

Research

von Willebrand factor and D-dimer are elevated in cirrhosis with spur cell anemia

Deepika^{1,2,*}

Abstract

The aim of the study is to assess the concentrations of von Willebrand factor (vWF) and D-dimer in patients with liver cirrhosis and spur cell anemia (SCA), and to evaluate their correlation with the proportion of spur cells. A total of 3 ml blood samples were collected in citrate tubes from 27 patients with Child C chronic liver disease (CLD), divided into two groups: group 1 (<10% SCA, n=20) and group 2 (>10% SCA, n=7). Plasma was separated by centrifugation at 3000 rpm for 10 minutes for ELISA based measurements of vWF and D-dimer. Clinical data and laboratory parameters, including indicators of liver dysfunction and the MELD-Na (Sodium - Model of End-Stage Liver Disease) score, were evaluated. Immunohistochemistry was performed to evaluate the expression of vWF in liver tissue. The blood plasma levels of vWF were significantly higher in group 2 compared to group 1 (7.96 ± 1.82 vs 5.76 ± 2.22 ; $p=0.0231$). D-dimer levels were also higher in group 2 but not statistically significant (72.80 ± 34.44 vs. 42.36 ± 28.53 ; $p=0.103$). Sonoclot assay results indicated that platelet function (PF) was increased in group 2 (2.07 ± 1.49 vs. 0.92 ± 0.89 ; $p=0.039$). In contrast, the clot rate and activated clotting time (ACT) showed no significant differences between groups (28.36 ± 8.91 vs 24.63 ± 14.18 , $p=0.065$; 189.33 ± 30.72 vs 215.86 ± 50.42 , $p=0.2311$). Other parameters such as hemoglobin (7.82 ± 1.71 vs 7.43 ± 1.1 , $p>0.05$) and platelet count (70.11 ± 23.75 vs 68 ± 29 , $p>0.05$) were comparable. Patients with higher proportions of spur cells in Child C advanced cirrhosis show elevated levels of VWF, D-Dimer, and PF, suggesting a prothrombotic state potentially driven by endothelial activation and microvascular dysfunction.

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Introduction

Cirrhosis of the liver leads to intricate changes in the hematological system, which affects both hemostasis and anemia (Privitera & Meli, 2016). SCA is a persistent type of anemia recognized as a secondary condition in cirrhosis and typically linked with a poor prognosis. Anemia in cirrhosis results from a complicated interaction of multiple factors, including impaired red blood cell production, increased sequestration in the spleen, chronic blood loss, deficiencies in nutrition, and systemic inflammation (Qamar & Grace, 2009; Qamar *et al.*, 2009). Spur cells are red blood cells with spiny projections on their surface caused by changes in their membrane fat (lipid) composition make them broad, inflexible, and prone to hemolysis (Arienti *et al.*, 1995).

vWF remains high in cirrhosis due to endothelial damage stimulated by endotoxemia or due to its increased synthesis by the diseased liver and correlates with higher stages of cirrhosis (Ferro *et al.*, 1996; Reiner *et al.*, 2001; Yilmaz *et al.*, 2015). vWF is a glycoprotein consisting of large multimers, produced by endothelial cells and bone marrow, considered to be a marker of endothelial disturbance (Blann, 1993).

It plays an essential role in blood coagulation; it functions as a linker molecule to prevent blood leakage at sites of vascular damage through regular platelet adhesion and under conditions of high shear stress, it enhances platelet aggregation, thereby affecting the risk of arterial and venous thromboembolism (Swystun & Lillicrap, 2018). D-dimer is a soluble product resulting from the degradation of fibrin, released during the breakdown of a blood clot by plasmin (Weitz *et al.*, 2017). It is also associated with an increased risk of in-hospital mortality among patients with cirrhosis (Violi *et al.*, 1993; Rautou *et al.*, 2014; Dai *et al.*, 2015; Drolz *et al.*, 2016; Gragnano *et al.*, 2017; Li *et al.*, 2017).

Nonetheless, the relationship between D-dimer and vWF concerning the condition of SCA has yet to be investigated. Therefore, we aimed to assess the levels of vWF and D-dimer in patients with liver cirrhosis and SCA. We propose that levels of vWF and D-dimer are increased in SCA and are associated with the severity of the liver disease as a result of endothelial dysfunction and microvascular thrombosis.

