

World Journal of *Gastroenterology*

World J Gastroenterol 2019 September 21; 25(35): 5220-5402



**OPINION REVIEW**

- 5220** How does *Helicobacter pylori* cause gastric cancer through connexins: An opinion review
Li H, Xu CX, Gong RJ, Chi JS, Liu P, Liu XM

REVIEW

- 5233** Colorectal cancer: Parametric evaluation of morphological, functional and molecular tomographic imaging
Mainenti PP, Stanzione A, Guarino S, Romeo V, Ugga L, Romano F, Storto G, Maurea S, Brunetti A

MINIREVIEWS

- 5257** Sarcopenia and cognitive impairment in liver cirrhosis: A viewpoint on the clinical impact of minimal hepatic encephalopathy
Nardelli S, Gioia S, Faccioli J, Riggio O, Ridola L

ORIGINAL ARTICLE**Basic Study**

- 5266** Significance of tumor-infiltrating immunocytes for predicting prognosis of hepatitis B virus-related hepatocellular carcinoma
Chen QF, Li W, Wu PH, Shen LJ, Huang ZL
- 5283** Long non-coding RNA highly up-regulated in liver cancer promotes exosome secretion
Cao SQ, Zheng H, Sun BC, Wang ZL, Liu T, Guo DH, Shen ZY
- 5300** Circular RNA PIP5K1A promotes colon cancer development through inhibiting miR-1273a
Zhang Q, Zhang C, Ma JX, Ren H, Sun Y, Xu JZ
- 5310** LncRNA-ATB promotes autophagy by activating Yes-associated protein and inducing autophagy-related protein 5 expression in hepatocellular carcinoma
Wang CZ, Yan GX, Dong DS, Xin H, Liu ZY

Case Control Study

- 5323** Liver stiffness and serum markers for excluding high-risk varices in patients who do not meet Baveno VI criteria
Zhou H, Long J, Hu H, Tian CY, Lin SD

Retrospective Study

- 5334** Pathological response measured using virtual microscopic slides for gastric cancer patients who underwent neoadjuvant chemotherapy
Kawai S, Shimoda T, Nakajima T, Terashima M, Omae K, Machida N, Yasui H

- 5344** Feasibility of endoscopic treatment and predictors of lymph node metastasis in early gastric cancer
Chu YN, Yu YN, Jing X, Mao T, Chen YQ, Zhou XB, Song W, Zhao XZ, Tian ZB

SYSTEMATIC REVIEWS

- 5356** *De novo* malignancies after liver transplantation: The effect of immunosuppression-personal data and review of literature
Manzia TM, Angelico R, Gazia C, Lenci I, Milana M, Ademoyero OT, Pedini D, Toti L, Spada M, Tisone G, Baiocchi L

META-ANALYSIS

- 5376** Gastric neuroendocrine neoplasms type 1: A systematic review and meta-analysis
Tsolakis AV, Ragkousi A, Vujasinovic M, Kaltsas G, Daskalakis K

CASE REPORT

- 5388** Autoimmune hepatitis in human immunodeficiency virus-infected patients: A case series and review of the literature
Chaiteerakij R, Sanpawat A, Avihingsanon A, Treeprasertsuk S

ABOUT COVER

Editorial board member of *World Journal of Gastroenterology*, Cesare Tosetti, MD, Doctor, Professor, Department of Primary Care, Health Care Agency of Bologna, Porretta Terme 40046, Bologna, Italy

AIMS AND SCOPE

The primary aim of *World Journal of Gastroenterology* (WJG, *World J Gastroenterol*) is to provide scholars and readers from various fields of gastroenterology and hepatology with a platform to publish high-quality basic and clinical research articles and communicate their research findings online.

WJG mainly publishes articles reporting research results and findings obtained in the field of gastroenterology and hepatology and covering a wide range of topics including gastroenterology, hepatology, gastrointestinal endoscopy, gastrointestinal surgery, gastrointestinal oncology, and pediatric gastroenterology.

INDEXING/ABSTRACTING

The WJG is now indexed in Current Contents®/Clinical Medicine, Science Citation Index Expanded (also known as SciSearch®), Journal Citation Reports®, Index Medicus, MEDLINE, PubMed, PubMed Central, and Scopus. The 2019 edition of Journal Citation Report® cites the 2018 impact factor for WJG as 3.411 (5-year impact factor: 3.579), ranking WJG as 35th among 84 journals in gastroenterology and hepatology (quartile in category Q2). CiteScore (2018): 3.43.

RESPONSIBLE EDITORS FOR THIS ISSUE

Responsible Electronic Editor: *Yu-Jie Ma*

Proofing Production Department Director: *Yun-Xiaojuan Wu*

NAME OF JOURNAL

World Journal of Gastroenterology

ISSN

ISSN 1007-9327 (print) ISSN 2219-2840 (online)

LAUNCH DATE

October 1, 1995

FREQUENCY

Weekly

EDITORS-IN-CHIEF

Subrata Ghosh, Andrzej S Tarnawski

EDITORIAL BOARD MEMBERS

<http://www.wjgnet.com/1007-9327/editorialboard.htm>

EDITORIAL OFFICE

Ze-Mao Gong, Director

PUBLICATION DATE

September 21, 2019

COPYRIGHT

© 2019 Baishideng Publishing Group Inc

INSTRUCTIONS TO AUTHORS

<https://www.wjgnet.com/bpg/gerinfo/204>

GUIDELINES FOR ETHICS DOCUMENTS

<https://www.wjgnet.com/bpg/GerInfo/287>

GUIDELINES FOR NON-NATIVE SPEAKERS OF ENGLISH

<https://www.wjgnet.com/bpg/gerinfo/240>

PUBLICATION MISCONDUCT

<https://www.wjgnet.com/bpg/gerinfo/208>

ARTICLE PROCESSING CHARGE

<https://www.wjgnet.com/bpg/gerinfo/242>

STEPS FOR SUBMITTING MANUSCRIPTS

<https://www.wjgnet.com/bpg/GerInfo/239>

ONLINE SUBMISSION

<https://www.f6publishing.com>



Case Control Study

Liver stiffness and serum markers for excluding high-risk varices in patients who do not meet Baveno VI criteria

Hong Zhou, Jun Long, Han Hu, Cai-Yun Tian, Shi-De Lin

ORCID number: Hong Zhou (0000-0002-5580-6744); Jun Long (0000-0001-7595-3840); Han Hu (0000-0001-7604-4008); Cai-Yun Tian (0000-0002-6847-4400); Shi-De Lin (0000-0001-8803-4069).

Author contributions: Zhou H and Long J contributed equally to this work; Zhou H, Long J, Hu H, Tian CY, and Lin SD performed the research; Zhou H and Lin SD wrote the manuscript; Long J and Lin SD performed the biostatistics analysis; Hu H, Tian CY, and Lin SD analyzed the data; all authors discussed the results and commented on the manuscript.

Supported by the National Natural Science Foundation of China, No. 81860114.

Institutional review board

statement: This study was approved by the Institutional Review Board of Affiliated Hospital of Zunyi Medical University, Guizhou Province, China.

Informed consent statement: All patients were informed in writing of the use of their data for clinical research purposes and accepted.

