

Original Article



# Comparison of the serum fibrinogen level and international normalized ratio in the assessment of gastrointestinal bleeding risk in decompensated cirrhosis

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## Abstract

**Introduction:** Gastrointestinal (GI) bleeding is one of the most severe complication of cirrhosis and its predicting is crucial for the management of cirrhotic patients. The current study aimed to assess the relationship between international normalized ratio (INR) and serum fibrinogen level and the risk of GI bleeding in patients with cirrhosis.

**Methods:** In the present cross-sectional study, 78 cirrhotic patients were enrolled. We assessed demographic, biochemical, and hematologic parameters in all patients. Underlying diseases and the etiology of cirrhosis were documented. The cirrhosis severity was assessed using Child-Pugh and the model for end-stage liver disease (MELD) scores. The history of bleeding episodes within 6 months before inclusion were recorded. A blood sample was drawn and fibrinogen and prothrombin time (PT) were measured and INR was calculated.

**Results:** The patients' mean age was 51.23±15.08 years and 40 (51.3%) were male. About 17 patients (21.7%) had a history of GI bleeding within 6 months before the study. The significant difference was detected between the two groups who experienced bleeding and who did not regarding the fibrinogen level ( $P < 0.05$ ). The fibrinogen level of more than 182.5 could significantly predict the bleeding risk in cirrhotic patients (AUC: 0.87) with the sensitivity of 77%, and specificity of 94%.

**Conclusion:** According to the results, the fibrinogen level is a better predictor of bleeding in patients with liver cirrhosis compared with INR.

## Introduction

Cirrhosis is defined as a final stage of chronic liver disease and is described by advanced fibrosis and distortion of hepatic architecture.<sup>1</sup> Patients with cirrhosis are at increased risk of a variety of complications such as jaundice, ascites, hepatic encephalopathy, hepatorenal syndrome, and variceal hemorrhage.<sup>1</sup> Coagulopathy is another complication of cirrhosis that is related with increased risk of bleeding in these patients.<sup>2</sup>

The most common and serious site of bleeding is the gastrointestinal (GI) tract including gastroesophageal varices and portal hypertensive gastropathy.<sup>3</sup> The mortality rate related to GI bleeding due to variceal bleeding is about 30%.<sup>4</sup> Hemostasis and coagulation abnormalities in chronic liver disease are identified based on routine coagulation parameters such as international normalized ratio (INR), fibrinogen, the activated partial thromboplastin time (aPTT), and platelet.<sup>5</sup>

Previous studies showed that bleeding and clot tendency are not well measured by the conventional prothrombin

time (PT) or the related INR.<sup>2</sup> PT is revealed the procoagulant activity but not the anticoagulant activity.<sup>2</sup> Therefore, routine laboratory tests mislead clinicians and correcting the INR or the PT alone prompt to unnecessary volume expansion and especially overuse of plasma, worsening portal hypertension, and then unintended complications such as bleeding.<sup>2,6,7</sup>

Recent studies demonstrated a close relationship between the severity of cirrhosis and hemostatic changes such as hypofibrinogenemia.<sup>6</sup> However, it is uncertain whether reversal of hypofibrinogenemia decreases the bleeding risk in cirrhotic patients especially the risk of bleeding following invasive procedures.<sup>6,8,9</sup> Some studies aimed to assess the association between fibrinogen level and bleeding risk in cirrhotic patients and reported conflicting results.<sup>3,6,9</sup>

Considering the importance of accurate determination of the bleeding risk in cirrhotic patients and lack of studies in this regard, we aimed to investigate the relationship between INR and plasma fibrinogen level and the GI

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bleeding risk in patients with cirrhosis.

## Methods

This cross-sectional study included 78 patients with cirrhosis from Imam Reza hospital of the Tabriz University of Medical Science. The patients were included if they aged 18-80 years with the B or C Child-Pugh score. The Patients who had malignancies, nephrotic syndrome or renal insufficiency, infections, chronic inflammatory diseases, known coagulation disorders, or using anticoagulant or anti-platelet drugs or if they experienced bleeding within one month before enrolling study were excluded.

We assessed demographic (age, gender), biochemical (serum bilirubin, serum albumin, serum creatinine, INR), and hematologic (platelet count) parameters in all patients. Moreover, the underlying diseases were assessed and documented. The severity of cirrhosis was defined based on the Child-Pugh and the model for end-stage liver disease (MELD) scores. Patients were asked for the history of bleeding event within 6 months before being included in the study.

Bleeding was defined as episodes of GI tract bleeding such as gastroesophageal varices or other lesions like esophagitis, peptic ulcer disease, and Mallory-Weiss tears.<sup>3</sup>

About 5 mL of blood was drawn for the determination of fibrinogen and other biochemical tests. The fibrinogen and PT were measured by the coagulation method using Fibriprest-2, supplied by Diagnostica Stago, France.