Material & Methods

A prospective study was conducted involving patients who have advanced cirrhosis (Child C) of various etiologies, admitted to the Institute of Liver & Biliary Sciences (ILBS) hospital in New Delhi from September 2018 to March 2019 due to various complications like jaundice, fever, anemia, ascites, spontaneous bacterial peritonitis was analyzed for the existence of spur cells. Individuals with conditions such as non-liver disease, hepatocellular carcinoma, hemoglobinopathies, a positive direct Coombs test, chronic renal failure, sepsis, or active bleeding were not included in the study. All patients were informed about the study purpose, and written informed consent was obtained prior to blood sample collection. The study protocol was approved by the Institutional Ethics Committee and conducted in accordance with the Declaration of Helsinki.

In clinical studies of liver cirrhosis, patients are frequently classified based on the percentage of spur cells (acanthocytes) observed in peripheral blood smears. A commonly used threshold stratifies patients into two groups: those with <10% and those with >10% spur cells. Individuals with <10% typically show evidence of liver dysfunction without meeting the diagnostic criteria for spur cell anemia (SCA), whereas >10% spur cells is considered diagnostic of SCA, a severe hemolytic anemia associated with advanced liver disease and poor prognosis. This 10% cutoff is widely accepted in literature as clinically meaningful.

In this study, a total of 27 patients aged 18–65 years, diagnosed with SCA, were included. Based on the percentage of spur cells, they were categorized into two groups: group 1 consisted of 20 patients with <10% spur cells, and group 2 included 7 patients with >10% spur cells (Figure 1). Given the study's focus on assessing the impact of spur cell burden on endothelial and coagulation markers within patients of cirrhosis, a healthy control group was not included. Instead, patients were categorized based on spur cell percentage to investigate internal correlations of vWF and D-dimer with disease severity.

Clinical parameters

Laboratory examination including complete liver function test (LFT), blood count test (CBC), kidney function test (KFT), Prothrombin (PT-INR), and other clinical findings including ascites, encephalopathy, esophagus varices examined by endoscopy or

severe portal gastropathy showing signs of visible blood loss were evaluated and documented. The severity of liver disease was assessed by Na-MELD score.

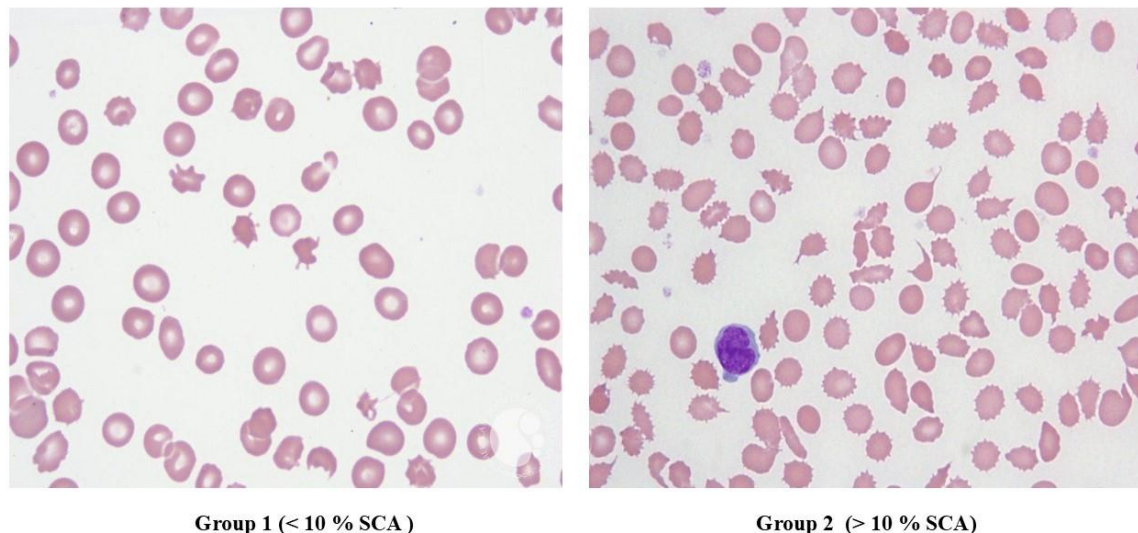


Figure 1. Representative microscopic image of spur cells observed in a peripheral blood smear from a patient with cirrhosis. The smear was stained using Wright–Giemsa and visualized under 10× magnification.

