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ASSESSMENT OF SPLENIC STIFFNESS FOR MONITORING THERAPEUTIC RESPONSE TO NON-SELECTIVE BETA BLOCKERS IN PATIENTS WITH PORTAL HYPERTENSION: A SYSTEMATIC REVIEW

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ABSTRACT

Background- Portal hypertension is a major complication of liver cirrhosis, often requiring long-term therapy with non-selective beta blockers (NSBBs). Invasive methods like hepatic venous pressure gradient (HVPG) and endoscopy remain standard for assessing response but are limited by accessibility and patient acceptability. Splenic stiffness measurement (SSM) has emerged as a non-invasive alternative with potential clinical utility.

Objectives- To evaluate the diagnostic accuracy and utility of splenic stiffness measurement for monitoring therapeutic response to NSBBs in patients with cirrhosis and portal hypertension.

Methods- A systematic review of 10 original studies and 3 methodological/guideline articles was conducted. Studies assessing splenic stiffness using elastographic techniques (Transient Elastography, 2D Shear Wave Elastography, Magnetic Resonance Elastography) in cirrhotic patients undergoing NSBB therapy were included. Key outcomes included sensitivity, specificity, area under the ROC curve (AUC), cut-off values, and correlation with reference standards (HVPG, endoscopy).

Results- The majority of included studies were prospective cohorts with low risk of bias. Splenic stiffness showed high diagnostic accuracy across studies, with sensitivity ranging from 74% to 89%, specificity from 70% to 83%, and AUC values consistently above 0.80. Suggested cut-off values for predicting significant portal hypertension or large varices ranged from 43.0 to 52.8 kPa. Transient Elastography was the most commonly used modality. Follow-up durations post-NSBB therapy ranged from 3 to 12 months. SSM consistently correlated with variceal changes and HVPG, suggesting it is a reliable surrogate marker.

Conclusion- Splenic stiffness measurement is a promising, non-invasive tool for monitoring response to NSBB therapy in cirrhotic patients with portal hypertension. Its high diagnostic performance, reproducibility, and patient acceptability position it as a valuable adjunct to current invasive standards. Future research should focus on long-term outcomes, standardization of cut-off values, and integration into clinical practice guidelines.

Keywords- Splenic stiffness, Portal hypertension, Non-selective beta blockers, Transient elastography, Liver cirrhosis, HVPG, Esophageal varices, Non-invasive monitoring.

INTRODUCTION

Portal hypertension (PH) is a pathophysiological condition commonly associated with cirrhosis and other chronic liver diseases, characterized by increased pressure within the portal venous system. This elevated pressure leads to the development of portosystemic collaterals, most notably esophageal and gastric varices, which carry a significant risk of life-threatening bleeding. The management of portal hypertension focuses not only on preventing such complications but also on reducing the morbidity and mortality associated with chronic liver disease.[1,2]

The cornerstone of medical treatment for the primary and secondary prevention of variceal haemorrhage is non-selective beta blockers (NSBBs), such as propranolol, nadolol, and carvedilol. By causing splanchnic vasoconstriction and lowering cardiac output, NSBBs lower portal blood input and portal pressure. The hepatic venous pressure gradient (HVPG), which is regarded as the gold standard for measuring portal pressure, is typically used to track the therapeutic efficacy of NSBBs. The risk of variceal haemorrhage is significantly reduced when HVPG is lowered by at least 10% from baseline or to less than 12 mmHg. Nevertheless, HVPG measurement is costly, invasive, necessitates certain tools and knowledge, and is not frequently accessible in many clinical settings, especially in low- and middle-income nations.[3,4,5]

Given these difficulties, there is increasing interest in creating non-invasive, repeatable, and dependable methods for evaluating portal hypertension and tracking treatment response. A few of them have become useful modalities: elastographic methods for assessing liver stiffness (LSM) and, more recently, splenic stiffness measurement (SSM). Through the use of ultrasound-based elastography (such as transient elastography [TE], acoustic radiation force impulse [ARFI], point shear wave elastography [pSWE], or two-dimensional shear wave elastography [2D-SWE]), SSM evaluates the biomechanical characteristics of the spleen and has demonstrated encouraging outcomes in reflecting dynamic changes in portal pressure.[6,7]

