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Prevalence of Bleeding and Thrombosis in Critically Ill Patients with Chronic Liver Disease

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Abstract

Introduction Hemorrhage and venous thromboembolism (VTE) are recognized complications of chronic liver disease (CLD), but their prevalence and risk factors in critically ill patients are uncertain.

Patients and Methods We studied a retrospective cohort of patients with CLD nonelectively admitted to a specialist intensive care unit (ICU) determining the prevalence and timing of major bleeding and VTE (early, present on admission/diagnosed within 48 hours; later, diagnosed >48 hours post-ICU admission). Associations with baseline clinical and laboratory characteristics, multiorgan failure (MOF), blood product administration, and mortality were explored. Odds ratios (ORs) and 95% confidence intervals (CIs) were calculated using logistic regression.

Results Of 623 patients with median age 52, bleeding (>48 hours after admission) occurred in 87 (14%) patients. Bleeding was associated with greater illness severity and increased mortality. Gastrointestinal bleeding accounted for 72% of events, secondary to portal hypertension in >90%. Procedure-related bleeding was uncommon. VTE occurred in 125 (20%) patients: early VTE in 80 (13%) and involving the portal vein in 85%. Later VTE affected 45 (7.2%) patients. Hepatocellular carcinoma (HCC) and nonalcoholic liver disease were independently associated with early VTE (OR: 2.79, 95% CI: 1.5–5.2 and OR: 2.32, 95% CI: 1.4–3.9, respectively), and HCC, sepsis, and cryoprecipitate use with late VTE (OR: 2.45, 95% CI: 1.11–5.43; OR: 2.26, 95% CI: 1.2–4.3; and OR: 2.60, 95% CI: 1.3–5.1).

Conclusion VTE was prevalent on admission to critical care and less commonly developed later. Bleeding was associated with MOF and increased mortality. Severe MOF was not associated with an increased rate of VTE which was linked with HCC, and specific etiologies of CLD.

Keywords
- liver disease
- critical care
- hemorrhage
- venous thromboembolism

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Introduction

Current paradigms of chronic liver disease (CLD) are of natural history in which a patient with cirrhosis may progress from a state of "stable cirrhosis" (SC) without complications, to a decompensated state in which manifestations of liver failure with jaundice or encephalopathy may be present, or with the development of complications of portal hypertension, ascites, and variceal bleeding.[1] The majority of hospitalized patients are in an "acutely decompensated" (AD) state with progression from SC, often following a precipitating insult. A proportion of those with AD will deteriorate further with the development of multiple extrahepatic organ systems failure and the syndrome of acute-on-chronic liver failure (ACLF) which frequently requires critical care organ support and has high short term mortality.[2–4]

Progression from SC to AD and finally ACLF is paralleled by worsening of laboratory measures of liver synthetic and metabolic function, and by increasing derangement of standard laboratory measures of coagulation and worsening thrombocytopenia.[5] CLD has thus historically been considered a bleeding diathesis. However, laboratory studies utilizing global hemostatic assays that better reflect in vivo hemostatic status suggest that loss of hepatically synthesized procoagulant factors is balanced by concurrent reductions in anticoagulant factors, leading to an overall rebalanced but fragile system.[6,7] Additionally, recent observational studies suggest that much of the bleeding tendency seen in cirrhosis is secondary to portal hypertension.[8,9] Studies also now demonstrate an apparent thrombotic tendency in some patients with cirrhosis, worsening in patients with decompensated disease, with splanchnic vein thrombosis particularly common.[10] Amongst those admitted to hospital, venous thromboembolisms (VTEs) are reported to develop in up to 7%, and may show variation by etiology of CLD.[9,11,12] This thrombotic tendency is poorly characterized and recent studies using global hemostatic assays suggest that there may not be a linear progression of hypercoagulability from SC to AD to ACLF. Although a thrombotic tendency may be seen in many patients with SC, and further exaggerated in those with AD, in ACLF the situation may be more complex, with patients demonstrating functional phenotypes with both hypo- and hypercoagulable features, and with marked variation in fibrinolysis.[5,13]

In acutely ill patients with cirrhosis, additional factors such as infection, renal impairment, and procedural intervention may lead to an increased risk of both bleeding and thrombosis with important clinical implications on the use of both pro- and antihemostatic therapies.[6,14,15] However, data in this setting are very limited and may not reflect either the definitions now used to describe patient state or the effect of current practice on bleeding and thrombotic complications. Over time, the incidence of bleeding in both acute liver failure (ALF) and CLD appears to have significantly decreased.[15] Although portal hypertensive bleeding may often be a precipitant to intensive care unit (ICU) admission, a recent series suggests that later bleeding occurs in only 17% of patients.[16] The current prevalence of thrombotic complications in this setting is unknown.

We therefore evaluated the prevalence of bleeding and thrombosis in a large cohort of patients with cirrhosis admitted to ICU with AD or ACLF. We characterized bleeding and thrombotic complications in relation to nature and severity of liver disease and according to site and timing relative to ICU admission, seeking to describe factors associated with bleeding and thrombosis risk, and the relationship with survival.

Patients and Methods

Setting

A 19-bedded specialist liver intensive therapy unit (LITU) at the Institute of Liver Studies, King's College Hospital—a high-volume liver transplant center and regional referral center for complex hepatology for the South of England. A low threshold for admission is maintained for patients with CLD deteriorating on general wards, and it is the principal site for emergency endoscopic procedures for gastrointestinal bleeding in patients with liver disease.

