Original Article

A Meta-analysis of the Value of vWF in the Diagnosis of Liver Cirrhosis with Portal Hypertension

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Abstract

Background and Aims: Studies have indicated that serum von Willebrand factor (vWF) has a positive correlation with hepatic venous pressure gradient. However, information on the value of vWF in the diagnosis of liver cirrhosis with portal hypertension has been lacking. The purpose of this meta-analysis was to assess the value of vWF in the diagnosis of liver cirrhosis with portal hypertension. ***Methods:*** Studies that analyzed the sensitivity, specificity, diagnostic odds ratio combined with likelihood ratios and test for heterogeneity of vWF in the diagnosis of liver cirrhosis with portal hypertension were found in the Cochrane Library, Ovid, VOS-SCI, CNKI, PubMed, Medline, EMBASE, CMB and Wanfang databases. In the end, the data was used to draw the summary receiver operating characteristic curve and to calculate the area under the curve. ***Results:*** Four studies involving 662 patients were analyzed. The results showed that serum vWF in liver cirrhosis with portal hypertension were significantly higher than in those without portal hypertension. Sensitivity combined was 0.823 (95% CI: 0.788, 0.855). Specificity combined was 0.782 (95% CI: 0.708, 0.845). +LR combined was 3.777 (95% CI: 2.794, 5.107). -LR combined was 0.221 (95% CI: 0.180, 0.272). Diagnostic odds ratio combined was 18.347 (95% CI: 11.725, 28.708). The area under the curve was 0.8896. ***Conclusions:*** Serum vWF can be used as an effective and feasible method for noninvasive diagnosis of liver cirrhosis with portal hypertension. However, further studies are still needed to evaluate the severity of liver cirrhosis with portal hypertension.

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Introduction

Liver cirrhosis is a chronic liver disease, which is caused by one or more factors, such as virus infection, drugs and toxicants, heavy drinking, metabolic disorders, liver hemodynamic disorders, high fat diet, and so on. These factors have a long-term effect on liver tissue, leading to diffuse fibrosis of the liver, pseudo lobules, and regenerative nodules.[1] It is the final outcome of many kinds of liver diseases.

Cirrhosis combined with portal hypertension (HP) is an important manifestation of cirrhosis progression to decompensation. Complications associated with PH severely reduce the prognosis and survival rate of patients with cirrhosis. Therefore, the early diagnosis and effective treatment of PH are particularly important. The study of the effective evaluation index and early intervention of PH are expected to improve the life cycle and quality-of-life of patients with the disease.

The current hepatic venous pressure gradient (HVPG) is still the gold standard for evaluating portal pressure.[2,3] Normal portal pressure is defined as the range of 1 to 5 mmHg, according to HVPG. When the HVPG range of 6 to 9 mmHg is reached, PH is defined as subclinical PH, whereas HVPG ≥10 mmHg is diagnosed as clinically significant PH.[2,3] At this time, the risk of cirrhosis-related complications increases significantly.[3] Yet, HVPG is a kind of invasive operation characterized by high risk and needs for advanced equipment, high level of operation skill of medical workers, high price and difficult follow-up, all of which limit its universal application in China. It is still necessary to find a simple and noninvasive method for predicting PH in cirrhosis to guide the diagnosis and treatment of it.

von Willebrand factor (vWF), as a marker of vascular endothelial damage, is a macromolecular glycoprotein, mainly composed of endothelial cells and bone marrow megakaryocytes.[4] The plasma levels of vWF are related to stress, vascular endothelial damage, activation of platelets, and hepatic sinusoidal endothelial system clearance.[5] In addition, as a component of the extracellular matrix, vWF has been shown to play an active role in regulating vascular proliferation, liver injury and repair, and to play an important role in the occurrence and development of cirrhosis with PH.[6,7] Studies have shown that serum vWF levels and HVPG in patients with cirrhosis and PH have a positive correlation and can predict clinical outcome in such patients.[6,7] However, the value of vWF in the diagnosis of PH in liver cirrhosis are not yet clear.