Spur cell quantification

Spur cells were manually quantified by an experienced hematologist using Wright–Giemsa-stained peripheral blood smears. At least 500 RBCs were evaluated per slide under light microscopy to calculate the percentage of spur cells.

Enzyme-linked immunosorbent assay (ELISA)

Plasma was extracted using the centrifugation method at a speed of 3000 r·min⁻¹ for a duration of 10 minutes, which was utilized for vWF and D-dimer analysis. ELISA assay according to manufacture's protocol (BioRad). Minimum detectable concentrations of vWF & D-dimer were determined by the manufacturer as 0.13 ng/ml & 0.08 pg/ml.

Immunohistochemistry (IHC)

Paraffin-embedded liver tissue sections from cirrhosis patients were stained using an anti-human von Willebrand factor (vWF) antibody (Novus Biologicals, Cat# NB600-586, 0.1 ml). Following deparaffinization and rehydration, antigen retrieval was performed using citrate buffer (pH 6.0). Endogenous peroxidase activity was blocked, and sections were incubated overnight at 4°C with the primary antibody (1:100 dilution). Detection was carried out using an HRP-conjugated secondary antibody and DAB substrate. Hematoxylin was used for counterstaining, and sections were visualized under a light microscope.

Sonoclot assay

Sonoclot assays were conducted using a fresh blood sample from the patient following the acquisition of their consent. The Sonoclot assay quantitatively measures activated clotting time (ACT), which is defined as the time in seconds until fibrin formation begins. The rate at which fibrin forms from fibrinogen is indicated by the gradient of the primary slope (R1), referred to as the clot rate (CR), and is

expressed in units per minute. The secondary slope (R2) reflects fibrin polymerization and the interaction between platelets and fibrin. The decline seen in slope R3 following the peak occurs as platelets cause the completed clot to contract. Therefore, the gradient of the R3 slope assesses the availability of platelets and the extent of platelet function, which the analyzer records as platelet function (PF) (Dai *et al.*, [2015](#)).

Statistical analysis

All statistical analyses were performed using Microsoft Excel. Data are presented as mean $\pm$ standard deviation. Comparisons between the two independent groups were made using the unpaired t-test or the Mann–Whitney U test, depending on the distribution and variance of the data. Unequal variances were assumed. A two-tailed p-value of <0.05 was considered statistically significant.

Table 1. Baseline demographic and clinical characteristics of patients with cirrhosis, comparing group 1 ($<10\%$ spur cells) and group 2 ($>10\%$ spur cells).

	SCA ($<10\%$)	SCA ($>10\%$)	P value
N (no. of patients)	20	7	-
Age (in years)	43.6 $\pm$ 10.1	45.3 $\pm$ 10.3	0.86
Gender (Male : Female)	18 : 2	7 : 0	-
Hemoglobin (13-17 gm/dl)	7.82 $\pm$ 1.71	7.43 $\pm$ 1.1	0.58
TLC (4–11 $\times 10^9$ /L)	10.06 $\pm$ 4.44	9.2 $\pm$ 3.68	0.62
Platelets (150-400 $\times 10^9$ /L)	70.11 $\pm$ 23.75	68 $\pm$ 29	0.85
PT - INR	2.87 $\pm$ 0.7	2.71 $\pm$ 0.63	0.6
Serum bilirubin (0.3-1.2 mg/dl)	12.98 $\pm$ 8.73	21.77 $\pm$ 11.97	0.04 *
AST (5-40 IU/L)	77.17 $\pm$ 47.27	100.67 $\pm$ 24.95	0.14
ALT (10-40 IU/L)	38.28 $\pm$ 21.50	46.71 $\pm$ 16.96	0.32
SAP (32-92 IU/L)	116 $\pm$ 60.31	74.14 $\pm$ 26.11	0.02 *
GGT (7-64 IU/L)	20.63 $\pm$ 12.46	42.57 $\pm$ 24.66	0.06
Creatinine (0.2-1 mg/dl)	1.03 $\pm$ 0.76	1.83 $\pm$ 1.19	0.14
Sodium (Na) (136-145 mmol/L)	129.54 $\pm$ 5.33	129.43 $\pm$ 3.32	0.95
Na-MELD score	23.52 $\pm$ 4.3	23.71 $\pm$ 2.98	0.91