Study Cohort

We studied a cohort of consecutive patients of $\geq$18 years of age with CLD nonelectively admitted to the LITU from March 2009 to November 2016. Underlying diseases, comorbidities, and reasons for admission were assessed. Patients with previous liver transplantation, ALF (without CLD), and ICU admission of $<$8 hours were excluded. We also excluded those admitted following elective procedures including liver transplantation, nontransplant surgery, and those transplanted from ICU or with a missing hospital outcome. Details of inclusion of patients are shown in ►**Fig. 1**. Cirrhosis was defined by the presence of characteristic clinical, radiological, or histological criteria. Patients were stratified into those with AD and ACLF utilizing the CANONIC study with grading by number of organ failures.[17] Laboratory parameters were determined on admission to ICU and at days 3 and 5 in ICU and admission. Illness severity scores determined included the sequential organ failure assessment score (SOFA), its chronic liver failure variant (CLIF-SOFA), and the model of end-stage liver disease (MELD).[18] Radiology reports relevant to each admission and details of thromboprophylaxis (TP) and blood product use were obtained from the patient medical record, the electronic patient record (Allscripts Sunrise, Chicago), and a prospective critical care database maintained by trained audit personnel with regular validation.

During the study period, no formal protocol existed for the timing of initiation of TP within ICU; however, patients had daily individual assessment of risk–benefit and typically commenced TP within 1 week of admission. In the absence of bleeding, cirrhosis patients requiring therapeutic anticoagulation received a continuous intravenous infusion of unfractionated heparin to maintain activated partial thromboplastin time ratio (APTR) values usually in the range of 2.0 to 2.5 The threshold for packed red blood cell

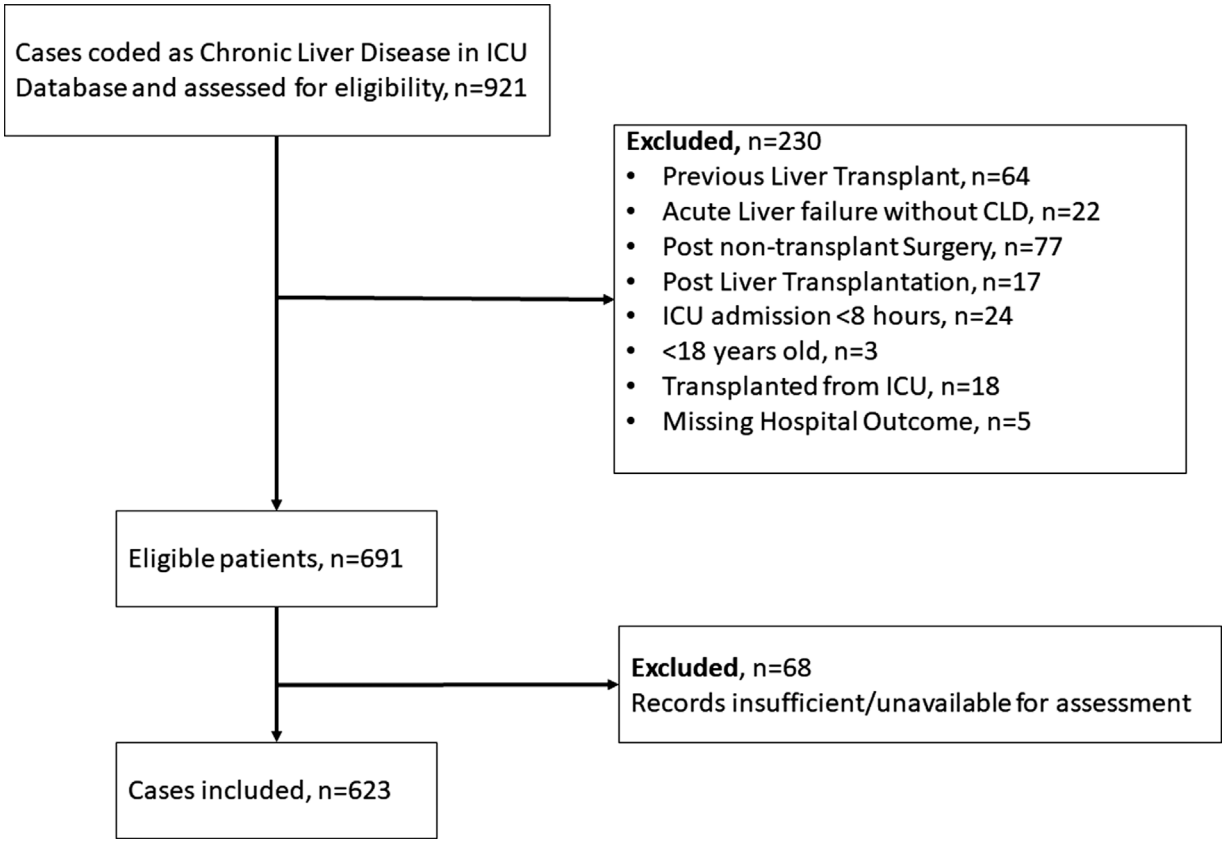

Fig. 1 Study flow chart.

transfusion was hemoglobin less than 7 g/L, except in patients with known coronary heart disease where a threshold below 8 g/dL was used. Administration of coagulation products was primarily limited to patients with active bleeding. However, patients with platelet counts $<10 \times 10^9$/L received substitution of platelets. Prophylactic substitution of coagulation products prior to interventional procedures assessed as low risk was not routinely performed. Patients received stress ulcer prophylaxis with proton pump inhibitors until enteral feed was successfully established when continued use was reviewed. All nonelective admissions to the unit undergo abdominal radiological evaluation with either Doppler ultrasound or triphasic computed tomography within 24 hours of arrival. Later imaging to identify vascular complications was at the discretion of the treating intensivist.

