Thromboelastography for Assessing the Risk of Bleeding in Patients With Cirrhosis—Moving Closer

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Background and aims: Conventional coagulation tests (CCTs) in patients with cirrhosis only assess procoagulant factors and are poor predictors of bleeding risk. In spite of this knowledge, they are routinely used prior to invasive procedures, and attempts are made to correct these abnormalities before invasive procedures. These practices are not supported by the evidence and are harmful to the patients. **Methods:** This prospective study included 150 patients of cirrhosis undergoing invasive procedures. CCTs [bleeding time (BT), clotting time (CT), international normalized ratio (INR), activated partial thromboplastin time (aPTT) and platelet count], thromboplastin generation time (TGT) and thromboelastography (TEG) were done in all patients, and they were observed for post procedural bleeding. None of the patients received prophylactic transfusion before the procedure. **Results:** BT, CT and TGT were normal in all 150 patients. One of 150 patients developed clinically significant post procedural bleeding. No statistically significant association was seen among INR, aPTT, platelet count and Child class with bleeding. TEG values (R time and MA value) were normal in 61% and 75% patients respectively in spite of abnormal CCTs in most of them. Comparison of abnormal TEG values (R time and MA value) with INR and platelet count, respectively, in patients with no bleeding showed a statistically significant lower percentage of abnormal values of R time and MA value compared to INR and platelet count. **Conclusion:** Abnormal CCTs in patients of cirrhosis do not predict bleeding risk. TEG may be useful in patients undergoing invasive procedures to assess bleeding risk and prevents erroneous prophylactic transfusions. (J CLIN EXP HEPATOL 2017;7:284–289)

Coagulation cascade in patients with cirrhosis is delicately balanced between deficiency of anti and procoagulant factors. Conventional coagulation tests (CCTs) which includes, prothrombin time and international normalized ratio (PT/INR), activated partial thromboplastin time (aPTT) and platelet count only assess procoagulant factors and are poor predictors of bleeding risk. In spite of this knowledge, they are routinely used prior to invasive procedures, and attempts are made to correct these abnormalities before invasive procedures. These practices are not supported by the evidence, and they are also harmful to the patients.

A recent work on coagulation in liver disease has led to a paradigm shift in our understanding, and we have this modern concept of rebalanced haemostasis in patients with liver disease; in this state, abnormalities in prohemostatic drivers are compensated for by commensurate changes in antihemostatic drivers.^{1,2} However, patients

with liver disease maintain a more fragile balance of haemostasis than normal subjects due to deficiencies in both prohemostatic and antihemostatic drivers, as well as the presence of other conditions that commonly accompany liver failure, such as renal failure, infection, and endothelial dysfunction.

This clearly suggests that standard laboratory tests of haemostasis such as aPTT, INR and platelet count do not adequately assess this state of rebalance, and more global assays may be very informative. PT INR and aPTT can tell us whether a patient is deficient in one (or more) procoagulant, but not whether this deficiency is counterbalanced by a concomitant deficiency of the anti-coagulants.

Plasma coagulation is not abnormal in cirrhosis when assessed with global tests reflecting the function of both pro- and anti-coagulants. When patients are assessed by means of global tests such as the thrombin generation test (TGT), the results do not show hypocoagulability.^{3,4} The usefulness of CCTs in assessing hemorrhagic risk in cirrhosis and use of procoagulant agents to correct the coagulopathy is in question as it has been known that efficacy of activated FVII to stop bleeding in cirrhosis is poor. CCTs results are poorly correlated with the onset and duration of bleeding after liver biopsy or other potentially hemorrhagic procedures.⁵

For judging the risk of bleeding, we need tests for global evaluation of coagulation-like thromboelastography (TEG), sonorheometry, and INR calibrated for cirrhosis of liver. TEG measures clot formation, clot strength, and

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Abbreviations: BT: bleeding time; CT: clotting time; TGT: thromboplastin generation time

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clot dissolution but does not measure vascular tone. It accesses global haemostasis. The modern TEG, which combines new computer technology with new materials and equipment, is popular during surgical interventions such as liver transplantation.³ In spite of this knowledge that CCTs are poor predictors of bleeding risk, they are routinely used prior to invasive procedures especially in nonacademic institutes and attempts are made to correct these abnormalities before invasive procedures. These practices are not supported by the evidence, and they are also harmful to the patients.

