Original article

The relationship between coagulation disorders and the risk of bleeding in cirrhotic patients

Asma Labidi [a],[*], Héla Baccouche [b], Monia Fekih [a], Sonia Mahjoub [b], Nadia BenMustapha [a], Meriem Serghini [a], Neila BenRomdhane [b], Jalel Boubaker [a]

[a] Department of Gastroenterology and Hepatology, Rabta Hospital, Faculty of Medicine of Tunis, University of Tunis El Manar, Tunis, Tunisia
[b] Department of Hematology, Rabta Hospital, Faculty of Medicine of Tunis, University of Tunis El Manar, Tunis, Tunisia

ARTICLE INFO

ABSTRACT

Introduction and Objectives: For long, bleeding in cirrhotic patients has been associated with acquired coagulation disorders. The aim of our study was to investigate the impact of acquired coagulation disorders on bleeding risk in cirrhotic patients.

Materials and methods: Blood samples were collected from 51 cirrhotic patients with (H+) or without (H−) bleeding events and 50 controls matched by age and sex. Thrombin generation was assessed as endogenous thrombin potential (ETP). Hemostatic balance was assessed by means of ratios of pro- to anticoagulant factors and by ETP ratio with/without protein C (PC) activator (ETP ratio).

Results: Bleeding events occurred in 9 patients (17.6%). Compared with controls, VIII/anticoagulant factors, VII/PC and XII/PC were significantly higher in (H+) patients. No significant difference as regards all ratios across patient groups was detected. ETP ratio was significantly higher in (H+) patients than in controls ($p = 0.017$). However, there was no significant difference between patient groups as regards ETP ratio.

Conclusion: Hemostatic balance is shifted toward a hypercoagulability state even in cirrhotic patients who experienced bleeding. These findings provide evidence against traditional concept of hemostasis-related bleeding tendency in cirrhotic patients.

1. Introduction

Bleeding often complicates the clinical course of cirrhosis. The most frequent and potentially life-threatening site of bleeding is the gastrointestinal tract. It could result from a variety of lesions including gastro-esophageal varices and portal hypertensive gastropathy or other lesions seen in the general population like esophagitis, Mallory-Weiss tears and peptic ulcer disease. Mortality rates related to gastrointestinal bleeding are high; up to 30% of initial variceal bleeding episodes are fatal [1]. Patients with cirrhosis may also experience cutaneous or mucosa-associated bleeding including bruising, purpura, epistaxis, gingival bleeding, menorrhagia, and bleeding associated with invasive procedures such as liver biopsy. For long, this increased hemorrhagic risk has been thought to be related to acquired hemostatic disorders in cirrhotic patients. In fact, liver synthesizes almost all coagulation factors with the exception of factor VIII. It has been thought that the reduced synthesis of clotting factors was responsible for abnormal conventional laboratory tests exploring global clotting activation, such as prothrombin time (PT) and activated partial thromboplastin (aPTT). However it has been noted that despite prolonged PT and aPTT, many cirrhotic patients do not experience bleeding even after liver biopsy or other potentially hemorrhagic procedures [2]. Furthermore, some cirrhotic patients do experience thromboembolic events despite abnormal conventional laboratory tests. Thus far, only few studies have investigated the impact of coagulation disorders on bleeding risk in cirrhotic patients [3,4].

This study aims to assess the relationship between hemostatic disorders and the risk of bleeding in cirrhotic patients through investigating hemostatic balance in cirrhotic patients with and without bleeding in comparison with controls.

2. Materials and methods

The study was performed in accordance with the Declaration of Helsinki of the World Medical Association and was approved by the local ethics committee. All patients gave their informed consent prior to inclusion in the study.

* Corresponding author at: Rabta Hospital, Faculty of Medicine of Tunis, University of Tunis El Manar, Jabbari Street, 1007 Tunis, Tunisia.
  E-mail addresses: asma.labidy@gmail.com, asma.labidi@fmt.utm.tn (A. Labidi).