Outcome Definitions

Bleeding complications were defined as per the International Society on Thrombosis and Haemostasis definition for major bleeding encompassing fatal bleeding, symptomatic bleeding in a critical area or organ (intracranial, intraspinal, intraocular, retroperitoneal, intra-articular or pericardial, intramuscular bleeding with compartment syndrome), and/or bleeding causing a fall in hemoglobin level of $\geq$2 g/dL or leading to transfusion of $\geq$2 units of packed red cells.[19] Bleeding was further classified according to time of onset (present on admission, i.e., with bleeding requiring medical or surgical intervention at the time of admission to LICU versus later onset, bleeding occurring at any time following admission to LICU), location of bleeding, whether the bleeding was secondary to a procedure or spontaneous, and related to portal hypertension or not.[16] VTE required objective confirmation with imaging and was classified according to time of onset as early (prior to or within 48 hours of admission) or later (diagnosed >48 hours after admission) and location (portal/splanchnic vein thrombosis, limb thrombosis, or pulmonary embolism).[20] The duration of follow-up was until hospital discharge or death, whichever was sooner.

Statistical Analysis

Continuous variables are reported as median and interquartile range (IQR). Nominal data were compared between groups with Chi-square and Fisher's exact test as appropriate and are presented as number (percentage). Binary logistic regression was performed to explore independent associations with bleeding or thrombotic events and to calculate odds ratios (ORs) with 95% confidence intervals (CIs). Variables of interest included age, gender, severity of liver disease (AD or ACLF, MELD, and ACLF-SOFA score), alcohol versus nonalcohol etiology, presence/absence of hepatocellular carcinoma (HCC), mortality, and laboratory variables (bilirubin, creatinine, sodium, international normalized ratio [INR], APTR, fibrinogen, platelet count). For later VTE events, use of tranexamic acid, fresh frozen plasma (FFP), and cryoprecipitate was also considered. All variables associated with a $p < 0.2$ in univariable analysis were evaluated for

inclusion in the final multivariable model, with additional inclusion of the year of admission to adjust for "era" of treatment. The final multivariable model was developed using backward elimination and included only those variables that were associated with a $p < 0.05$. All statistical analysis was undertaken utilizing IBM SPSS version 25 software (IBM, Armonk, New York, United States). Use of de-identified data was approved by the King's College Hospital Research Ethics Committee.

Results

Six-hundred and twenty-three patients meeting the inclusion criteria were studied. Median length of ICU stay was 5 days (IQR: 2–11) and hospital stay 17 days (IQR: 8–35). Baseline characteristics and underlying etiology of liver disease are summarized in ►**Table 1**. Median age was 52 years (IQR: 43–61) and 61% were male; 47% had alcohol as the primary cause of CLD, 19% chronic viral infection, and in 34% other causes were responsible. Seventy-seven (12%) of patients had HCC. The median MELD score was 26 (17–33) and CLIF-SOFA 11 (9–13). On admission, 30% ($n = 187$) fulfilled criteria for AD and 70% ($n = 436$) for ACLF. The distribution of patients by illness severity and mortality is illustrated in ►**Fig. 2**. Hospital mortality was 44% ($n = 275$) overall, lowest in those admitted with AD at 15% (28 of 187) and highest at 73% (159 of 219) in those in ACLF 3.

Data on TP were available for 538/623 (86%) of the study cohort. Overall, 111/538 (21%) received heparin as TP—though this increased over time from 9% of admissions in 2009 to 40% of those admitted in 2016.

Bleeding Events

Two-hundred sixty-eight (43%) patients were admitted with bleeding; this was predominantly gastrointestinal ($n = 233$, 86%), with 90% of these bleeds secondary to portal

Table 1 Clinical characteristics of study cohort according to hospital survival

	Total	Survivors	Nonsurvivors
N	623	348	275
Age (y), median (IQR)	52 (43–61)	51 (41–60)	53 (45–61)
Male gender, *n* (%)	383 (61%)	214 (61%)	169 (61%)
Etiology			
Alcohol, *n* (%)	317 (51%)	189 (54%)	128 (47%)
Viral, *n* (%)	92 (15%)	46 (13%)	46 (17%)
Autoimmune/cholestatic, *n* (%)	106 (17%)	57 (16%)	49 (18%)
Nonalcoholic fatty liver disease, *n* (%)	43 (7%)	23 (7%)	20 (7%)
Other, *n* (%)	65 (10%)	33 (10%)	32 (12%)
HCC, *n* (%)	77 (12%)	38 (11%)	39 (14%)
Sepsis on admission, *n* (%)	242 (39%)	115 (33%)	127 (46%)
Illness severity scores			
MELD, median (IQR)	26 (17–33)	21 (14–28)	31 (24–37)
CLIF-SOFA, median (IQR)	11 (9–13)	10 (8–11)	13 (11–15)
ACLF grade			
AD, *n* (%)	187 (30%)	159 (46%)	28 (10%)
ACLF 1, *n* (%)	73 (12%)	47 (14%)	26 (9%)
ACLF 2, *n* (%)	144 (23%)	82 (24%)	62 (23%)
ACLF 3, *n* (%)	219 (35%)	60 (17%)	159 (58%)
Admission laboratory parameters			
Bilirubin (mmol/L), median (IQR)	116 (48–264)	73 (39–172)	207 (86–389)
Creatinine (mmol/L), median (IQR)	120 (79–187)	99 (70–152)	156 (106–236)
Sodium (mmol/L), median (IQR)	136 (131–140)	136 (132–140)	136 (130–140)
INR, median (IQR)	2 (1.6–2.7)	1.8 (1.5–2.3)	2.3 (1.8–3.2)
APTR, median (IQR)	1.53 (1.3–1.9)	1.4 (1.3–1.7)	1.7 (1.4–2.1)
Fibrinogen (g/dL), median (IQR)	1.8 (1.4–2.4)	1.9 (1.4–2.6)	1.6 (1.2–2.2)
Platelet count ($\times 10^9$/L), median (IQR)	87 (58–126)	89 (62–125)	85 (53–129)

Abbreviations: ACLF, acute-on-chronic liver failure; ADA, acute decompensation; APTR, activated partial thromboplastin time ratio; CLIF-SOFA, chronic liver failure-sequential organ failure assessment score; HCC, hepatocellular carcinoma; INR, international normalized ratio; IQR interquartile range; MELD, model for end-stage liver disease.