Few studies comparing the CCTs and TEG have been published; a recently published study by Shah et al.⁶ strongly suggested that deranged CCTs do not predict risk of bleeding in cirrhotics. Whenever indicated, any invasive procedure could be safely carried out in patients with cirrhosis without prior correction of coagulation abnormalities. In another recently published randomized controlled trial done by Lesley et al.,⁷ they found that TEG-guided transfusion strategy leads to a significantly lower use of blood products compared to standard of care (transfusion guided by INR and platelet count), without an increase in bleeding complications. Remarkably, even in patients with significant coagulopathy, post-procedure bleeding was rare indicating that TEG thresholds should be reevaluated. A recently published review article on management of critically ill patients with cirrhosis also suggests to avoid prophylactic blood transfusions before procedures and recommends use of TEG for guiding the blood product transfusions before invasive procedures but the level of recommendation is low because of lack of trials.⁸ We conducted this study to compare the utility of TEG and CCTs in assessing the risk of bleeding in cirrhotic patients undergoing invasive procedure.

MATERIALS AND METHODS

Study Design

This endeavor is a prospective longitudinal hospital-based study. It initially included 207 patients of cirrhosis of liver attending liver clinic (inpatient and outpatient) from May 2014 to April 2016. Of 207 patients, 57 patients were excluded from the study as 18 of them received blood transfusion before the procedure for low hemoglobin (less than 7gm/dl) and 39 patients did not give consent for TEG. So we prospectively enrolled 150 patients with cirrhosis of liver of all age groups including any Child class and any etiology undergoing any invasive procedures. Initially, 100 patients underwent all CCTs such as bleeding time (BT), clotting time (CT), aPTT, PT/INR, platelet count and TGT; since BT, CT and TGT were normal in all 100 patients we stopped doing them in subsequent 50 patients. TEG was done in all 150 patients. None of the patients received prophylactic blood product transfusion.

All these patients were observed for post procedural bleeding. Clinically significant bleeding was defined as any bleeding requiring: additional and unexpected haemostatic measures; blood transfusions; hospitalization for patients in whom the procedure was carried out as outpatients, and bleeding-related extension of hospital stay.⁹ In case of bleeding, we planned to use following recommendations used across transplant centers for correction of TEG parameters: 2 units of plasma for an R-time greater than 15 min, 10 units of platelets for a maximum amplitude less than 40 mm.¹⁰

Safety Assessment

At the end of the procedure, the patients were clinically reassessed. Any bleeding episode was recorded, in case of transfusion, amount of blood and transfusion-related side effect were recorded. Each procedure was performed by an expert operator/team according to guidelines.

Inclusion Criteria

All the patients with Cirrhosis of liver

- Diagnosis of cirrhosis was based on clinical, biochemical, endoscopic and imaging findings. Patients with histological evidence of cirrhosis were also included.
- The diagnosis of alcoholic cirrhosis was made on the basis of history of any form of daily alcohol consumption of >80 g/dl in men and >40 g/dl in women for 10yrs.
- History, clinical examination, complete blood count with platelet count, liver profile, renal profile, oesophagogastroduodenoscopy, complete coagulation profile [BT, CT, aPTT, PT INR, Platelet count and TGT] and TEG was done.

Exclusion Criteria

The patients who had received prophylactic any blood product transfusions or receiving anticoagulants within last 7 days were excluded.

Methods and Instruments used: Thromboelastography: Blood samples were collected with the double-syringe technique from a clean venipuncture at the antecubital fossa. The first 6 ml of each sample were discarded. Whole blood 3.5 ml was then collected into a 5 ml syringe and in accordance with manufacturer recommendation, analyzed within 4 min from sampling. TEG was performed using TEG 5000® (Haemoscope, Haemonetics corporation, USA) expert operator blinded to patient's data. Clot formation was triggered by contact activation without the addition of activators. TEG parameters used to guide blood product transfusion were as follows: R time value: it is the time from the start of the TEG tracing until the TEG trace amplitude reaches 2 mm. This represents the rate of initial fibrin formation and is functionally related to plasma clotting factors and circulating inhibitor activity (normal range: 2–8 min). Prolongation of the R time may be a result of coagulation factor deficiencies or severe hypofibrinogenemia. For the study, an R > 15 minutes (mins) was indication for FFP transfusion. MA value: It is the maximum