Based on this background, to explore the value of vWF in the diagnosis of PH in liver cirrhosis, we made a meta-analysis of the published studies of vWF in the diagnosis of PH in liver cirrhosis. The databases of Cochrane Library, Ovid, VOS-SCI, CNKI, PubMed, Medline, EMBASE, CMB and Wanfang were searched. We discovered that serum vWF could be used as an effective and feasible method for non-invasive diagnosis of liver cirrhosis with PH. However, further studies are still needed to evaluate the severity of liver cirrhosis with PH.

Methods

Literature search

The literature available in the Cochrane Library, Ovid, VOS-SCI, CNKI, PubMed, Medline, EMBASE, CMB and Wanfang databases was searched. The subject words and reference words used were determined by the subject word list of Medicine (commonly known as MeSH terms) and the Chinese version of key words. According to the characteristics of the different databases, combinations of the corresponding subject words and reference words were used to search. The reference literature was searched at the same time.

Inclusion and exclusion criteria

Inclusion criteria for the meta-analysis were as follows. (1) Prospective study, continuity research or retrospective study. (2) Diagnosis of cirrhosis based on pathological examination or clinical diagnosis according to physical signs, ultrasound, CT and biochemical indexes. It included hepatic sinusoidal obstruction syndrome, chronic alcoholic liver disease, autoimmune liver disease, hereditary metabolic liver disease, liver cirrhosis caused by various viral infections, combined esophageal and gastric variceal bleeding, intractable ascites, hypersplenism, liver cancer, and patients with PH that had persistent treatment. The diagnosis of PH was made on the basis of HVPG≥10mmHg. (3) All subjects had measures of serum vWF. (4) The study could have listed quadruple tabular form.

Patient populations were excluded if they featured: (1) increasing serum vWF not due to liver cirrhosis; (2) diagnosis of PH not based on HVPG; (3) data about the serum vWF and HVPG unable to be extracted.

Literature collection and selection

The search was based on the search strategy described in the previous session. First, according to the topic of the literature, we eliminated the literature which was obviously inconsistent with the inclusion criteria. Secondly, we read the summary part of the literature, and suspicious literature was temporarily left. Finally, we read the literature carefully, according to the inclusion and exclusion criteria to ultimately determine the literature selected.

Quality evaluation

The QUADAS tool was used to assess the methodological quality of the selected studies. This tool is a validated quality checklist containing 14 items that address the most important sources of bias and variation in diagnostic accuracy studies.[8] The detailed explanations of the 14 items are elaborated in Table 3. The reviewers who assessed and extracted data were well-trained in the use of the QUADAS checklist. Each item in the checklist was categorized as "Yes" for low risk of bias, "No" for high risk of bias, or "Unclear" if there was insufficient information to make an unbiased judgment.[8]

Statistical analysis

The data extracted from the included literature are listed in a four-fold table. First, Meta software was used to analyze the sensitivity (SEN), specificity (SPE) and 95% confidence interval (CI) of vWF in the diagnosis of PH in liver cirrhosis. Then, Meta-DiSc1.4 software was used to analyze SEN, SPE, positive (+) likelihood ratio (LR), negative (-)LR, diagnostic odds ratio (DOR) combined and test for heterogeneity. We considered significant heterogeneity having been met when the X^2 value was within the 10% level of significance ($p < 0.10$). In the end, the data was used to draw summary receiver operating characteristic (SROC) curves and to calculate the area under the curve (AUC).