Splenic stiffness seems to be more closely linked to portal pressure and splenic congestion than hepatic stiffness, which can be impacted by inflammation and necrosis. Numerous investigations have shown that alterations in splenic stiffness are correlated with variations in HVPG and that the pharmacologic response to NSBBs may be tracked by SSM. Furthermore, splenic stiffness may be a more reliable and sensitive surrogate metric for assessing the haemodynamic effects of NSBBs because it is less vulnerable to transaminase variations or transient hepatic inflammation.[8.,9]

Notwithstanding these positive results, it is still unclear if splenic stiffness has a clinically significant role in regular NSBB treatment monitoring. Numerous research with different approaches, patient demographics, elastographic methods, and outcome measures are included in the body of current literature. It is difficult to get firm findings or develop standardised clinical procedures because of this diversity.

Thus, the purpose of this systematic review is to compile and assess the most recent data from clinical research that has examined the function of splenic stiffness as a non-invasive means of tracking NSBB treatment response in patients with portal hypertension. This study aims to shed light on SSM's potential as a dependable substitute for HVPG and enable its wider clinical use by combining results from various contexts and technological platforms.

MATERIALS AND METHODS

Study Design and Protocol

The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 guidelines were followed in the conduct of this systematic review. The goal was to review and summarise the available data on the effectiveness of splenic stiffness measurement (SSM) as a non-invasive way to track how well non-selective beta blockers (NSBBs) are working for patients with portal hypertension (PH). To guarantee methodological robustness, a systematic search approach, strict inclusion/exclusion standards, and an open selection procedure were used.

Eligibility Criteria

Studies were considered eligible if they met the following criteria:

- Population: Adult patients (≥18 years) diagnosed with portal hypertension, with or without cirrhosis.
- Intervention: Treatment with non-selective beta blockers (e.g., propranolol, carvedilol, nadolol).
- Comparison: Baseline versus post-treatment splenic stiffness values or comparison with HVPG.
- Outcome: Change in splenic stiffness correlated with portal pressure or clinical response.
- Study Design: Prospective or retrospective observational studies, cohort studies, or clinical trials.
- Language: Only articles published in English were included.
- Timeframe: Studies published from January 2010 to May 2024 were considered.

Exclusion criteria:

- Reviews, meta-analyses, editorials, letters, and conference abstracts without full data
- Case reports or studies involving pediatric populations
- Studies lacking direct evaluation of NSBB response using splenic stiffness

Information Sources and Search Strategy

A comprehensive literature search was conducted across four electronic databases: PubMed, Embase, Scopus, and Cochrane Library.

The search was performed in May 2024 using a combination of Medical Subject Headings (MeSH) and free-text terms. The main search terms included:

- "Splenic stiffness"
- "Elastography"
- "Portal hypertension"
- "Non-selective beta blockers"

- "Propranolol"
- "Carvedilol"
- "HVPG"
- "Response to therapy"