2.1. Patient population and study design

Fifty-one cirrhotic patients constituted the group of cases and 50 healthy controls matched for age and sex were included in a cross-sectional study. Data regarding bleeding episodes, characteristics of cirrhosis and medication were abstracted from medical records. The severity of cirrhosis was estimated according to Child Turcotte Pugh score. Patients who had bleeding episodes within 2 months before or after inclusion were identified. For each of these patients, site and severity of bleeding were determined. Patients who experienced bleeding with deglobulisation (fall of the hemoglobin of 2 g/dl or more) requiring or not a transfusion were considered as having severe hemorrhage. Exclusion criteria were hepatocellular carcinoma or any other malignancy, bacterial infection, chronic inflammatory disease, nephrotic syndrome, renal failure, known inherited coagulation abnormalities and use of anticoagulant or anti-platelet drugs. Patients were divided into two groups: (H+) group included patients who experienced bleeding episodes and (H−) group included patients who did not.

2.2. Blood collection

Blood sample was drawn through venipuncture into plastic tubes containing 3.2% sodium citrate as an anticoagulant in the proportion of one to nine parts of anticoagulant/blood. Poor platelet plasma (PPP) was obtained after a double blood centrifugation at $2500 \times g$ for 15 min. PPP was aliquoted and frozen at $-80\,^{\circ}C$ until coagulation tests were performed.

2.3. Laboratory tests

2.3.1. Conventional laboratory tests

The prothrombin time (PT) and activated partial thromboplastin time (aPTT) were measured, respectively, with the human thromboplastin (neoplastin, STAGO) and the automated APTT reagent (APTT, STAGO). The fibrinogen was measured with (STA fibrinogen, STAGO).

2.3.2. Pro and anticoagulant factors

The pro and anticoagulant factor activities were determined as functional activities using STAGO reagents: Factor VIII and XII activities were measured with standard aPTT based clotting assays (respectively with DEFICIENT VIII and IMMUNODEF XII). Factor VII, factor V and factor II activities were measured with PT based clotting assays (respectively with DEFICIENT VII, DEFICIENT V, IMMUNODEF II). Protein C (PC) and Protein S (PS) activities were measured using clotting assays (STACLOT PC and STACLOT PS). Antithrombin (AT) activity was determined using chromogenic assay (STACHROM AT). All tests were performed on STA COMPACT MAX (STAGO; Asnières France). Platelet count was performed on the hematology analyzer (SYSMEX XT 2000i; Cobe, Japan).

2.3.3. Thrombin generation

Thrombin generation (TG) was measured by means of calibrated automated thrombin method (thrombiniscope-Thermosystem). The coagulation was triggered in the PPP after addition of tissue factor 1 pmol/L and phospholipids (PPP reagent low-STAGO) into two steps: in the absence then in the presence of protein C activator (PROTAC; STACLOT PC STAGO). Registration of the thrombin generated over time was carried out with a fluorogenic substrate (FLUCAT, STAGO). The TG was expressed as endogenous thrombin potential (ETP) in nmol × min.

Table 1
Comparison between patients groups as regards conventional laboratory tests.

Parameters	H+	H−	p-Value
Platelet count (/mm³)	62,888 ± 33,650	110,317 ± 70,483	0.01[a]
PT (%)	52.7 ± 10.8	62 ± 21.3	0.1
aPTT (ratio)	1.40 ± 0.3	1.26 ± 0.3	0.16
Fibrinogen (g/L)	2.12 ± 0.6	2.6 ± 0.9	0.21

H+: cirrhotic patients who experienced bleeding; H−: cirrhotic patients who did not experienced bleeding; PT: prothrombin time; aPTT: activated partial thromboplastin.

[a] $p < 0.05$.

2.3.4. Hemostatic balance

Hemostatic balance was assessed by means of procoagulant to anticoagulant factor ratios and ETP ratio with/without PC activator.