Conflict-of-interest statement: The authors declare that they have no conflicts of interest in this study.

STROBE statement: The authors have read the STROBE Statement-checklist of items, and the manuscript was prepared and revised according to the STROBE Statement-checklist of items.

Open-Access: This article is an

Hong Zhou, Jun Long, Han Hu, Cai-Yun Tian, Shi-De Lin, Department of Infectious Diseases, Affiliated Hospital of Zunyi Medical University, Zunyi 563003, Guizhou Province, China

Hong Zhou, Department of Infectious Diseases, Suining Central Hospital, Suining 629000, Sichuan Province, China

Corresponding author: Shi-De Lin, MD, Occupational Physician, Professor, Department of Infectious Diseases, Affiliated Hospital of Zunyi Medical University, 201 Dalian Street, Zunyi 563003, Guizhou Province, China. linshide6@zmu.edu.cn

Telephone: +86-851-28609183

Fax: +86-851-28609183

Abstract

BACKGROUND

The Baveno VI criteria for predicting esophageal varices, *i.e.*, liver stiffness measurement (LSM) < 20 kPa and platelet (PLT) count > 150 × 10⁹/L, identify patients who can safely avoid gastroscopy screening. However, they require further refinement.

AIM

To evaluate the utility of LSM and serum markers of liver fibrosis in ruling out high-risk varices (HRV) in patients who do not meet Baveno VI criteria.

METHODS

Data from 132 patients with hepatitis B virus (HBV)-related compensated liver cirrhosis who did not meet the Baveno VI criteria were retrospectively reviewed. MedCalc 15.8 was used to calculate receiver operating characteristic (ROC) curves, and the accuracy of LSM, PLT count, aspartate aminotransferase (AST)-to-PLT ratio index, Fibrosis-4, and the Lok index in predicting HRV were evaluated according to the area under each ROC curve (AUROC). The utility of LSM, PLT, and serum markers of liver fibrosis stratified by alanine transaminase (ALT) and total bilirubin (TBil) levels was evaluated for ruling out HRV.

RESULTS

In all patients who did not meet the Baveno VI criteria, the independent risk factors for HRV were LSM and ALT. Only the AUROC of Lok index was above 0.7 for predicting HRV, and at a cutoff value of 0.4531 it could further spare 24.2% of gastroscopies without missing HRVs. The prevalence of HRV was significantly lower in patients with ALT or TBil ≥ 2 upper limit of normal (ULN) (14.3%) than in patients with both ALT and TBil < 2 ULN (34.1%) (*P* = 0.018). In

open-access article which was selected by an in-house editor and fully peer-reviewed by external reviewers. It is distributed in accordance with the Creative Commons Attribution Non Commercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited and the use is non-commercial. See: <http://creativecommons.org/licenses/by-nc/4.0/>

Manuscript source: Unsolicited manuscript

Received: May 29, 2019

Peer-review started: May 30, 2019

First decision: July 21, 2019

Revised: July 30, 2019

Accepted: August 24, 2019

Article in press: July 21, 2019

Published online: September 21, 2019

P-Reviewer: El-Karakasy H, Fouad YM, Thomopoulos K

S-Editor: Yan JP

L-Editor: Wang TQ

E-Editor: Ma YJ



the 41 patients with ALT and TBil < 2 ULN, LSM had an AUROC for predicting HRV of 0.821. LSM < 20.6 kPa spared 39.0% of gastroscopies without missing HRVs. In the 91 patients with ALT or TBil \geq 2 ULN, the Lok index and PLT had AUROCs of 0.814 and 0.741, respectively. Lok index \leq 0.5596 or PLT > $100 \times 10^9/L$ further spared 39.6% and 43.9% of gastroscopies, respectively, without missing HRVs.

CONCLUSION

In HBV-related compensated cirrhosis patients who do not meet Baveno VI criteria, the LSM, PLT, or Lok index cutoff stratified by ALT and TBil accurately identifies more patients without HRV.

Key words: Baveno VI; Esophageal varices; Liver cirrhosis; Liver stiffness measurement; Serum markers of liver fibrosis

©The Author(s) 2019. Published by Baishideng Publishing Group Inc. All rights reserved.

Core tip: In patients with hepatitis B virus (HBV)-related compensated cirrhosis who did not meet the Baveno VI criteria, the prevalence of high-risk varices among patients with alanine transaminase (ALT) or total bilirubin (TBil) \geq 2 upper limit of normal (ULN) was significantly lower compared to patients with ALT and TBil < 2 ULN. In the 41 patients with ALT and TBil < 2 ULN, liver stiffness measurement (LSM) < 20.6 kPa spared 39.0% of gastroscopies without missing high-risk varices (HRVs). In the 91 patients with ALT or TBil \geq 2 ULN, Lok index \leq 0.5596 or platelet (PLT) > $100 \times 10^9/L$ further spared 39.6% and 43.9% of gastroscopies, respectively, without missing HRVs.

Citation: Zhou H, Long J, Hu H, Tian CY, Lin SD. Liver stiffness and serum markers for excluding high-risk varices in patients who do not meet Baveno VI criteria. *World J Gastroenterol* 2019; 25(35): 5323-5333

URL: <https://www.wjgnet.com/1007-9327/full/v25/i35/5323.htm>

DOI: <https://dx.doi.org/10.3748/wjg.v25.i35.5323>

INTRODUCTION

About 30% of cases of liver cirrhosis worldwide result from chronic hepatitis B virus (HBV) infection^[1]. Esophageal varices (EV) and esophagogastric variceal bleeding (EVB) are major complications among patients with liver cirrhosis and are associated with high morbidity and mortality^[2]. Six-week mortality rates range between 15% and 25% in patients with EVB^[3,4]. High-risk varices (HRV) are medium or large EV or small EV with red wale signs. Prophylactic therapy with beta-blockers or elastic band ligation benefits patients with HRV and is the standard of care in patients with cirrhosis to identify those with HRV^[5,6].

Gastroscopy is the gold standard for diagnosing EV and assessing bleeding risk^[7]. However, gastroscopy is an invasive and expensive procedure with associated risks^[6]. In the last 10 years, evidence has accumulated regarding the usefulness of non-invasive methods for stratifying EV risk in patients with compensated advanced chronic liver disease^[8]. The 2015 Baveno VI consensus workshop recommended that patients with liver stiffness measurement (LSM) < 20 kPa and platelet (PLT) count > $150 \times 10^9/L$ could safely avoid gastroscopy screening^[3,4]. These criteria were verified in several clinical studies and can safely spare 20%-30% of liver cirrhosis patients from undergoing gastroscopy^[9,10]. The American Association for the Study of Liver Disease recently recommended using the Baveno VI criteria to stratify EV risk in patients with liver cirrhosis^[3]. However, up to 40% of gastroscopies are still unnecessary^[11]. It is therefore imperative to finding a new strategy to identify more patients without HRV.