amplitude on the TEG tracing. It reflects the strength of the clot and is a direct result of platelet function and plasma factors and their interaction (normal range: 45–63 mm). For the study, an MA < 40 mm was considered an indication for platelet transfusion. The cost of TEG is Rupees 1400 (USD ~22) per patient. TGT was done manually using adsorbed plasma. PT/INR and aPTT were done by using an automated blood coagulation analyzer CA-500 series, manufactured by Sysmex Corporation, Kobe, Japan. Test was done on 0.2 ml of plasma collected by double-syringe technique from a clean venipuncture at the antecubital fossa. Platelet count was done using Coulter LH 750 analyzer manufactured by Beckman Coulter India PVT LTD. Test was done on 0.5 ml of whole blood collected by double-syringe technique from a clean venipuncture at the antecubital fossa.

RESULTS AND OBSERVATIONS

In this longitudinal prospective study, a total of 150 consecutive patients with cirrhosis of liver undergoing invasive procedure were enrolled [mean age of 52 years, 69% Males, Alcohol (34%) as most common etiology followed by in nonalcoholic steatohepatitis (NASH)/cryptogenic (21%), Hepatitis C (14%), Hepatitis B (9%) and others (23%)]. Patients in Child class A, B and C were 37, 51 and 62 respectively (Table 1). Invasive procedures included 45 liver biopsies (34 percutaneous USG guided and 11 transjugular liver biopsies) and 105 other invasive procedures which included pleural tapping ($n = 6$), Intercostal drain insertion ($n = 3$), central venous catheter insertion ($n = 59$), haemodialysis catheter insertion ($n = 6$), pulmonary angiography and coiling ($n = 1$), hepatic angiography with middle hepatic vein stenting ($n = 1$), transarterial chemoembolization (TACE) ($n = 4$), transjugular intrahepatic portosystemic shunt (TIPS) ($n = 6$), coronary angiography

($n = 1$), dental extraction ($n = 3$), fissurectomy ($n = 1$), haemorrhoidectomy ($n = 1$), pigtail drainage of liver abscess ($n = 2$), umbilical hernia surgery ($n = 1$), rectal polypectomy ($n = 2$), CT scan guided renal abscess drainage ($n = 1$), left hemiarthroplasty ($n = 1$), hysterectomy ($n = 1$), diagnostic laparoscopy ($n = 1$), arthroscopy ($n = 1$), coronary artery bypass grafting ($n = 1$), umbilical hernia surgery ($n = 1$) and laparoscopic Cholecystectomy ($n = 1$). All the procedures were done on the indoor basis.

Only one of these 150 patients developed clinically significant bleeding requiring blood transfusion for post procedural (internal jugular venous catheter insertion) bleeding and this patient also had sepsis and renal failure along with cirrhosis of liver.

BT, CT and TGT were normal in initial 100 patients so these tests were not done on subsequent patients. Median aPTT levels were 53 s (control = 28 s), 50% patients have aPTT levels of more than double of control but no association was seen between aPTT levels and bleeding. Normal INR levels (<1.5) were normal in 58 patients, while abnormal levels were seen in 92 patients (between 1.5–1.8 in 53 and >1.8 in 39 patients). Platelet count was normal ($>150 \times 10^3/\mu\text{L}$) in 21 patients, while it was low in remaining 129 patients ($<50 \times 10^3/\mu\text{L}$ in 23, $50\text{--}100 \times 10^3/\mu\text{L}$ in 66 and $100\text{--}150 \times 10^3/\mu\text{L}$ in 40). In patient who developed post procedural bleeding had an aPTT of 48 seconds, INR of 1.98, and platelet count $58 \times 10^3/\mu\text{L}$.