2.4. Statistical analysis

Statistical Package for Social Science (SPSS) software version 21.0 (IBM Corp., Armonk. New York, USA) was used for analysis of data. Data were summarized as mean and percentage. Study groups were compared using the χ^2 test for qualitative variables. Student's t and ANOVA tests were used for analysis of parametric data. Mann–Whitney U and Kruskal–Wallis H tests were used for analysis of non-parametric data. p-Value less than or equal to 0.05 was considered significant.

3. Results

Mean age of patients at inclusion was 57.8 years (16–91 years). Mean age at diagnosis of cirrhosis was 55 years (6–88 years). There were 24 males and 27 females. Major etiology of cirrhosis was viral hepatitis (64.7%). Patients were categorized according to Child–Pugh score as class A in 14 patients (27.5%), class B in 22 patients (43.2%), and class C in 15 patients (29.3%). (H+) group included 9 patients (17.6%). Bleeding episodes were variceal hemorrhage ($n = 6$), gastrointestinal bleeding secondary to gastric ($n = 1$) and duodenal ($n = 1$) ulcers and gingivorrhagia ($n = 1$). Hemorrhage was judged mild to moderate in 6 patients and severe in 3 others. Both patient groups were comparable regarding age, sex and Child–Pugh score.

Obviously, as regards controls, no bleeding episodes occurred within 2 months before or after inclusion.

3.1. Conventional laboratory tests

There was no significant difference in mean levels of PT, aPTT and fibrinogen between (H+) and (H−) groups. Platelet count was significantly lower in (H+) patients than in (H−) patients ($p = 0.01$) (Table 1).

3.2. Procoagulant and anticoagulant factors

Mean levels of pro-and anticoagulant factors were significantly lower in cirrhotic patients who experienced bleeding episodes (H+) than in controls. However, factor VIII was significantly higher in cirrhotic patients than in controls (166% vs. 94.5%; $p = 0.045$). There was no significant difference between both (H+) and (H−) groups as regards levels of pro- and anticoagulant factors (Table 2).

3.3. Thrombin generation

There was no significant difference between (H+) patients and controls as regards ETP mean level without PC activator (716.1 vs. 811 nmol × min respectively; $p = 0.5$). In the presence of PC

Table 2
Comparison between patients groups and controls as regards procoagulant and anticoagulant factors.

Parameters	H+	Controls	p value[a]	H−	p-Value[b]
Factor II (%)	38.38 ± 17.46	89.82 ± 15.5	<0.0001	43.38 ± 20.4	0.519
Factor V (%)	34.5 ± 24.6	93.98 ± 21.3	<0.0001	51.35 ± 29.7	0.157
Factor VII (%)	38.25 ± 23.8	94.98 ± 23.8	<0.0001	58.09 ± 43.3	0.188
Factor XII (%)	52.38 ± 37.2	84.49 ± 25.9	0.008	60.53 ± 28.26	0.357
Factor VIII (%)	166 ± 123.9	94.5 ± 38.9	0.045	133.57 ± 96.5	0.433
Protein C (%)	34.86 ± 29.3	116.54 ± 28	<0.0001	47.08 ± 24.4	0.146
Protein S (%)	41.71 ± 19.5	76.07 ± 19.7	0.001	52.39 ± 21.8	0.187
Antithrombin (%)	48 ± 29.5	99.81 ± 15.9	<0.0001	49.75 ± 26.4	0.714

H+: cirrhotic patients who experienced bleeding; H−: cirrhotic patients who did not experienced bleeding.

[a] (H+) group vs. controls.
[b] (H+) vs. (H−) group.

Table 3
Comparison between patients groups and controls as regards ratios of pro to anticoagulant factors.

