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Original article

Hyperfibrinolysis and the risk of hemorrhage in stable cirrhotic patients

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Background: Bleeding is an important complication of cirrhosis. Currently, there is no coagulation test that can reliably predict clinical hemorrhage. However, previous studies demonstrated significant correlations between hyperfibrinolysis and following bleeding in advanced cirrhotic patients.

Objectives: Estimate the prevalence of hyperfibrinolysis in cirrhotic patients at stable conditions and to assess its role in predicting subsequent hemorrhage.

Methods: The prospective cohort study included 58 consecutive cirrhotic patients at the Liver Clinic, Chulalongkorn Hospital. Assays for liver functions, PT, APTT, fibrinogen, fibrin degradation products (FDPs) and euglobulin lysis time (ELT) were performed at baseline. The subjects were followed-up for 10 months to observe clinical hemorrhage and survival.

Results: The mean age was 56.4 years and 47% were male. The etiologies of liver diseases were virus (62.1%), alcohol (24.1%) or unknown (8.6%). Hyperfibrinolysis as reflected by ELT<120 minutes or FDPs>10 μg/mL was present in 32.8% and 74.1%, respectively. Fibrinolytic activity was significantly correlated with platelet counts and coagulation times, but not as much with liver function tests. By 10 months, 13 cases (22.4%) showed hemorrhagic episodes and 7 (12.1%) were expired, including 2 from bleeding. The significant predictors for death were Child class B or C, presence of ascites, hyperbilirubinemia, hypoalbuminemia, and prolonged APTT. However, none of the clinical, biochemical, or hemostatic factors was associated with clinical bleeding.

Conclusion: Hyperfibrinolysis is common in cirrhotic outpatients. However, it cannot predict subsequent hemorrhage or survival. Novel hemostatic tests are required to assess the probability of bleeding in this disorder.

Keywords: Bleeding, cirrhosis, euglobulin lysis time, hyperfibrinolysis, survival

Hemorrhagic events are common in patients with cirrhosis. The mechanisms comprise both local gastrointestinal lesions and systemic bleeding tendency. Hemorrhagic diathesis in chronic liver diseases is characterized by the combination of multiple components. These include 1) thrombocytopenia from splenomegaly and thrombopoietin deficiency, 2) coagulation factor deficiency from synthetic failure, 3) consumptive coagulopathy from reduced synthesis of natural anticoagulants and decreased activated clotting factor elimination and 4) enhanced fibrinolysis from decreased tissue plasminogen activator (t-PA) clearance [1-4] and low levels of thrombin-activatable fibrinolysis inhibitor [5, 6]. High fibrin degradation products (FDPs) from fibrinolysis can interfere with platelet functions and fibrin polymerization aggravating bleeding symptoms.

Although the pathogenesis is seemingly well-known, the associations of available hemostatic test results and clinical bleeding in cirrhotic patients are controversial [7, 8] Conflicting positive and negative data have been reported. Interestingly, hyperfibrinolysis, as defined by markedly shortened clot lysis time and/or elevated FDPs or D-dimer, has been found to predict subsequent clinical

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hemorrhage. Violi et al. [9] found a relationship between hyperfibrinolysis (FDPs over 10 μg/mL) and fatal bleeding. This association has been confirmed in subsequent single-center [10] and multicenter [11] studies suggesting that hyperfibrinolysis was a strong risk factors for gastrointestinal bleeding in advanced cirrhosis. Furthermore, the shortened euglobulin lysis time (less than 120 minutes) was found in up to 36% of hospitalized cirrhotic patients and showed the associations with hepatic decompensation and mucocutaneous hemorrhage [12].

Nevertheless, the data on less advanced cirrhotic patients in outpatient clinics are still lacking. Currently, prophylactic endoscopic measures to prevent first and recurrent variceal bleeding are frequently applied. Bleeding may largely depend on systemic diathesis as esophageal varices become less common. This study was undertaken to investigate the prevalence of hyperfibrinolysis in cirrhosis at stable condition, and to assess the roles of fibrinolysis, as well as other coagulation tests, in predicting subsequent hemorrhage and survival.

