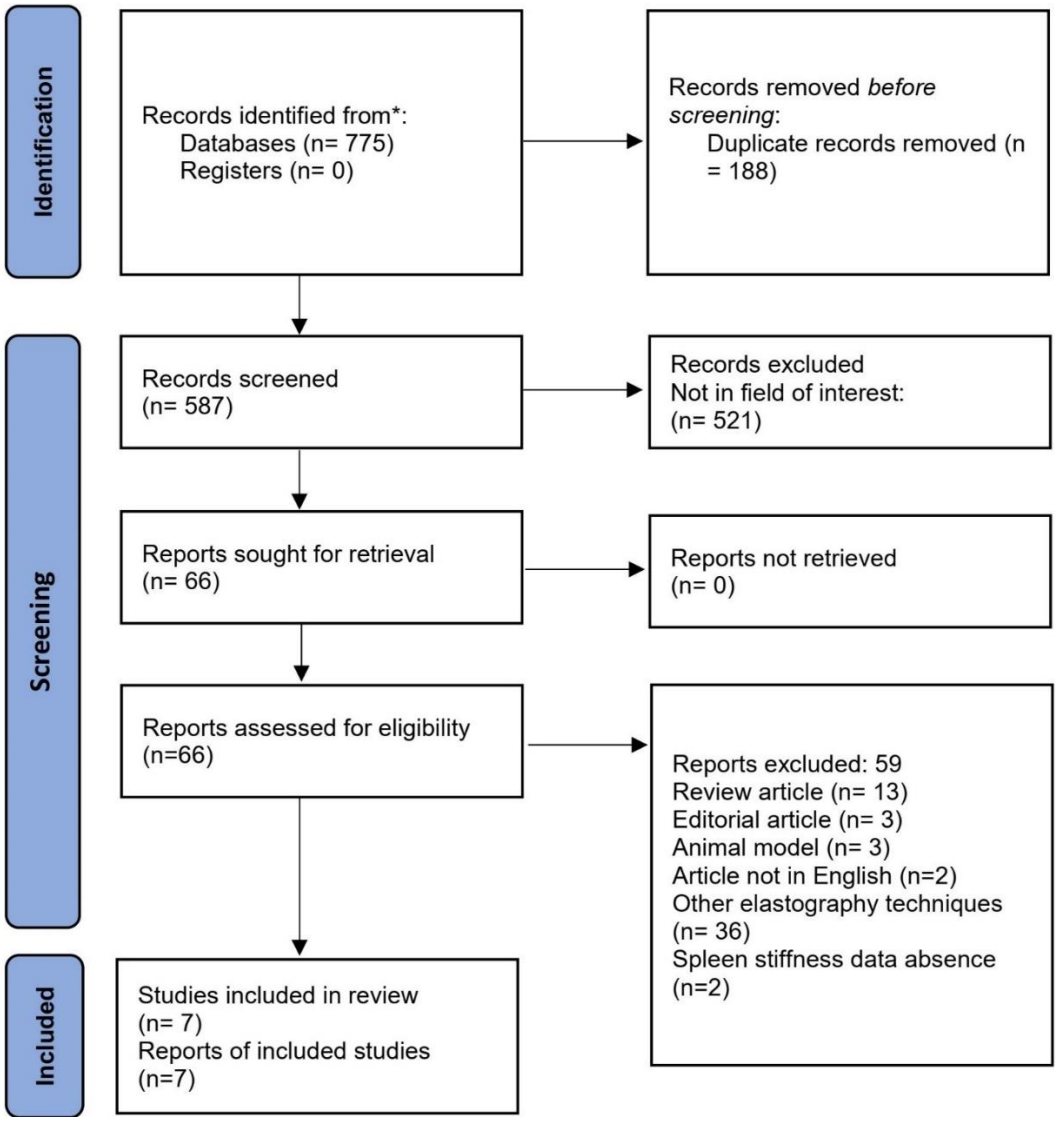

Fig. 1: Prisma flowchart depicting the results of the literature search and study selection

Risk of bias

The Quality Assessment of Diagnostic Accuracy Studies (QUADAS-2) tool was used for evaluating the quality of included articles.

Publication bias

The chances of publication bias were measured through visual representation using a funnel plot with the y-axis representing the standard error (SE) of each study. In addition, the x-axis represents the mean of each study.