INR was calculated using the raising prothrombin time ratio (PTR) which is the ratio of plasma level of PT and the mean normal PT to the power of the international sensitivity index.

## Statistical analysis

Data analysis was conducted by Statistical Package for Social Science (SPSS) software version 21.0, and STATA 16. Continuous data were presented as mean and standard deviation and the categorical and nominal data were reported as number and percentages.

Receiver operating characteristic (ROC) curve was used to identify the diagnostic value of studied parameters for bleeding. The specificity, sensitivity, and the best cut-off

value for fibrinogen in predicting the risk of GI bleeding were obtained after adjusting for the platelet level. A *P* value of less than 0.05 was considered significant.

## Results

A total of 78 cirrhotic patients with the mean age of 51.23±15.08 were enrolled in this study. About 51% of patients were male and 67% had the Child-Pugh class B. Other demographic and clinical characteristics are shown in Table 1.

Table 2 reports the biochemical, hematological, and coagulation indices stratified according to the history of bleeding. As can be seen, in the patients with bleeding history, the fibrinogen (159.65 mg/dL vs. 242 mg/dL, *P* = 0.001), and platelet count ( $85.67 \times 10^3$  vs.  $103.61 \times 10^3$ , *P* =

**Table 1.** Patients' demographic and clinical characteristics

Variables	Value
Gender n (%)	
Male	40 (51.3%)
Female	38 (48.7%)
Age (mean ± SD)	51.23±15.08
Albumin (g/dL) (mean ± SD)	3.1±0.63
Bilirubin (mg/dL) (mean ± SD)	2.09±1.12
Creatinine (mg/dL) (mean ± SD)	1.04±0.23
MELD score (mean ± SD)	13.55±4.36
Child-Pugh, No. (%)	
Class B	53 (67%)
Class C	25 (32%)
Etiology of cirrhosis n (%)	
Cryptogenic	28 (35.9%)
Hepatitis B	23 (29.5%)
Hepatitis C	3 (3.8%)
NASH	4 (5.1%)
Autoimmune	18 (23.1%)
Primary biliary cholangitis	2 (2.6%)
Platelet (n*10 <sup>3</sup> )	96±32.62
INR (mean ± SD)	1.38±0.32
Fibrinogen (mg/dL) (mean ± SD)	209.65±77.39

MELD: model for end-stage liver disease; INR: international normalized ratio; NASH: non-alcoholic steatohepatitis.

**Table 2.** Main biochemical, hematological, and coagulation parameters of patients

Variables	Patients with a history of bleeding (17)	Patients without a history of bleeding (61)	<i>P</i> -value*
INR (Mean±SD)	1.46±0.33	1.33±0.29	0.07
Fibrinogen (mg/dl) (Mean±SD)	159.65±35.13	242.64±80.15	0.001
Platelet (n*10 <sup>3</sup> ) (Mean±SD)	85.67±22.7	103.61±36.25	0.01
MELD score (Mean±SD)	14.90±4.20	12.66±4.27	0.02
Child-Pugh n (%)			
Class B	12 (70.6%)	41 (67.2%)	
Class C	50 (29.4%)	20 (32.8%)	

MELD: Model for End-stage Live Disease. INR: International Normalised Ratio. Hep B: B hepatitis, PBC: Primary Biliary Cholangitis, NASH: Non-Alcoholic Steatohepatitis.

\*Independent t-test

0.01) were significantly lower compared with patients with no bleeding history. There were no significant differences between groups regarding INR values (1.46 vs. 1.33,  $P = 0.07$ ).

Figure 1 explains the ROC curve analysis of fibrinogen (A), INR (B), and fibrinogen + INR (C) in predicting bleeding in cirrhotic patients after adjusting for platelet as a confounding variable. As evidenced, fibrinogen (0.87 [95% CI: 0.78, 0.97]) and INR + fibrinogen (0.90 [95% CI: 0.83, 0.97]) had higher AUC compared with INR (0.55 [CI: 0.41, 0.70]) in predicting bleeding in cirrhotic patients.

A fibrinogen level of 182.5 mg/dL had a sensitivity of 77% and a specificity of 94% for prediction of bleeding in the cirrhotic patient

## Discussion

Bleeding is one of the most severe complications of liver cirrhosis that mostly occurs in the GI tract.<sup>10</sup> Routine laboratory tests are misleading the clinicians to assess bleeding risk in these patients.<sup>1,2</sup> So this study was aimed

to assess the predictive value of coagulation indexes for predicting bleeding in patients with cirrhosis. Our result indicated that fibrinogen had significantly more AUC compared with INR in predicting bleeding risk in these patients and INR value was not associated with bleeding in cirrhotic patients. This finding is in line with the result of some of the previous studies. Horvatits et al showed that low fibrinogen and platelet counts were the strong predictors of major bleeding during the ICU stay in cirrhotic patients.<sup>11</sup> However, INR was not significantly associated with bleeding risk in cirrhotic patients. In addition, Giannini et al showed that the cirrhotic patients with the lower level of fibrinogen were at higher threat of bleeding after prophylactic EVBL.<sup>9</sup> The researchers reported that fibrinogen level of 179 mg/dL or less had a sensitivity and specificity of 83.3% and 73%, respectively. In accordance with the finding of this study, we also showed that the fibrinogen level of 182.5 had a sensitivity of 77% and specificity of 94% in predicting bleeding in cirrhotic patients. In another study, Siddiqui et al showed a significant relationship between low fibrinogen level and the risk of GI bleeding in cirrhotic patients.<sup>12</sup>