Materials and methods

This is a prospective cohort observational study. The inclusion criteria were cirrhotic patients who attended the outpatient Liver Clinic, Division of Gastroenterology, Department of Medicine, King Chulalongkorn Memorial Hospital between February and May 2006. Cirrhosis was diagnosed by hepatic ultrasonography or liver biopsy. Exclusion criteria were known hepatocellular carcinoma or other active cancers, vitamin K or blood product infusion within 1 week, uses of anti-platelets and/or anticoagulants, platelet count lower than $50x10^9$/L, active bleeding, use of tranexamic acid within two weeks, and patients with active infection.

All patients were evaluated by history taking and physical examinations. After informed consent, blood samples were taken for laboratory tests at baseline. They included complete blood count (CBC), liver function tests, prothrombin time (PT), partial thromboplastin time (PTT), euglobulin lysis time (ELT), fibrinogen and FDPs. The time of blood draws was between one and three p.m. because it was the clinic time. For the coagulation tests, blood was anti-coagulated in 3.2% buffered citrate, centrifuged within one hour, and plasma was stored in -70°C until tests. ELT was performed according to Copley et al. [13]. FDPs were measured by a semi-quantitative latex agglutination method using monoclonal antibody (Dade Behring, Marburg, Germany). Blood for FDP tests was put in the special tube containing *Bothrops atrox* venom provided by the manufacturer. The definition of hyperfibrinolysis was the complete euglobulin dissolution before 120 minutes. The normal values for ELT in our laboratory were more than 90 minutes for initial lysis and over 240 minutes for complete lysis.

Patients were followed for clinical bleeding and death from all causes at two, four, six and 10 months after initial evaluation. The ELTs were repeated when the patients had clinical bleeding when available.

For descriptive purposes, data were expressed as means and standard deviations (SD). Student's t-test was used to compare the numerical data between groups. Chi square test was used for the comparisons of categorical data. Pearson correlation coefficients were utilized to examine data correlation. A value of $p < 0.05$ was considered as significant. All statistical calculations were performed using the SPSS 16.0 for window software.

Results

Baseline characteristics

Fifty-five consecutive patients were included in the cohort during the study period. The mean age was 56.4±13.1, ranging from 24-84 years. Twenty-seven (46.6%) of them were male. The etiologies of liver diseases were viral hepatitis B (34.5%), viral hepatitis C (27.6%), alcohol (24.1%), and unknown (8.6%). Two patients with autoimmune hepatitis and one patient with primary biliary cirrhosis were included. The distribution of Child-Pugh class was 40 (68.9%), 15 (25.9%), and three (5.2%) for class A, B, and C, respectively. Eleven (19.0%) of them exhibited ascites detectable on physical examinations.

The baseline laboratory values were displayed in **Table 1**. Each liver function was abnormal in approximately half of the cases. Fibrinolytic activations were the most common hemostatic abnormalities (high FDPs and/or shortened ELT), followed by thrombocytopenia, prolonged PT, hypofibrinogenemia, and prolonged activated partial thromboplastin time (APTT), respectively. Hyperfibrinolysis, defined as markedly shortened ELT and elevated FDPs, was present in 32.8% and 74.1% of the patients, respectively. All cases with ELT below 120 showed FDP of 10 μg/mL or greater.

Table 1. Baseline laboratory data (n=58).