Statistical analysis

A systematic review of the literature was conducted with the help of Rayyan systematic review and Zotero software. A meta-analysis was carried out as fixed effect and random effects models using R opensource software. The packages of R used for meta-analysis were metafor, meta and openxlsx. Visual representation of the meta-analysis was depicted using Forest plots. The impact of the model was chosen based upon the level of heterogeneity (I^2). The standard mean difference (SMD) was calculated for continuous

outcomes that were measured using the same methodology.

Results

Study selection

The literature search of various databases yielded 775 studies, of which 188 were removed due to duplication of records. Out of the remaining 587 studies screened, 521 were excluded for being beyond the field of interest. The number of studies assessed for eligibility was 66. The reasons for exclusion and the number of papers excluded are summarised as follows: review articles (n= 13), editorial articles (n= 3), animal model studies (n= 3), non-English articles (n=2), studies dealing with other elastography techniques (n= 28), and studies with no data on spleen stiffness (n=2). Table 1 lists the characteristics of the final 7 studies (13-19) selected for inclusion. Of the selected studies, 2 studies were conducted in South Korea (14, 15) and each from France (13), Germany (16), USA (17), Japan (18) and Taiwan (19). Among those, 4 studies (14, 15, 18, 19) were reported from the retrospective and 3 studies (13, 16, 17) are based on the prospective study design. Overall, 332 portal hypertensive patients were analyzed for this study from the included studies.

Table 1: Baseline characteristics of included studies

Author Year	Country	pHTN patients (total)	Study design	Age(Y) Mean / Median	Gender Male/ Female	BMI (kg/ m2) Mean/ Median	Etiology	Child-Pugh class score A/B/C	Reference standard
Ronot 2014 (13)	France	36 (36)	Prospective	56	28/8	26	44% alcohol, 25% HCV, 17% HBV, 11% NASP, 3% others	7/13/16	HVPG and Esophageal varices
Yoon 2019 (14)	South Korea	6 (22)	Retrospective	10.4	10/12	17.1	NR	NR	Esophageal varices
Shin 2014 (15)	South Korea	139 (139)	Retrospective	57	102/NR	NR	HRG: 26 HBV, 10 HCV, 4 Alcoholism, 2 PBC, 1 RPC, 1 AH, 2 unknown	NR	Esophageal varices
Guo 2015(16)	Germany	8 (10)	Prospective	60.5	5/5	26.3	NR	1/8/1	Esophageal varices
Dillman 2019 (17)	USA	35 (44)	Prospective	15.2	23/NR	NR	52% AH, 30% PSC, 18% ASC	NR	Splenomegaly Radiologic portal hypertension (any of ascites, varices)
Morisaka 2015 (18)	Japan	44 (93)	Retrospective	69	59/34	20	NR	25/4/1	Esophageal varices
Jhang 2021 (19)	Taiwan	64(263)	Retrospective	60.9	178/85	NR	NR	NR	Esophageal varices

CHC: chronic hepatitis C; CHB: chronic hepatitis B; NASH: non-alcoholic steatohepatitis; HBV: Hepatitis B virus; HCV: Hepatitis C virus; PBC: Primary biliary cirrhosis; RPC: Recurrent pyogenic cholangitis; AH: Autoimmune hepatitis, ASC: autoimmune sclerosing cholangitis; NR: not reported; Y: Year; BMI: Body mass index; pHTN: Portal hypertension.

Quality assessment of selected studies

The details of the QUADAS-2 assessment are shown in Table 2. With reference to risk of bias and applicability concerns, there were low risks for patient selection and reference standard. However, the index test showed either high risk or was unclear to some extent. The flow and timing was unclear or high risk for some studies.

Table 2: Results of QUADAS-2 assessment for risk of bias in individual studies

Study	*Risk of bias*				*Applicability concerns*		
	Patient selection	Index test	Reference standard	Flow and timing	Patient selection	Index test	Reference standard
Ronot et al., 2014 (13)	1	2	1	3	1	2	1
Yoon et al., 2019 (14)	1	2	1	1	1	2	1
Shin et al., 2014 (15)	1	2	2	1	1	2	2
Guo et al., 2015 (16)	1	2	1	3	1	2	1
Dillman et al., 2019 (17)	1	2	1	1	1	2	1
Morisaka, 2015 (18)	1	3	1	1	1	3	1
Jhang et al., 2021 (19)	1	2	1	2	1	2	1

1= Low risk 2= High risk 3= Unclear

Publication bias

Dispersion of studies in the funnel plot showed that all the studies were outliers, indicating low accuracy of the studies included for the subgroup analysis, with reference to spleen stiffness, age and continent (Figs. 2, 3 and 4). The small number of studies included in this meta-analysis also could have contributed to publication bias.