Several studies reported that adjusting the LSM and PLT thresholds could spare more patients from undergoing gastroscopy. The expanded Baveno VI criteria (PLT > $110 \times 10^9/L$ and LSM < 25 kPa) further spare 19% of gastroscopies compared to the original Baveno VI criteria, with a risk of missing 1.6% of HRV cases^[12]. Jangouk *et al*^[9] recently reported a 12% increase in spared gastroscopies (with no additional HRV cases missed) by expanding the Baveno VI criteria to include a Model for End-Stage

Liver Disease (MELD) score of 6. Using cutoff values of $\text{LSM} \leq 25 \text{ kPa}$ and $\text{PLT} \geq 100 \times 10^9/\text{L}$, Ding *et al*^[13] found that 21% of gastroscopies were spared. However, these criteria have not been confirmed.

Because liver inflammation can significantly increase LSM, it is recommended that the interpretation of LSM is based on the levels of alanine transaminase (ALT) and total bilirubin (TBil)^[14,15]. Clinically, most patients with HBV-related liver cirrhosis have concomitant liver inflammation. However, it remains unknown whether adjusting the LSM and PLT cutoffs according to ALT and TBil levels would increase the number of spared gastroscopies among patients who do not meet the Baveno VI criteria.

Serum markers of liver fibrosis such as PLT count, aspartate aminotransferase (AST)-to-PLT ratio index (APRI), Fibrosis-4 (FIB-4), and the Lok index are useful in predicting severe liver fibrosis or cirrhosis^[16-18], EV risk, and variceal bleeding risk in patients with HBV infection^[19]. It remains unknown whether these serum markers of liver fibrosis can identify patients without HRV among those who do not meet the Baveno VI criteria. In this study, we aimed to evaluate the utilities of LSM, PLT count, APRI, FIB-4, and the Lok index stratified by ALT and TBil levels for ruling out HRV in patients with HBV-related compensated cirrhosis who did not meet the Baveno VI criteria.

MATERIALS AND METHODS

Study population

From September 2016 to June 2018, we applied the Baveno VI criteria to patients with compensated liver cirrhosis who were admitted to the Affiliated Hospital of Zunyi Medical University and Suining Central Hospital. All the patients with compensated liver cirrhosis who did not meet the Baveno VI criteria underwent gastroscopy screening during this period. We retrospectively reviewed records of 183 hospitalized patients with HBV-related compensated liver cirrhosis who underwent a FibroScan procedure and gastroscopy within 6 months and had complete clinical, laboratory, and imaging data. A total of 132 patients were included in the study. The remaining 51 were excluded from the study because they had the following concomitant conditions: 19, alcoholic liver disease; 15, hepatocellular carcinoma; 6, invalid LSM; 4, human immunodeficiency virus infection; 3, cardiovascular disease; 3, splenectomy; and 1, primary biliary cholangitis.

Diagnostic criteria for HBV-related compensated liver cirrhosis

The diagnosis of cirrhosis was based on previous liver biopsy findings or a composite of clinical signs and findings provided by laboratory tests, gastroscopy, radiologic imaging, and FibroScan procedures. Decompensated liver cirrhosis was defined as the presence of one of the following: New onset of hepatic encephalopathy, EVB, or ascites^[2].

Two professionally trained operators performed each transient elastography (TE) measurement using a FibroScan device (Echosens, Paris, France). The M probe was used in all measurements. Only cases with 10 valid measurements obtained with a success rate $\geq 60\%$ and an interquartile range-to-median ratio $\leq 30\%$ were considered valid. The median valid LSM value is expressed in kPa.

Grading criteria for EV

Gastroscopy procedures were performed by two experienced endoscopists who were unaware of the LSM results. EV stage was classified as none (no veins above the esophageal mucosal surface; F0), small (minimally elevated veins above the esophageal mucosal surface; F1), medium (large tortuous veins occupying $< 1/3$ of the lumen; F2), or large (large coil-shaped veins occupying $\geq 1/3$ of the lumen; F3). HRV was defined as F2/F3 EV or F1 EV with red wale signs^[20].

Candidate predictor variables

Laboratory parameters included white blood cell (WBC) count, PLT count, ALT, AST, gamma-glutamyl transpeptidase (GGT), TBil, albumin (ALB), globulin (GLB), prothrombin (PT), prothrombin time activity (PTA), international normalized ratio (INR), HBV DNA, serum sodium (Na^+), blood urea nitrogen (BUN), creatinine (Cr), and alpha-fetoprotein (AFP). For patients with multiple laboratory parameter measurements, we used the results obtained nearest in time to the TE procedure.

The serum markers of liver fibrosis were calculated according to the following formulas: $\text{APRI} = [\text{AST}/\text{upper limit of normal (ULN)}] \times 100/\text{PLT}$; $\text{FIB-4} = (\text{age} \times \text{AST})/(\text{PLT} \times \text{square root of ALT})$; $\text{Lok index} = \exp(\log \text{odds})/[1 + \exp(\log \text{odds})]$, $\log \text{odds} = -5.56 - 0.0089 \times \text{PLT} + 1.26 \times (\text{AST}/\text{ALT}) + 5.27 \times \text{INR}$. The following formula

was used for calculating the MELD scores: MELD score = $3.8 \times \ln[\text{Tbil (mg/dL)}] + 11.2 \times \ln(\text{INR}) + 9.6 \times \ln[\text{Cr (mg/dL)}] + 6.4 \times (\text{constant for liver disease etiology: 0 if cholestatic or alcoholic, otherwise 1})$.

Ethics statement

The protocol conformed to the provisions of the Declaration of Helsinki and was approved by the Human Ethical Committee of the Affiliated Hospital of Zunyi Medical University and Suining Central Hospital. All patients were informed in writing regarding the potential use of their data for clinical research purposes, and all accepted.

Statistical analysis

Statistical analyses were performed using SPSS 19.0 (SPSS, Chicago, IL, USA) and MedCalc® 15.8 (MedCalc Software BVBA, Ostend, Belgium). Patient characteristics were compared between patients with and without HRV, using χ^2 tests for categorical variables, *t*-tests for variables with normal distributions, and Mann-Whitney U tests for variables with non-normal distributions. Logistic regression analysis was used for univariate and multivariate analyses. MedCalc 15.8 was used to calculate receiver operating characteristic (ROC) curves, and the accuracy of each diagnostic criterion was evaluated according to the area under each ROC curve (AUROC). Given that the aim of this study was to identify patients without HRV, we defined the cutoff values of LSM, PLT, MELD score, and serum markers of liver fibrosis based on the values corresponding to a negative predictive value (NPV) of 100%. The main results calculated were sensitivity, specificity, positive predictive value (PPV), and positive likelihood ratio (PLR) as well as the number of unnecessary gastroscopy procedures. Since we set the cutoff values based on an NPV of 100%, we did not calculate the negative likelihood ratio (NLR). *P* < 0.05 was considered statistically significant.

RESULTS

Patient characteristics and HRV prevalence

Among the 132 patients enrolled in the study, 59 (44.7%) had EV. Among them, 32 (24.2%) had small EV without red wale signs and 27 (20.5%) had HRV (medium or large EV). Regarding Child-Pugh class, 95 and 37 patients had classes A and B, respectively. Of the 132 patients, 99 (26 with HRV) did not meet the Baveno VI criteria due to having both $\text{LSM} \geq 20 \text{ kPa}$ and $\text{PLT} \leq 150 \times 10^9/\text{L}$; 11 (1 with HRV) due to having only $\text{LSM} \geq 20 \text{ kPa}$; and 22 (0 with HRV) due to having only $\text{PLT} \leq 150 \times 10^9/\text{L}$. As shown in Table 1, PT, INR, LSM, and MELD score were significantly higher in patients with HRV than in those without, whereas ALT, AST, GGT, PLT, PTA, and HBV DNA levels were significantly lower.

