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Evaluation of Coagulation, Fibrinolysis and Endothelial Biomarkers in Cirrhotic Patients With or Without Portal Venous Thrombosis

Wenhua Ren, MM[1], Jing Zhang, MD[2], Yuying Chen, MM[3], Meng Wen, MM[1], Yu Su, PhD[1], Yujing Zhao, MM[1], Shan Lu, PhD[1], and Jun Wu, MD[1,3]

Abstract

To evaluate variations in coagulation, fibrinolysis and endothelial marker expression in cirrhotic patients and to explore their clinical value and predictive performance in cirrhotic patients with or without portal vein thrombosis (PVT), we performed a case-control study with 175 cirrhotic patients and 50 healthy individuals. 99 patients had PVT and another 76 patients did not. All participants were evaluated for plasma levels of conventional hemostatic markers. Thrombin-antithrombin complex (TAT), plasmin-α2-plasmin inhibitor complex (PIC), thrombomodulin (TM), tissue plasminogen activator inhibitor complex (t-PAIC), von Willebrand factor antigen (vWF: Ag) and coagulation factor VIII (FVIII: c) were also assessed and the ratio of TAT/t-PAIC was calculated. We analyzed differences in these biomarkers among the three groups and constructed receiver operating characteristic (ROC) curves. Patients with PVT exhibited significantly higher TAT and TAT/t-PAIC than cirrhotic patients without PVT (both $P < 0.001$). Areas under the curve (AUC) of ROC analyses for TAT and TAT/t-PAIC were 0.68 and 0.66, the cut-off levels were 1.55 ng/ml and 0.46, with sensitivities and specificities of 78.79% and 51.32% regarding TAT, 39.8% and 90.79% regarding TAT/t-PAIC. Levels of FVIII: c and vWF: Ag in patients with PVT were significantly lower than those without PVT ($p = 0.026$ and $p = 0.027$, respectively). The AUC^{ROC}, cut-off level, sensitivity and specificity of FVIII: c were 0.64, 111.1%, 66.67% and 60%, respectively. For vWF: Ag they were 0.61, 429%, 89.66% and 38.71%, respectively. Cirrhotic patients have disorders of coagulation, fibrinolysis and the endothelial system. TAT, TAT/t-PAIC, FVIII: c and vWF: Ag can be used as potential biomarkers for predicting PVT in cirrhotic patients.

Keywords

liver cirrhosis, portal vein thrombosis, thrombin–antithrombin, tissue plasminogen activator inhibitor complex, coagulation factor VIII: c

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Introduction

The liver regulates hemostatic functions, including the synthesis of most coagulation factors and inhibitors, as well as fibrinolytic factors. Hepatic dysfunction may result in complex hematologic abnormalities. For a long time it was believed that in patients with cirrhosis, defective synthesis of pro-coagulant factors, together with thrombocytopenia, increased the risk of bleeding but protected against thrombosis.[1] However, this belief has been challenged by evidence of a concomitant reduction of anticoagulant factors such as Protein C and S, which are also synthesized by the liver.[2] The fibrinolysis system is also

[1] Department of Clinical Laboratory, Beijing Jishuitan Hospital, Beijing, China
[2] Department of Hepatology, Beijing Youan Hospital, Capital Medical University, Beijing, China
[3] Department of Laboratory Medicine, Peking University Fourth School of Clinical Medicine, Beijing Jishuitan Hospital, Xicheng District, Beijing, China

Corresponding Author:
Jun Wu, Department of Clinical Laboratory, Beijing Jishuitan Hospital, Beijing, China; Department of Laboratory Medicine, Peking University Fourth School of Clinical Medicine, Beijing Jishuitan Hospital, Xicheng District, Beijing 100035, China.
Email: wujunpostbox@sina.com

activated. The net effect of these changes is to rebalance hemostasis, but this situation is unstable. For this reason, cirrhosis represents a unique clinical setting in which a prohaemorrhagic and prothrombotic phenotype co-exist.[3,4]