Parameters	H+	Controls	p value[a]	H−	p-Value[b]
II/PS	1.37 ± 1.0	1.16 ± 0.3	0.926	1.05 ± 1.1	0.493
II/PC	1.41 ± 0.7	0.75 ± 0.2	0.25	1.15 ± 0.7	0.233
II/AT	0.86 ± 0.2	0.92 ± 0.2	0.531	0.95 ± 0.3	0.651
V/PS	1.31 ± 1.3	1.27 ± 0.4	0.694	1.24 ± 1.4	0.885
V/PC	1.38 ± 1.3	0.84 ± 0.25	0.414	1.42 ± 1.0	0.756
V/AT	0.77 ± 0.5	1.01 ± 0.3	0.073	1.07 ± 0.5	0.128
VII/PS	1.51 ± 1.5	1.29 ± 0.4	0.437	1.45 ± 1.8	0.984
VII/PC	1.27 ± 0.5	0.82 ± 0.2	0.030[c]	1.34 ± 0.8	0.664
VII/AT	0.88 ± 0.4	1.02 ± 0.3	0.160	1.15 ± 0.6	0.261
XII/PS	2.06 ± 2.0	1.17 ± 0.5	0.910	1.28 ± 0.7	0.810
XII/PC	1.69 ± 0.6	0.77 ± 0.3	0.001[c]	1.78 ± 1.5	0.470
XII/AT	1.12 ± 0.3	0.92 ± 0.3	0.249	1.38 ± 0.6	0.307
VIII/PS	3.45 ± 1.7	1.12 ± 0.4	0.004[c]	2.97 ± 2.7	0.506
VIII/PC	4.31 ± 3.2	0.7 ± 0.2	<0.0001[c]	3.88 ± 4.7	0.598
VIII/AT	2.88 ± 1.8	0.85 ± 0.3	0.003[c]	3.26 ± 2.5	0.922

PS: protein S; PC: protein C; AT: antithrombin.

[a] (H+) group vs. controls.
[b] (H+) vs. (H−) group.
[c] $p < 0.05$.

activator, ETP was surprisingly higher in (H+) patients than in controls (725 vs. 387 nmol × min; $p = 0.05$).

However, there was no significant difference between patient groups as regards ETP with and without PC activator.

3.4. Hemostatic balance

3.4.1. The ratios of pro- to anticoagulant factors

Compared with controls, VIII/anticoagulant factors (VIII/PC, VIII/PS, VIII/AT), VII/PC and XII/PC were significantly higher in (H+) patients. All other ratios were roughly at the same levels.

No significant difference as regards all ratios between patients who experienced bleeding (H+) and those who did not (H−) was detected (Table 3).

3.4.2. ETP ratio

ETP ratio with/without PC activator was significantly higher in (H+) patients than in controls (0.97 vs. 0.51; $p = 0.017$) (Fig. 1A).

However, there was no significant difference between patient groups as regards ETP ratio (Fig. 1B).

4. Discussion

The current study showed that the hemostatic balance assessed by ratios of pro- to anticoagulant factors and ETP ratio with/without PC activator was in favor of a hypercoagulability state even in cirrhotic patients who experienced bleeding events. When comparing both patient groups, cirrhotic patients who had bleeding generated roughly as much thrombin as those who had not. To our knowledge, there were no published studies investigating the impact of thrombin generation assay in assessing the bleeding risk in cirrhosis.

However, the main limitation of this study is the small number of cirrhotic patients who experienced bleeding.

The bleeding tendency in cirrhotic patients namely in those with advanced liver disease was supported by many clinical observations [5]. The most relevant hemorrhagic events in such patients result from esophageal varices rupture and portal hypertensive gastropathy [6]. Bleeding may occur also from the same lesions seen in the general population such as peptic ulcer, epistaxis, gingivorrhagia, bruising or from invasive procedures. In our study, variceal bleeding was the most common site of hemorrhage as it occurred in two-thirds of patients.

Historically, hemostatic abnormalities due to liver failure such as prolonged PT and aPTT were assumed to reflect bleeding disorders that frequently occur in cirrhotic patients. Thus, PT has frequently been corrected by means of fresh frozen plasma prior to liver biopsy or other potentially hemorrhagic procedures [7].