Results

An overview of and quality analysis of the literature included

A total of 27 studies were identified and screened for retrieval by using the strategies described above. After screening the title or abstract, 11 studies were excluded and 14 were retrieved and subjected to detailed evaluation. By adhering to the inclusion criteria, 10 of those studies were excluded. Finally, 4 cohort studies[6,9–11] were chosen for inclusion in the meta-analysis, which comprised a total of 662 patients (Fig. 1).
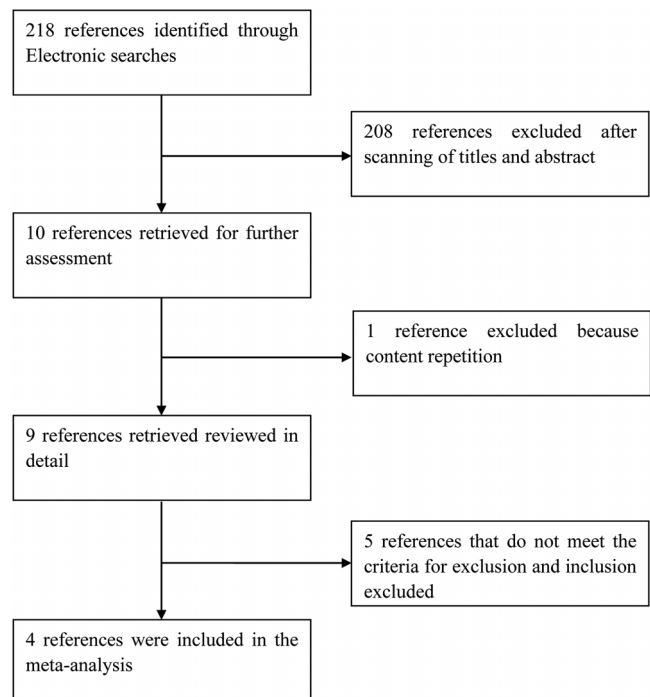

Fig. 1. Literature search flow sheet.

Table 1. The basic information of the literature included

Study	Monika Ferlitsch	Stephanie Hametner	Hao Wu	M. Homonclik
Year of publication	2012	2016	2015	2017
Sample size	286	236	60	81
Male/Female	201/65	170/66	43/17	67/14
Age	55 (48-62)	57.9 (50-60)	49 (45-52)	54
Etiology	–	ALD 93; HCV 67; NASH 29; other 19; unknown 28	HBV	ALD, HCV, cryptogenic
CPS (A/B/C)	48/104/34	140/56/18	28/19/13	–
Compensation	189	136	–	–
Decompensation	97	100	–	–

According to the Review Manager 5.2 diagnostic test system evaluation criteria, we needed to independently evaluate the research characteristics and retrieve relevant information, including sample size, sample characteristics and research type. The basic characteristics of each of the 4 studies are listed in Table 1. Of the 4 studies, 1 study[9] was composed of Chinese and the other 3[6,10,11] were composed of Australians. The population size for each of the studies ranged from 60 to 286. The mean age ranged from 49 to 57.9 years old. The percentage of males ranged from 70.3% to 82.7%.

According to the 14 criteria of QUADAS used evaluate the quality of the literature, the literature of Monika Ferlitsch and Stephanie Hametner have the highest quality, while that of M. Homonclik has the lowest quality (Table 2).

The serum vWF expression increased significantly in cirrhotic patients with PH

The 4 studies are based on the HVPG measurement of liver cirrhosis, and the patients were divided into PH group and group without PH. Then, the serum vWF was detected. By comparing the serum vWF (Table 3) in the group without PH

Table 2. Quality assessment

Study	Monika Ferlitsch	Stephanie Hametner	Hao Wu	M. Homonclik
Was the spectrum of patients representative of the patients who will receive the test in practice?	Yes	Yes	Yes	Yes
Were selection criteria clearly described?	Yes	Yes	Yes	Yes
Is the reference standard likely to correctly classify the target condition?	Yes	Yes	Yes	Yes
Did patients receive the same reference standard regardless of the index test result?	Yes	Yes	Yes	Yes
Was the reference standard independent of the index test?	Yes	Yes	Yes	Yes
Were the reference standard results interpreted without knowledge of the results of the index test?	Yes	Yes	Yes	Yes
Were the same clinical data available when test results were interpreted as would be available when the test is used in practice?	Yes	Yes	Yes	Yes
Were withdrawals from the study explained?	Yes	Yes	Yes	Yes
Were the index test results interpreted without knowledge of the results of the reference standard?	No	No	No	No
Is the time period between reference standard and index test short enough to be reasonably sure that the target condition did not change between the two tests?	Yes	Yes	Unclear	Unclear
Did the whole sample or a random selection of the sample, receive verification using a reference standard of diagnosis?	Yes	Yes	Yes	Yes
Was the execution of the index test described in sufficient detail to permit replication of the test?	Yes	Yes	Yes	No
Was the execution of the reference standard described in sufficient detail to permit its replication?	Yes	Yes	Yes	No
Were uninterpretable/ intermediate test results reported?	Yes	Yes	Yes	No