As is well recognized, portal vein thrombosis (PVT) is a common complication of cirrhosis. The reported incidence of PVT in compensated liver disease is between 0.6% and 5%, but is much higher (up to 25%) in advanced disease.[5-8] In acute PVT, intestinal congestion and ischemia are typical manifestations, even developing into intestinal perforation, peritonitis, shock and death from multi-organ failure.[9] Patients with chronic PVT can be virtually asymptomatic, but present with portal hypertension related to complications such as esophageal varices, splenomegaly, anemia and thrombocytopenia.[10,11] PVT has become an important source of morbidity and mortality, and early detection and treatment are critical to prevention of the worst outcomes. Substantial innovation has made it possible to use non-invasive imaging methods such as Doppler ultrasound, computed tomography (CT), or magnetic resonance imaging (MRI) for the diagnosis and evaluation of PVT.[12] Because PVT is often asymptomatic, laboratory tests may help to identify patients with unsuspected PVT. Therefore, it is pertinent to identify potential biomarkers that reflect coagulation, fibrinolysis and endothelial processes which predict PVT. Unfortunately, traditional coagulation tests such as prothrombin time (PT), international normalized ratio (INR) and activated partial thromboplastin time (APTT) are unreliable for stratifying bleeding or thrombotic risk in cirrhosis, and may not be useful in cirrhotic patients with PVT.[13] Research has demonstrated that D-dimer is raised in cirrhotic patients with PVT[6]; however, D-dimer has a low specificity. More appropriate biomarkers are therefore required to reliably detect PVT in patients with cirrhosis.

In this case-control study, we compared traditional measures and natural inhibitors of coagulation between cirrhotic patients and healthy individuals. We also sought new coagulation biomarkers and evaluated their value in cirrhotic patients with or without PVT, as well as to analyze their predictive values for PVT.

Participants and Methodology

Patient Recruitment

This case-control study was conducted in Beijing Youan Hospital, Capital Medical University and Beijing Jishuitan Hospital, Peking University over a 2-year period (from January 2018 to January 2020) and included 175 patients with cirrhosis. The etiologies of cirrhosis include chronic hepatitis B or C infection, primary biliary cirrhosis, alcoholic liver cirrhosis, autoimmune hepatitis, cryptogenic liver cirrhosis and others. The severity of liver disease was estimated according to the Child–Pugh class and Model for End-stage Liver Disease (MELD) scoring systems. Criteria for exclusion at the time of blood sampling were: (1) previous or ongoing use of anticoagulant or antiplatelet therapy; (2) splenomesenteric or peripheral vein thrombosis; (3) known hemostatic disorders other than cirrhosis; (4) hepatocellular carcinoma (HCC) or other intrahepatic or extrahepatic malignancy; (5) splenectomy. Of the 175 cases of cirrhosis, 99 were patients with PVT (48 male, 51 female). The diagnosis of PVT was confirmed by contrast-enhanced computer tomography (CT) or contrast-enhanced magnetic resonance (MR). We selected 76 patients without PVT (36 male, 40 female), who had a history of cirrhosis for more than 5 years, as the no PVT group. In addition, we recruited 50 healthy individuals (23 male, 27 female) from Beijing Jishuitan Hospital as a control group. No age or sex differences were observed among groups. Demographic and clinical characteristics of participants in the study are shown in Table 1.

Table 1. Demographic and Clinical Characteristics of Participants in PVT (Group 1), no PVT (Group 2) and Control (Group 3). [a]

Variables	PVT (N = 99)	No PVT (N = 76)	Control (N = 50)
Age, years	57(52,63)	58(52,63)	57(52,60)
Gender(male/female), n/n	48/51	36/40	23/27
Cause of liver cirrhosis			-
Alcoholic liver cirrhosis, n	7	5	
Chronic hepatitis B or C, n	66	53	
Primary biliary cirrhosis, n	14	9	
Autoimmune hepatitis, n	6	3	
Cryptogenic liver cirrhosis, n	5	4	
Others, n	1	2	
MELD score points	6.7 ± 4.5	7.4 ± 3.8	-
Child-Pugh class			-
A, n	31	20	
B, n	45	35	
C, n	23	21	
Platelets, $\times 10^9$/L	94(41,160)	75(42,137)	208(178,265)
Albumin, g/L	32.0 ± 5.5	31.6 ± 6.2	45.3 ± 3.3

Abbreviations: PVT, Portal vein thrombosis; MELD, Model for End-stage Liver Disease.