However, a previous study did not show a significant difference in fibrinogen level between cirrhotic patients who had bleeding and that of patients without bleeding.<sup>3</sup> The discrepancies between different studies may be due to the differences in the disease stages or etiology of cirrhosis (we excluded the alcoholic liver disease).

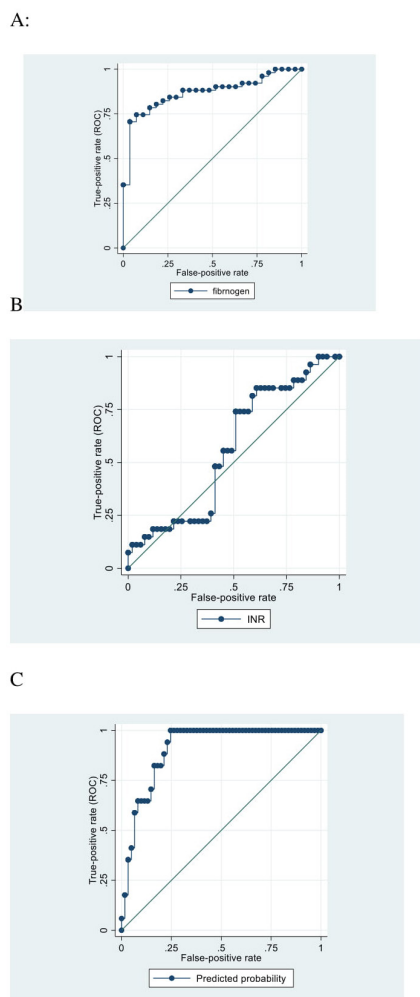
The negative association between the fibrinogen level and bleeding risk in cirrhotic patients may be due to the fact that fibrinogen is considered as an important mediator of platelet aggregation.<sup>3</sup>

We also found that there was no association between the INR level and bleeding risk in cirrhotic patients. Tripodi et al in a review study indicated compared with patients with abnormal INR, cirrhotic patients with near-normal INR were more susceptible for bleeding.<sup>13</sup> The observed no association between INR level and bleeding risk in cirrhotic patients is maybe owing to that the patients with the end-stage-liver disease suffer both from procoagulant and anticoagulant deficiency and INR can only reflect the procoagulant activity.<sup>14</sup>

Our study suffers from some limitations such as the cross-sectional study design and the small number of patients who had bleeding.

## Conclusion

Our results indicated the significant lower level of fibrinogen in cirrhotic patients who experienced GI bleeding compared with those who did not have bleeding history. Moreover, the fibrinogen level was a better predictor of bleeding in cirrhotic patients than INR. However, considering the limitations of the study, cohort investigations are needed with a higher sample size to approve these preliminary results.



**Figure 1.** Receiver operating characteristic curve of fibrinogen (A), INR (B), and fibrinogen +INR (C) according to bleeding after adjusting for platelet count as a confounding variable.

## Study Highlights

### What is current knowledge?

- GI bleeding is the most life-threatening complication of cirrhosis and its predicting is crucial for the management of cirrhotic patients.
- Routine laboratory tests such as International normalized ratio (INR) mislead clinicians for assessing coagulation status of cirrhotic patients
- Considering that bleeding and clot tendency is not well measured with INR, it is necessary to consider other coagulation parameters to assess bleeding tendency in cirrhotic patients.

### What is new here?

- The fibrinogen level was significantly lower in cirrhotic patients who experienced bleeding compared with that of those who did not experience
- The fibrinogen was a better predictor of bleeding in cirrhotic patients than INR
- The fibrinogen level of 182.5 had a sensitivity of 77% and specificity of 94% in predicting bleeding in cirrhotic patients

## Conflict of Interest

The authors declare no competing interest.

## Ethical Approval

The protocol of the current research was accepted by the Ethics Committee of Tabriz University of Medical Sciences (IR.TBZMED.REC.1398.930) and the patients gave a written informed consent.

## Authors' Contribution

MHS, MFD, and LA were responsible for the conception and design of the study. SA and AR were responsible for data acquisition. ZN was responsible for data analysis. ZN, LA, SA were responsible for data interpretation. SA and ZN drafted the manuscript; all other authors revised and commented on the draft. All authors read and approved the final version of the manuscript.

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