In the present study, there was not any significant difference between patients who experienced bleeding and those who did not as regards PT and aPTT mean levels. Our results are in accordance with those of many papers suggesting these conventional tests are not as good at predicting bleeding in acquired as compared with congenital coagulopathies [8]. In fact, Segal et al. found no evidence to conclude that prolonged PT could predict bleeding during invasive diagnostic procedures [9]. Furthermore, Tripodi noted that, paradoxically, cirrhotic patients with near-normal PT could bleed whereas patients with relatively abnormal PT commonly did not [10]. The lack of its bleeding predictive power can best be explained by the fact that only the procoagulant but not the anticoagulant activity (PC, PS, AT) is being reflected by PT [11]. Since both procoagulant and anticoagulant factors are decreased
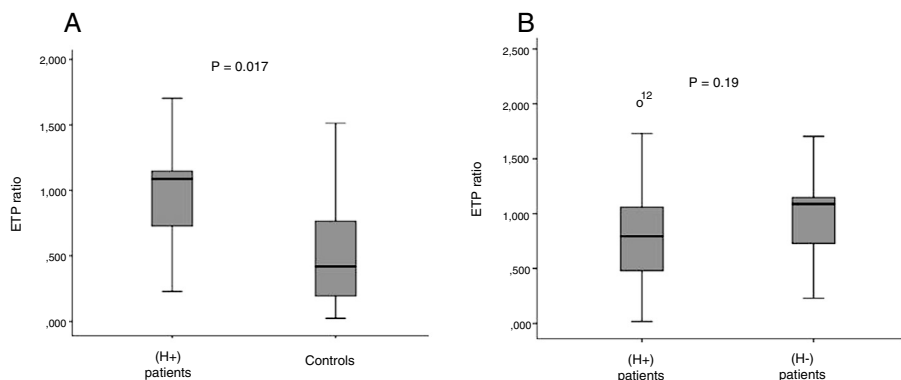
Fig. 1. Comparison of ETP ratio between (H+) patients and controls (A), and between (H+) and (H−) patients (B). H+: cirrhotic patients who experienced bleeding; H−: cirrhotic patients who did not experienced bleeding; ETP: endogenous thrombin potential.

in cirrhosis, PT and aPTT could not represent the balance between pro-and anticoagulant factors [5].

With regard to platelet count assessed in the present study, patients who experienced bleeding had significantly lower levels than patients who did not ($p = 0.01$). Our results were in agreement with those of El Bokl et al. where platelet count was found to be significantly lower in cirrhotic patients who experienced hematemesis and melena than those who did not have bleeding episodes ($p < 0.0001$) [3]. These findings could be supported by the multiple quantitative and qualitative alterations that could affect platelets in patients with chronic liver disease. Increased platelet sequestration in the spleen caused by portal hypertension and decreased thrombopoietin production by the diseased liver are main mechanisms of thrombocytopenia in cirrhotic patients [12]. Besides thrombocytopenia, defective platelet function has also been found since adhesion, aggregation and then capacity to support thrombin generation are impaired in cirrhotic patients. These findings were supported by several clinical observations showing that a platelet count <60,000/mm^3 was associated with a significantly increased risk of bleeding related to invasive procedures [13]. Thus, platelet count seems to be more reliable than other hemostatic conventional tests (TP or aPTT) in assessing bleeding risk. Although there is no prospective studies determining the threshold platelet count for prophylactic transfusion in cirrhotic patients, AASLD guidelines for liver biopsy recommend consideration of platelet transfusion prior to liver biopsy for a platelet count <50,000–60,000/mm^3 (Class I level C) [7].

In the current study, there was not any difference between (H+) and (H−) patients with regard to plasma fibrinogen level. However, Siddiqui et al. found significant correlation for decreased fibrinogen level with gastrointestinal bleeding in cirrhotic patients (RR = 1.47; 95% CI, 0.64–3.35) [4].

In fact, hypofibrinogenemia which is frequently seen in patients with advanced cirrhosis is thought to increase bleeding risk since fibrinogen serves both as a precursor of fibrin and a mediator of platelet aggregation [14]. Bleeding risk is considered particularly high when fibrinogen levels are below 1 g/L [15]. In the present study, our results as regards fibrinogen levels could be explained by the fact that the majority of patients had stable liver disease.