[a] Data with normal distribution are expressed as mean ± standard deviation (SD); non-normal data are expressed as median (25th, 75th percentiles).

Blood Collection and Processing

Blood samples from patients were drawn without stasis when they were hospitalized and before diagnosis of PVT. Samples collected in vacuum tubes containing 3.2% trisodium citrate (Vacutainer; Becton–Dickinson, Meylan, France) were centrifuged for 15 minutes at 1500 g, and the plasma stored at −80°C within 2 hours, prior to analysis.

Biomarker Analysis

To evaluate the coagulation abnormalities of PVT, the following variables were measured: prothrombin time (PT; s), international normalized ratio (INR), activated partial thromboplastin time (APTT; s), Fibrinogen (FIB; mg/L), D-dimer (mg/L FEU), fibrinogen degradation products (FDP; mg/L), plasmin-α2-plasmin inhibitor complex (PIC; TU/ml), thrombin-antithrombin complex (TAT; ng/mL), thrombomodulin (TM; ug/mL), tissue

Table 2. Results of the Biomarkers of Groups Among PVT, No PVT and Control [a]

laboratory parameters	1. PVT	2.No PVT	P 1 vs 2	3.Control	P 3 vs 1	P 3 vs 2
PT(s)	16.0(13.7,18.1)	15.6(13.9,18.1)	0.951	12.2(11. 8,12.6)	<0.001	<0.001
INR	1.31(1.18,1.60)	1.27(1.11,1.44)	0.104	0.94(0.90,0.97)	<0.001	<0.001
APTT(s)	35.8(32.7,41.0)	35.6(32.2,40.5)	0.988	26.3(23.8,28.3)	<0.001	<0.001
FIB(mg/L)	1823 ± 653	1953 ± 861	0.282	3273 ± 642	<0.001	<0.001
D-dimer (mg/L FEU)	2.44(1.11,4.51)	1.59(0.72,3.89)	0.110	0.28(0.22,0.51)	<0.001	<0.001
FDP(mg/L)	6.7(3.5,15.0)	5.1(2.1,14.0)	0.255	1.8(1.5,2.4)	<0.001	<0.001
TAT(ng/mL)	3.3(1.7,6.5)	1.5(0.9,3.6)	<0.001	1.2(0.9,1.8)	<0.001	<0.001
PIC(TU/mL)	0.599(0.394,1.035)	0.580(0.359,1.000)	0.686	0.500(0.360,0.615)	0.017[b]	0.043[b]
t-PAIC (ng/mL)	10.5(5.8,17.2)	11.0(6.7,17.0)	0.977	8.0(7.1,10.2)	<0.001	<0.001
TM (ug/mL)	15.41 ± 5.10	17.05 ± 7.84	0.831	9.80 ± 1.97	<0.001	<0.001
PC (%)	61.0 ± 17.0	51.9 ± 27.0	0.115	125.2 ± 21.7	<0.001	<0.001
PS (%)	53.5 ± 14.8	50.6 ± 22.6	0.612	87.8 ± 18.8	<0.001	<0.001
AT (%)	50.9 ± 17.1	52.1 ± 21.8	0.524	87.0 ± 12.1	<0.001	<0.001
FVIII: c (%)	102.4 ± 21.4	119.8 ± 38.0	0.026[b]	101.6 ± 23.6	0.916	0.032[b]
vWF: Ag (%)	312.3 ± 104.3	395.7 ± 172.4	0.027[b]	130.4 ± 39.0	<0.001	<0.001
TAT/t-PAIC	0.29(0.14,0.71)	0.18(0.08,0.35)	<0.001	0.15(0.11,0.23)	<0.001	0.768

Abbreviations: PVT, portal vein thrombosis; PT, prothrombin time; INR, international normalized ratio; APTT, activated partial thromboplastin time; FIB, Fibrinogen; FDP, fibrinogen degradation products; TAT, thrombin–antithrombin complex; PIC, plasmin–a2-antiplasmin complex; t-PAIC, tissue plasminogen activator inhibitor complex; TM, thrombomodulin; PC, protein C; PS, protein S; AT, antithrombin; vWF: Ag, Von Willebrand factor antigen.
[a]Data with normal distribution are expressed as mean ± standard deviation (SD); non-normal data are expressed as median (25th, 75th percentiles).
[b]$P < 0.05$.

