Dealing with the High Bleeding and Thrombosis Risks in Critically Ill Patients with Chronic Liver Disease: A Dilemma in the Clinical Practice

Jo-Nan Liao[1,2,3] Tze-Fan Chao[1,2,3]

[1] Division of Cardiology, Department of Medicine, Taipei Veterans General Hospital, Taipei, Taiwan
[2] Institute of Clinical Medicine, National Yang Ming Chiao Tung University, Taipei, Taiwan
[3] Cardiovascular Research Center, National Yang Ming Chiao Tung University, Taipei, Taiwan

Address for correspondence Tze-Fan Chao, MD, PhD, Division of Cardiology, Department of Medicine, Taipei Veterans General Hospital, No. 201, Sec. 2, Shih-Pai Road, Taipei, Taiwan (e-mail: eyckeyck@gmail.com).

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Chronic liver disease (CLD) is prone to both thrombosis and bleeding because of altered hemostasis marked by impaired regulation of platelet function/aggregation, and a decrease in both procoagulation and anticoagulation factors.[1] The old belief that CLD was associated with increased bleeding and a lower risk of thrombosis has been revisited given that an increased prevalence of thrombosis has been recognized in CLD.[2] Additional critical factors such as infection, renal impairment, or procedural intervention would further exacerbate the imbalance of hemostasis.[3] Of note, standard laboratory tests such as prothrombin time and international normalized ratio (INR) may not be useful in discriminating between hypo- and hypercoagulability or predicting the risk of bleeding/thrombosis at this time. Furthermore, correction of INR levels does not necessarily convey decreased bleeding risk since it is associated with the risk of transfusion-associated complications without a clear benefit. In general, hemostasis and coagulopathy are far more complex in critically ill conditions superimposed on CLD.

Although some studies about hemorrhage and thrombosis in patients with CLD have been reported,[4–6] data in CLD patients in critically ill conditions are scarce (►**Table 1**).[7–10] One retrospective analysis including 67 critically ill cirrhotic patients observed a mortality rate of 40.9%, 48.5% of hemorrhage, and 13.7% of thrombotic complications, with variceal bleeding and portal vein (PV) thrombosis responsible for most hemorrhage and thrombotic events. Factors associated with bleeding episodes included kidney injury, infection, and thrombosis, and factors associated with thrombotic risk were ascites, infection, and bleeding.[8] Cho et al, on the other hand, reported a lower rate of hemorrhage (12.2%) in 205 cirrhotic patients admitted to intensive care unit (ICU) and gastrointestinal (GI) bleeding was the most common origin of bleeding. A low platelet count at admission and sepsis were independent risk factors of major bleeding.[9] Another study by Al-Dorzi et al reported a surprisingly high mortality rate of 80% in 75 critically ill cirrhotic patients, suggesting the wide variation of available data currently.[10]

In this issue of *Thrombosis and Haemostasis*, Ow and colleagues reported the prevalence of hemorrhage and thrombosis in 623 critically ill patients with CLD and the temporal trends of bleeding/thrombosis.[7] A high hospital mortality rate up to 44% was observed, highlighting the frailty of this patient population. Forty-three percent of patients were admitted for bleeding and 14% of patients had later bleeding (>48 hours after admission), with GI bleeding accounting for 72% of later bleeding events. Later bleeding was associated with illness severity and increased hospital mortality. On the other hand, procedure-related bleeding was uncommon. Therefore, procedure-related bleeding should not be a concern to postpone necessary procedures in critically ill patients with CLD. Meanwhile, venous thromboembolism (VTE) appeared in up to 20% of patients and most of them belonged to early VTE (prior to/on admission to ICU), with 85% involving the PV. Risk factors of early and later VTE were different but hepatocellular carcinoma was a common risk factor. Neither early nor later VTE was associated with increased mortality. In this field full of uncertainty, Ow et al did provide a comprehensive picture based on a large study population.

While medication use was less addressed in the current analysis, this is a difficult issue in CLD patients with critically ill conditions. The fact that CLD sometimes coexists with certain cardiovascular diseases further poses medication use complicated. For example, atrial fibrillation (AF), which is the most

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Table 1 Studies about hemorrhage and thrombosis in critically ill patients with chronic liver disease

Studies	Patient (No.)	Mortality rate	Bleeding	Characteristics or risk factors of hemorrhage	Thrombosis	Characteristics or risk factors of thrombosis
Ow et al[7]	623	44%	Early bleeding 43% Later bleeding 14%	• GI bleeding accounts for 72% of later bleeding (mostly secondary to portal hypertension)	20% (13% early VTE; 7.2% later VTE)	• 85% involving portal vein • Risk factors of early VTE: nonalcoholic etiologies of CLD, HCC • Risk factors of later VTE: HCC, administration of cryoprecipitate, bilirubin level
Muciño-Bermejo et al[8]	67	40.9%	48.5%	• Variceal bleeding accounts for 78.1% of hemorrhage • Risk factors: kidney injury, infection, and thrombosis	13.66%	• PV thrombosis accounts for 77.7% of thrombosis • Risk factors: ascites, infection, and bleeding.
Cho et al[9]	205	71.2%	12.2%	• GI bleeding accounts for 64% of hemorrhage • Risk factors: a low platelet count at admission, sepsis	NR	NR
Al-Dorzi et al[10]	75	80%	NR	NR	2.7%	• Thrombosis prophylaxis in 55 patients

Abbreviations: CLD, chronic liver disease; GI, gastrointestinal; HCC, hepatocellular carcinoma; No., number; NR, not reported; PV, portal vein; VTE, venous thromboembolism.