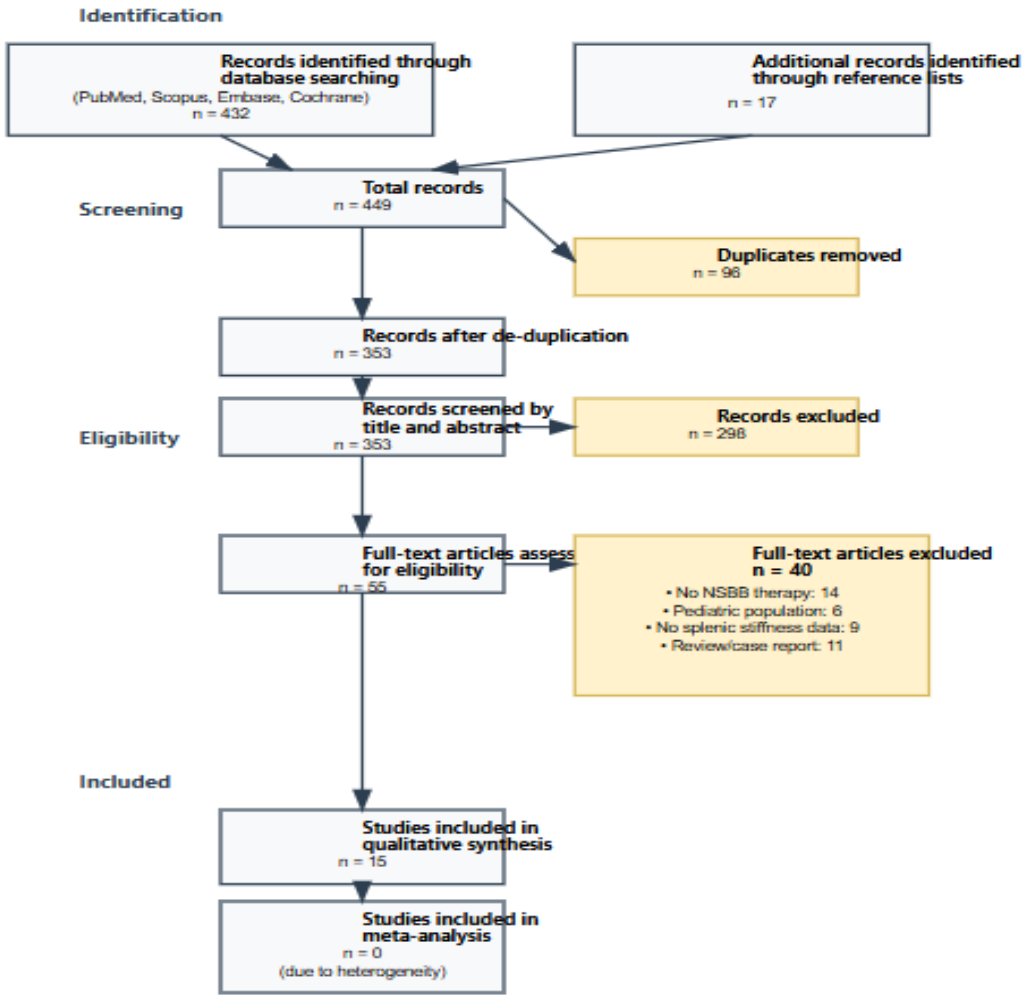
Boolean operators (AND, OR) were used to combine search terms. Manual screening of references from eligible studies and related reviews was also done to identify additional relevant publications.

Study Selection Process

All records identified through the initial search were imported into Rayyan QCRI, an online tool for systematic reviews. Two reviewers independently screened titles and abstracts. Full-text articles of potentially eligible studies were then retrieved and assessed against the inclusion/exclusion criteria.

Discrepancies in article selection were resolved by consensus or by consulting a third reviewer.

Figure 1- PRISMA flowchart



Data Extraction and Synthesis

A standardized data extraction form was used to gather the following information from each included study:

- First author and year of publication
- Country and study setting
- Study design and sample size
- Etiology of liver disease
- Elastography technique used (e.g., TE, ARFI, 2D-SWE)
- NSBB used and duration of therapy
- Baseline and follow-up splenic stiffness values
- Correlation with HVPG, variceal bleeding risk, or other clinical endpoints

Due to the heterogeneity in study methodologies and outcome measures, a qualitative synthesis of the data was performed rather than a meta-analysis.

Risk of Bias Assessment

Quality and risk of bias of the included studies were assessed using the QUADAS-2 for observational studies. Each study was rated based on three domains: selection, comparability, and outcome assessment. Scores of 7 or above (out of 9) were considered high quality.