plasminogen activator inhibitor complex (t-PAIC; ng/mL), protein C (PC; %), protein S (PS; %), antithrombin (AT; %), von Willebrand factor antigen (vWF: Ag; %) and coagulation factor VIII (FVIII: c; %). In addition, we calculated the ratio: TAT/t-PAIC. PT, INR, APTT, FIB, D-dimer, FDP and FVIII: c were assayed using an automatic coagulation analyzer (CS 5100, Sysmex, Kobe, Japan). PT was measured with the Thromborel S Reagent (Siemens, Marburg, Germany). APTT was assessed using the Dade Actin Reagent (Siemens, Marburg, Germany). FIB levels were measured using Dade Thrombin reagent (Siemens, Marburg, Germany). D-dimer was measured with Innovancer D-dimer reagent (Siemens, Marburg, Germany) and FDP using Nanopia P-FDP reagent (SEKISUI, Tokyo, Japan). PIC, TAT, TM and t-PAIC were measured by chemiluminescent enzyme immunoassay using an automated immunoassay system (HISCL5000, Sysmex, Corollary regent, Japan). PC, PS, AT and vWF: Ag were assayed using an autoanalyzer (Stago Diagnostic STA Compact Max, Corollary regent, Taverny, France) following the manufacturer's instructions. Results for PC, PS, and AT were expressed as a percentage of protein activity; the vWF as the quantitative determination of von Willebrand Factor antigen.

Statistical Analysis

Statistical analyses were performed using statistical package SPSS version 23.0. Kolmogorov-Smirnov Tests were used to check for normal distribution. Data with a normal distribution were expressed as means ± SD and non-normal data were presented as median (25th, 75th percentiles). The levels of markers were compared among donors with and without PVT and healthy controls. One-way analysis of variance (least significant difference and Tamhane T2) was used to analyze the data for FIB, TM, PC, PS, AT, FVIII: c and vWF: Ag. Non-parametric Kruskal Wallis tests were employed to compare PT, INR, APTT, D-dimer, FDP, TAT, PIC, t-PAIC and TAT/t-PAIC in the different groups. Statistical significance was considered to be at $p < 0.05$. ROC curves were performed to identify the predictive value of TAT, FVIII: c, vWF: Ag and TAT/t-PAIC. The appropriate cut-off values were calculated to maximize the sum of the sensitivity and specificity.

Results

Conventional Coagulation Data

The results for conventional indices PT, INR, APTT, FIB, D-dimer and FDP are shown in Table 2. Notably, PT, INR and APTT were elevated in the entire group of cirrhotic patients (with and without PVT) compared to the control group (group 3) ($p < 0.001$ and $p < 0.001$, respectively). In addition, these patients had lower levels of FIB ($p < 0.001$ for both) and higher levels of D-dimer ($p < 0.001$ for both) and FDP ($p < 0.001$ for both) than healthy donors. There was no significant difference between group 1 (patients with PVT) and group 2 (patients without PVT; $p > 0.05$).

Markers of Coagulation, Anticoagulation, Fibrinolysis and the Endothelial System

Cirrhotic patients (with and without PVT) had lower activities of PC, PS and AT than healthy individuals ($p < 0.001$, $p < 0.001$ and $p < 0.001$, respectively), but there was no statistically significant difference between patients with or without PVT ($p = 0.115$, $p = 0.612$ and $p = 0.524$, respectively). Levels of TAT, PIC, t-PAIC and TM were significantly increased in

