Use of prothrombin complex concentrates in patients with decompensated liver cirrhosis is associated with thromboembolic events

To the Editor:

With great interest we have read the outstanding Grand Rounds article by Dhar *et al.*, published recently in the *Journal of Hepatology*.[1] In their article, the authors describe a patient with decompensated liver cirrhosis who experienced a fatal pulmonary embolism, which may have been prevented by prophylactic anticoagulation measures. Dhar and colleagues describe nicely that patients with advanced liver diseases are not only burdened with the well-recognized increased risk of bleeding events, but also with a substantial risk of thromboembolic complications. Importantly, the international normalized ratio (INR) – which is commonly used to define coagulation failure in patients with liver cirrhosis – neither accurately reflects the risk of bleeding nor of thromboembolic events in patients with advanced liver cirrhosis.[2,3]

The difficulty of assessing the individual risk of bleeding and thromboembolic events in patients with liver cirrhosis does not only result in challenges with respect to the use of anticoagulants, as highlighted by Dhar *et al.*, but also with respect to prevention and management of spontaneous or procedure-related bleeding. Common strategies aiming to improve coagulation in patients with advanced liver cirrhosis include transfusion of platelets or fresh frozen plasma, or substitution of prothrombin complex concentrates (PCCs) or other coagulation factors.[4] Yet, there are limited data on how these measures should be applied to prevent or stop bleeding events in patients with liver cirrhosis without unnecessarily increasing the risk of thromboembolism.

Therefore, we aimed to assess the association of PCC substitution with the risk of thromboembolic events in patients with decompensated liver cirrhosis. To this end, patients with advanced liver cirrhosis who were admitted to the Hepatology Unit of the Goethe University Hospital Frankfurt between 2007 and 2015 and who had received 4 factor PCCs, including factor II, VII, IX, X, as well as protein C+S, were retrospectively analyzed. The vast majority of patients were treated in an intermediate or intensive care setting. The decision to substitute PCCs was made by the responsible physician in order to treat active bleeding or prevent bleeding before invasive procedures. PCCs dosage was defined on the basis of the INR and bodyweight of patients, according to the label of the agents. A predefined follow-up time of 4 weeks after application of PCCs was applied. Patients with insufficient data documentation (lacking follow-up), liver transplantation during the follow-up period, previous thromboembolic events, or usage of antithrombotic agents were excluded.

A total of 347 patients with liver cirrhosis receiving PCCs for the prevention or treatment of bleedings were identified. The median model for end-stage liver disease score of the cohort, calculated directly before PCCs administration, was 24 (range 7–40). Alcohol-related liver disease was the most common cause of cirrhosis (44%), followed by chronic hepatitis C (19%) and B (18%). Additional baseline characteristics are shown in Table 1. Within 4 weeks of follow-up, 19 patients (5.5%) from the entire cohort experienced a *de novo* thromboembolic event. The most frequent thromboembolic event was portal vein thrombosis (n = 8; 42%), followed by deep vein thrombosis/pulmonary embolism (n = 7; 37%), and arterial thrombosis (n = 5; 26%; 2 cases of myocardial infarction, 2 cases of stroke, 1 case of hepatic artery thrombosis), including 1 patient with development of both portal vein thrombosis and stroke. The only factors associated with the risk of thromboembolic events after PCCs administration in uni- and multivariate analyses were serum albumin (multivariate $p = 0.09$) and PCCs dosage (multivariate $p = 0.03$), but neither INR nor the model for end-stage liver disease score (Table 1).

In summary, a rationale usage of procoagulant therapeutics in patients with advanced liver cirrhosis remains challenging, in particular because commonly used agents like PCCs are not specifically designed for this patient group.[4] In the present study of patients with liver cirrhosis who had received PCCs to treat or prevent bleeding events, an association of PCC dosage with occurrence of thromboembolic events during short term follow-up has been identified. It is noteworthy that the preparations of PCCs used in our clinic contain protein C and protein S, but not anti-thrombin, suggesting an imperfect balance of pro- and anticoagulants. Although the retrospective design of our study does not enable us to establish causal associations, our finding is in line with previous reports showing that the usage of PCCs in patients on vitamin K antagonists is associated with a risk of thromboembolic events.[5] In addition, a retrospective study analyzing 51 patients with acute liver failure or liver cirrhosis who received PCCs reported the occurrence of 3 PCC-related thromboembolic events.[6] Furthermore, 2 recent studies has shown that PCCs may be less efficient in decreasing INR and in achieving hemostasis in patients with liver disease (though only the study by Huang *et al.* contained a control group), which may result in the application of high doses of PPCs in this patient collective.[7,8] Collectively, prospective trials to define the optimal usage of procoagulant agents in patients with liver cirrhosis are required.