Table 3. The serum levels of vWF in the included studies

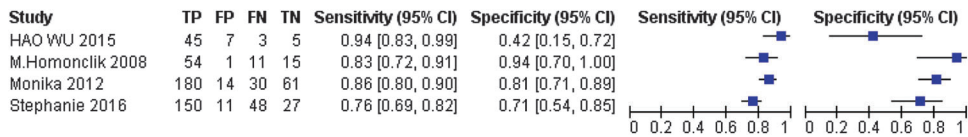| vWF	Cirrhosis without portal hypertension (HVPG<10 mmHg)	Cirrhosis with portal hypertension (HVPG≥10 mmHg)	Cutoff
Monika Ferlitsch	197% (158%-228%)	346% (275%-441%)	241%
Stephanie Hametner	200% (157%-236%)	306% (227%-373%)	226%
M. Homonclik	210% (176%-243%)	355% (322%-388%)	264%
Hao Wu	1240±470.3 mU/mL	2430±760.3 mU/mL	1510.5 mU/mL (231%)

Fig. 2. Forest map of the meta-analysis.

and the PH group, the expression of serum vWF in the cirrhosis PH group was found to be significantly higher than that in the liver cirrhosis without PH group.

Meta-analysis

The 4 studies did not directly provide four-fold tables (i.e. true positive number, false positive number, false negative number and true negative number), but the effective data were extracted by statistical processing through the SEN and SPE of the positive and negative results obtained by the

evaluation test method; in this way, the four-fold table was generated,[12] and then RevMan5.2 software was used for meta-analysis. The SEN, SPE and 95%CI were calculated (Fig. 2).

Meta-analysis of diagnostic test in Meta-DiSc software

Threshold effect: Testing heterogeneity is the key factor that clears the possible factors affecting the accuracy and determines whether the accuracy of different studies is appropriate.[12] In the meta-analysis of diagnostic tests, the
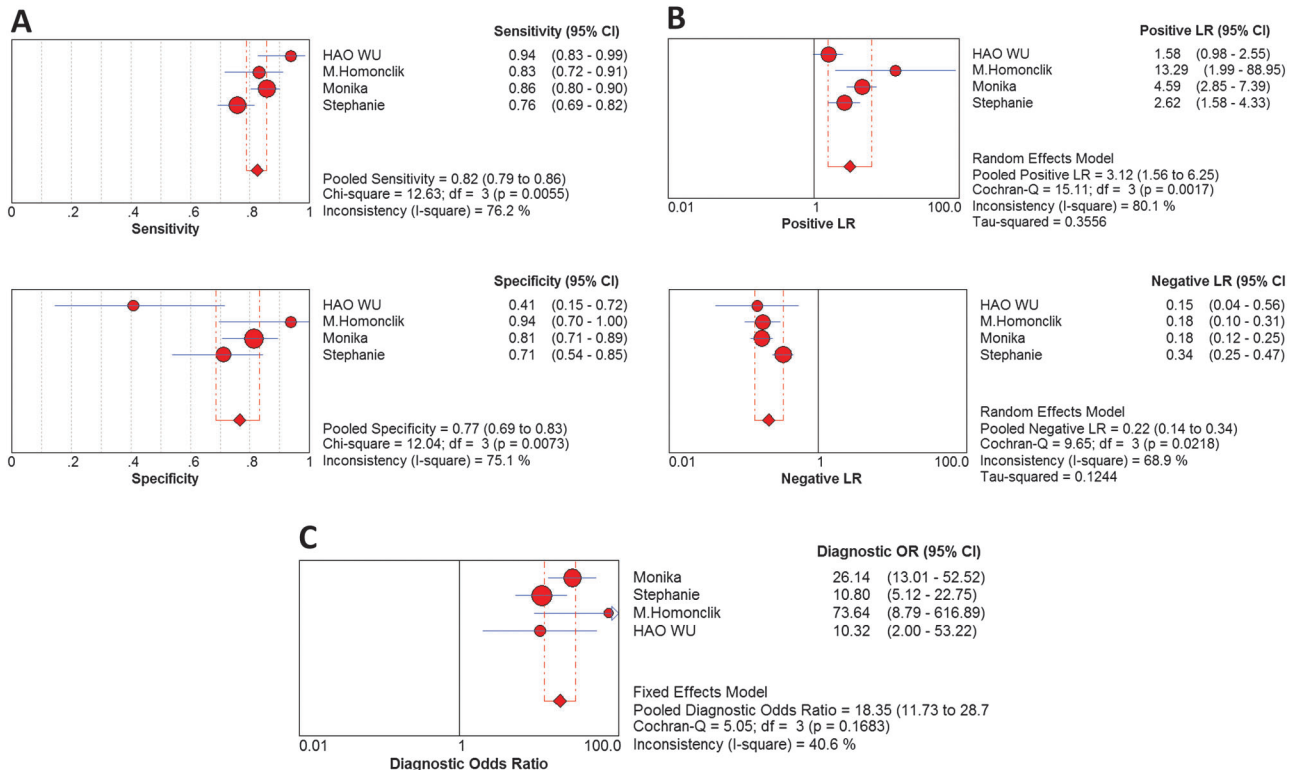