common sustained cardiac arrhythmia in the world, shares common risk factors with CLD.[11–13] AF increases the risk of thromboembolism and ischemic stroke and the coexistence with CLD further raises the risk.[2] Oral anticoagulants (OACs) are sometimes needed to treat liver disease–related VTE or to prevent ischemic stroke/thromboembolism.[14,15] Vitamin K antagonist (VKA) is often the main OAC in patients with CLD, but the narrow therapeutic range, the need for frequent INR monitoring, risk of intracranial hemorrhage, and drug–drug interactions are major problems with VKA use. Besides, an intrinsic INR level above 2.0 is common in patients with advanced CLD even before OAC treatment. The non-VKA OACs (NOACs) have replaced VKA as the mainstream therapy for stroke prevention in AF,[16,17] as recommended by contemporary guidelines.[18] However, the benefit of NOACs in CLD with AF has not been fully established given that most NOACs undergo certain degrees of hepatic metabolism[19] and AF patients with CLD were excluded from the large-scale randomized controlled trials (RCTs) of NOACs, not to mention the scarcity of evidence regarding NOAC use in CLD patients in critical conditions. Besides, patients with advanced anemia or thrombocytopenia, the conditions which were frequently present in CLD patients in critical conditions, were also excluded from RCTs of NOACs.

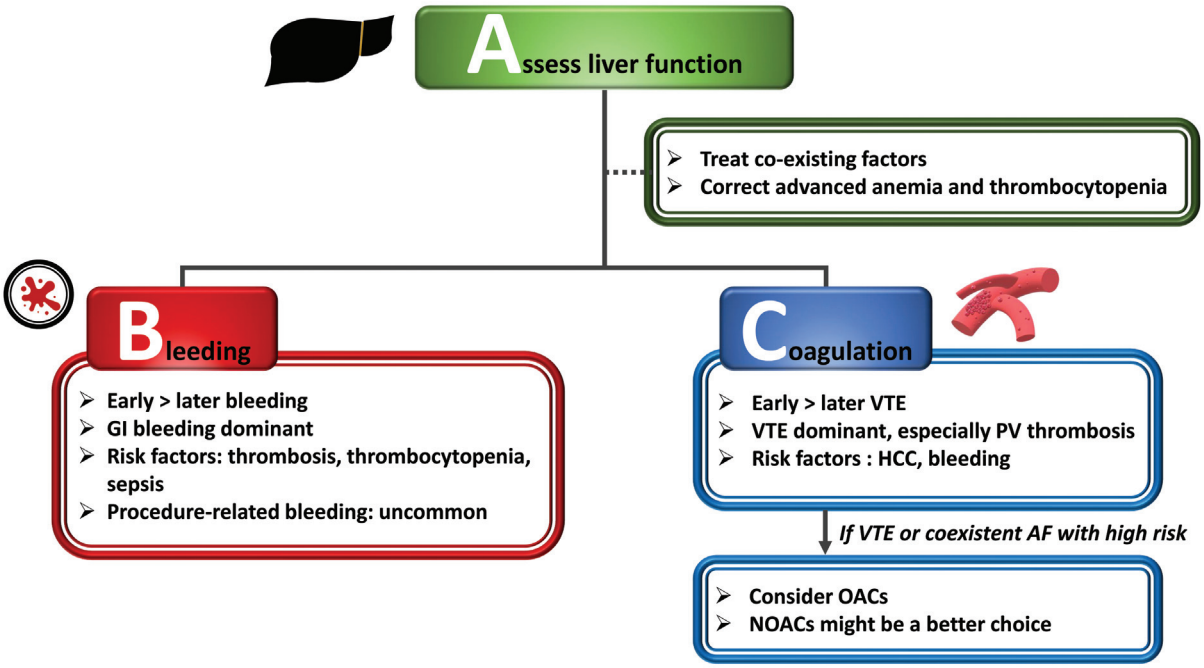

Fig. 1 Key information and considerations of bleeding and coagulation in critically ill patients with chronic liver disease. AF, atrial fibrillation; GI, gastrointestinal; HCC, hepatocellular carcinoma; NOACs, nonvitamin K antagonist oral anticoagulants; OACs, oral anticoagulants; PV, portal vein; VTE, venous thromboembolism.

However, real-world cohort studies have shown better effectiveness and safety of NOACs than VKA or no OAC use in AF patients with CLD. Small series of retrospective analyses have recently examined the safety of NOACs in patients with cirrhosis and showed comparable safety profiles between NOACs and traditional OACs.[20–23] Besides, reversal agents are available for certain NOACs in case of emergent surgeries or major bleeding. Finally, the management issues related to CLD in AF patients can be put into perspective of the guideline-recommended holistic or integrated care approach to AF management,[24] beyond anticoagulation alone.[18] Indeed, adherence to such an approach has been associated with improved clinical outcomes.[25]

In summary, a critical condition would predispose patients with CLD to increasing risks of both hemorrhage and thrombosis. A thorough evaluation of liver function as well as predisposing and coexisting risk factors should be done to identify potentially correctable factors. OACs might be needed in patients with VTE or coexistence of AF with high risk of stroke and judicious decisions for the choice of OACs are necessary. Key information and considerations of bleeding and coagulation in critically ill patients with CLD are summarized as the acronym of "ABC" (A: assess liver function; B: bleeding events; and C: coagulation) (►**Fig. 1**).

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Conflict of Interest
None declared.

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