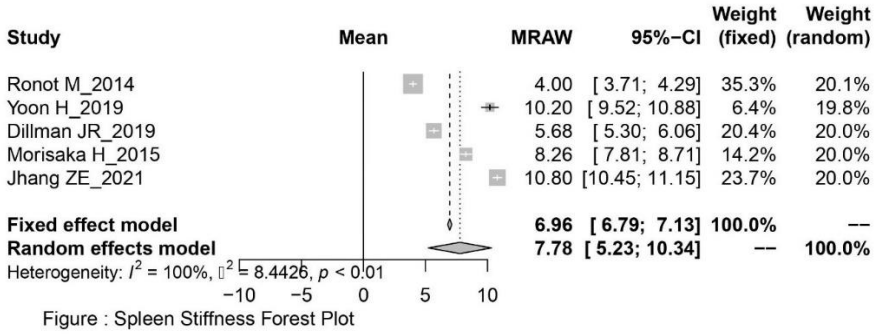

Fig. 2: Subgroup analysis with reference to spleen stiffness towards hypertension

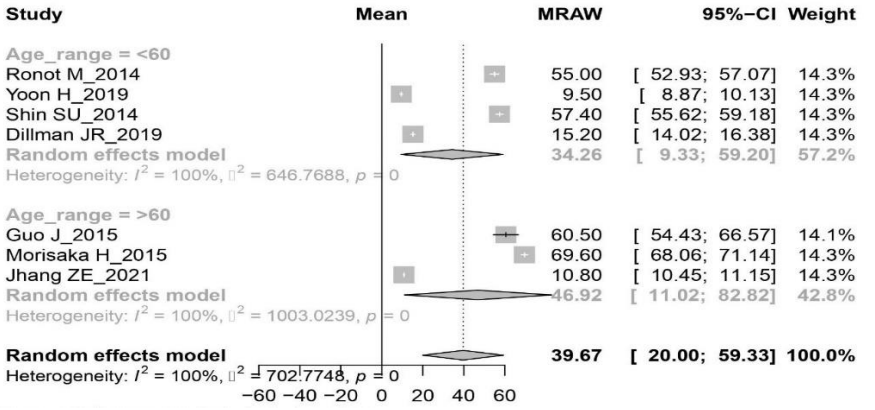

Fig. 3: Subgroup analysis with reference to age

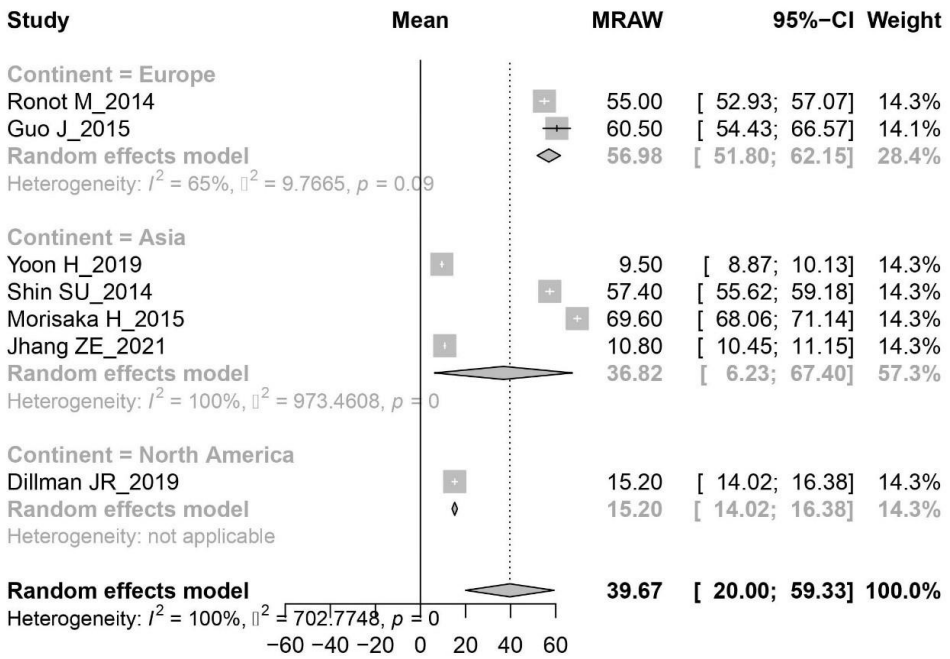

Fig. 4: Subgroup analysis with reference to continent

Subgroup analysis of spleen stiffness towards the prediction of PH

A subgroup analysis with reference to spleen stiffness as a predictor of PH revealed raw mean difference (RMD) of 7.78% (95% CI 5.23-10.34, *P*<0.01). The overall residual heterogeneity by subgroup analysis was estimated to be I^2= 100%, τ^2=8.4426, indicating the highly heterogenous nature of the included studies. Two studies (15, 16) were excluded from the analysis based on the outliers caused by the studies due to the lack of spleen stiffness measurement.

Subgroup analysis (age)

A subgroup analysis with reference to age revealed raw mean difference (RMD) of 39.67% (95% CI 20.00 -59. 33, *P*=0). The overall residual heterogeneity by subgroup analysis was calculated as I^2= 100%, τ^2=702.77. The association observed for <60 yr and >60 yr yielded RMD of 34.26% (95% CI 9.33- 59.20, I^2=100%, τ^2=646.7688, *P*=0), and 46.92% (95% CI 20-59.33, I^2=97%, τ^2=1003.023, *P*=0) respectively. The heterogeneity was found to be highly significant for both age groups.

Subgroup analysis (regions)