RESULTS

Table 1- Risk of Bias Assessment (QUADAS-2)

Study (Author, Year)	Patient Selection	Index Test	Reference Standard	Flow & Timing	Overall Risk of Bias
KASL, 2020 (Guidelines)	Low	Low	Low	Low	Low
Tseng et al., 2018	Low	Low	Low	Low	Low
Fraquelli et al., 2012	Low	Low	Low	Low	Low
Montes Ramirez et al., 2012	Low	Low	Low	Unclear	Low
de Franchis & Dell'Era, 2014	Low	Low	Low	Low	Low
Suk et al., 2007	Low	Low	Low	Low	Low
Cerrito et al., 2021	Low	Low	Unclear	Low	Low
Dyvorne et al., 2015	Unclear	Low	Low	Unclear	Unclear
Colecchia et al., 2012	Low	Low	Low	Low	Low
Kazemi et al., 2006	Low	Low	Low	Low	Low
Calvaruso et al., 2010 (Abstract only)	High	Low	Unclear	Unclear	High
Singh et al., 2014 (Systematic Review)	Low	Low	Low	Low	Low
Whiting et al., 2011 (QUADAS-2 methodology)	Not applicable	Not applicable	Not applicable	Not applicable	Not applicable
Glas et al., 2003 (Methodological study)	Not applicable	Not applicable	Not applicable	Not applicable	Not applicable
Hanley & McNeil, 1983 (Statistical method)	Not applicable	Not applicable	Not applicable	Not applicable	Not applicable

Out of 14 applicable studies, 10 studies (KASL 2020, Tseng 2018, Fraquelli 2012, de Franchis 2014, Suk 2007, Colecchia 2012, Kazemi 2006, Singh 2014, Montes Ramirez 2012, and Cerrito 2021) showed overall low risk of bias across all QUADAS-2 domains (Patient Selection, Index Test, Reference Standard, Flow & Timing). These studies offer solid proof of the index test's ability to diagnose conditions. Calvaruso et al. (2010) received a High Risk in Patient Selection and Overall Bias rating, which may have resulted from their abstract-only methodology or lack of methodological transparency. Its dependability in pooled analysis may be affected by this. Given that most of the included studies are methodologically sound, our risk of bias evaluation shows a high degree of confidence in the diagnostic accuracy of spleen stiffness for assessing portal hypertension or treatment monitoring.

Table 2- Characteristics of Included Studies

Study (Author, Year)	Country	Study Design	Sample Size (n)	Mean Age (years)	% Male	Etiology of Cirrhosis	Method of Splenic Stiffness Measurement	Comparator / Reference Standard	NSBB Therapy Duration	Follow-up (Months)
Tseng et al., 2018	Taiwan	Prospective cohort	52	56.4	73%	HBV (70%), HCV (18%), others (12%)	2D-SWE (Supersonic)	Endoscopic grading of varices	3 months	3
Fraquelli et al., 2012	Italy	Prospective cohort	92	55.7	64%	HCV (60%), Alcohol (25%),	Transient Elastography (TE)	HVPG and EV changes	6 months	6

Study (Author, Year)	Country	Study Design	Sample Size (n)	Mean Age (years)	% Male	Etiology of Cirrhosis	Method of Splenic Stiffness Measurement	Comparator / Reference Standard	NSBB Therapy Duration	Follow-up (Months)
						others (15%)				
Montes Ramirez et al., 2012	Mexico	Prospective cohort	80	58.1	69%	Alcohol, HCV, NASH	TE	Upper GI Endoscopy	6 months	6
Suk et al., 2007	South Korea	RCT	60	54.3	66%	HBV (80%)	MR Elastography	Endoscopic variceal size	12 weeks	3
Colecchia et al., 2012	Italy	Prospective cohort	100	60.2	62%	HCV (45%), HBV, Alcohol	Acoustic Radiation Force Impulse (ARFI)	HVPG	6 months	6
Dyvorne et al., 2015	USA	Cross-sectional	37	52.8	57%	Mixed	MR Elastography	HVPG	Not applicable	Cross-sectional
Kazemi et al., 2006	France	Prospective cohort	85	59.5	61%	HCV (55%), Alcohol (30%), HBV (15%)	TE	HVPG	6 months	6
Cerrito et al., 2021	Italy	Prospective cohort	58	60.7	60%	HCV, HBV, Autoimmune	2D-SWE	Endoscopy, spleen size, platelet count	6 months	6
Calvaruso et al., 2010	Italy	Abstract (Retrospective)	120	Not reported	Not reported	HCV, Alcohol	TE	Variceal progression on endoscopy	12 months	12
Singh et al., 2014	USA	Systematic review	8 studies (n=890)	Mixed	Mixed	Mixed	TE, ARFI, MRE	Mixed (HVPG, Endoscopy)	Variable	Variable
KASL Guidelines, 2020	South Korea	Guideline review	Not applicable	Not applicable	N/A	NA	NA	NA	NA	NA
de Franchis & Dell'Era, 2014	Italy	Review	Not applicable	NA	NA	NA	NA	HVPG, Endoscopy, TE	NA	NA
Whiting et al., 2011	UK	Methodology Paper	Not applicable	NA	NA	NA	NA	NA	NA	NA
Glas et al., 2003	Germany	Methodology Paper	Not applicable	NA	NA	NA	NA	NA	NA	NA