Independent risk factors for HRV and performance of LSM and serum markers of liver fibrosis for ruling out HRV

As shown in Table 2, the risk factors for HRV in patients who did not meet the Baveno VI criteria included PT, PLT, ALT, GGT, LSM, and MELD score. Independent risk factors for HRV were LSM and ALT. We then explored whether adjusting the LSM and PLT cutoff values and using serum markers of liver fibrosis could exclude more patients without HRV among those who did not meet the Baveno VI criteria. As shown in Table 3, the Lok index had an AUROC of 0.753 [95% confidence interval (CI): 0.671-0.824]. The AUROCs of LSM, APRI, FIB-4, and MELD score were all < 0.7. The Lok index cutoff value of 0.4531 could further spare 32/132 (24.2%) of gastroscopies without missing HRVs. Although PLT had an AUROC of 0.712 (95%CI: 0.627-0.787), $\text{PLT} > 151 \times 10^9/\text{L}$ could only spare 10/132 (7.6%) of gastroscopies without missing HRVs. The AUROC of LSM was 0.637 (95%CI: 0.548-0.718), and $\text{LSM} < 20.9 \text{ kPa}$ could spare 31/132 (23.5%) of gastroscopies without missing HRVs.

If the expanded Baveno VI criteria ($\text{LSM} < 25 \text{ kPa}$ with a $\text{PLT count} > 110 \times 10^9/\text{L}$) were applied to patients who did not meet the Baveno VI criteria, they only spared 8 (6.1%) gastroscopies without missing HRVs. In our study, only 7 patients had an MELD score of 6, and a stepwise strategy using $\text{PLT} > 150 \times 10^9/\text{L}$ and $\text{MELD} = 6$ only led to 7/132 (5.3%) additional patients avoiding gastroscopies without missing HRVs. Using cutoff values of $\text{LSM} \leq 25 \text{ kPa}$ and $\text{PLT} \geq 100 \times 10^9/\text{L}$, as suggested by Ding *et al*^[13], only led to 16/132 (12.1%) more patients avoiding gastroscopies without missing HRVs.

Effects of ALT and Tbil on LSM in patients who did not meet the Baveno VI criteria

LSM in patients with $\text{ALT} < 2 \text{ ULN}$ ($26.77 \pm 12.08 \text{ kPa}$) was significantly lower than

Table 1 Biochemical characteristics of patients with hepatitis B virus-related liver cirrhosis with and without high-risk varices

Variable	Without high-risk varices (n = 105)	With high-risk varices (n = 27)	P-value
Age	46.32 ± 11.83	46.74 ± 11.17	0.869 ¹
Male	88 (83.81)	25 (92.59)	0.246 ²
BMI (kg/m ²)	24.6 ± 3.53	23.8 ± 2.96	0.912 ¹
HBeAg: Positive	59 (56.19)	11 (40.74)	0.151 ²
HBV DNA (log 10, copies/mL)	6.27 ± 1.43	5.08 ± 1.46	0.002 ¹
Na ⁺ (mmol/L)	137.56 ± 13.80	139.12 ± 3.07	0.560 ¹
ALT (U/L)	177.0 (64.0-318.0)	54.0 (33.0-92.0)	0.000 ³
AST (U/L)	144.0 (55.5-266.5)	60.0 (37.0-136.9)	0.001 ³
GGT (U/L)	105.0 (68.4-198.0)	60.0 (35.0-93.0)	0.000 ³
TBil (μmol/L)	24.4 (16.75-37.5)	27.8 (15.5-48.2)	0.676 ³
ALB (g/L)	37.35 ± 5.74	36.07 ± 5.74	0.305 ¹
GLB (g/L)	31.4 (28.55-35.65)	34.6 (28.6-39.1)	0.101 ³
AFP (ng/mL)	16.47 (6.66-74.73)	13.6 (7.00-30.1)	0.422 ³
BUN (mmol/L)	4.64 ± 1.28	4.71 ± 1.29	0.801 ¹
Cr (μmol/L)	73.0 (62.0-80.5)	73.0 (69.0-90.0)	0.277 ³
PT (s)	13.0 (11.8-14.4)	15.4 (12.5-16.3)	0.002 ³
INR	1.08 (0.98-1.17)	1.23 (1.04-1.38)	0.003 ³
PTA (%)	85.05 ± 21.33	74.52 ± 20.25	0.022 ¹
WBC (10 ⁹ /L)	4.21 (3.28-5.34)	3.64 (2.68-4.50)	0.052 ³
PLT (10 ⁹ /L)	98.35 ± 46.49	67.00 ± 28.29	0.000 ¹
LSM (kPa)	28.93 ± 12.41	35.42 ± 14.44	0.021 ¹
Child-Pugh score	5.00 (5.00-7.00)	6.00 (5.00-7.00)	0.508 ³
MELD	8.83 (7.50-11.76)	11.33 (8.81-13.18)	0.025 ³

Data are presented as the mean ± SD, or median (interquartile range).

¹t-test results;

²Chi square test results;

³Mann-Whitney *U* test results.

P < 0.05 was statistically significant. AFP: Alpha-fetoprotein; ALB: Albumin; ALT: Alanine aminotransferase; AST: Aspartate aminotransferase; BMI: Body mass index; BUN: Urea nitrogen; Cr: Creatinine; GGT: Glutamine transpeptidase; GLB: Globulin; HBeAg: Hepatitis B e-antigen; HBV DNA: Hepatitis B virus DNA; INR: International normalized ratio; LSM: Liver stiffness measurement; MELD: Model for End-Stage Liver Disease; Na⁺: Sodium; PLT: Platelet; PT: Prothrombin time; PTA: Prothrombin activity; TBil: Total bilirubin; WBC: White blood cell.

that in patients with ALT ≥ 2 ULN (32.59 ± 13.25 kPa) (*P* = 0.011). The mean LSM value in patients with TBil < 2 ULN (26.40 ± 8.66 kPa) was also significantly lower than that in patients with TBil ≥ 2 ULN (38.80 ± 16.77 kPa) (*P* = 0.000). The LSM in patients with both ALT and TBil < 2 ULN (23.66 ± 8.44 kPa) was significantly lower than that in patients with ALT or TBil ≥ 2 ULN (33.23 ± 13.71 kPa) (*P* = 0.000).

LSM and serum markers of liver fibrosis for ruling out HRV in patients with ALT and TBil < 2 ULN

To explore the possibility of increasing the number of patients spared gastroscopy by adjusting the cutoff values of LSM and PLT according to ALT and TBil levels, we divided them into patients with ALT and TBil < 2 ULN (*n* = 41) and patients with ALT or TBil ≥ 2 ULN (*n* = 91). Among the 41 patients with both ALT and TBil < 2 ULN, 14 (34.1%) had HRV. As shown in Table 4, LSM had an AUROC of 0.821 (95%CI: 0.670-0.923, *P* < 0.0001). At a cutoff value of 20.6 kPa, LSM further spared 16/41 (39.0%) of gastroscopies without missing HRVs. PLT, Lok index, MELD score, APRI, FiB-4, and PLT had no predictive value for HRV.