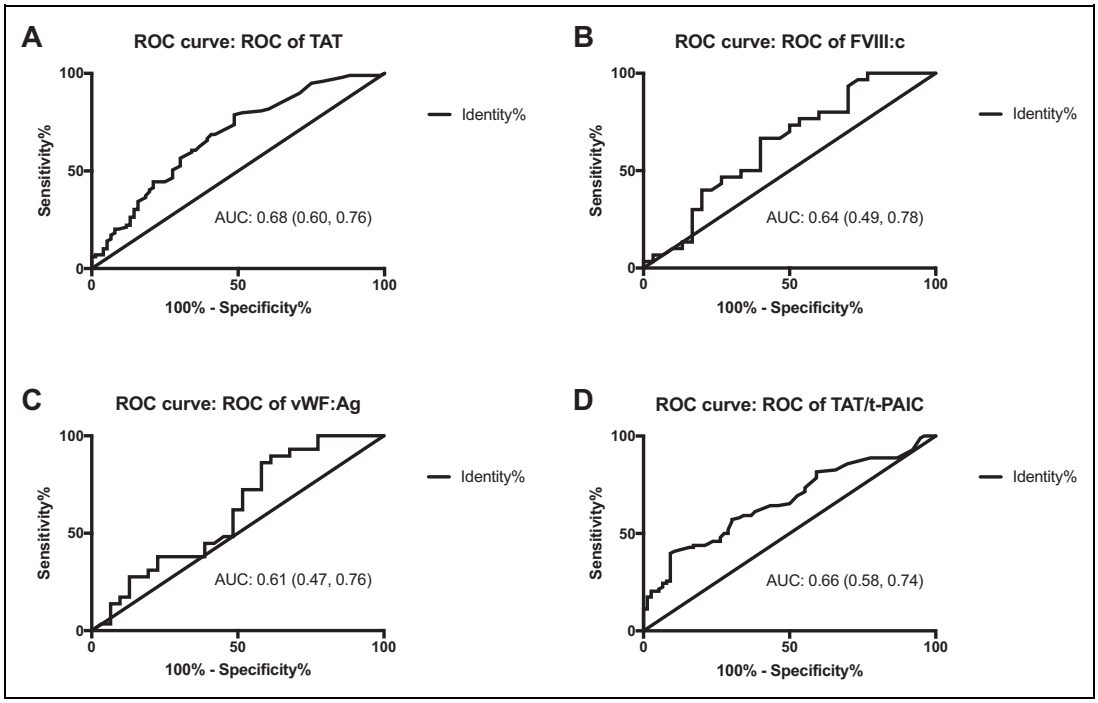

Figure 1. (A-D) Receiver operating characteristic (ROC) curves for TAT, FVIII: c, vWF: Ag and TAT/t-PAIC to predict PVT in cirrhotic patients.

patients with cirrhosis (with and without PVT) compared to controls ($p < 0.001$, $p < 0.05$, $p < 0.001$ and $p < 0.001$, respectively). Patients who developed PVT exhibited higher levels of TAT and TAT/t-PAIC than those without PVT ($p < 0.001$ for both). In addition, levels of FVIII: c and vWF: Ag in patients without PVT were significantly higher than those with PVT ($p = 0.026$ and $p = 0.027$, respectively).

Predictive Values of TAT, FVIII: c, vWF: Ag and TAT/t-PAIC

To investigate the usefulness of TAT, FVIII: c, vWF: Ag and TAT/t-PAIC to predict PVT in cirrhotic patients, ROC curve analysis was performed in the PVT and non-PVT groups. As shown in Figure 1, the data showed that optimum sensitivity and specificity were obtained at a TAT value of 1.55 ng/ml, giving a sensitivity of 78.79%, specificity of 51.32%, and AUC of 0.68 (95% CI 0.60-0.76). The AUC for FVIII: c was 0.64 (95% CI 0.49-0.78), and its cut-off level was 111.1%, with sensitivity and specificity of 66.67% and 60%, respectively. AUC, cut-off level, sensitivity, and specificity for vWF: Ag were 0.61 (95% CI 0.47-0.76), 429%, 89.66% and 38.71%, respectively. Lastly, the AUC of TAT/t-PAIC was 0.66 (95% CI 0.58-0.74) and its cut-off level was 0.46, with sensitivity and specificity of 39.8% and 90.79%, respectively.