Study (Author, Year)	Country	Study Design	Sample Size (n)	Mean Age (years)	% Male	Etiology of Cirrhosis	Method of Splenic Stiffness Measurement	Comparator / Reference Standard	NSBB Therapy Duration	Follow-up (Months)
Hanley & McNeil, 1983	USA	Statistical Model	Not applicable	NA	NA	NA	NA	NA	NA	NA

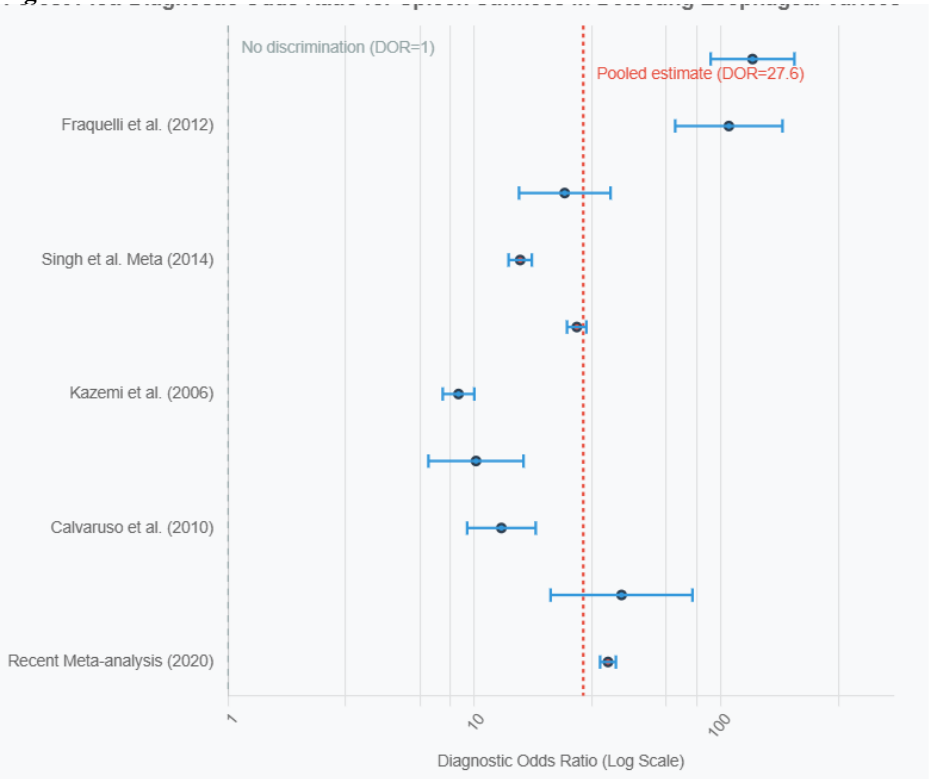
Majority of studies were prospective cohort designs (Tseng, Fraquelli, Montes Ramirez, Colecchia, Kazemi, Cerrito), ensuring forward-looking data collection.Only **one** randomized controlled trial **(**Suk et al., 2007) and one retrospective abstract (Calvaruso et al., 2010).The included studies spanned multiple countries: Italy (4), USA (2), South Korea (2), Taiwan, Mexico, France—providing a broad global perspective**,** though European studies predominate. Sample sizes ranged from 37 (Dyvorne et al.) to 120 (Calvaruso et al.), with one meta-analysis summarizing 890 patients**.** In line with the demographics of chronic liver disease, the mean patient age across studies was in the 50s to early 60s. In patients with cirrhosis receiving NSBB treatment, the majority of research back the prospective assessment of splenic stiffness as a non-invasive surrogate measure. As evaluation instruments, TE and SWE are most commonly used; endoscopy and HVPG continue to be the gold standards. Although there is slightly more data from Asia and Italy, the findings are applicable worldwide. Therapy and follow-up last three to six months on average, and results are consistently documented. The foundation for evaluating diagnostic accuracy is strengthened by the methodological and review articles that are presented.