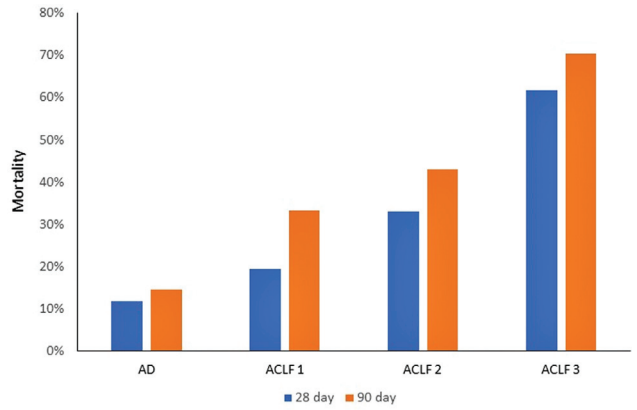

Fig. 2 28- and 90-day mortality in study cohort according to acute decompensation (AD) or acute on chronic liver failure (ACLF) grade on intensive care unit admission. Note: AD: $n = 187$, ACLF 1: $n = 73$, ACLF 2: $n = 144$, ACLF 3: $n = 219$.

hypertension (based on endoscopy and/or imaging findings) ($n = 210$). There were 35 nongastrointestinal bleeding events which included 4 from ruptured HCC, 4 intracranial bleeds, and 10 procedure-related bleeds precipitating admission: 3 complicated paracentesis, 2 followed ERCP (endoscopic retrograde cholangiopancreatography) with sphincterotomy, 1 after liver biopsy, 2 after surgical procedures, and 2 after vascular and urinary catheter removal.

Eighty-seven patients (14%) had later bleeding events at a median of 9 (4–16) days after admission, of which 72% ($n = 60$) were gastrointestinal bleeds with 91% ($n = 55$) secondary to portal hypertension. Of the 23 (28%) nongastrointestinal bleeds, 10 were secondary to procedures (following paracentesis, $n = 5$, two complicating line insertion, $n = 2$, liver biopsy, $n = 1$, bladder catheterization, $n = 1$, and thoracentesis, $n = 1$) with 13 spontaneous events (intracranial, $n = 2$; pulmonary, $n = 3$, retroperitoneal, $n = 4$, and other, $n = 4$).

Characteristics of patients with bleeding are summarized in ►**Table 2**. Late bleeding occurred in 25 of 268 (9%) of those admitted with bleeding as compared with 62 of 354 (18%) of those admitted for nonbleeding indications ($p < 0.005$). Patients with later bleeding were more often admitted in ACLF (83 vs. 68%, $p < 0.001$) with higher MELD scores (28 [21–33] vs. 25 [15–33], $p < 0.001$), and higher bilirubin, INR, and APTR values with lower fibrinogen and higher mortality (60 vs. 42%, $p < 0.005$). Heparin administration was not associated with late bleeding (18 vs. 12%, $p = 0.07$).

Table 2 Characteristics of patients in study cohort according to development of bleeding on or after ICU admission

	Admission bleeding event			Later bleeding event		
	Yes	No	*p*-Value	Yes	No	*p*-Value
N	268	354		87	536	
Age, y (IQR)	51 (41–61)	52 (44–62)		50 (42–57)	52 (43–61)	ns
Male gender, *n* (%)	173 (65%)	210 (59%)	ns	61 (70%)	322 (60%)	ns
AD, *n* (%)	120 (45%)	67 (19%)	<0.001	15 (17%)	172 (32%)	<0.001
ACLF, *n* (%)	148 (55%)	287 (81%)	<0.001	72 (83%)	364 (68%)	<0.001
Etiology						
Alcohol, *n* (%)	154 (57%)	162 (46%)	0.004	47 (54%)	270 (50%)	ns
Nonalcohol, *n* (%)	114 (43%)	192 (54%)	0.004	40 (46%)	266 (50%)	ns
HCC, *n* (%)	35 (13%)	42 (12%)		8 (9%)	69 (13%)	ns
Sepsis on admission, *n* (%)	36 (13%)	205 (58%)	<0.001	42 (48%)	27 (5%)	<0.001
MELD (IQR)	21.6 (14–31)	27.9 (21–34)		28.2 (21–33)	24.9 (15–33)	<0.001
CLIF-SOFA (IQR)	10 (8–12)	12 (10–14)		12 (10–14)	11 (9–13)	<0.001
In-hospital mortality, *n* (%)	98 (37%)	176 (50%)	0.001	52 (60%)	223 (42%)	<0.005
Admission laboratory parameters						
Bilirubin, μmol/L	91 (43–230)	125 (53–300)	0.02	162 (56–322)	113 (47–250)	0.01
Creatinine, μmol/L	102 (69–164)	137 (92–203)	<0.001	148 (108–194)	116 (76–184)	<0.001
Sodium, mmol/L	137 (134–141)	135 (130–138)	<0.001	136 (132–140)	136 (131–140)	0.06
INR (IQR)	1.8 (1.5–2.2)	2.3 (1.7–3.0)	<0.001	2.1 (1.6–2.9)	2.0 (1.6–2.7)	<0.01
APTR (IQR)	1.38 (1.3–1.6)	1.7 (1.4–2.0)	<0.001	1.6 (1.4–1.9)	1.5 (1.3–1.9)	<0.001
Fibrinogen, g/dL (IQR)	1.8 (1.4–2.4)	1.6 (1.2–2.5)	0.07	1.6 (1.4–2.2)	1.8 (1.4–2.5)	0.05
Platelet count, $\times 10^9$/L (IQR)	90 (60–130)	85 (57–121)		92 (61–128)	87 (57–126)	ns

Abbreviations: ACLF, acute-on-chronic liver failure; AD, acutely decompensated; APTR, activated partial thromboplastin ratio; CLIF-SOFA, chronic liver failure-sequential organ failure assessment score; HCC, hepatocellular carcinoma; ICU, intensive care unit; INR, international normalized ratio; IQR, interquartile range; MELD, model of end-stage liver disease.