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Conflict of interest

The authors declare no conflicts of interest that pertain to this work.

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Table 1. Baseline characteristics and regression analyses of thromboembolic events of patients with liver cirrhosis receiving PCCs.

Variable	No event during follow-up (n = 327)	Thromboembolic event during follow-up (n = 19)	Regression analyses of thromboembolic events	
			p value (univariate)	*p* value; OR (95% CI) (multivariate)
Age (years), mean ± SD	56.01 ± 11.86	57.58 ± 9.56	0.83	
MELD score, mean (range)	25.5 (7–40)	24.8 (13–40)	0.62	
Sodium (mmol/L), mean ± SD	136 ± 5.819	135.7 ± 7.95	0.78	
Creatinine (mg/dl), mean ± SD	1.96 ± 3.38	1.97 ± 1.72	0.58	
Bilirubin (mg/dl), mean ± SD	9.03 ± 10.25	6.64 ± 8.78	0.36	
AST (mg/dl), mean ± SD	111.62 ± 473.86	151.42 ± 310.87	0.72	
Albumin (g/dl), mean ± SD	2.72 ± 0.67	2.97 ± 0.77	0.077	0.09; 1.83 (0.89–3.75)
Hb (g/dl), mean ± SD	9.11 ± 2.22	8.98 ± 2.3	0.96	
Platelet (/nl), mean ± SD	93.49 ± 67.52	95.42 ± 90.32	0.37	
INR, mean ± SD	2.29 ± 1.17	2.4 ± 0.86	0.66	
PCC dosage (IU), mean ± SD	6,888 ± 14,024	13,747 ± 15,147	0.01	0.028; 2.46 (1.10–5.50)

AST, aspartate aminotransferase; Hb, hemoglobin; INR, international normalized ratio; MELD, model for end-stage liver disease; OR, odds ratio; PCC, prothrombin complex concentrates. P values were calculated by means of chi-square contingency tables or Wilcoxon-Mann-Whitney-U-tests for dichotomous or continuous variables, respectively.

Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jhep.2018.11.019.

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Outcome of critically ill cirrhotic patients admitted to the ICU: The role of ACLF

To the Editor:

We read with great interest the study by Meersseman *et al.*,[1] which demonstrated an excellent outcome for cirrhotic patients with acute-on-chronic liver failure (ACLF) admitted to the intensive care unit (ICU), equal to that of matched patients without cirrhosis, although indications for ICU admission among control groups were heterogeneous, spanning from cardiac surgery to acute liver failure.

Considering patients with ACLF, 11% of cases had ACLF grade I, whereas in the whole cohort serum bilirubin was unexpectedly low (median 3.7 mg/dl). The in-ICU and in-hospital mortality rates of 25% and 35% differed from previously published data (in-ICU 39%–66% and in-hospital 52–70%).[2–4] Moreover, given that 70% of patients had an infection at the time of ICU admission, this should have further impaired survival.[5]

The authors used the APACHE-II score to compare the severity of illness among patients with and without cirrhosis at ICU admission. This score was demonstrated to be superior to sequential organ failure assessment (SOFA), Child-Pugh and model for end-stage liver disease scores,[6] but inferior to more specific scores, such as chronic liver failure (CLIF)-SOFA and CLIF-Consortium ACLF (CLIF-C ACLF)[7,8] in predicting ICU-prognosis among patients with ACLF.[9] At multivariate analysis, APACHE-II score, but not the presence of ACLF, was significantly associated with the ICU outcome. However, ICU liver transplant-free mortality and 90-day liver transplant-free mortality were