LSM and serum markers of liver fibrosis for ruling out HRV in patients with ALT or TBil ≥ 2 ULN

Among the 91 patients with ALT or TBil ≥ 2 ULN, the prevalence of HRV (13/91, 14.3%) was significantly lower than that among patients with ALT and TBil < 2 ULN (14/41, 34.1%, *P* < 0.05). As shown in Table 5, only the AUROC of the Lok index for identifying HRV was > 0.800. The AUROC of LSM was significantly reduced to 0.672, which was lower than those for the Lok index (0.814), PLT (0.741), and MELD score (0.735).

Using a Lok index cutoff ≤ 0.5596 could spare 36/91 (39.6%) of gastroscopies

Table 2 Univariate and multivariate analyses of risk factors associated with high-risk varices in patients who did not meet the 2015 Baveno VI criteria

Variable	Univariate analysis				Multivariate analysis			
	β	OR	95%CI	P-value	β	OR	95%CI	P-value
PT	0.289	1.335	1.117-1.595	0.001				
PLT	-0.025	0.975	0.960-0.990	0.001				
ALT	-0.008	0.992	0.987-0.997	0.003	-0.007	0.993	0.987-0.999	0.029
GGT	-0.013	0.987	0.979-0.996	0.003				
LSM	0.035	1.035	1.004-1.068	0.025	0.077	1.080	1.030-1.132	0.001
MELD	0.091	1.096	1.002-1.198	0.045				

ALT: Alanine aminotransferase; CI: Confidence interval; GGT: Glutamine transpeptidase; LSM: Liver stiffness measurement; MELD: Model for End-Stage Liver Disease; OR: Odds ratio; PLT: Platelet; PT: Prothrombin time. $P < 0.05$ was statistically significant.

without missing HRVs. Using $PLT > 100 \times 10^9/L$ could spare 40/91 (43.9%) of gastroscopies without missing HRVs. An MELD score ≤ 7 could only spare 10/91 (11.0%) of gastroscopies without missing HRVs. These results suggested that the Lok index and PLT performed satisfactorily in identifying patients without HRV among patients with ALT or TBil ≥ 2 ULN.

DISCUSSION

Although many studies have validated the accuracy of the Baveno VI criteria for ruling out HRV^[9,21-23], studies have also found that the criteria are conservative and need to be refined to accurately identify more patients without HRV^[10,24,25]. In this study, we focused on patients with HBV-related compensated liver cirrhosis who did not meet the 2015 Baveno VI criteria because the prevalence of HRV is relatively high in this population and the possible HRV risk factors may be different from those for patients who fulfill the 2015 Baveno VI criteria^[3,26]. We found that only 20.5% of the patients had HRV. Moreover, among the 91 patients with ALT or TBil ≥ 2 ULN, only 14.3% had HRV. Thus, our results demonstrated that many unnecessary gastroscopies are conducted in patients with HBV-related compensated liver cirrhosis despite excluding patients at low risk for EV using the 2015 Baveno VI criteria, especially among patients with ALT or TBil ≥ 2 ULN.

Although LSM was still one of the independent factors associated with HRV, it only had an AUROC of 0.637 for predicting HRV among patients who did not meet the Baveno VI criteria. This result indicated that LSM was not a good predictor of HRV in the overall cohort of patients who did not meet the Baveno VI criteria.

We also found that ALT was independently negatively associated with HRV, because most patients in our study had concomitant liver inflammation. Previous studies showed that LSM can be elevated by liver inflammation and cholestasis^[27,28]. Our results suggested that concomitant liver inflammation might be an important factor that interfered with the predictive accuracy of LSM in patients with HBV-related compensated liver cirrhosis who did not meet the Baveno VI criteria.

It was previously unknown whether adjusting the LSM cutoff value according to ALT and TBil levels could improve its utility for predicting HRV among patients with compensated liver cirrhosis and obvious liver inflammation. We found that LSM could accurately identify patients with HRV in those with ALT and TBil < 2 ULN. By slightly increasing the LSM cutoff to 20.6 kPa, LSM further spared 16/41 (39.0%) of gastroscopies without missing HRVs. PLT, Lok index, MELD score, APRI, FIB-4, and PLT had no value for predicting HRV. However, in the patients with ALT or TBil ≥ 2 ULN, LSM had no HRV predictive value.

Previous studies have found that serum markers of liver fibrosis have moderate value for predicting liver cirrhosis in patients with HBV infection^[29,30]. However, there is disagreement on the performance of serum markers of liver fibrosis in EV or HRV prediction^[8,19,31]. In this study, we found that APRI and FIB-4 could not predict HRV. We also found that PLT and the Lok index performed better in predicting HRV in patients with ALT or TBil ≥ 2 ULN compared with ALT and TBil < 2 ULN. As previous studies found that the Lok index could better predict liver fibrosis in patients with a slightly higher ALT level compared with a normal ALT level^[16,32], it is

Table 3 Performance of liver stiffness measurement and serum markers of liver fibrosis in predicting high-risk varices in patients who did not meet the 2015 Baveno VI criteria

Variable	AUROC (95%CI)	P-value	Cutoffvalue	Se (%)	Sp (%)	PPV (%)	PLR	Spared gastroscopies, n = 132, (%)
LSM	0.637 (0.548-0.718)	0.0141	20.9	100	29.52	26.7	1.42	31/132 (23.5)
PLT	0.712 (0.627-0.787)	< 0.0001	151.0	100	9.52	22.1	1.11	10/132 (7.6)
Lok index	0.753 (0.671-0.824)	< 0.0001	0.4531	100	30.48	27.0	1.44	32/132 (24.2)
MELD	0.644 (0.556-0.726)	0.0122	6.0	100	6.67	21.6	1.07	7/132 (5.3)
APRI	0.586 (0.497-0.671)	0.1453						
FIB-4	0.585 (0.496-0.670)	0.1281						

APRI: Aspartate aminotransferase-to-platelet ratio index; AUROC: Area under the receiver operating characteristic curve; CI: Confidence interval; MELD: Model for End-Stage Liver Disease; PLT: Platelet; PLR: Positive likelihood ratio; PPV: Positive predictive value; Se: Sensitivity; Sp: Specificity. $P < 0.05$ was statistically significant.

reasonable that the Lok index performed better in predicting HRV in patients with ALT or TBil ≥ 2 ULN. However, it is difficult to explain the different performances of PLT in patients with ALT or TBil ≥ 2 ULN *vs* < 2 ULN. The different prevalence rates of HRV in these two groups may be a possible explanation, as the prevalence in the patients with ALT and TBil < 2 ULN (34.1%) was significantly higher compared to that in patients with ALT or TBil ≥ 2 ULN (14.3%). Indeed, previous studies reported that the utility of serum markers of liver fibrosis in predicting EV or HRV is greatly affected by the prevalence^[29,33,34]. Because patients with ALT or TBil ≥ 2 ULN had obvious liver inflammation, which could elevate LSM, they were difficult to fulfill the Baveno VI criteria, and as a result, the prevalence rate of HRV in patients with ALT or TBil ≥ 2 ULN was lower than that in patients with ALT and TBil < 2 ULN.