All values are represented in mean $\pm$ SD; Significant difference $P < 0.05$ (*)

Results & Discussion

A total of 27 patients with SCA with chronic liver disease were analyzed. Baseline demographic and clinical characteristics of the two groups are summarized in Table 1. There was no significant difference found between the groups in terms of age, gender, hemoglobin, total leukocyte count (TLC), platelets, creatinine, aspartate aminotransaminase (AST), alanine aminotransferase (ALT), serum Alkaline phosphatase (SAP), gamma-glutamyl transpeptidase (GGT), or Na-MELD score. However, serum bilirubin ($p = 0.04$) and SAP ($p = 0.02$) levels were significantly higher in group 2 (patients with >10% SCA). Mortality rates were comparable between the two groups.

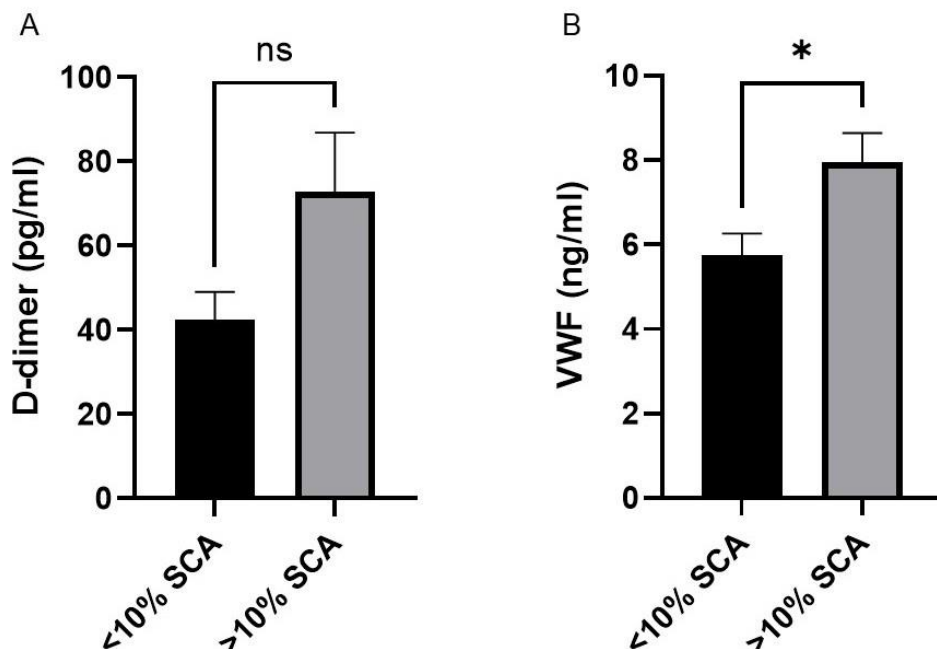


Figure 2. Graphical representation of ELISA test results for D-dimer levels (pg/ml) (A) and von Willebrand factor (vWF) (ng/ml) (B), comparing group 1 (<10% spur cells, n=20) and group 2 (>10% spur cells, n=7).

Results from the ELISA indicated that mean plasma vWF levels were significantly higher in group 2 compared to group 1 (5.76 ± 2.22 vs 7.96 ± 1.82 , $p=0.0231$), while D-dimer levels were elevated but not statistically significant (42.36 ± 28.53 vs 72.80 ± 34.44 , $p=0.103$) (Figure 2). The Sonoclot analysis demonstrated a significant increase in platelet function in group 2 (0.92 ± 0.89 vs 2.07 ± 1.49 , $p=0.039$), whereas the clot rate and activated clotting time (ACT) showed no significant differences between the groups (Clot rate: 28.36 ± 8.91 vs 24.63 ± 14.18 , $p=0.065$; ACT: 189.33 ± 30.72 vs 215.86 ± 50.42 , $p=0.2311$) (Figure 3). IHC analysis further confirmed overexpression of vWF in liver endothelial cells of group 2 patients (Figure 4).

These findings suggest that patients with higher SC percentages exhibit a prothrombotic and inflammatory phenotype. In our study, Patient with more than 10% SCA had higher plasma vWF and D-dimer levels, indicating an intravascular prothrombotic state in patients with cirrhosis (Figure 2). Although not statistically significant, D-dimer levels were higher in patients with >10% spur cells, suggesting a potential trend toward increased fibrinolytic activity and intravascular coagulation.