Thrombotic Events

Thrombotic complications (VTE) occurred in 125 (20%) patients; 80 (13%) with events identified prior to/on admission to ICU. Of these, 41 patients (6.5%) had events diagnosed prior to admission with 37 (90%) portal vein thrombosis (PVT), 1 (2.4%) deep vein thrombosis (DVT), and 6 other events. VTE was diagnosed within 48 hours of admission in 39 patients: 31 (79%) PVT, 3 (7.7%) DVT, and 12 other events: 10 spleno-mesenteric venous thromboses (8 in the context of new PVT), 1 caval thrombosis, and 1 cortical vein thrombosis.

Forty-five (7.2%) new VTEs were diagnosed >48 hours after ICU admission at a median of 10 (IQR: 6–16) days. PVT accounted for 55% ($n = 25$), with 9 DVT (20%), 8 PE (17%), and 16 other thrombotic events. These comprised 8 spleno-mesenteric thromboses (6 in the context of PVT), 3 caval thromboses, 3 hepatic venous thromboses, 1 cortical vein thrombosis, and 1 atrial thrombosis.

Comparison of patients who developed early or later VTE is shown in ►**Table 3**. Neither was associated with increased mortality. As compared with those without VTE on admission, those identified with VTE before or early on admission were older, more often had nonalcoholic etiologies of CLD (69 vs. 46%, $p < 0.001$), and had HCC (30 vs. 9%, $p < 0.001$). There were no significant differences in laboratory markers examined. Later VTE was also associated with HCC (22 vs. 12%, $p < 0.05$) but not age, etiology of CLD, or laboratory markers. During ICU stay cryoprecipitate was administered to 21 of 45 (47%) of those developing late VTE as compared with 183 of 578 (32%) who did not ($p < 0.05$). The median amount of cryoprecipitate administered was 4 (2–9) pools and median time to VTE diagnosis after cryoprecipitate administration was 2 (range: 1–7) days. Comparison of patients who did or did not receive cryoprecipitate is shown in ►**Supplementary Tables S1** and **S2** (available in the online version). Data on tranexamic acid use were incomplete but were not associated with VTE risk alone or in combination with cryoprecipitate/FFP use as shown in ►**Supplementary Table S3** (available in the online version).

On multivariable regression analysis, independent association with early VTE remained with HCC (OR: 2.79, 95% CI: 1.49–5.21) and nonalcoholic etiology (OR: 2.38, 95% CI: 1.4–4.04) (►**Table 4**). Independent association with late VTE was seen with HCC (OR: 2.46, 95% CI: 1.11–5.44), sepsis on admission (OR: 2.26, 95% CI: 1.19–4.27), administration of cryoprecipitate (OR: 2.60, 1.34–5.1), and bilirubin (OR: 0.995, 95% CI: 0.992–0.998) (►**Table 5**).

Comparison of prevalence of early and late VTE by etiology of CLD is shown in ►**Fig. 3**. After exclusion of patients with HCC ($n = 77$), significant differences in prevalence were seen between etiologies in early but not late VTE, with the highest proportions of early VTE seen in nonalcoholic fatty liver disease (NAFLD; 18.2%), primary sclerosing cholangitis (PSC; 20%), and viral hepatitis (12.7%), and lowest in alcoholic liver disease (5.8%).

Discussion

In our study in a specialist liver critical care unit, we found that bleeding events were common in critically ill patients with cirrhosis, with major hemorrhage affecting 55% of all patients admitted. However, this high figure likely reflects the admission practices of our specialist unit, where emergency endoscopic procedures for gastrointestinal bleeding are performed. Later bleeding was uncommon, seen in only 14% of admissions and as a complication of advanced CLD with patients having higher MELD, severe ACLF, and greater mortality. While overall mortality in this cohort was high (44%), this is consistent with previous observations.[2] The frequency of later bleeding parallels Drolz and colleagues' observations of later bleeding in 17% of an ICU cohort.[16] Like Drolz et al, we also found that gastrointestinal bleeding secondary to portal hypertension predominated and that significant procedure-related bleeding was very uncommon, seen in only 3% of patients overall and representing 6% of bleeding events. Procedural bleeding was more frequent in the late bleeding group but remained uncommon representing 11% of all late bleeds, a figure lower than that seen in the Drolz et al's cohort (20%). We noted increased use of heparin for VTE prophylaxis over time but this was not associated with increased late bleeding events, confirming findings in noncritically ill patients with liver disease.[21]

Blood product use was common in our cohort, with nearly two-thirds (62%) of patients receiving FFP and a third (34%) cryoprecipitate. English national audit of blood product use in hospitalized patients with cirrhosis reported 30% (391/1,313) received blood products during admission with 10% receiving FFP, 5% platelets, and <1% cryoprecipitate. The majority of transfusion (61%) was for treatment of bleeding with the remainder transfused prophylactically (of which 39% was in the peri-procedural setting).[22] The need for peri-procedural blood product support is now increasingly questioned and the practice that we report from this cohort must be regarded as historic. The majority of procedures performed in patients with cirrhosis carry a low bleeding risk.[23] Abnormal standard hemostatic markers have not been consistently associated with bleeding risk.[15] Additionally recent small randomized controlled trials of viscoelastic-test-guided blood product use highlight that high bleeding risk procedures can be safely performed without blood product support.[24,25] International guidance documents now recommend against the use of FFP in this setting, with platelet support restricted to high-risk procedures only.[23,26] In CLD patients with acute gastrointestinal bleeding, it has been demonstrated that a restrictive approach to red cell replacement is associated with lower portal pressure gradients, less variceal rebleeding, and improved survival.[27] The current approach to major bleeding in cirrhosis requires further evaluation; the optimal target ratios of red cells to plasma and/or thresholds for platelet/fibrinogen support are extrapolated from other settings, where bleeding-associated coagulopathy is evident. Given routine hemostatic markers are often abnormal in patients with cirrhosis prior to bleeding, whether these targets are appropriate is unknown. Small studies suggest that both thrombin generation and fibrin stability are preserved in bleeding patients with cirrhosis (compared with nonbleeding patients).[13,28] Future studies should