In the present study, procoagulant (II, V, VII and XII) and anticoagulant factors (PC, PS and AT) were significantly lower in cirrhotic patients who had bleeding than in controls. However, FVIII was markedly increased in the former group. Several previous studies were in agreement with our results regardless of bleeding or thrombotic status of cirrhotic patients [16–18].

When comparing (H+) and (H−) patients, no difference in levels of pro-and anticoagulant factors was detected. In line with our results, El Bokl et al. showed no significant difference between both patient groups as regards FVIII level. However, paradoxically, PC was significantly lower in cirrhotic patients who experienced bleeding in comparison with those who did not (36.4% vs. 65%; $p = 0.018$) [3]. These findings suggest that bleeding events in cirrhotic patients are not related to plasma levels of coagulation factors. Indeed, randomized controlled trials provide evidence against effectiveness of recombinant activated factor VII infusion in controlling bleeding from varices or during hepatectomy [19,20].

In the present study, regarding hemostatic balance, VIII/anticoagulant factors (VIII/PC; VIII/PS and VIII/AT), VII/PC and XII/PC were significantly higher in (H+) patients than in controls. All other ratios were roughly at the same levels between (H+) patients and controls. Similarly, previous studies showed that ratios pro- to anticoagulant factors (II/PC, V/PC, VIII/PC and VIII/AT) were significantly higher in cirrhotic patients than in controls [16,17,21].

In the current study, all ratios of pro- to anticoagulant factors were at the same levels between both patient groups. However, El Bokl et al. showed paradoxically a significant higher level of FVIII/PC in cirrhotic patients who had bleeding events than in patients who had not [3].

With regard to thrombin generation assessed in the current study, there was no difference across controls and patient groups.

After activation of PC, ETP ratio was significantly higher in (H+) patients than in controls ($p = 0.017$). These findings were in agreement with those of Tripodi et al. suggesting a state of resistance to the anticoagulant effect of activated PC in cirrhotic patients [17,18]. This "hypercoagulability status" could even have a protective effect against bleeding in cirrhotic patients. In the same context, ETP ratio did not reach statistical significance between both patient groups. This finding provides an additional argument against the traditional tenet holding that coagulation disorders detected in cirrhotic patients are predictors of bleeding.

It appears that gastrointestinal bleeding may be explained by hemodynamic alterations related to portal hypertension. Advanced liver disease, large varices, variceal wall tension and the presence of red wale marking have been reported as risk factors for variceal bleeding in cirrhotic patients [22]. Endothelial dysfunctions, bacterial infections and renal failure may also contribute to gastrointestinal bleeding [23]. Other bleeding events such as epistaxis, gingivorrhagia and bruising may be explained by thrombocytopenia, which is in turn mainly due to portal hypertension [23].

Before concluding, it is worth noting that in patients with chronic liver disease, vitamin k deficiency is one of the main factors implicated in coagulation disorders described above. Indeed, vitamin K deficiency may result in, not only decreased synthesis of coagulation factors but also in producing under-carboxylated

precursors of these proteins that are functionally inactive. These proteins are known as proteins induced by vitamin K absence (PIVKA) such as undercaboxylated prothrombine (PIVK-II) which has been shown to be secreted by hepatocellular carcinoma cells in cirrhotic patients [24,25]. Although it has been reported in some previous studies that the administration of vitamin K in such patients did not improve coagulation disorders, data regarding the sensitivity of under-carboxylated prothrombin are still conflicting [26,27]. Hence, we could speculate that it would probably be wise not to administer vitamin K in cirrhotic patients in order to prevent a significant decrease of the level of undercarboxylated prothrombin which may play a role in the early diagnosis of hepatocellular carcinoma in such patients [28].