Laboratory tests	Mean ± SD (Normal range)	Cases with abnormalities (%)
Liver function tests		
Total bilirubin (mg/dL)	1.92 ± 1.61 (0.2-1.7)	24 (41.4%)
Albumin (g/dL)	3.45 ± 0.55 (3.5-5.4)	30 (51.7%)
AST (U/L)	15.0 ± 49.6 (10-40)	37 (63.8%)
ALT (U/L)	52.9 ± 44.0 (10-40)	28 (48.3%)
Hemostatic tests		
Platelet count (10^9/L)	105 ± 45 (150-450)	49 (84.5%)
PT (INR)	1.18 ± 1.14 (0.9-1.2)	23 (39.7%)
APTT ratio	1.10 ± 0.13 (0.88-1.24)	9 (15.5%)
Fibrinogen (g/L)	2.31 ± 0.66 (1.7-4.5)	10 (17.2%)
ELT initial (minute)	84.0 ± 41.3 (>90)	37 (63.8%)
ELT complete (minute)	166.5 ± 63.3 (>240)	49 (84.5%)
FDP (μg/mL)	26.6 ± 17.8 (0-5)	54 (93.1%)
Hyperfibrinolysis		
ELT <120 minutes		19 (32.8%)
FDP >10 μg/mL		43 (74.1%)

Correlations of fibrinolysis and clinical, coagulation and biochemical variables

Cases with hyperfibrinolysis, as defined by ELT less than 120 minutes, showed significantly longer PT ($p<0.001$), longer APTT ($p=0.002$), lower platelet counts ($p=0.001$) and lower albumin levels ($p=0.048$). There were more child B and C patients who displayed hyperfibrinolysis compared with child A (44.4% *vs.* 27.5% respectively), but the difference was not statistically significant ($p=0.203$). There was no difference in hyperfibrinolysis in the presence vs. absence of ascites on physical examinations (27.3% *vs.* 34.0%, respectively). In contrast, none of these showed statistical difference, if the hyperfibrinolysis was defined by FDPs over 10 μg/mL.

The correlation coefficients of coagulation, fibrinolytic and biochemical variables were displayed in **Table 2**. There were significant correlations between coagulation values and platelet counts with ELTs. However, the associations with FDP levels were not evident. Fibrinolytic activities were poorly correlated with liver functions except for bilirubin, while coagulation times (PT and APTT), fibrinogen levels, and platelet counts were correlated with liver functions.

Predictors for death and bleeding

During the 10-month follow-up time, 13 cases (22.4%) suffered from hemorrhagic episodes and 7 patients (12.1%) expired. The sites of bleeding and causes of death categorized according to hyperfibrinolytic states were shown in **Table 3**.

Eight bleeding patients had available repeated ELT on the hemorrhagic episodes and three of them (37.5%) showed hyperfibrinolysis. The presence or absence of hyperfibrinolysis was consistent in seven out of eight cases. In the remaining case, ELT changed from 280 to 115 minutes, and he had mucosal bleeding. In these eight cases, the mean ELTs were shortened from 189 ± 62 at baseline to 137 ± 57 minutes at the time of bleeding. This difference was statistically significant ($p=0.021$, Wilcoxon signed rank test).

Using univariate analysis, none of the clinical, hemostatic, fibrinolytic or biochemical variables could predict clinical bleeding (**Table 4**). On the other hand, child class B or C, presence of ascites, prolonged APTT, total bilirubin over 2.0 mg/dL and low albumin levels were significantly associated with poor survival (**Table 5**), while hyperfibrinolysis was not associated with clinical bleeding or fatal outcomes.

Table 2. Correlation coefficients among laboratory values.

	ELTinitial	ELTcomplete	FDPs	PlateletCount	PT-INR	APTT	Fibrinogen	Bilirubin	Albumin	AST
ELT complete	+0.450***									
FDPs	-0.443***	-0.202								
Platelet count	+0.066	+0.325***	+0.137							
PT-INR	-0.203	-0.492***	+0.137	-0.420***						
APTT	-0.244	-0.317*	+0.057	-0.280*	+0.658***					
Fibrinogen	+0.308*	+0.239	-0.115	+0.465***	-0.420**	-0.475***				
Bilirubin	-0.005	-0.269*	+0.301*	-0.242	+0.522***	+0.484***	-0.528***			
Albumin	+0.066	-0.243	-0.047	+0.318*	+0.572***	-0.437**	+0.370**	-0.522***		
AST	-0.104	-0.096	+0.082	+0.361**	+0.207	+0.361**	-0.467***	+0.227	-0.221	
ALT	-0.097	+0.034	-0.017	-0.182	+0.011	+0.267*	-0.427**	+0.077	-0.010	+0.885***

*p <0.05, **p <0.01, ***p <0.00

Table 3. Bleeding and death at 10 month.