Our study had several limitations. First, it was a two-center, retrospective study based on LSM assessed and gastroscopies performed by different operators, although all were experienced. Second, because we only included the patients with HBV-related compensated liver cirrhosis who did not meet the Baveno VI criteria, the number of patients in this study was small, and the cutoff values were not tested in a validation cohort. Further studies are required to verify our findings.

In conclusion, our study found that in patients with HBV-related compensated cirrhosis who did not meet the Baveno VI criteria, using the cutoff value of LSM, PLT, or the Lok index stratified by ALT and TBil levels accurately identified more patients without HRV. An algorithm-based screening process for HRV in patients with HBV-related compensated liver cirrhosis is shown in [Figure 1](#).

Table 4 Performance of liver stiffness measurement and serum markers of liver fibrosis in predicting high-risk varices in patients with alanine aminotransferase and total bilirubin < 2 upper limit of normal

Variable	AUROC (95%CI)	P-value	Cutoffvalue	Se (%)	Sp (%)	PPV (%)	PLR	Spared gastroscopies, <i>n</i> = 41, (%)
LSM	0.821 (0.670-0.923)	< 0.0001	20.60	100	66.7	60.9	3.00	16/41 (39.0)
PLT	0.628 (0.464-0.774)	0.1928						
Lok index	0.638 (0.473-0.782)	0.1407						
MELD	0.644 (0.479-0.787)	0.1449						
APRI	0.569 (0.405- 0.722)	0.4667						
FIB-4	0.608 (0.444-0.757)	0.2474						

APRI: Aspartate aminotransferase-to-platelet ratio index; AUROC: Area under the receiver operating characteristic curve; CI: Confidence interval; MELD: Model for End-Stage Liver Disease; PLT: Platelet; PLR: Positive likelihood ratio; PPV: Positive predictive value; Se: Sensitivity; Sp: Specificity. *P* < 0.05 was statistically significant.

Table 5 Performance of liver stiffness measurement and serum markers of liver fibrosis in predicting high-risk varices in patients with alanine aminotransferase or total bilirubin ≥ 2 upper limit of normal

Variable	AUROC (95%CI)	P-value	Cutoffvalue	Se (%)	Sp (%)	PPV (%)	PLR	Spared gastroscopies, <i>n</i> = 91, (%)
LSM	0.672 (0.565-0.766)	0.0508						
PLT	0.741 (0.639-0.827)	< 0.0001	100.0	100	51.28	25.5	2.05	40/91 (43.9)
Lok index	0.814 (0.718-0.888)	< 0.0001	0.5596	100	47.44	24.1	1.90	36/91 (39.6)
MELD	0.735 (0.632-0.822)	0.0003	7.0	100	12.82	16.0	1.15	10/91 (11.0)
APRI	0.532 (0.424-0.637)	0.7256						
FIB-4	0.576 (0.468-0.679)	0.3329						

APRI: Aspartate aminotransferase-to-platelet ratio index; AUROC: Area under the receiver operating characteristic curve; CI: Confidence interval; MELD: Model for End-Stage Liver Disease; PLT: Platelet; PLR: Positive likelihood ratio; PPV: Positive predictive value; Se: Sensitivity; Sp: Specificity. *P* < 0.05 was statistically significant.

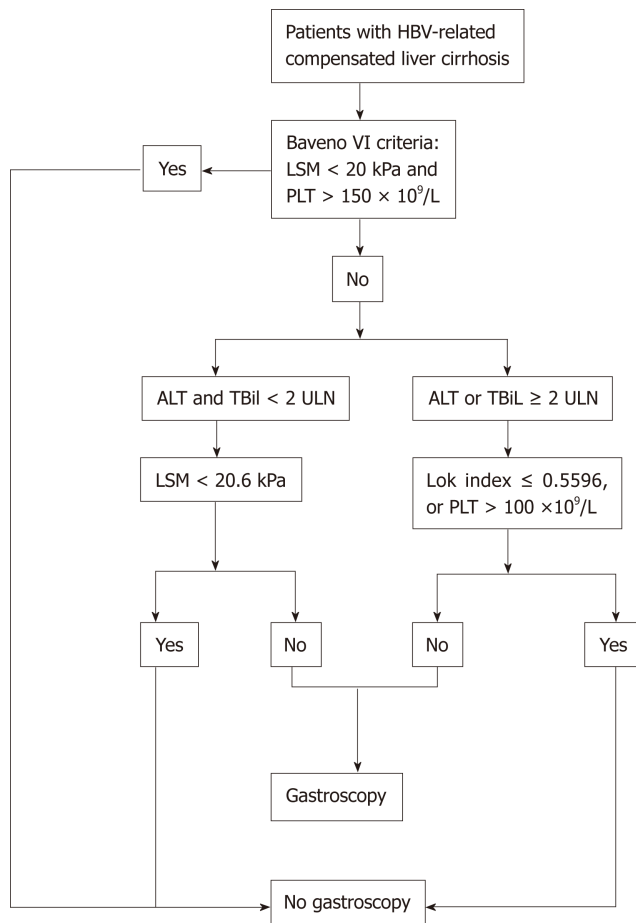


Figure 1 Algorithm-based screening process for high-risk varices in patients with HBV-related compensated liver cirrhosis. ALT: Alanine aminotransferase; HBV: Hepatitis B virus; LSM: Liver stiffness measurement; PLT: Platelet; TBil: Total bilirubin; ULN: Upper limit of normal.

ARTICLE HIGHLIGHTS

Research background

The 2015 Baveno VI consensus workshop recommended that patients with liver stiffness measurement (LSM) < 20 kPa and platelet (PLT) count >150 × 10⁹/L could safely avoid gastroscopy screening. However, studies have also found that such criteria are conservative and need to be refined to accurately identify more patients without high-risk varices (HRV).

Research motivation

It is recommended that the interpretation of LSM is based on the levels of alanine transaminase (ALT) and total bilirubin (TBil), but it remains unknown whether the LSM, PLT and serum markers of liver fibrosis stratified by ALT and TBil levels can identify more patients without HRV among those who do not meet the Baveno VI criteria.

Research objectives

To evaluate the utility of LSM and serum markers of liver fibrosis in ruling out high-risk varices (HRV) in patients who do not meet Baveno VI criteria.

Research methods

Data from 132 patients with hepatitis B virus (HBV)-related compensated liver cirrhosis who did not meet the Baveno VI criteria were retrospectively reviewed. The accuracy of LSM, PLT count, aspartate aminotransferase (AST)-to-PLT ratio index, Fibrosis-4, and the Lok index in predicting HRV was evaluated. The utility of LSM, PLT, and serum markers of liver fibrosis stratified by ALT and TBil levels was evaluated for ruling out HRV.

Research results

The prevalence of HRV was significantly lower in patients with ALT or TBil ≥ 2 upper limit of normal (ULN) (14.3%) than in patients with both ALT and TBil < 2 ULN (34.1%) (*P* = 0.018). In the 41 patients with ALT and TBil < 2 ULN, LSM < 20.6 kPa spared 39.0% of gastroscopies without missing HRVs. In the 91 patients with ALT or TBil ≥ 2 ULN, Lok index ≤ 0.5596 or PLT > 100 × 10⁹/L further spared 39.6% and 43.9% of gastroscopies, respectively, without missing HRVs.