The elevated expression of vWF, particularly near the portal tracts, may indicate endothelial activation and microvascular injury, which could hinder hepatic blood flow (Figure 4). Platelets are crucial elements in the blood that help prevent bleeding by forming clots. In our study, both groups showed decreased platelet counts, a condition known as thrombocytopenia, which is frequently observed in cirrhosis because of compromised bone marrow activity. Interestingly, group 2 had increased platelet function despite low counts. However, the lower clot rate suggests a disconnect between platelet activation and fibrin formation. This suggests that even though platelets are effectively activated and aggregated, likely influenced by elevated vWF levels observed in the >10% SCA group, the formation of the fibrin network may be delayed or obstructed, possibly due to reduced or ineffective clotting factors typically associated with severe liver disease.

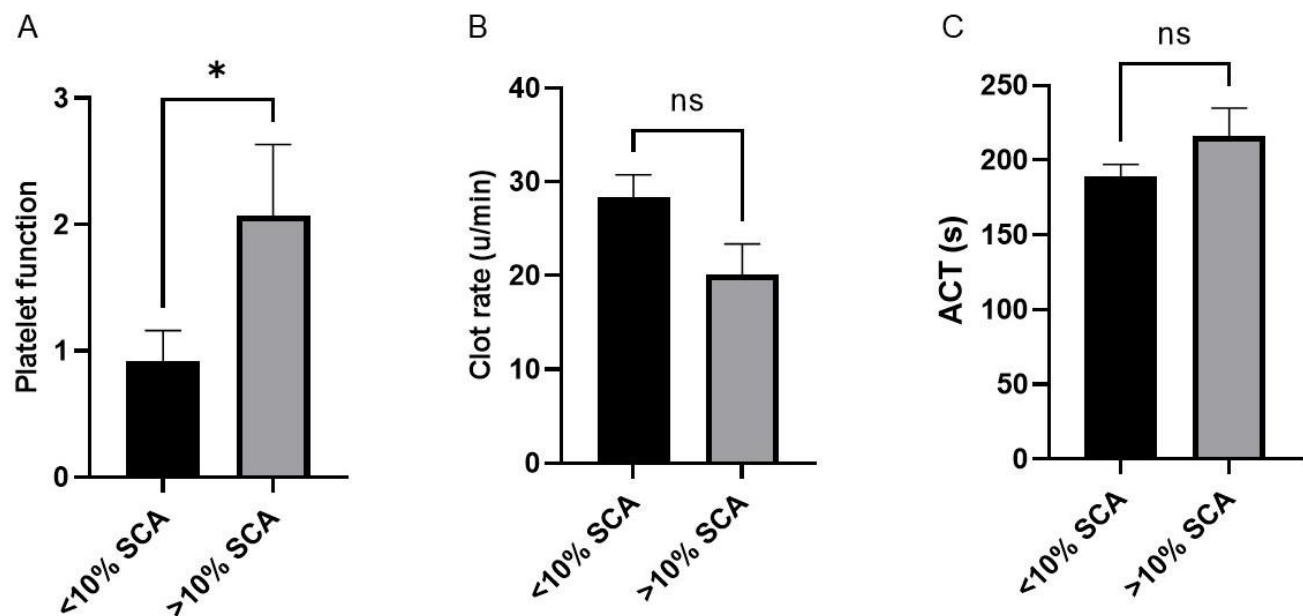


Figure 3. Graphical representation of Sonoclot assay parameters comparing group 1 (<10% spur cells, n=20) and group 2 (>10% spur cells, n=7) in patients with cirrhosis. Platelet function (A) is shown as a dimensionless unit reflecting the mechanical contribution of platelets to clot formation. Clot rate (B), measured in units per minute (u/min), indicates the speed of clot development. Activated clotting time ACT (C) is measured in seconds and represents the time to initial fibrin formation. ACT: Activated clotting time; ns: non-significant.

vWF is crucial in numerous vascular inflammatory processes, facilitating the recruitment of leukocytes and platelets to the inflamed area, altering vascular permeability and contributing to fibrin clot formation. These processes together contribute to the formation of microvascular obstruction & thrombotic microangiopathy (TMA), which has been associated with organ dysfunction in various settings (Gragnano *et al.*, 2017). In cirrhosis, elevated shear stress and endothelial activation frequently induced by systemic inflammation, may upregulate vWF expression and activity.