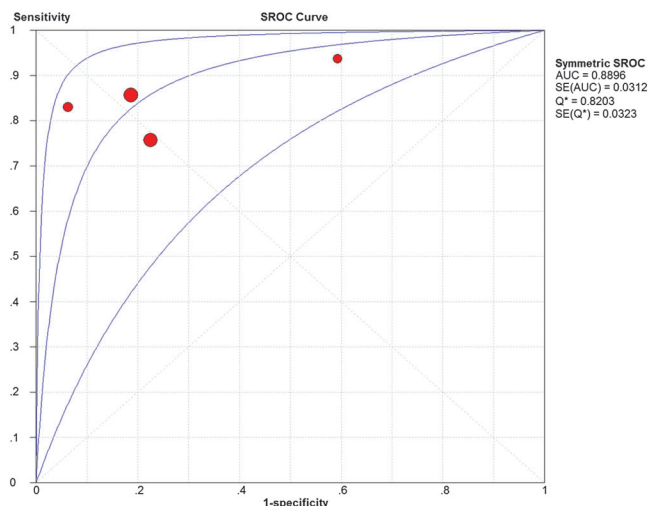**Fig. 3. Forest map of diagnostic odds ratio.**

Fig. 4. Summary receiver operating characteristic curve.

threshold effect is one of the important reasons underlying heterogeneity. When there is a negative correlation between the logarithm of SEN and the logarithm of SPE (or the logarithm of SEN is positively correlated with the logarithm of 1- SPE), it indicates a threshold effect. In our test, the Spearman correlation coefficient between the logarithm of SEN and the logarithm of 1- SPE was 0.400 ($r = 0.400$), indicting a positive correlation. But, $p = 0.600$ (>0.1) indicated that there is no statistical significance, that is to say there was no threshold effect.

Combined effect sizes and discussed heterogeneity: Meta-DiSc1.4 software, which used the random effect model to analyze SEN, SPE, +LR, -LR (Fig. 3A-B), and DOR combined, drew a forest map of the DOR and test for heterogeneity (Fig. 3C). As shown in Figure 3C, the findings of $p = 0.1683$, $I^2 = 40.6\%$, $p > 0.10$ and $I^2 < 50\%$ indicated no heterogeneity.

Drawing of the SROC curve: The Mantel-Haenszel model of Meta-DiSc1.4 was used to combine the DOR and calculate the total SEN, SPE and 95%CI. Then, the SROC curve was drawn and the AUC was calculated. Figure 4 shows the AUC of 0.8896 and Q index of 0.8203, indicating higher accuracy and better diagnostic efficiency.