Research conclusions

In HBV-related compensated cirrhosis patients who do not meet Baveno VI criteria, the LSM, PLT, or Lok index cutoff stratified by ALT and TBil accurately identified more patients without HRV.

Research perspectives

Our study found that in patients with HBV-related compensated cirrhosis who did not meet the Baveno VI criteria, using the cutoff value of LSM, PLT or the Lok index stratified by ALT and TBil levels accurately identified more patients without HRV.

REFERENCES

- 1 **Terrault NA**, Lok ASF, McMahon BJ, Chang KM, Hwang JP, Jonas MM, Brown RS, Bzowej NH, Wong JB. Update on prevention, diagnosis, and treatment of chronic hepatitis B: AASLD 2018 hepatitis B guidance. *Hepatology* 2018; **67**: 1560-1599 [PMID: [29405329](#) DOI: [10.1002/hep.29800](#)]
- 2 **European Association for the Study of the Liver**. EASL Clinical Practice Guidelines for the management of patients with decompensated cirrhosis. *J Hepatol* 2018; **69**: 406-460 [PMID: [29653741](#) DOI: [10.1016/j.jhep.2018.03.024](#)]
- 3 **Garcia-Tsao G**, Abraldes JG, Berzigotti A, Bosch J. Portal hypertensive bleeding in cirrhosis: Risk stratification, diagnosis, and management: 2016 practice guidance by the American Association for the study of liver diseases. *Hepatology* 2017; **65**: 310-335 [PMID: [27786365](#) DOI: [10.1002/hep.28906](#)]
- 4 **de Franchis R**; Baveno VI Faculty. Expanding consensus in portal hypertension: Report of the Baveno VI Consensus Workshop: Stratifying risk and individualizing care for portal hypertension. *J Hepatol* 2015; **63**: 743-752 [PMID: [26047908](#) DOI: [10.1016/j.jhep.2015.05.022](#)]
- 5 **Fukui H**, Saito H, Ueno Y, Uto H, Obara K, Sakaida I, Shibuya A, Seike M, Nagoshi S, Segawa M, Tsubouchi H, Moriwaki H, Kato A, Hashimoto E, Michitaka K, Murawaki T, Sugano K, Watanabe M, Shimosegawa T. Evidence-based clinical practice guidelines for liver cirrhosis 2015. *J Gastroenterol* 2016; **51**: 629-650 [PMID: [27246107](#) DOI: [10.1007/s00535-016-1216-y](#)]
- 6 **Garcia-Tsao G**, Sanyal AJ, Grace ND, Carey W; Practice Guidelines Committee of the American Association for the Study of Liver Diseases; Practice Parameters Committee of the American College of Gastroenterology. Prevention and management of gastroesophageal varices and variceal hemorrhage in cirrhosis. *Hepatology* 2007; **46**: 922-938 [PMID: [17879356](#) DOI: [10.1002/hep.21907](#)]
- 7 **de Franchis R**; Baveno V Faculty. Revising consensus in portal hypertension: Report of the Baveno V consensus workshop on methodology of diagnosis and therapy in portal hypertension. *J Hepatol* 2010; **53**: 762-768 [PMID: [20638742](#) DOI: [10.1016/j.jhep.2010.06.004](#)]
- 8 **Sebastiani G**, Tempesta D, Fattovich G, Castera L, Halfon P, Bourliere M, Noventa F, Angeli P, Saggioro A, Alberti A. Prediction of oesophageal varices in hepatic cirrhosis by simple serum non-invasive markers: Results of a multicenter, large-scale study. *J Hepatol* 2010; **53**: 630-638 [PMID: [20615567](#) DOI: [10.1016/j.jhep.2010.04.019](#)]
- 9 **Jangouk P**, Turco L, De Oliveira A, Schepis F, Villa E, Garcia-Tsao G. Validating, deconstructing and refining Baveno criteria for ruling out high-risk varices in patients with compensated cirrhosis. *Liver Int* 2017; **37**: 1177-1183 [PMID: [28160373](#) DOI: [10.1111/liv.13379](#)]
- 10 **Sousa M**, Fernandes S, Proença L, Silva AP, Leite S, Silva J, Ponte A, Rodrigues J, Silva JC, Carvalho J. The Baveno VI criteria for predicting esophageal varices: Validation in real life practice. *Rev Esp Enferm Dig* 2017; **109**: 704-707 [PMID: [28776387](#) DOI: [10.17235/reed.2017.5052/2017](#)]
- 11 **Silva MJ**, Bernardes C, Pinto J, Loureiro R, Duarte P, Mendes M, Calinas F. Baveno VI Recommendation on Avoidance of Screening Endoscopy in Cirrhotic Patients: Are We There Yet? *GE Port J Gastroenterol* 2017; **24**: 79-83 [PMID: [28848787](#) DOI: [10.1159/000452693](#)]
- 12 **Augustin S**, Pons M, Maurice JB, Bureau C, Stefanescu H, Ney M, Blasco H, Procopet B, Tsochatzis E, Westbrook RH, Bosch J, Berzigotti A, Abraldes JG, Genesca J. Expanding the Baveno VI criteria for the screening of varices in patients with compensated advanced chronic liver disease. *Hepatology* 2017; **66**: 1980-1988 [PMID: [28696510](#) DOI: [10.1002/hep.29363](#)]
- 13 **Ding NS**, Nguyen T, Iser DM, Hong T, Flanagan E, Wong A, Luiz L, Tan JY, Fulforth J, Holmes J, Ryan M, Bell SJ, Desmond PV, Roberts SK, Lubel J, Kemp W, Thompson AJ. Liver stiffness plus platelet count can be used to exclude high-risk oesophageal varices. *Liver Int* 2016; **36**: 240-245 [PMID: [26212020](#) DOI: [10.1111/liv.12916](#)]
- 14 **Shiha G**, Ibrahim A, Helmy A, Sarin SK, Omata M, Kumar A, Bernstien D, Maruyama H, Saraswat V, Chawla Y, Hamid S, Abbas Z, Bedossa P, Sakhuja P, Elmahatab M, Lim SG, Lesmana L, Sollano J, Jia JD, Abbas B, Omar A, Sharma B, Payawal D, Abdallah A, Serwah A, Hamed A, Elsayed A, AbdelMaqsood A, Hassanein T, Ihab A, GHaziuan H, Zein N, Kumar M. Asian-Pacific Association for the Study of the Liver (APASL) consensus guidelines on invasive and non-invasive assessment of hepatic fibrosis: A 2016 update. *Hepatol Int* 2017; **11**: 1-30 [PMID: [27714681](#) DOI: [10.1007/s12072-016-9760-3](#)]
- 15 **Singh S**, Muir AJ, Dieterich DT, Falck-Ytter YT. American Gastroenterological Association Institute Technical Review on the Role of Elastography in Chronic Liver Diseases. *Gastroenterology* 2017; **152**: 1544-1577 [PMID: [28442120](#) DOI: [10.1053/j.gastro.2017.03.016](#)]
- 16 **Dong M**, Wu J, Yu X, Li J, Yang S, Qi X, Mao R, Zhang Y, Yu J, Zhu H, Yang F, Qin Y, Zhang J. Validation and comparison of seventeen noninvasive models for evaluating liver fibrosis in Chinese hepatitis B patients. *Liver Int* 2018; **38**: 1562-1570 [PMID: [29314613](#) DOI: [10.1111/liv.13688](#)]
- 17 **Lok AS**, Ghany MG, Goodman ZD, Wright EC, Everson GT, Sterling RK, Everhart JE, Lindsay KL, Bonkovsky HL, Di Bisceglie AM, Lee WM, Morgan TR, Dienstag JL, Morishima C. Predicting cirrhosis in patients with hepatitis C based on standard laboratory tests: Results of the HALT-C cohort. *Hepatology* 2005; **42**: 282-292 [PMID: [15986415](#) DOI: [10.1002/hep.20772](#)]
- 18 **Ma J**, Jiang Y, Gong G. Evaluation of seven noninvasive models in staging liver fibrosis in patients with chronic hepatitis B virus infection. *Eur J Gastroenterol Hepatol* 2013; **25**: 428-434 [PMID: [23358121](#) DOI: [10.1097/MEG.0b013e32835cb5dd](#)]
- 19 **Rockey DC**, Elliott A, Lyles T. Prediction of esophageal varices and variceal hemorrhage in patients with acute upper gastrointestinal bleeding. *J Investig Med* 2016; **64**: 745-751 [PMID: [26912006](#) DOI: [10.1136/jim-2015-000047](#)]