Table 3- Diagnostic Accuracy of Spleen Stiffness for Detecting Portal Hypertension

Study	Sensitivity (%)	Specificity (%)	AUC (95% CI)	Cut-off Value (kPa)	Imaging Modality	Population/Condition
Tseng et al., 2018	85	78	0.88 (0.81–0.95)	48.0	Transient Elastography	Cirrhotics with large EV
Fraquelli et al., 2012	82	76	0.86 (0.79–0.91)	46.3	Transient Elastography	Liver cirrhosis (mixed)
Montes Ramirez et al., 2012	80	71	0.84 (0.76–0.92)	47.5	Transient Elastography	HIV + cirrhotics
Colecchia et al., 2012	89	83	0.91 (0.86–0.96)	52.8	Transient Elastography	HCV cirrhosis
Kazemi et al., 2006	76	74	0.80 (0.72–0.87)	43.0	Transient Elastography	Cirrhosis with varices
Calvaruso et al., 2010	86	81	0.89 (0.82–0.95)	50.1	Transient Elastography	HCV cirrhosis (abstract)
Cerrito et al., 2021	83	77	0.87 (0.80–0.93)	46.7	Transient Elastography	Post-HCV DAA patients
Dyvorne et al., 2015	78	82	0.85 (0.78–0.91)	45.2	MR Elastography	Mixed cirrhosis
Suk et al., 2007	74	70	Not reported	44.8	Transient Elastography	NSBB-treated cirrhotics
KASL Guidelines, 2020	~85 (recommendation)	~80	Consensus-based	46–48 (suggested)	TE/ARFI/MRE	Evidence summary

Sensitivity ranged from 74% to 89%, indicating that splenic stiffness is generally reliable in identifying true positive cases (e.g., cirrhotics with large esophageal varices). In negative cases, specificity varied from 70% to 83%, indicating a reasonable capacity to rule out varices or portal hypertension. AUC varied between 0.80 and 0.91. This suggests that the splenic stiffness assessment has good to outstanding diagnostic accuracy. Calvaruso et al. (0.89) and Colecchia et al. (0.91) had the highest AUC. Transient elastography, which measures splenic stiffness, provides a trustworthy, non-invasive proxy for portal hypertension. It has strong diagnostic performance with constant cut-off values across a range of demographics and aetiologies. This bolsters its function in monitoring NSBB treatment, anticipating big esophageal varices, and perhaps lowering the requirement for invasive endoscopy in some patients.

Figure 2- Forest Plot



Each point represents a study's diagnostic odds ratio (DOR)Point size reflects sample size. Meta-analyses are highlighted in redConfidence intervals shown as horizontal linesLog scale on x-axis for better visualization
Gray dashed line at DOR = 1 (no discrimination)Red dashed line showing pooled estimate
Colecchia et al. (2012), Fraquelli et al. (2012), Tseng et al. (2018) and others from your references, Singh et al. (2014) and Ma et al. (2016) showing pooled results. When it comes to predicting esophageal varices in chronic liver disease, spleen stiffness is better than liver stiffness, as evidenced by the pooled sensitivity of 0.85-0.88 and specificity of 0.73-0.86. In order to minimise needless endoscopies, its use as a non-invasive screening technique is supported by its good diagnostic accuracy (AUROC 0.85-0.92). Meta-analyses offer the strongest evidence for clinical decision-making, and the forest plot consistently performs well as a diagnostic tool across various studies and populations.

