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ORIGINAL ARTICLE

Performance of spleen stiffness measurement in prediction of clinical significant portal hypertension: A meta-analysis

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KEYWORDS
Spleen stiffness;
Elastography;
Portal hypertension;
Chronic liver disease;
Correlation coefficient

Summary
Aim: Our purpose was to evaluate the correlation between spleen stiffness (SS) measured by ultrasound-based elastography and hepatic venous pressure gradient (HVPG) and assess the accuracy of SS in detecting clinical significant portal hypertension (CSPH) and severe portal hypertension.
Method: Nine studies were included from thorough literature research and selection processes. A random model was used to analyze the correlation between HVPG and SS. We adopted the bivariate mixed effects model to assess the diagnostic performance.
Results: Regarding to correlation between SS and HVPG, the summary correlation coefficient was 0.72 (95% confidence interval [CI], 0.63–0.80). In detection of CSPH, the sensitivity, specificity, AUC and DOR were: 0.88 (0.70–0.96), 0.84 (0.72–0.92), 0.92 (0.89–0.94) and 38 (17–84) for CSPH, respectively; and 0.92 (0.82–0.96), 0.79 (0.72–0.85), 0.87 (0.84–0.90) and 41 (17–100) for severe portal hypertension, respectively.
Conclusion: Correlation between SS and HVPG was good. Although SS showed good sensitivity and specificity, the different cut-off values and techniques among studies might limit the impact of our results on clinical practice. Therefore, more high-quality prospective studies are required to evaluate the role of SS in predicting portal hypertension.

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Introduction

Portal hypertension is defined by an increase in hepatic venous pressure gradient (HVPG) and results from the development of liver cirrhosis caused by chronic liver disease (CLD). Dominating complications of liver cirrhosis such as hepatorenal syndrome, varices bleeding, and hepatic encephalopathy related to portal hypertension are important cause of death on patients with cirrhosis [1]. Hence it is necessary to detect portal hypertension for sufficient therapy which will improve the prognosis and reduce mortality of portal hypertension related complications [2].

HVPG measurement is a reference standard to evaluate portal hypertension in patients with cirrhosis. Response to therapy of portal hypertension can also be assessed through this method [3]. When high HVPG presents ($\geq$ 10 mmHg), clinically significant portal hypertension (CSPH), which increases risk of developing varices, is defined [4]. Patients with severe portal hypertension (HVPG $\geq$ 12 mmHg) are at risk for variceal bleeding [5]. However, measurement of HVPG is invasive and related with complications [6]. Further, applicability of HVPG measurement is limited by deficiency of technique outside liver units. Thus a safe and convenient method is needed to assess the progression of portal hypertension accurately.

Ultrasound elastography is a non-invasive tool to measure value of liver/spleen stiffness which could predict the presence of portal hypertension [7—10]. Recent studies have revealed that spleen stiffness (SS) value measured by ultrasound elastography correlated HVPG well and SS value was a promising method to diagnose CSPH in CLD with high diagnostic accuracy [11—13]. To our knowledge, there is no meta-analysis discussing SS value on diagnosis of CSPH. The purpose of our study is to perform a systematic review and meta-analysis to assess the correlation between SS value and HVPG and the diagnostic accuracy of ultrasound-based SS value on prediction of CSPH in patients with CLD.

Materials and methods

Selection criteria

Articles would be selected in our meta-analysis when they contain the following features: (1) being performed in patients with chronic liver disease; (2) selecting ultrasound elastography (e.g. transient elastography) as index test; (3) using HVPG as the reference standard for diagnosing CSPH; (4) providing sufficient information to calculate the number of patients of true positive (TP), false positive (FP), true negative (TN), and false negative (FN) for SS value on prediction of CSPH or severe portal hypertension; (5) providing correlation coefficient regarding the correlation between SS and HVPG.

Search strategy

In the present meta-analysis, online literature searching was carried out. Searches were implemented on MEDLINE (Pubmed), Embase (Ovid), Web of Science. Keywords used in the search included ''spleen'', ''elastography'', and ''portal hypertension''. Only studies written by English were included in our meta-analysis. The full electronic strategy was showed in Supplementary document.

Data extraction

Potentially eligible articles would be identified by two authors. If there were discrepancies, a senior reviewer would resolve the problems. The search included articles published before March 2017. We tried to extract following data: authors' name, year of publication, country, number of patients, mean age of patients, sex ratio, body mass index (BMI), constituent ratio of etiology, proportion of cirrhosis, measuring techniques and correlation coefficient. Optimal cut-off value based on ROC, sensitivity, specificity, positive predictive value and negative predictive value for SS on diagnosis of CSPH and severe portal hypertension were also extracted. The number of TP, FP, FN and TN results of SS on diagnosis of CSPH and severe portal hypertension was calculated on basis of sensitivity, specificity, positive predictive value and negative predictive value.

Quality assessment

We used QUADAS-2 tool to assess the quality of the included study [14]. This tool evaluated bias risks of the study in 4 domains including patient selection, index test, reference standard, flow and timing. Applicability was also estimated in the first 3 domains. In this study, the reference standard referred to HVPG and index test was SS measurement.

Statistical methods for correlation between SS measurement and HVPG measurement

A Fisher *z* transformation of the correlation coefficient was used to calculate correlation coefficient (*r*) between SS and HVPG [15]. According to this method, the Pearson or Spearman correlation coefficients were converted to *z* transforms. After the pooled *z* score with a 95% confidence interval (CI) was calculated, it was transformed back to the pooled with a 95% CI through both fixed and random effects models. Chi-square test with significance was used to assess the heterogeneity quantitatively and a *P*-value less than 0.10 was consider as significant heterogeneous. I^2 statistic was used to quantify heterogeneity and an I^2 above 50% was also considered as significant heterogeneous. If significant heterogeneity was found in included studies, we would adopt a random effect model to obtain the summary correlation coefficient and its 95% CI. For statistical analysis, STATA 14 (Stata Corp., TX, USA) was used.

Analysis regarding diagnostic accuracy of SS in the meta-analysis was based on the number of TP, FP, FN and TN results of SS on diagnosis of CSPH and severe portal hypertension. Pooled sensitivity and pooled specificity were used as standard measures. The diagnostic odds ratio (DOR) was selected to evaluate diagnostic test accuracy which combined both sensitivity and specificity. The summary ROC (SROC) curve was also performed. We performed Fagan's nomogram to assess the post-test probabilities presuming pre-test probability of 25%, 50% and 75%. Chi-square test

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