Table 3 Characteristics of patients in study cohort according to development of venous thromboembolism before/on or later after ICU admission

	Prior/admission thrombotic event			Later thrombotic event		
	Yes	No	*p*-Value	Yes	No	*p*-Value
N	80	543		45	578	
Median age, y (IQR)	58 (48–63)	51 (42–60)	0.02	53 (47–60)	51 (42–61)	ns
Male gender, *n* (%)	53 (66%)	330 (61%)	ns	30	353	ns
AD, *n* (%)	28 (35%)	159 (29%)	ns	9	178	ns
ACLF, *n* (%)	52 (65%)	384 (71%)		36	400	
Etiology						
Alcohol, *n* (%)	25 (31%)	292 (54%)	<0.001	22	295	ns
Nonalcohol, *n* (%)	55 (69%)	251 (46%)	ns	23	283	
HCC, *n* (%)	24 (30%)	53 (9%)	<0.001	10 (22%)	67 (12%)	<0.05
Admission for bleeding, *n* (%)	34 (43%)	234 (43%)		17 (38%)	251 (43%)	ns
Sepsis on admission, *n* (%)	25 (31%)	217 (40%)	ns	24 (53%)	218 (38%)	<0.05
Median MELD (IQR)	25.8 (17–32)	25.7 (17–33)	ns	26.1 (17–31)	25.8 (17–33)	ns
Median CLIF-SOFA (IQR)	10 (8–13)	11 (9–14)	ns	11 (9–13)	11 (9–14)	ns
In-hospital mortality, *n* (%)	27 (34)	238 (44)	ns	21 (47)	254 (44)	ns
Admission laboratory parameters						
Median bilirubin, μmol/L (IQR)	80 (43–196)	121 (50–282)	ns	81 (30–147)	121 (48–282)	0.005
Median creatinine, mmol/L (IQR)	132 (82–193)	119 (79–186)	ns	142 (94–221)	119 (79–182)	ns
Median sodium, mmol/L (IQR)	135 (129–139)	136 (132–140)	ns	137 (131–140)	136 (131–140)	ns
Median INR (IQR)	2.0 (1.6–2.9)	2.0 (1.6–2.7)	ns	2.0 (1.5–2.4)	2.0 (1.6–2.7)	ns
Median APTR (IQR)	1.5 (1.3–2)	1.5 (1.3–1.9)	ns	1.53 (1.3–1.9)	1.5 (1.3–1.8)	ns
Median fibrinogen, g/dL (IQR)	1.6 (1.2–2.5)	1.8 (1.4–2.5)	ns	1.8 (1.4–2.6)	1.8 (1.4–2.4)	ns
Median platelet count, $\times 10^9$/L (IQR)	86 (64–112)	87 (57–127)	ns	89 (51–171)	87 (59–123)	ns
Blood product use						
FFP[a], *n*/total (%)	42/77 (55%)	336/541 (62%)	ns	27/44 (61%)	351/574 (61%)	ns
Cryoprecipitate[a], n/total (%)	26/77 (34%)	178/541 (33%)	ns	21/44 (48%)	183/574 (32%)	0.04

Abbreviations: ACLF, acute-on-chronic liver failure; AD, acutely decompensated; APTR, activated partial thromboplastin ratio; CLIF-SOFA, chronic liver failure-sequential organ failure assessment score; HCC, hepatocellular carcinoma; ICU, intensive care unit; INR, international normalized ratio; IQR, interquartile range; MELD, model of end-stage liver disease.
[a]Data missing for up to 4 patients per group, total patients with data reported.

prospectively evaluate the optimal utilization of blood product support in both the management and peri-procedural prevention of bleeding and confirm whether alternate hemostatic assays are of use in these settings.

Overall, we found thrombosis to be common, affecting 20% of our study cohort. However, the majority of VTE was identified either prior to or on admission to critical care, with VTE present in 13% of admissions. Later thrombosis was identified in 7% of admissions, a figure that closely parallels the previously reported prevalence in a hospitalized cohort of patients with decompensated CLD.[9] The higher prevalence in patients before or on admission may suggest that while patients with AD but without the requirement of organ support have an increased prothrombotic tendency, this is

Table 4 Uni- and multivariable logistic regression analysis of variables associated with VTE identified <48 hours after admission

	Univariate			Multivariate[a]		
Variable	**OR**	**95% CI**	***p*-Value**	**OR**	**95% CI**	***p*-Value**
Clinical features						
Age	1.017	0.997–1.037	0.089			
Male gender	2.87	0.77–2.07	0.789			
Nonalcohol etiology	2.559	1.549–4.228	<0.001	2.32	1.387–3.871	0.001
HCC	3.954	2.268–6.894	<0.001	2.79	1.492–5.213	0.001
Bleeding on admission	0.973	0.605–1.564	0.910			
Sepsis on admission	0.683	0.886–2.422	0.137			
MELD	1.005	0.983–1.027	0.669			
CLIF-SOFA	0.964	0.888–1.046	0.379			
Laboratory values						
Bilirubin	0.999	0.998–1.001	0.274			
Sodium	0.965	0.936–0.996	0.027			
Creatinine	1	0.997–1.002	0.666			
INR	1.102	0.950–1.278	0.200			
APTR	0.984	0.853–1.136	0.830			
Fibrinogen	0.936	0.734–1.193	0.592			
Platelets	0.999	0.996–1.002	0.561			
Blood product use						
FFP	0.732	0.453–1.184	0.204			
Cryoprecipitate	0.987	0.598–1.629	0.960			

Abbreviations: APTR, activated partial thromboplastin time ratio; 95% CI, 95% confidence interval; CLIF-SOFA; chronic liver failure-sequential organ failure assessment score; FFP, fresh frozen plasma; HCC, hepatocellular carcinoma; INR; international normalized ration; MELD, model for end-stage liver disease; OR: odds ratio.