	Hyperfibrinolysis (n=19)	Without hyperfibrinolysis (n=39)
Bleeding (n=13)	4 (21.1%)	9 (23.1%)
Mucocutaneous bleeding	3	5
Bleeding per wound	-	1
Gastrointestinal bleeding	1	2
Bleeding hepatoma	-	1
Death (n=7)	3 (15.8%)	4 (10.3%)
Sepsis	2	2
Liver failure	1	-
Gastrointestinal bleeding	-	1
Bleeding hepatoma	-	1

Table 4. Associations of clinical and laboratory variables and bleeding.

Variables	Bleeding (n=13)	Relative risks (95% Confident interval)	P-value
Child class			
A	7/40 (17.5%)		
B+C	6/18 (33.3%)	1.90 (0.75-4.85)	0.181
Ascites			
No ascites	11/47 (23.4%)		
Ascites	2/11 (18.2%)	0.78 (0.20-3.01)	0.708
PT (INR)			
≤1.2	6/35 (17.1%)		
>1.2	7/23 (30.4%)	1.78 (0.68-4.61)	0.235
PTT			
≤1.24	10/49 (20.4%)		
>1.24	3/9 (33.3%)	1.63 (0.56-4.78)	0.393
Fibrinogen			
≥1.7 g/L	11/48 (22.9%)		
<1.7 g/L	2/10 (20.0%)	0.87 (0.23-3.34)	0.841
ELT			
> 120 minutes	9/39 (23.1%)		
≤ 120 minutes	4/19 (21.1%)	0.91 (0.32-2.58)	0.862
FDP			
≤10 μg/mL	4/15 (26.7%)		
>10 μg/mL	9/46 (20.9%)	0.78 (0.28-2.18)	0.646
Platelet count			
≥100 x10^9/L	7/28 (25.0%)		
<100 x10^9/L	6/30 (20.0%)	0.80 (0.31-2.09)	0.648
Total billirubin			
≤2.0 mg/dL	7/41 (17.1%)		
>2.0 mg/dL	6/17 (35.3%)	2.07 (0.81-5.26)	0.130
Albumin			
≥3.5 g/dL	6/28 (21.4%)		
<3.5 g/dL	7/30 (23.3%)	1.09 (0.42-2.85)	0.862

Table 5. Associations of clinical and laboratory variables and survival.

Variables	Death within 10 months (n=7)	Relative risk (95% Confident interval)	P-values
Child class			
A	2/40 (5.0%)		
B+C	5/18 (27.8%)	5.55 (1.19-26.32)	0.014
Ascites			
No ascites	3/47 (6.4%)		
Ascites	4/11 (36.4%)	5.68 (1.48-21.74)	0.006
PT (INR)			
≤1.2	3/35 (8.6%)		
>1.2	4/23 (17.4%)	2.03 (0.50-8.26)	0.313
APTT ratio			
≤1.24	4/49 (8.2%)		
>1.24	3/9 (33.3%)	4.08 (1.09-15.15)	0.033
Platelet count			
≥100 x10^9/L	2/28 (7.1%)		
<100 x10^9/L	5/30 (16.7%)	2.33 (0.49-11.11)	0.266
ELT			
> 120 minute	4/39 (10.3%)		
≤ 120 minute	3/19 (15.8%)	1.54 (0.38-6.21)	0.544
FDP			
≤ 10 μg/mL	1/15 (6.7%)		
> 10 μg/mL	6/43 (14%)	2.09 (0.27-15.87)	0.456
Total bilirubin			
≤2.0 mg/dL	2/41 (4.9%)		
>2.0 mg/dL	5/17 (29.4%)	6.02 (1.29-27.78)	0.009
Albumin			
≥ 3.5 g/dL	0/28 (0.0%)		
<3.5 g/dL	7/30 (23.3%)	NA*	0.006

*Not available because it could not be calculated.