In conclusion, although our findings should be interpreted cautiously due to the small number of (H+) patients, they may support the concept that abnormal conventional laboratory tests such as prolonged PT and aPTT do not correlate with bleeding risk in cirrhotic patients. However, platelet count seems to be a better predictor of bleeding than PT and aPTT. The hemostatic balance is shifted toward a hypercoagulability state even in cirrhotic patients who experienced bleeding. We surmise that gastrointestinal bleeding in such patients is mainly hemodynamic due to portal hypertension. Further studies should take into account the fibrinolytic system. In fact, hyperfibrinolysis has been reported in some cases as a cause of bleeding in cirrhotic patients, although this concept remains controversial [10].

Abbreviations

ETP   endogenous thrombin potential
PC   protein C
PT   prothrombin time
aPTT   activated partial thromboplastin
PPP   poor platelet plasma
PS   protein S
AT   antithrombin
TG   thrombin generation

Copyright assignment

Authorship responsibility

I, the undersigned author, certify that I have participated sufficiently in the intellectual content, the analysis of data, if applicable, and the writing of the Article, to take public responsibility for it. I have reviewed the final version of the Article, believe it represents valid work, and approve it for publication. As an author of this Article, I certify that none of the material in the manuscript has been published previously, is included in another manuscript, or is currently under consideration for publication elsewhere. I also certify that the Article has not been accepted for publication elsewhere, nor have I assigned any right or interest in the Article to any third party.

Financial disclosure

Institutional Review Board/Animal Care Committee Approval

I, the undersigned author, certify that my institution has approved the protocol for any investigation involving humans or animals and that all experimentation was conducted in conformity with ethical and humane principles of research.

Author contributions

Asma labidi, Hela Baccouche, Monia Fekih and Neila BenRomdhane designed the study.
Hela Baccouche carried out biological tests.
Asma Labidi and Hela Baccouche analyzed the data.
Asma labidi wrote the manuscript with the support of Hela Baccouche.
All authors discussed the results and contributed to the final manuscript.

Conflict of interest

None.

Informed consent

All patients gave their informed consent for publication of the case details.

References

[1] Sharara AI, Rockey DC. Gastroesophageal variceal hemorrhage. N Engl J Med 2001;345:669–81.
[2] Violi F, Ferro D, Basili S, Quintarelli C, Musca A, Cordova C, et al. Hyperfibrinolysis resulting from clotting activation in patients with different degrees of cirrhosis. The CALC Group. Coagulation abnormalities in liver cirrhosis. Hepatology 1993;17:78–83.
[3] El Bokl MA, Shawky A, Riad GS, Abdel Fattah HS, Shalaby H, Nady A, et al. Procoagulant versus anticoagulant factors in cirrhotic patients. Arab J Gastroenterol 2014;15:123–9.
[4] Siddiqui SA, Ahmed M, Ghani MH, Memon MA, Mustafa G, Ghori MA. Coagulation abnormalities in patients with chronic liver disease in Pakistan. J Pak Med Assoc 2011;61:363–7.
[5] Lisman T, Porte RJ. Rebalanced hemostasis in patients with liver disease: evidence and clinical consequences. Blood 2010;116:878–85.
[6] Odelowo OO, Smoot DT, Kim K. Upper gastrointestinal bleeding in patients with liver cirrhosis. J Natl Med Assoc 2002;94:712–5.
[7] Rockey DC, Caldwell SH, Goodman ZD, Nelson RC, Smith AD. Liver biopsy. Hepatology 2009;49:1017–44.
[8] Tripodi A, Chantarangkul V, Mannucci PM. Acquired coagulation disorders: revisited using global coagulation/anticoagulation testing. Br J Haematol 2009;147:77–82.
[9] Segal JB, Dzik WH. Paucity of studies to support that abnormal coagulation test results predict bleeding in the setting of invasive procedures: an evidence-based review. Transfusion (Paris) 2005;45:1413–25.
[10] Tripodi A, Primignani M, Mannucci PM, Caldwell SH. Changing concepts of cirrhotic coagulopathy. Am J Gastroenterol 2017;112:274–81.
[11] Saner FH, Gieseler RK, Akiz H, Canbay A, Gorlinger K. Delicate balance of bleeding and thrombosis in end-stage liver disease and liver transplantation. Digestion 2013;88:135–44.
[12] Giannini EG. Review article: thrombocytopenia in chronic liver disease and pharmacologic treatment options. Aliment Pharmacol Ther 2006;23:1055–65.
[13] Giannini EG, Greco A, Marenco S, Andorno E, Valente U, Savarino V. Incidence of bleeding following invasive procedures in patients with thrombocytopenia and advanced liver disease. Clin Gastroenterol Hepatol 2010;8:899–902, quiz e109.