A subgroup analysis based on the continent in which the study was conducted revealed an overall RMD of 39.67% (95% CI 20.00-59.33, P=0). The overall residual heterogeneity by subgroup analysis was calculated as I^2= 100%, τ^2=702.774. The corresponding RMDs observed for Asia and Europe were 36.82% (95% CI 6.23-67.40, I^2=100%, τ^2=973.460, *P*=0) and 56.98% (95% CI 51.80 – 62.15, I^2=65%, τ^2=9.7665, *P*=0.09). The heterogeneity was highly significant for Asia, but not significant for Europe. Estimation of heterogeneity was not applicable for groups having only one study, hence the subgroup analysis for North America was not carried out.

Sensitivity and specificity of MRE in evaluating PH

The sensitivity and specificity of MRE in determining PH, noted in various studies with corresponding 95% confidence limits, have been depicted in Fig. 5. The overall residual heterogeneity calculated for the studies considered for estimating specificity was I^2= 81%, τ^2=1.8037

(P<0.01) and that for sensitivity was I^2= 55%, τ^2=0.1688 (P<0.07). The estimated random effect models for specificity and sensitivity were 0.938 and 0.842. Different studies were excluded based on outliers caused, with respect to sensitivity and specificity. Although sensitivity and specificity were correlated, the results obtained from both were different. Heterogeneity and inherent difference in the magnitude of the study population were greater; hence, the studies by Guo et al. (16) and Morisaka et al. (18) were removed from the sensitivity and specificity analyses respectively. The receiver operating characteristic (ROC) curve was obtained by plotting the false-positive rate against the true-positive rate (one minus specificity). The corresponding specificity and sensitivity noted were 0.721 and 0.747 with area under the curve of 0.788 (Fig. 6).