A recent study demonstrated that under shear stress, stressed erythrocytes interact fiercely with vWF through Annexin V and A1 domain of vWF to initiate the development of ultra-large vWF fibers (ULvWFs)/erythrocytes aggregates. These aggregates are implicated in the development of TMA and organ injury, including

renal dysfunction (Nicolay *et al.*, 2018). Interestingly, we found an increased expression of vWF near the portal tract, indicating that blood from the portal vein and hepatic artery struggled to navigate the sinusoidal network and reach the central vein leading to compromised hepatic perfusion. When we integrate these findings, we observe that group 2 patients—who had higher inflammation and greater spur cell burden probably faced more significant hepatic microvascular obstruction caused by cytokine induced endothelial activation and subsequent thrombosis.

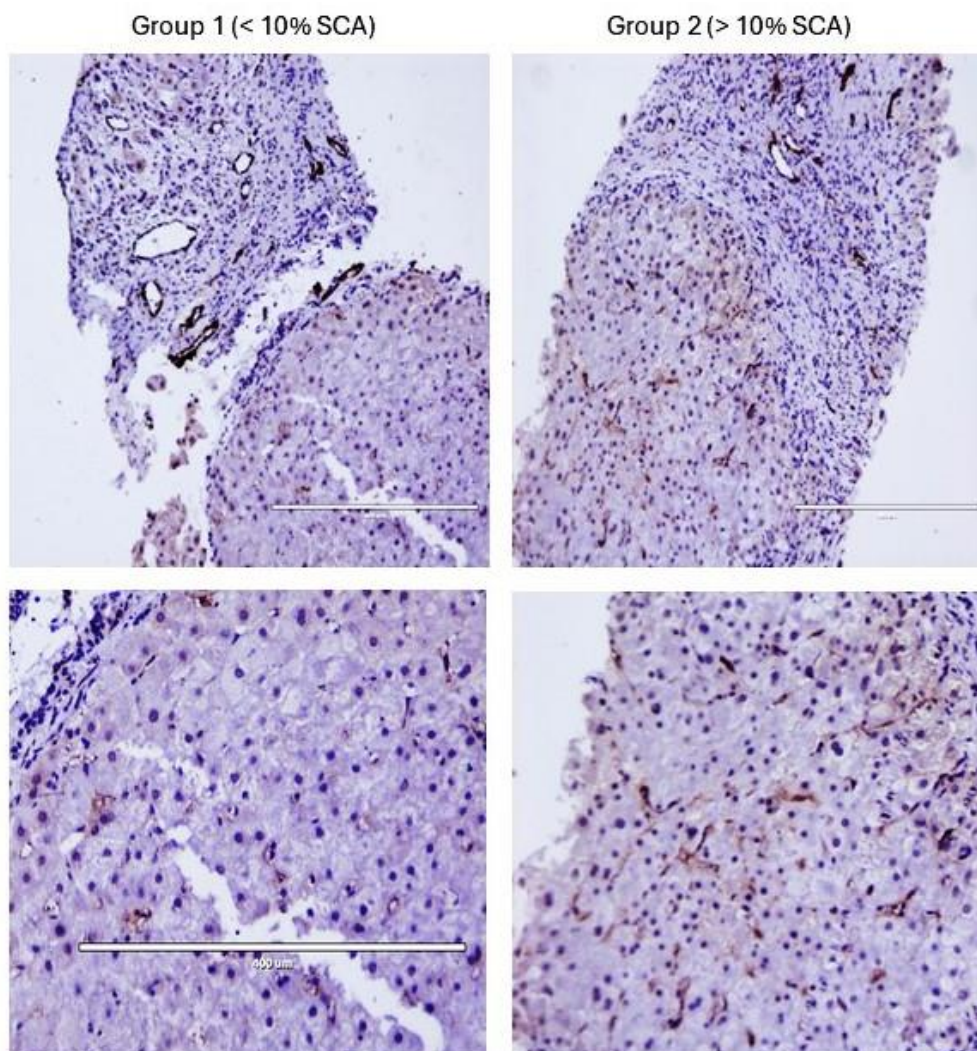


Figure 4. Immunohistochemical staining of cirrhotic liver tissue sections using an anti–von Willebrand factor (vWF) antibody. Increased vWF expression (brown staining) is observed in group 2 (>10% spur cells) compared to group 1 (<10% spur cells), indicating elevated endothelial activation. Hematoxylin was used as a counterstain to visualize cell nuclei (violet). The upper panel shows original images captured at a scale of 400 μm , while the lower panel presents magnified views of the boxed regions for detailed visualization.