[14] Fries D, Martini WZ. Role of fibrinogen in trauma-induced coagulopathy. Br J Anaesth 2010;105:116–21.

[15] Dymock IW, Tucker JS, Woolf IL, Poller L, Thomson JM. Coagulation studies as a prognostic index in acute liver failure. Br J Haematol 1975;29:385–95.

[16] Baccouche H, Labidi A, Fekih M, Mahjoub S, Kaabi H, Hmida S, et al. Haemostatic balance in cirrhosis. Blood Coagul Fibrinolysis 2017;28:139–44.

[17] Tripodi A, Primignani M, Chantarangkul V, Dell'Era A, Clerici M, de Franchis R, et al. An imbalance of pro- vs anti-coagulation factors in plasma from patients with cirrhosis. Gastroenterology 2009;137:2105–11.

[18] Tripodi A, Primignani M, Lemma L, Chantarangkul V, Dell'Era A, Iannuzzi F, et al. Detection of the imbalance of procoagulant versus anticoagulant factors in cirrhosis by a simple laboratory method. Hepatology 2010;52:249–55.

[19] Bosch J, Thabut D, Albillos A, Carbonell N, Spicak J, Massard J, et al. Recombinant factor VIIa for variceal bleeding in patients with advanced cirrhosis: a randomized, controlled trial. Hepatology 2008;47:1604–14.

[20] Planinsic RM, van der Meer J, Testa G, Grande L, Candela A, Porte RJ, et al. Safety and efficacy of a single bolus administration of recombinant factor VIIa in liver transplantation due to chronic liver disease. Liver Transpl 2005;11:895–900.

[21] Tripodi A, Salerno F, Chantarangkul V, Clerici M, Cazzaniga M, Primignani M, et al. Evidence of normal thrombin generation in cirrhosis despite abnormal conventional coagulation tests. Hepatology 2005;41:553–8.

[22] Mucino-Bermejo J, Carrillo-Esper R, Uribe M, Mendez-Sanchez N. Coagulation abnormalities in the cirrhotic patient. Ann Hepatol 2013;12:713–24.

[23] Caldwell SH, Hoffman M, Lisman T, Macik BG, Northup PG, Reddy KR, et al. Coagulation disorders and hemostasis in liver disease: pathophysiology and critical assessment of current management. Hepatology 2006;44: 1039–46.

[24] Huisse MG, Leclercq M, Belghiti J, Flejou JF, Suttie JW, Bezeaud A, et al. Mechanism of the abnormal vitamin K-dependent gamma-carboxylation process in human hepatocellular carcinomas. Cancer 1994;74:1533–41.

[25] Saja MF, Abdo AA, Sanai FM, Shaikh SA, Gader AG. The coagulopathy of liver disease: does vitamin K help? Blood Coagul Fibrinolysis 2013;24:10–7.

[26] Liebman HA, Furie BC, Tong MJ, Blanchard RA, Lo KJ, Lee SD, et al. Des-gamma-carboxy (abnormal) prothrombin as a serum marker of primary hepatocellular carcinoma. N Engl J Med 1984;310:1427–31.

[27] Carr BI, Wang Z, Wang M, Wei G. Differential effects of vitamin K1 on AFP and DCP levels in patients with unresectable HCC and in HCC cell lines. Dig Dis Sci 2011;56:1876–83.

[28] Volk ML, Hernandez JC, Su GL, Lok AS, Marrero JA. Risk factors for hepatocellular carcinoma may impair the performance of biomarkers: a comparison of AFP, DCP, and AFP-L3. Cancer Biomark 2007;3:79–87.