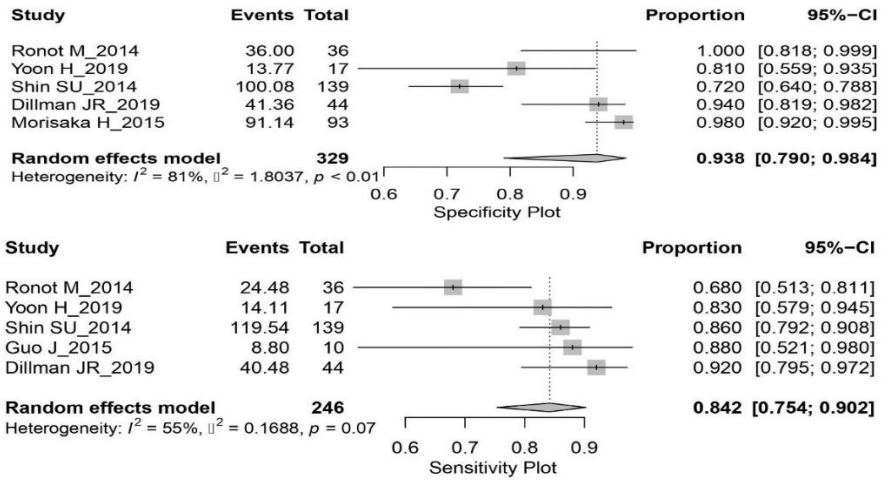

Fig. 5: Specificity and sensitivity of MRI noted in various studies on PH

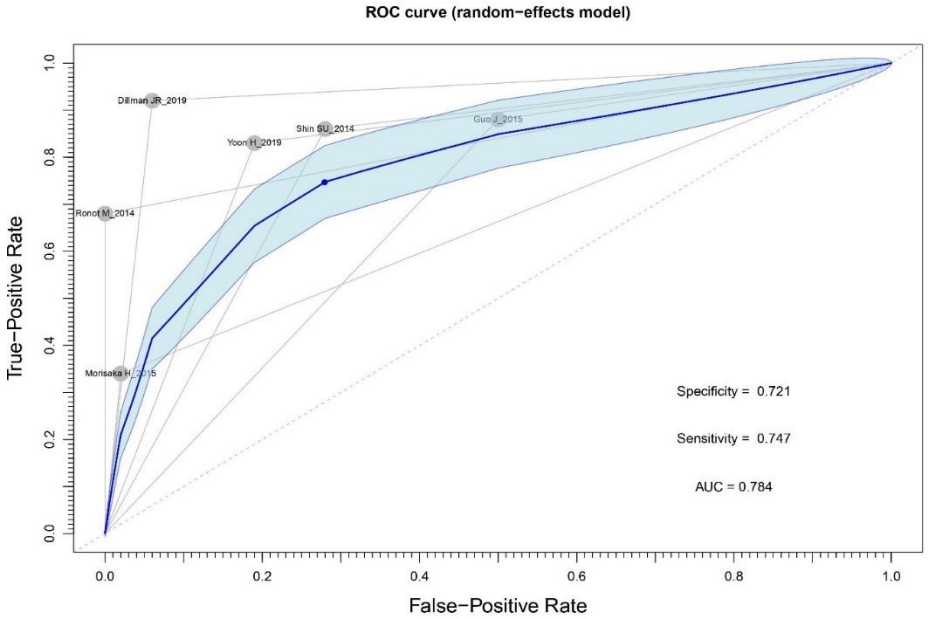

Fig. 6: ROC curve demonstrating the specificity and sensitivity of MRI in various studies

Discussion

The present meta-analysis found that the specificity and sensitivity (0.721 and 0.747) of MRE in determining spleen stiffness is acceptable. Age and ethnicity may influence the MRE-based evaluation of spleen stiffness. This finding holds significant relevance, as there is a lack of studies that have conducted age and geographical evaluation of studies on PH.

Table 3 shows the MRE techniques and their characteristics involved in the selected studies. Mostly, the 1.5-T MRI system was used as an instrument for the diagnosis of spleen stiffness. A systematic review and meta-analysis (20) comprehensively evaluated the diagnostic accuracy of spleen stiffness, measured by various techniques including MRE, in detecting CSPH, SPH, esophageal varices, and high-risk esophageal varices in patients with chronic liver diseases.

Table 3: MRE techniques and characteristics

Author, Year	*Instrument*	*Manufacturer*	*Cut-off value of SSM (kPa)*	*Success rate of SSM (%)*	*ROI*
Ronot 2014 (13)	1.5-T MRI system	Philips	4.20	86.0	1
Yoon 2019 (14)	3T system	GE	9.90	NR	1
Shin 2014 (15)	1.5- T MRI Scanner	GE	7.23	96.8	3
Guo 2015 (16)	1.5-T MRI scanner	Siemens	6.50	NR	NR
Dillman 2019 (17)	1.5-T MRI scanner	Philips	7.30	NR	4
Morisaka 2015 (18)	1.5 T MRI scanner	GE	10.1	NR	1
Jhang 2021 (19)	1.5 T MR scanner	Aera, Siemens, Erlangen	9.53	80.4	2

SSM: spleen stiffness measurement; ROI = number of regions of interest in the target organ measured for calculation of stiffness value, NR: not recorded

Measurement of spleen stiffness is a good non-invasive surveillance tool for the management of chronic liver diseases and may be beneficial as an initial screening method for excluding the presence of high-risk esophageal varices, thereby avoiding unnecessary endoscopy. The study also validated the high sensitivity and specificity of spleen stiffness in diagnosing CSPH and SPH in patients with chronic liver diseases (20).