Discussion

Most of the patients in this series showed some degrees of fibrinolytic system activation. Remarkably, almost all cases had elevated FDPs. The frequency of hyperfibrinolysis (32.8%) is comparable to previous series with more advanced liver diseases admitted in the hospital [12]. The prevalence is even higher if FDP levels are used as a cut-off point. The data suggest that hyperfibrinolysis is common even in less advanced cirrhosis. Although prior investigations indicated that ascites might be the source of hyperfibrinolysis in plasma [14, 15], our study could not demonstrate the association of laboratory fibrinolysis, and the physical signs of ascites. There is also no association between hyperfibrinolysis and the etiologies of cirrhosis (data not shown).

This study intended to evaluate the prognostication of patients with cirrhosis using relatively simple and clinically available hemostatic tests. Analysis of correlation coefficients suggests that coagulation times are better correlated with liver functions than fibrinolytic tests. One possible explanation is that coagulation time prolongation reflects only impaired synthesis of clotting factors, while a fibrinolytic test comprises the delicate balance between profibrinolytic and antifibrinolytic components. Several studies demonstrated that t-PA is universally elevated in cirrhosis, but its inhibitor, plasminogen activator inhibitor-1 (PAI-1), levels are variable. PAI-1 may be unchanged, reduced, or elevated [3, 16, 17]. This partly depends on the deterioration of liver functions and the acute phase reactions that can decrease [18] and increase [19] the PAI-1 levels, respectively. Furthermore, the fibrinolytic tests have been well-known for their variability including the diurnal variation.[20] Therefore, this study has limited the

venepuncture time to a fixed period. In addition, there are fibrinolytic activity variations affected by several factors, for examples, age, sex, diet, exercise, and medications [20]. These made fibrinolytic tests difficult to be standardized and, thus, probably less useful in routine clinical practice.

Our data confirmed that Child-Pugh class, as well as its components (albumin, bilirubin and presence of ascites), is strongly correlated with survival in cirrhosis consistent with the extensive systematic review of previous studies [21]. Interestingly, among all the hemostatic tests, we found that only prolonged APTT was a significant risk factor of death. In our series, APTT was less commonly prolonged than PT and all prolonged APTT cases also had prolonged PT. These APTT abnormalities might indicate the further decline of liver ability to produce clotting factors in the common and intrinsic pathways because the fibrinogen level was not predictive for survival. We propose that most, if not all, current hemostatic tests in cirrhosis may just be indicators of liver damages and do not directly signify hemostatic functions. Although some of abnormal tests were more commonly found in cases with bleeding, the differences were not significant (**Table 4**). This may partly due to the small sample size of the study.

In contrast to previously published reports [9-12], hyperfibrinolysis could not predict the hemorrhagic episodes in our study. Of note, bleeding rate in our series was relatively low, probably due to less advanced cirrhosis and the routine prophylactic endoscopic ligation of esophageal varices. One of eight who had second tests months later exhibited temporal variation in fibrinolysis. He developed hyperfibrinolysis, as well as mucosal bleeding, few months after entering the study. In addition, the mean ELT at hemorrhagic episodes was significantly shorter than that of the baseline. These observations might suggest a possible association of fibrinolysis and bleeding or only a sign of progressively impaired hepatic functions. Nevertheless, this challenges the values of single test and the predictive roles of serial assays over time remained to be determined.

Conclusion

We could not identify the clinical and laboratory variables that were associated with hemorrhage in cirrhosis. The inability of all current hemostatic tests to reliably predict bleeding in cirrhosis may reflect the complex mechanisms of this phenomenon. Novel laboratory assays that integrate all hemostatic aspects showed promising roles in some studies [22, 23].These 'global tests' still need standardization, and future clinical investigations to correlate with bleeding are required.

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