Statistical analysis of the data was done to look association between different variables and presence of bleeding. No statistically significant association was seen between age and sex of the patients and bleeding ($P = 0.674$ and $P = 0.395$ respectively). Also no statistically significant association was seen between INR levels (<1.5, 1.6–1.8 and >1.8) and platelet count ($<50 \times 10^3/\mu\text{L}$, $50\text{--}100 \times 10^3/\mu\text{L}$, $100\text{--}150 \times 10^3/\mu\text{L}$, $>150 \times 10^3/\mu\text{L}$) with bleeding ($P = 0.239$ and $P = 1.000$ respectively) individually amongst different values of INR and platelet count. On comparing combined INR and platelet count amongst four groups namely; group A ($n = 7$): Platelet count $<50 \times 10^3/\mu\text{L}$ and INR > 1.8, group B ($n = 95$): Platelet count $\geq 50 \times 10^3/\mu\text{L}$ and INR ≤ 1.8 , group C ($n = 31$): Platelet count $\geq 50 \times 10^3/\mu\text{L}$ and INR > 1.8, group D ($n = 16$): Platelet count $<50 \times 10^3/\mu\text{L}$ and INR ≤ 1.8 no statistically significant difference is seen in any of the groups and bleeding. One patient who developed post procedural bleeding belongs to group C. There was no association seen between Child class [A ($n = 37$), B ($n = 51$) and C ($n = 61$)] and bleeding ($P = 0.489$). Patient who had post procedural bleeding was in Child class C.

TEG values R time and MA value were normal in 91 (60.66%) and 113 (75.33%) patients respectively including one patient who had post procedural bleeding and they were abnormal in 59 (39.33%) and 37 (24.67%) patients respectively. While INR and platelet count were normal in only 58 (38.67%) and 21 (14%) respectively (Table 2).

Table 1 Demographics and Baseline Characteristics.

	<i>n = 150</i>
Age (mean $\pm$ SD), years	52 $\pm$ 12
Male, <i>n</i> (%)	104 (69)
Etiology, <i>n</i> (%)	
Alcoholic liver disease	51 (34)
NASH/cryptogenic	31 (21)
Hepatitis C	21 (14)
Hepatitis B	13 (9)
Others	34 (23)
CTP CLASS, <i>n</i> (%)	
A	37
B	51
C	62

Table 2 Abnormal and Normal TEG Values Comparing with INR and Platelet Count.

TEG	R time		MA value		INR		Platelet count	
	No.	%	No.	%	No.	%	No.	%
Abnormal	59	39.33	37	24.67	92	61.33	129	86
Normal	91	60.66	113	75.33	58	38.67	21	14
Total	150	100	150	100	150	100	150	100

Even the TEG values (R time and MA value) showed no association with bleeding ($P = 0.815$ and $P = 0.063$ respectively). On comparison of patients with abnormal TEG values R time and MA value with INR and Platelet count respectively in patients with no bleeding by dividing them in various groups. Comparison of all R time with INR values and MA values with platelet count amongst all the groups showed statistically significant lower percentage of abnormal values of R time and MA value compared to INR and platelet count respectively in patients with no bleeding. Only group of patients with platelet count $<50 \times 10^3/\mu\text{L}$ and MA value <40 mm shows a higher percentage of patients (15% vs 24%) showing abnormal values of TEG value in patients without bleeding but that is not statistically significant.

DISCUSSION

There is a major change in the understanding of process of coagulation in patients with cirrhosis. Liver cirrhosis is now considered as a prothrombotic rather than naturally hemorrhagic state. The bleeding risk associated with invasive procedures is over estimated and addressed differently depending on expertise and confidence in treating these patients. Accordingly, most clinicians facing patients with coagulopathy transfuse the patients with fresh frozen plasma (FFP) and/or platelets, fearing that the impaired clotting will translate in a higher risk of bleeding. Review of literature has shown very few prospective trials for bleeding in routine procedures on cirrhotic patients with coagulopathy. In particular, there is little evidence for the effectiveness of the prophylactic use of FFP. There are no clear guidelines for cut off values of CCTs beyond which invasive procedures should be avoided.

In 2007, results from a study done by Armando tripod et al. showed that in cirrhosis, PT/INR did not predict the bleeding risk, and it provides a robust measure of liver function. So, need for alternate tests to predict bleeding risk was realized.¹¹ Previous studies have shown that even with abnormal CCTs patients undergoing abdominal paracentesis and central venous catheter insertion have not required pre or post procedure blood transfusion and incidence of post procedural bleeding has been low except in patients with associated renal failure.^{12,13} Similarly, abnormal coagulation tests are not a contraindication for liver biopsy. These results call into question the

common use of prophylactic procoagulants in the elective setting. In a systematic review it was noted that most clinical uses of FFP currently recommended by practice guidelines, are not supported by evidence from randomized trials.¹⁴

Armando Tripodi et al. in 2009 showed that thromboelastometry is suitable for investigating bleeding risk in stable cirrhosis.¹⁵ Although many studies are observational and small in size, it is clear that VET provide additional information that is in keeping with the new concepts of how coagulation is altered in these patients. There are very few prospective studies which compare CCTs and global tests of coagulation like TEG.