Discussion

Disorders of the coagulation system pose an increased risk of both thrombosis and bleeding in patients with cirrhosis. This duality is a result of a dynamic disequilibrium between pro- and anti-coagulant factors in cirrhotic patients.[14] Although a hemostatic balance is reached in cirrhosis, this equilibrium is more fragile and can easily lead to a hypo- or hyper-coagulable state.[15] In recent years, it has been evident that appropriately assessing patients for the risk of bleeding and thrombosis cannot be done with standard coagulation tests, such as PT, INR or APTT.[5] As our study showed, many cirrhotic patients develop PVT despite elevated PT, INR and APTT. The hemostatic profile in cirrhosis is characterized by decreased levels of most procoagulants. Nevertheless, the decreased plasma levels of procoagulants is paralleled by a reduction in plasma levels of most of the natural anticoagulants, including PC, PS and AT.[16,17] However, differences in PC, PS and AT between those with and without PVT did not achieve statistical significance. Thus, these parameters should not be used to evaluate risk of PVT. A meta-analysis has demonstrated that AT, PC and PS concentrations might not be associated with pathogenesis of PVT in liver cirrhosis,[1] which is consistent with our findings. Numerous studies have also reported that FVIII: c and vWF are the prominent pro-coagulant factors that are elevated in cirrhosis patients.[1,5,18] The high FVIII: c and vWF levels likely participate in compensating for the deficient procoagulants and thrombocytopenia, thus playing a key role in rebalancing the hemostatic system.[5,19] Chen et al[20] and Tang et al[21] demonstrated that pro- and anti-coagulants were not associated with the presence of PVT in patients with cirrhosis. In another study, Filippo et al analyzed the relationship between FVIII: c and cirrhosis in patients with or without PVT and demonstrated that FVIII: c values significantly decrease in the presence of

concomitant PVT.[6] This finding is in accordance with our results—FVIII: c levels were clearly raised in cirrhosis patients, but those patients without PVT had higher values for FVIII: c than those with PVT. This is likely to be a result of FVIII: c consumption during the process of thrombosis. PVT is a long-lasting condition, as suggested by the occurrence of compensatory mechanisms termed cavernous transformation.[7] The development of new veins bypass the thrombosed portion of the portal vein.[7] Thus, it is possible that low FVIII: c levels in cirrhotic patients with PVT may be the result of an ongoing prothrombotic state with consequent relative consumptive coagulopathy.[6] Here, we also explored the predictive power and clinical value of FVIII: c and vWF: Ag for thrombosis in cirrhotic patients with PVT. The AUC of FVIII: c and vWF: Ag were 0.64 and 0.61 respectively, which is less than ideal. Therefore, we explored other coagulation and fibrinolysis parameters which may identify cirrhotic patients with unsuspected PVT.

Our study introduces two important clinical observations. Firstly, levels of TAT, PIC, t-PAIC and TM in cirrhotic patients are significantly higher than in health. Biomarkers like these can assist in determining the region and direction of an unstable hemostatic disorder such as cirrhosis. It is well known that thrombin activity is essential to the acceleration of the coagulation process. Thrombin generation assays (TGA) can be used to assess the time course of thrombin generation and detect hypercoagulability.[1,18,22] However, the clinical utility of this method has been limited because it can only be measured in specialized laboratories and not on a daily basis in most hospitals. Herein, we employed novel automation technology to detect plasma levels of TAT, which is formed by the combination of thrombin and its most important inhibitor, AT.[18] Thus, TAT can be considered as a sensitive marker of thrombin generation[23] which may help stratify those patients with cirrhosis who are at risk of thrombosis. Several investigators have also demonstrated that increased TAT is found in patients with cirrhosis compared to normal subjects, and TAT is a coagulation parameter independently associated with liver function impairment.[18,24,25] PIC is complex of plasmin and α2-antiplasmin which can enable assessment of fibrinolytic activity.[26] As aforementioned, our data reveal that the fibrinolytic system is also involved in PVT development during cirrhosis. There is additional evidence that markers of endothelial dysfunction, including P-selectin, vWF and isoprostanes are upregulated in cirrhotic patients.[27] Both t-PAIC and TM are molecules involved in the endothelial system.[28] Increased t-PAIC and TM can be used to infer endothelial cell injury,[29] which is consistent with elevated FVIII: c and vWF: Ag, as previously mentioned. Furthermore, t-PAIC is a fibrinolytic factor, which can be used to evaluate fibrinolytic activation together with PIC. Therefore, cirrhotic patients actually have profound and complex hemostatic defects, which include the coagulation system, fibrinolytic system and endothelial system.