[a]All variables associated with a $p < 0.2$ in univariable analysis were evaluated for inclusion in the final multivariable model. The final multivariable model was developed using backward elimination and included only those variables that were associated with a $p < 0.05$ and the year of admission to adjust for era effects.

not further exaggerated in those who develop ACLF—but does suggest that VTE may form or accompany precipitating events leading to the need for ICU admission. This also explains the inverse relationship observed with bilirubin, with higher levels associated with a lower risk of later VTE.

In common with previous reports, we found PVT to be the predominant manifestation of VTE, often with further complicating porto-mesenteric or splenic venous involvement, suggesting these vascular beds that are at principal risk of VTE in patients with CLD admitted to ICU. We also identified that the majority of later VTE were identified early in the second week of ICU admission. Critical illness is a dynamic process with changes over time in organ support requirements, immunological status, and systemic inflammation. It is likely that this is paralleled by changes in thrombotic risk, and the limited data available similarly suggest that more than half of VTE events in critical care patients with medical illness occur in the second week of ICU admission.[29] VTE TP should therefore be considered early in ICU admission. The lack of association between bleeding and heparin use is reassuring but likely reflects considered decision making regarding risk–benefit, given its use in less than half of the cohort. We also identified risk factors for VTE in these patients, and importantly they varied according to the timing of VTE. As expected, the presence of HCC was associated with markedly increased risk of both early and late VTE, but associations with etiology of CLD were apparent only in those with early VTE. An increased risk of VTE in certain etiologies including NAFLD, PSC, and chronic infection with hepatitis C virus has been previously reported[10,30,31] and we confirm this—but this association did not hold after ICU admission, potentially reflecting either changes in the prothrombotic state or the effects of therapy used during ICU admission. Sepsis at admission was associated with later VTE; infection and sepsis have been previously reported as a risk factor for VTE in critically ill patients.[32,33] Portal venous flow has been reported as an independent predictor of PVT development;[34,35] this was not routinely measured during the study period. We found no association between VTE/PVT and mortality. This conflicts with previous reports of increased mortality in both population-based studies of those awaiting liver transplant and prospective observational cohorts.[10,36,37] It is possible that the relatively high use of heparin in our cohort reflects

Table 5 Uni- and multivariable logistic regression analysis of variables associated with VTE identified >48 hours after admission

	Univariate			Multivariate[a]		
Variable	OR	95% CI	*p*-Value	OR	95% CI	*p*-Value
Clinical features						
Age	1.006	0.981–1.031	0.661			
Male gender	1.276	0.670–2.42	0.459			
Nonalcohol etiology	1.090	0.594–1.99	0.781			
HCC	2.175	1.03–4.593	0.042	2.457	−1.111–5.435	0.026
Bleeding on admission	0.789	0.422–1.473	0.456			
Sepsis on admission	1.887	1.026–3.47	0.041	2.257	1.192–4.274	0.012
MELD	0.987	0.959–1.016	0.367			
CLIF-SOFA	1.014	0.913–1.125	0.797			
Laboratory values						
Bilirubin	0.996	0.994–0.999	0.007	0.995	0.992–0.998	0.001
Sodium	1	0.996–1.003	0.927			
Creatinine	1.001	0.999–1.003	0.432			
INR	0.810	0.588–1.117	0.200			
APTR	0.794	0.443–1.422	0.438			
Fibrinogen	0.986	0.727–1.336	0.926			
Platelets	1.002	0.999–1.005	0.177			
Blood product use						
FFP	1.009	0.538–1.894	0.978			
Cryoprecipitate	1.889	1.025–3.481	0.041	2.604	1.335–5.102	0.005

Abbreviations: APTR, activated partial thromboplastin time ratio; 95% CI, 95% confidence interval; CLIF-SOFA; chronic liver failure-sequential organ failure assessment score; FFP, fresh frozen plasma; HCC, hepatocellular carcinoma; INR; international normalized ration; MELD, model for end-stage liver disease; OR: odds ratio.

[a]All variables associated with a $p < 0.2$ in univariable analysis were evaluated for inclusion in the final multivariable model. The final multivariable model was developed using backward elimination and included only those variables that were associated with a $p < 0.05$ and the year of admission to adjust for era effects.

provision of timely treatment, mitigating any potential impact on early survival, but it may also be that that any impact is on longer term survival.

A novel observation which may have practical implications was of the association between the administration of cryoprecipitate and late VTE. We found no such association with the administration of FFP. To confirm this association, we clarified both the temporal relationship to VTE and the dose of cryoprecipitate used and both were consistent with use prior to VTE and at standard doses. The principal indication for the use of cryoprecipitate in our unit was for the correction of hypofibrinogenemia in acute bleeding or prior to higher risk procedures. We did not collect serial fibrinogen levels and were unable to examine the effect of cryoprecipitate in correcting hypofibrinogenemia. Cryoprecipitate use in the context of liver transplantation has been associated with increased thrombotic complications in two independent retrospective cohorts,[38,39] with increased cryoprecipitate use noted following the implementation of viscoelastic testing.[39] Cryoprecipitate use was higher in our cohort (30%) than reported in national cohorts of hospitalized, noncritically ill patients with cirrhosis (<1%) and in those with variceal bleeding (7%).[22,40] A recent observational cohort found low fibrinogen to represent disease severity; while cryoprecipitate effectively increased fibrinogen, it did not reduce later bleeding.[41] Although the great majority of patients receiving cryoprecipitate did not develop VTE, these data suggest that caution should be applied to its use in critically ill patients with CLD, particularly if other risk factors for VTE are present. There is a need for further studies to confirm or refute this association. Given the lack of evidence to support a role for cryoprecipitate in either the management of major bleeding in patients with cirrhosis or the peri-procedural setting, randomized controlled studies should be undertaken to further evaluate the risk–benefit profile.