In a recently published randomized controlled trial by Lesley et al. they randomized 60 patients with cirrhosis and significant coagulopathy prior to invasive procedures, in two groups on received standard of care treatment and other received TEG guided transfusion. They found that TEG-guided transfusion strategy leads to a significantly lower use of blood products compared to standard of care (transfusion guided by INR and platelet count), without an increase in bleeding complications. Remarkably, even in patients with significant coagulopathy, post-procedure bleeding was rare indicating that TEG thresholds should be reevaluated.⁷ Authors in this study used pre-procedural transfusions as standard of care but there is no recommendation for prophylactic transfusion in cirrhotics undergoing invasive procedures. Prophylactic transfusions have not been beneficial on the contrary they have been harmful. As there was a very low incidence of bleeding in both the groups, it suggests need of a study without prophylactic correction of routine coagulation tests; which is what is done in our study. In a study recently published by our group, 338 patients enrolled in the study were divided into two groups (A and B) according to the presence or absence of abnormal coagulation parameters (defined as INR ≥ 1.5 and/or platelet count $\leq 50 \times 10^3/\mu\text{L}$) respectively. Low risk procedures and high risk procedures were performed on patients in both groups. No patient undergoing low risk procedure developed bleeding in either group. Three patients in group A underwent high risk procedures developed clinically significant bleeding, however, the difference was not statistically significant. None of the patients received pre procedural correction of abnormal coagulation parameters with plasma/platelet concentrate. So they concluded that deranged CCTs did

not predict clinically significant bleeding in cirrhosis and whenever indicated, any invasive procedure could be safely carried out in patients with cirrhosis without prior correction of coagulation abnormalities.⁶ On the basis of these results we conducted our present study.

In our study we included 150 patients of liver cirrhosis undergoing all routine invasive procedures in day to day clinical practice. The invasive procedures performed in this study cohort reflect the “real world” conditions. Only one of 150 patients who underwent invasive procedures required post procedural blood transfusion. And this single patient who developed post procedural bleeding was having severe sepsis and acute kidney injury in addition to decompensated cirrhosis of liver. BT, CT and TGT were normal in initial 100 patients so it was not done in the subsequent patients. There is no statistically significant association seen between risk of procedure related bleeding and any of the variables such as age, sex, Child class, deranged aPTT, INR and platelet count. These results suggest that risk of procedure related bleeding in cirrhotic patients is not related to abnormal coagulation tests, but is more dependent on severity of portal hypertension. Since only one patient developed bleeding.

TEG values (R time and MA value) were normal in 61% and 75% patients respectively in spite of abnormal CCTs in most of them. Comparison of deranged R time and MA value with the procedure related bleeding also is not statistically significant, this may be due to the fact that only one patient has developed procedure related bleeding. We compared the percentage of patients amongst various groups with abnormal TEG values and abnormal INR and platelet count amongst patients without bleeding, all other criteria showed statistically significant lower percentage of patients with abnormal of R time and MA value compared to INR and platelet count respectively in patients with no bleeding. Bleeding was not seen even in patient who had abnormal TEG values. These results show the usefulness of TEG as a test for predicting the risk of bleeding in cirrhotic patients undergoing invasive procedure but the needs further studies to re evaluate the cut off values of TEG parameters.

Earlier studies have showed that plasma from patients with cirrhosis generates as much thrombin (the final enzyme of coagulation) as plasma from healthy subjects; our study confirmed this finding with normal TGT in 100 patients.^{16,17}

A recently published guideline by Nadim et al. also recommend against routine prophylactic use of fresh frozen plasma.⁸ Based on this discussion we strongly recommend to, avoid prophylactic transfusions in patients of cirrhosis undergoing invasive procedures and wait for further studies for role of TEG in cirrhotic patients undergoing invasive procedure. Limitation of this study is only 23 patients had platelet count less than 50,000 and INR>1.8 was seen in only 38 patients. TEG is used mainly in liver

transplantation or during major surgeries; role of TEG before minor procedures in patients with cirrhosis is not yet established. TEG is usually available only at few academic institutes and cost is also a factor limiting its use.