Wannhoff *et al.* have previously reported that reduced platelet count or hematocrit and thrombocytopathy in patients with cirrhosis responsible for impaired primary hemostasis, which is partially compensated by increased vWF levels (Wannhoff *et al.*, 2014). Furthermore, vWF levels have a notable correlation with the severity of the disease and mortality in cases of decompensated cirrhosis (DC) and acute-on-

chronic liver failure (ACLF). In ACLF, VWF serves as a predictor for 30-day mortality with precision similar to that of conventional prognostic models (van den Boom *et al.*, 2023). As the severity of advanced chronic liver disease (ACLD) increases, the proportion of patients exhibiting significantly elevated vWF levels continues to rise. Although vWF levels do not indicate the hepatic venous pressure gradient (HVPG) in these individuals, they are associated with liver impairment and systemic inflammation. Notably, evaluating elevated values offers significant prognostic insights (Pomej *et al.*, 2022). vWF antigen (vWF-Ag) and its propeptide have been identified as effective markers for clinically relevant portal hypertension in compensated ACLD. Although no correlation was identified between ADAMTS13 activity and the severity of the disease, its reduction is linked with increased vWF procoagulant activity and adverse outcomes (Simbrunner *et al.*, 2023).

Based on these results, it is reasonable to conclude that increased levels of vWF contribute to thrombotic complications in SCA patients with cirrhosis. Although our research did not focus on treatment methods, the observed prothrombotic state suggests that anticoagulant options, like warfarin or low molecular weight heparin, might be worth investigating in subsequent studies.

D-dimer as a prognostic marker

In a retrospective analysis involving 132 individuals with HBV-related decompensated cirrhosis (HBV-DeCi), plasma D-dimer concentrations were significantly elevated in patients who did not survive compared to those who did survive within a one-month mortality timeframe (Zhou *et al.*, 2019). Elevated D-dimer has also emerged as an independent predictor for hepatorenal syndrome and adverse clinical outcomes in cirrhosis patients (Zhou *et al.*, 2024). Additionally, plasma D-dimer levels showed a positive correlation with Child-Pugh-Turcotte (CTP) scores and MELD scores in individuals with liver cirrhosis (Volkanovska *et al.*, 2023). In the context of HBV-DC, a higher D-dimer-to-platelet count ratio (DPR) was associated with a worse prognosis, suggesting its potential role as a prognostic biomarker (He & Ding, 2024).

Conclusion

In summary, our research emphasizes a clear association between elevated vWF and D-dimer levels with a prothrombotic and inflammatory state in patients with cirrhosis, especially those with >10% spur cells. D-dimer results may be not statistically significant but its biologically relevant and may serve as potential marker of subclinical thrombotic activity. The increased expression of vWF in liver endothelial cells indicate endothelial activation or dysfunction, which may lead to increased platelet adhesion, coagulation activation, and thrombotic events.

Despite thrombocytopenia in both groups, group 2 showed increased platelet function and reduced clot formation, indicating a possible imbalance between platelet activation and coagulation factor deficiency in advanced liver disease. These vascular alterations may not only worsen liver dysfunction but also contribute to extrahepatic complications such as renal impairment and worsened prognosis. Furthermore, the potential interaction between vWF and structurally abnormal erythrocytes (spur cells) raises the possibility of a role in thrombotic microangiopathy.

Collectively, these findings suggest a disturbed hemostatic environment in patients with high spur cell burden. However, given the observational nature and limited

sample size, further mechanistic and longitudinal studies are essential to validate these associations and explore whether modulating this prothrombotic state could offer clinical benefit.

Declarations

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Author Contribution: Deepika conceived of the idea or designed the study, conducted the research, analyzed the data, and wrote the manuscript.

Conflict of Interest: The author declare no conflict of interest.

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