Discussion

PH is an important sign of decompensation of liver cirrhosis. The increase of portal pressure can cause complications, such as upper gastrointestinal hemorrhage, massive ascites, splenomegaly, hypersplenism, hepatic encephalopathy, hepatorenal syndrome, and hepatopulmonary syndrome.[3] It is an important pathophysiological link to continuously accelerating liver function decline or even failure. Therefore, the severity of PH is also an important indicator to predict the risk of death in patients with cirrhosis.[13]

HVPG is used as a gold standard for the diagnosis of cirrhosis with PH.[3,10,14] The study showed that the risk of upper gastrointestinal bleeding, massive ascites, spontaneous peritonitis, hepatic encephalopathy, liver cancer and other related complications increased significantly when HVPG was more than 10 mmHg.[2,3,6,7] However, HVPG is an invasive method, associated with high cost and needs of advanced

equipment and technical skills for diagnosis of PH, so it is difficult to measure in clinic. Therefore, it is necessary to find noninvasive methods for detecting PH, and such will have a very important role in early diagnosis and prediction of significance.

vWF, which is a marker of vascular endothelial damage, plays an important role in the occurrence and development of cirrhosis with PH.[6,7] Studies showed that the serum vWF levels were significantly positively correlated with HVPG in cirrhosis patients with PH and were able to predict clinical outcome of cirrhosis patients with PH.[6,7,9–11] Abdelmoneim *et al.* and Ferlitsch *et al.* found that vWF can be used as a potential new biomarker and noninvasive serum marker to diagnosis cirrhosis PH.[6,10,14] However, the value of vWF levels in the diagnosis of PH in liver cirrhosis is not yet clear.

In this study, to explore the value of vWF in the diagnosis of PH of cirrhosis, we searched for relevant literature in the Cochrane Library, Ovid, VOS-SCI, CNKI, PubMed, Medline, EMBASE, CMB and Wanfang databases and extracted data to analyze the correlation between HVPG and serum vWF in patients with cirrhosis and PH. A total of 4 studies, comprised of 662 patients (Table 1), observed that the expression of serum vWF in liver cirrhosis with PH patients is significantly higher than that in liver cirrhosis without PH patients.

In addition, we used RevMan5.2 software for meta-analysis. In the case of no threshold effect, we combined SEN and SPE. The SEN of vWF diagnosis of PH was 82.3% and SPE was 78.2%, indicating that the rate of missed diagnosis was 17.6% and the misdiagnosis rate was 21.8%. +LR was 3.777 (>1), indicating the possibility of PH when vWF was positive in the diagnosis of PH; -LR was 0.22 (<1), indicating that the possibility of PH cannot be excluded when the vWF diagnosis of PH is negative. The forest map of DOR was drawn and heterogeneity analyzed. The values of $p = 0.1683$ (>0.1), $I^2 = 40.6\%$ (<50%) showed no heterogeneity. The odds ratio was 18.347, suggesting that vWF has high accuracy in differentiating cirrhosis with or without PH. Finally, the SROC curve was drawn. The AUC was 0.8896 and the Q index was 0.8203, indicating that vWF has a high diagnostic efficiency for cirrhosis with PH. Moreover, the results of this study showed that in the diagnosis of vWF, the variation range of SEN in the diagnosis of cirrhosis with PH was not significant (0.788–0.855), suggesting that the stability of diagnosis was good.

In conclusion, this study suggests that serum vWF could be used as an effective and feasible method of noninvasive marker testing for diagnosis of liver cirrhosis with PH. However, in this study, most of the research samples were too small; thus, serum vWF could not be found to evaluate the severity of liver cirrhosis with PH. Further studies are still needed to evaluate the role of vWF levels in indicating the severity of liver cirrhosis with PH.

Acknowledgments

Conflict of interest

The authors have no conflict of interests related to this publication.

Author contributions

Contributed equally to this study (XCD, WLM, MKL), conceived the study, drafted the manuscript and critically revised it for important intellectual content (XCD, WLM, MKL, LNM), all authors read and approved the final manuscript.

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