CONCLUSIONS

We recommend using TEG as a global test of coagulation to avoid unnecessary prophylactic transfusions in patients with cirrhosis of liver undergoing invasive procedures. But still further studies are required to assess the efficacy of TEG in predicting the risk of bleeding in cirrhotic patients undergoing invasive procedures.

CONFLICTS OF INTEREST

The authors have none to declare.

REFERENCES

1. Lisman T, Porte RJ. Rebalanced hemostasis in patients with liver disease: evidence and clinical consequences. *Blood*. 2010;12:878–885.
2. Lisman T, Bakhtiari K, Pereboom IT, et al. Normal to increased thrombin generation in patients undergoing liver transplantation despite prolonged conventional coagulation tests. *J Hepatol*. 2010;52:355–361.
3. Koh MB, Hunt BJ. The management of perioperative bleeding. *Blood Rev*. 2003;17:179–185.
4. Tripodi A, Chantarangkul V, Primignani M, et al. The international normalized ratio calibrated for cirrhosis (INR (liver)) normalizes prothrombin time results for model for end-stage liver disease calculation. *Hepatology*. 2007;46:520–527.
5. Stravitz RT. Potential applications of thromboelastography in patients with acute and chronic liver disease. *Gastroenterol Hepatol (NY)*. 2012;8:513–520.
6. Shah A, Amarapurkar D, Dharod M, et al. Coagulopathy in cirrhosis: a prospective study to correlate conventional tests of coagulation and bleeding following invasive procedures in cirrhotics. *Indian J Gastroenterol*. 2015;34(5):359–364.
7. De Pietri L, Bianchini M, Montalti R, et al. Thrombelastography-guided blood product use before invasive procedures in cirrhosis with severe coagulopathy. A randomized controlled trial. *Hepatology*. (September)2015;(September). <http://dx.doi.org/10.1002/hep.28148>.
8. Nadim M, Durand F, Kellum J, et al. Management of the critically ill patient with cirrhosis: a multidisciplinary perspective. *J Hepatol*. 2016;64:717–735.
9. Giannini EG, Greco A, Marengo S, et al. Incidence of bleeding following invasive procedures in patients with thrombocytopenia and advanced liver disease. *Clin Gastroenterol Hepatol*. 2010;8:899–902.
10. Segal JB, Dzik WH. Transfusion Medicine/Hemostasis Clinical Trials Network. Paucity of studies to support that abnormal coagulation test results predict bleeding in the setting of invasive procedures: an evidence-based review. *Transfusion*. 2005;45:1413–1425.
11. Tripodi A, Caldwell SH, Hoffman M, et al. Review article: the prothrombin time test as a measure of bleeding risk and prognosis in liver disease. *Aliment Pharmacol Ther*. 2007;26:141–148.

12. Grabau CM, Crago SF, Hoff LK, et al. Performance standards for therapeutic abdominal paracentesis. *Hepatology*. 2004;40:484–488.
13. Pache I, Bilodeau M. Severe haemorrhage following abdominal paracentesis for ascites in patients with liver disease. *Aliment Pharmacol Ther*. 2005;21:525–529.
14. Stanworth SJ, Brunskill SJ, Hyde CJ, et al. Is fresh frozen plasma clinically effective? A systematic review of randomized controlled trials. *Br J Haematol*. 2004;126:139–152.
15. Tripodi A, Primignani M, Chantarangkul V, et al. The coagulopathy of cirrhosis assessed by thromboelastometry and its correlation with conventional coagulation parameters. *Thromb Res*. 2009;124:132–136.
16. Tripodi A, Salerno F, Chantarangkul V, et al. Evidence of normal thrombin generation in cirrhosis despite abnormal conventional coagulation tests. *Hepatology*. 2005;41:553–558.
17. Muciño-Bermejo J, Carrillo-Esper R, Méndez-Sánchez N, et al. Thrombosis and hemorrhage in the critically ill cirrhotic patients: five years retrospective prevalence study. *Ann Hepatol*. 2015;14:93–98.