A meta-analysis found superiority of spleen stiffness over liver stiffness in detecting esophageal variances in patients with chronic liver diseases (21). The corresponding summary receiver operating characteristic curve noted for liver stiffness and spleen stiffness were 0.81 (95% CI: 0.77–0.84) and 0.88 (95% CI: 0.85–0.91), and the result was statistically significant (P<0.01) (19). In line with this finding, Morisaka et al. (OR 1.82, P=0.005) has reported more significant association of spleen stiffness with gastroesophageal variances in patients with chronic liver disease than liver stiffness (OR 1.52, P=0.006) and spleen volume (OR 1.01, P=0.016) (18).

A retrospective study concluded that measuring spleen stiffness using MRE (84.4% sensitivity and 73.7% specificity) is superior to liver stiffness in predicting esophageal variances (19). A review by Tang et al. discussed the respective strengths and limitations of MR Elastographies, noting that the diagnostic accuracy of MR Elastography is excellent and may be slightly superior to US-based techniques. However, the quality may be compromised in patients with significant iron deposition, and the accessibility is comparatively limited (19). In concurrence with the current study findings, the second part of the study conducted by the same group of researchers also found excellent diagnostic performance of MRI- based techniques. They have also highlighted the use of spleen stiffness as a marker of hypertension, and in predicting the risk of bleeding and the presence of esophageal variances. Further standardi-

sation of elastographic techniques is paramount to improving the reproducibility of measurements, comparison of diagnostic thresholds, and patient care (22). Another major finding of the current study is that spleen stiffness measurement by MRI showed significant difference with regard to age (<60 yr and >60 yr). In contrast to this result, no significant correlation was observed between spleen stiffness and age (P>0.05) and highlighted the need to evaluate the effect of age in a larger population (23).

According to the QUADAS-2 tool, almost all the studies were clear in terms of patient selection and reference standard. However, with reference to flow and timing, there was a lack of clarity or high risks in certain articles. The risk bias was high or unclear for nearly 90% of the articles with reference to the index test.

Strength and limitations of the study

A literature review highlighted the lack of sufficient studies on MRE of the spleen and the difficulty in ascertaining the role of MRE scans of the spleen for non-invasive prediction of esophageal varices (24). Liver and spleen stiffness on MRE could serve as a supplemental non-invasive assessment tool for detecting portal hypertension (25). However, the researchers did not limit their study selection to studies in the English language. The present meta-analysis adds to the literature evidence on MRI-based evaluation of spleen stiffness alone and not on liver stiffness. Studies were limited to a few continents based on the origin of the study. The oscillation frequency of MRE in hertz as well as the MRI strength of the included studies was not reported in this study, as it was not available in most of the studies. Subgroup analyses based on age and geographical location can be considered as another major strength of the current study. However, the study could not conduct a direct comparison of MR elastography with other techniques due to the diversity of studies. Due to the limited number and heterogeneity of the included studies, there is a requirement to further investigate the diagnostic performance of these two techniques in determining the role of spleen stiffness for predicting PH. Moreover, sensitivity and specificity analysis could not be carried out due to the non-availability of data. The presence of publication bias was another limitation of the study.

Many MRI-based elastographic studies have a high risk of bias with reference to the index test, heterogeneity, inherent difference and methodological limitations. This study may help investigators to improve study design and to reduce heterogeneity by a standardised interpretation of results. Moreover, it is essential to examine the prognostic relevance, reproducibility, safety, and affordability of the MRI-based elastographic evaluation method of spleen stiffness.

Conclusion

The present meta-analysis corroborates the acceptable diagnostic potential of real-time MRE, which could have significant implications in improving non-invasive disease diagnosis, and guidance for the treatment and outcomes. The study highlights the lacunae in literature evidence and the need for head-to-head clinical trials comparing the diagnostic performance of the MRE technique.

Journalism Ethics considerations

Ethical issues (Including plagiarism, informed consent, misconduct, data fabrication and/or falsification, double publication and/or submission, redundancy, etc.) have been completely observed by the authors.

Funding source

None.

Conflict of interest

The authors declare that there is no competing of interest.

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