Limitations

There are potentially important limitations to this study in that we report a single-center retrospective cohort, with incomplete data regarding the use of all hemostatic products (i.e., red blood cells, platelets, and tranexamic acid), the dose and timing of TP initiation, and lack of consistent formal protocol for use of FFP, cryoprecipitate, and TP over the

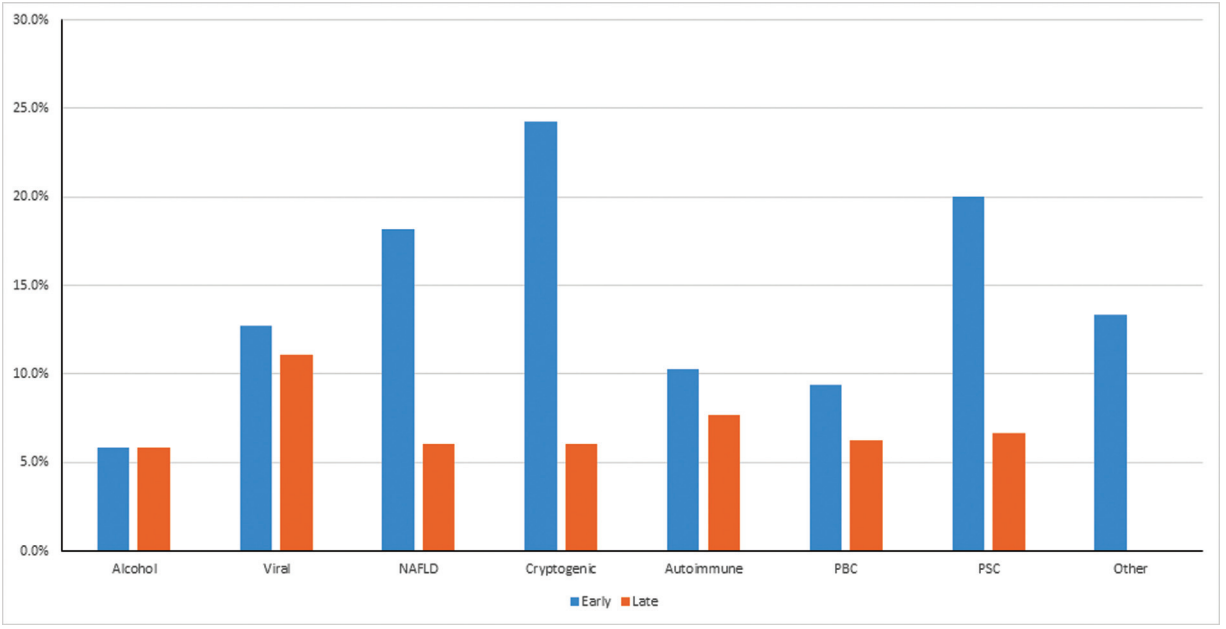

Fig. 3 Prevalence of early and late venous thromboembolism after intensive care unit admission according to primary etiology of chronic liver disease. Note: patients with hepatocellular cancer excluded. Comparison of prevalence of early VTE: $p < 0.01$; late: $p =$ ns. Alcohol: $n = 291$, viral: $n = 63$, nonalcoholic fatty liver disease (NAFLD): $n = 39$, cryptogenic: $n = 33$, autoimmune: $n = 39$, primary biliary cholangitis (PBC): $n = 32$, primary sclerosing cholangitis (PSC): $n = 30$. Other: $n = 30$ (Alagille syndrome: $n = 1$, alpha-1 antitrypsin deficiency: $n = 6$, biliary atresia: $n = 2$, cholestatic liver disease: $n = 2$, congenital hepatic fibrosis: $n = 1$, cystic fibrosis: $n = 1$, hemochromatosis: $n = 1$, hepatic venopathy: $n = 1$, schistosomiasis: $n = 1$, sickle hepatopathy: $n = 1$, secondary biliary cirrhosis: $n = 2$, Wilson's disease: $n = 4$).

course of the study period. Of note, tranexamic acid was used infrequently. The inclusion of early bleeding events may be a source of bias given local practice to admit all those with major bleeding to LICU as a site for endoscopic procedures.

Conclusion

Bleeding complications predominate in critically ill patients with cirrhosis, with later bleeding events adversely impacting on survival. Thrombosis, particularly PVT, is also common both on admission and later, but was not more common than in less severe illness and does not influence short-term survival.

What is known about this topic?

- Chronic liver disease (CLD) is associated with increased risk of both bleeding and thrombosis.
- These complications are less well studied in the critically ill subpopulation.

What does this paper add?

In critically ill patients with CLD:

- Bleeding events occurred in 14% and were associated with increased mortality.
- Bleeding secondary to procedures was uncommon (3% overall).
- Venous thromboembolism is commonly present on admission to ICU, but less frequent later in admission (7%) with no adverse impact on hospital survival.

Author Contributions

W.B. conceived and supervised the study and design, data analysis and interpretation, and critical review of the paper. T.-W.O. led data collection, interpretation, and writing of the manuscript. L.N.R. contributed to study design, data interpretation, and writing of the manuscript. E.F., L.R., S.N., and B.v.d.B. collected data. V.C.P., B.H., and M.M. interpreted the data and critically reviewed the manuscript. All authors revised and approved the final submission.

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Conflict of Interest

None declared.

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