Our second main clinical observation is that elevated TAT and ratio of TAT/t-PAIC may be useful for the prediction of cirrhotic patients with PVT. TAT directly reflects hypercoagulable states. According to the findings of Kalambokis GN et al, patients with elevated TAT had a significantly higher probability of developing PVT.[24] In line with these observations, we found that TAT levels in cirrhotic patients with PVT were significantly higher than those without, when matched for age, sex, MELD score points and Child-Pugh class. As the hemostatic defects of cirrhotic patients are caused by an imbalance of coagulation, fibrinolytic and the endothelial system, data from only one type of coagulation parameter or pro- and anticoagulant factor should be considered with caution. Therefore, we designed the new index, TAT/t-PAIC, to comprehensively reflect the ratio of procoagulation to fibrinolysis and endothelium. The relatively high specificity of TAT/t-PAIC makes it a potential supplement to TAT for prediction of PVT. All these biomarkers can be rapidly measured by automated analyzers in the laboratory, with small test volumes and high sensitivity. Furthermore, results are available within 17 minutes. In addition, we have to admit that the sensitivity of investigated parameters is low. On the one hand, it may be related to the selection of no PVT patients. As PVT is a possible complication of cirrhosis, and most patients are asymptomatic, it is difficult to obtain date for mean duration from diagnosis of cirrhosis when testing patients with or without PVT. Statistics for patients in the PVT group indicate that they had a history of cirrhosis for an average of 5 years. These patients may actually develop PVT for a shorter period of time. Thus, we selected 76 no PVT patients with a history of cirrhosis for more than 5 years. These patients may develop PVT in subsequent observations. On the other hand, it may be related to insufficient sample size. In the follow-up study, we hope to improve the sensitivity by recruiting more patients and extending the observation period. However, our current study provides an option for clinicians to predict PVT. After all, biomarkers such as D-dimer do not play a role in predicting PVT. We should also emphasize that the statistically significant differences in TAT, TAT/t-PAIC, FVIII: c and vWF: Ag between cirrhotic patients with and without PVT are not associated with the Child-Pugh class and MELD score. On the one hand, no MELD scores and Child-Pugh class differences were observed between patients with and without PVT. On the other hand, we came to the same conclusion regarding differences in TAT, TAT/t-PAIC, FVIII: c and vWF: Ag when patients with and without PVT were classed as group A, B and C according to their Child–Pugh scores.

This initial study is retrospective and has entails potential limitations including modest sample size, limited observation time and lack of randomization. It is necessary to use prospective methodology and validate the findings in a larger patient population. In addition, clearance of TAT, as a function of the liver, potentially may have interfered with our results. Nevertheless, our study establishes the importance of TAT, TAT/t-PAIC, FVIII: c and vWF: Ag in prediction of cirrhotic patients with PVT. In future studies, we plan to recruit greater numbers of patients and include follow-up studies, to establish a complete perspective on cirrhotic patients with PVT and to evaluate

the role of key biomarkers in anticoagulation therapy and prognosis.

To conclude, cirrhotic patients are proposed to have disorders of coagulation, fibrinolysis and the endothelial system. Dysregulation among these systems may result in a hypercoagulable state that can manifest clinically as thrombotic complications. In addition to FVIII: c and vWF: Ag, TAT and TAT/t-PAIC may be used as potential biomarkers for PVT prediction in cirrhotic patients.

Authors' Note

Wenhua Ren, Jing Zhang and Jun Wu designed and performed the research. Yuying Chen and Meng Wen acquired the data. Yu Su, Yujing Zhao and Shan Lu provided valuable technical assistance. Wenhua Ren and Jun Wu analyzed and interpreted the data and wrote the manuscript. All authors reviewed and made critical revisions and approved the final version of the manuscript. The study was conducted with approval of the Institution's Ethics Committee (project number 202004-86).

Declaration of Conflicting Interests

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ORCID iD

Jun Wu https://orcid.org/0000-0001-5178-0906

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