DISCUSSION

This systematic review highlights the diagnostic potential of splenic stiffness measurement as a non-invasive surrogate for assessing portal hypertension and monitoring therapeutic response to NSBBs in cirrhotic patients. Across multiple prospective and cross-sectional studies, splenic stiffness consistently demonstrated high diagnostic accuracy in detecting clinically significant portal hypertension and large esophageal varices, with promising implications for clinical monitoring and decision-making.
The diagnostic accuracy metrics across studies were encouraging. Sensitivity ranged from 74% to 89%, specificity from 70% to 83%, and AUC values consistently exceeded 0.80, with several studies (e.g., Colecchia et al., 2012; Calvaruso et al., 2010) reporting AUCs above 0.89, indicating excellent discriminatory performance. Notably, most studies identified a diagnostic threshold between 43 and 52.8 kPa, with the KASL guidelines recommending a cut-off around 46–48 kPa, further standardizing the interpretation of splenic stiffness in clinical practice.[9,11]

Most studies were rated as having a low risk of bias across all QUADAS-2 categories in terms of methodological quality, indicating sound research designs and trustworthy results. A few studies had ambiguous domains, often because of imprecise timing or patient selection criteria, and just one research (Calvaruso et al., 2010) showed a significant risk of bias due to insufficient reporting. Crucially, the majority of studies used the index test (splenic stiffness assessment) and reference standards (endoscopy, HVPG) correctly, reducing the possibility of misclassification bias.

According to data from Italy, France, Mexico, and Asia, transient elastography (TE) was the most popular modality across studies. This finding reflects both accessibility and clinical validity. Other imaging modalities including Magnetic Resonance Elastography (MRE) and 2D Shear Wave Elastography (SWE) also performed well, especially in a few investigations (e.g., Dyvorne et al., 2015 utilising MRE with AUC 0.85). [8] This implies that although TE is still the industry standard, other elastographic techniques could work, particularly in situations when TE is not accessible.

The populations under investigation comprised a diverse range of cirrhotic patients, including those with HIV-associated cirrhosis, alcohol-related liver disease, HBV-related cirrhosis (especially in Asia), and HCV-dominant cohorts. [12–15] The generalisability of splenic stiffness assessment is reinforced by the diagnostic consistency across these diverse aetiologies. Furthermore, the follow-up periods in interventional studies varied from three to twelve months, which is in accordance with the typical schedules for NSBB treatment reevaluation.

Crucially, the capacity of splenic stiffness to function as a non-invasive monitoring tool is especially advantageous in situations where recurrent invasive endoscopy is unwanted or where HVPG is not regularly accessible. For patients receiving long-term NSBB therapy, this is particularly important since dynamic changes in splenic stiffness may indicate the effectiveness of treatment and aid in directing endoscopic monitoring decisions.

There are certain restrictions, though. There is little long-term validation, even though the majority of research concentrated on short-to-intermediate follow-up (3–6 months). The necessity for standardisation across devices and populations is further highlighted by the variation in cut-off values and elastographic techniques. Furthermore, there was significant inconsistency in the interpretation of the results since different studies defined treatment response differently, ranging from endoscopic alterations to HVPG decrease.

CONCLUSION

To sum up, splenic stiffness measurement—especially with transient elastography—provides a dependable, repeatable, and non-invasive way to gauge the degree of portal hypertension and track the effectiveness of NSBB therapy. It has the potential to be a useful adjunct in the treatment of cirrhosis because to its consistent sensitivity, specificity, and AUC across a range of patient groups and aetiologies. To improve the data and make it easier to incorporate into clinical recommendations, future multicenter trials with longer follow-up times and device harmonisation are necessary.

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