- 20 **Beppu K**, Inokuchi K, Koyanagi N, Nakayama S, Sakata H, Kitano S, Kobayashi M. Prediction of variceal hemorrhage by esophageal endoscopy. *Gastrointest Endosc* 1981; **27**: 213-218 [PMID: 6975734 DOI: 10.1016/s0016-5107(81)73224-3]
- 21 **Marot A**, Trépo E, Doerig C, Schoepfer A, Moreno C, Deltenre P. Liver stiffness and platelet count for identifying patients with compensated liver disease at low risk of variceal bleeding. *Liver Int* 2017; **37**: 707-716 [PMID: 27862856 DOI: 10.1111/liv.13318]
- 22 **Stafylidou M**, Paschos P, Katsoula A, Malandris K, Ioakim K, Bekiari E, Haidich AB, Akriviadis E, Tsapas A. Performance of Baveno VI and Expanded Baveno VI Criteria for Excluding High-Risk Varices in Patients With Chronic Liver Diseases: A Systematic Review and Meta-analysis. *Clin Gastroenterol Hepatol* 2019; **17**: 1744-1755. e11 [PMID: 31077823 DOI: 10.1016/j.cgh.2019.04.062]
- 23 **Augustin S**, Pons M, Genesca J. Validating the Baveno VI recommendations for screening varices. *J Hepatol* 2017; **66**: 459-460 [PMID: 27826055 DOI: 10.1016/j.jhep.2016.09.027]
- 24 **Colecchia A**, Ravaoli F, Marasco G, Colli A, Dajti E, Di Biase AR, Bacchi Reggiani ML, Berzigotti A, Pinzani M, Festi D. A combined model based on spleen stiffness measurement and Baveno VI criteria to rule out high-risk varices in advanced chronic liver disease. *J Hepatol* 2018; **69**: 308-317 [PMID: 29729368 DOI: 10.1016/j.jhep.2018.04.023]
- 25 **Moctezuma Velázquez C**, Abalde JG. Non-invasive diagnosis of esophageal varices after Baveno VI. *Turk J Gastroenterol* 2017; **28**: 159-165 [PMID: 28492370 DOI: 10.5152/tjg.2017.16744]
- 26 **Maurice JB**, Brodtkin E, Arnold F, Navaratnam A, Paine H, Khawar S, Dhar A, Patch D, O'Beirne J, Mookerjee R, Pinzani M, Tsochatzis E, Westbrook RH. Validation of the Baveno VI criteria to identify low risk cirrhotic patients not requiring endoscopic surveillance for varices. *J Hepatol* 2016; **65**: 899-905 [PMID: 27388923 DOI: 10.1016/j.jhep.2016.06.021]
- 27 **Wong GL**, Wong VW, Choi PC, Chan AW, Chim AM, Yiu KK, Chan FK, Sung JJ, Chan HL. Increased liver stiffness measurement by transient elastography in severe acute exacerbation of chronic hepatitis B. *J Gastroenterol Hepatol* 2009; **24**: 1002-1007 [PMID: 19457152 DOI: 10.1111/j.1440-1746.2009.05779.x]
- 28 **Millonig G**, Reimann FM, Friedrich S, Fonouni H, Mehrabi A, Büchler MW, Seitz HK, Mueller S. Extrahepatic cholestasis increases liver stiffness (FibroScan) irrespective of fibrosis. *Hepatology* 2008; **48**: 1718-1723 [PMID: 18836992 DOI: 10.1002/hep.22577]
- 29 **Leung JC**, Loong TC, Pang J, Wei JL, Wong VW. Invasive and non-invasive assessment of portal hypertension. *Hepatol Int* 2018; **12**: 44-55 [PMID: 28361299 DOI: 10.1007/s12072-017-9795-0]
- 30 **Tan YW**, Zhou XB, Ye Y, He C, Ge GH. Diagnostic value of FIB-4, aspartate aminotransferase-to-platelet ratio index and liver stiffness measurement in hepatitis B virus-infected patients with persistently normal alanine aminotransferase. *World J Gastroenterol* 2017; **23**: 5746-5754 [PMID: 28883700 DOI: 10.3748/wjg.v23.i31.5746]
- 31 **Wang L**, Feng Y, Ma X, Wang G, Wu H, Xie X, Zhang C, Zhu Q. Diagnostic efficacy of noninvasive liver fibrosis indexes in predicting portal hypertension in patients with cirrhosis. *PLoS One* 2017; **12**: e0182969 [PMID: 28820885 DOI: 10.1371/journal.pone.0182969]
- 32 **Dong XQ**, Wu Z, Zhao H, Wang GQ; China HepB-Related Fibrosis Assessment Research Group. Evaluation and comparison of thirty noninvasive models for diagnosing liver fibrosis in chinese hepatitis B patients. *J Viral Hepat* 2019; **26**: 297-307 [PMID: 30380170 DOI: 10.1111/jvh.13031]
- 33 **Paternostro R**, Reiberger T, Bucsis T. Elastography-based screening for esophageal varices in patients with advanced chronic liver disease. *World J Gastroenterol* 2019; **25**: 308-329 [PMID: 30686900 DOI: 10.3748/wjg.v25.i3.308]
- 34 **Calès P**, Buisson F, Ravaoli F, Berger A, Carboni C, Marasco G, Festi D. How to clarify the Baveno VI criteria for ruling out varices needing treatment by noninvasive tests. *Liver Int* 2019; **39**: 49-53 [PMID: 30129700 DOI: 10.1111/liv.13945]



Published By Baishideng Publishing Group Inc
7041 Koll Center Parkway, Suite 160, Pleasanton, CA 94566, USA
Telephone: +1-925-2238242
E-mail: bpgoffice@wjgnet.com
Help Desk: <http://www.f6publishing.com/helpdesk>
<http://www.wjgnet.com>

