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# The Spectrum of Disease Severity in Cirrhosis and Its Implications for Hemostasis

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**Abstract**

Bleeding and thrombosis are both common complications that patients with advanced liver disease experience. While hemostatic pathways remain largely intact with cirrhosis, this balance can quickly shift in the direction of bleeding or clotting in an unpredictable manner. A growing body of literature is attempting to shed light on difficult scenarios that clinicians often face, ranging from predicting and mitigating bleeding risk in those who need invasive procedures to determining the best strategies to manage both bleeding and thrombotic complications when they occur. Studies examining hemostasis in those with advanced liver disease, however, often include heterogeneous cohorts with varied methodology. While these studies often select a cohort of all types and degrees of cirrhosis, emerging evidence suggests significant differences in underlying systemic inflammation and hemostatic abnormalities among specific phenotypes of liver disease, ranging from compensated cirrhosis to decompensated cirrhosis and acute-on-chronic liver failure. It is paramount that future studies account for these differing disease severities if we hope to address the many critical knowledge gaps in this field.

**Keywords**
► coagulation
► hemostasis
► cirrhosis
► acute-on-chronic liver failure

With advanced liver disease, progressive liver dysfunction and portal hypertension alter hemostatic pathways in a variety of ways. Deficiencies in hepatocyte-derived procoagulant and anticoagulant factors, abnormalities in platelet number and function, and dysregulation of the fibrinolytic system all contribute to the acquired coagulopathy seen in chronic liver disease.[1–3] It is now accepted that the hemostatic system is "rebalanced" in cirrhosis, with any clinical deterioration predisposing these patients to inappropriate bleeding or clotting.[4,5] In this setting, a growing body of literature is attempting to address a variety of challenging clinical scenarios that providers face when caring for these patients, including mitigating bleeding risk in those undergoing invasive procedures and developing strategies to manage both bleeding and thrombosis when they occur.

One limitation of the research in this field, however, is that patients with cirrhosis represent a very heterogeneous population, with differences not only in the etiology but also in the severity and complications of their underlying liver disease. While most studies performed to date involved cohorts that combined different causes of liver disease, a recent study comparing patients with Child–Turcotte–Pugh (CTP) A/B cirrhosis showed small differences in thrombin generation capacity and clot lysis times (CLTs) among different etiologies.[6] In addition, the progressive nature of liver disease to liver dysfunction and its effects on hemostatic pathways highlight the importance of differentiating patients based on disease severity.

Efforts to risk stratify patients according to underlying liver disease severity often include traditional tests of coagulation (e.g., the international normalized ratio [INR]) and date back to

the development of the CTP score in the 1970s.[7] Initially developed to predict surgical outcomes in patients with bleeding esophageal varices and now commonly used to assess liver disease severity and prognosis, this score includes the following five factors: three factors directly assessing the synthetic function of the liver (INR, bilirubin, and albumin) and two subjective criteria based on clinical assessment (ascites and encephalopathy). The Model for End-Stage Liver Disease (MELD) score was described 20 years ago as an alternate system for assessing liver disease severity using the serum bilirubin, creatinine, and INR.[8] While initially developed to predict mortality in those undergoing TIPS (transjugular intrahepatic portosystemic shunt) procedures, MELD has become the standard for prioritizing those listed for liver transplant and is now used by Eurotransplant and the United Network for Organ Sharing for the allocation of donor livers.[9,10] The use of MELD is ubiquitous throughout hepatology and is employed to risk stratify patients prior to surgery and survival in alcohol hepatitis.[11,12] Both models have become essential to daily clinical care of patients with cirrhosis, yet this reliance on INR as a measure of mortality has unfortunately created confusion and belies the emerging evidence that INR is not predictive of bleeding risk in cirrhosis.[5]

Beyond these commonly used scoring systems for liver disease severity, however, an important clinical distinction in patients with cirrhosis is now emerging. Patients with cirrhosis have multiple distinct phenotypes, ranging from stable and compensated cirrhosis to acutely decompensated (AD) cirrhosis and an increasingly recognized syndrome referred to as acute-on-chronic liver failure (ACLF) (►**Fig. 1**). The transition from compensated to decompensated cirrhosis (defined as the development of ascites, variceal bleeding, encephalopathy, or

jaundice) represents a critical moment in the natural history of cirrhosis: those with compensated cirrhosis have a median survival of more than 12 years compared with around 2 years for those who develop decompensations.[13] More recently, an increasing body of literature describes an entity referred to as ACLF, a clinical syndrome in which a patient with chronic liver disease has an acute insult, often infection or circulatory failure, that leads to a rapid deterioration in liver function.[14] ACLF carries a grave prognosis, with a 90-day mortality in excess of 50%.[14–16] In this setting, there is ongoing debate surrounding specific definitions for ACLF, with several of the more accepted definitions including criteria from the Chronic Liver Failure Consortium (CLIF-C), the Asian Pacific Association for the Study of the Liver-ACLF Research Consortium (AARC), and the North American Consortium for the Study of End-Stage Liver Disease (NACSELD).

In the context of hemostasis and thrombosis in patients with liver disease, it is important to note that patients with compensated cirrhosis, decompensated cirrhosis, AD, and ACLF represent different populations with differing degrees of underlying systemic inflammation. Studies looking at inflammatory markers have shown that while patients with compensated cirrhosis have relatively normal baseline inflammatory markers, patients with AD cirrhosis have progressively abnormal profiles of inflammatory markers and those with ACLF have an intense systemic inflammatory response.[17,18] Importantly, these inflammatory markers have been associated with poor outcomes in both AD cirrhosis and ACLF.[17,19–21] Patients with AD cirrhosis and ACLF also likely undergo unique and progressive changes in the hemostatic system, which may place them at an increased risk of both bleeding and thrombotic complications.[2,22–24] With this evidence, it is now apparent that most



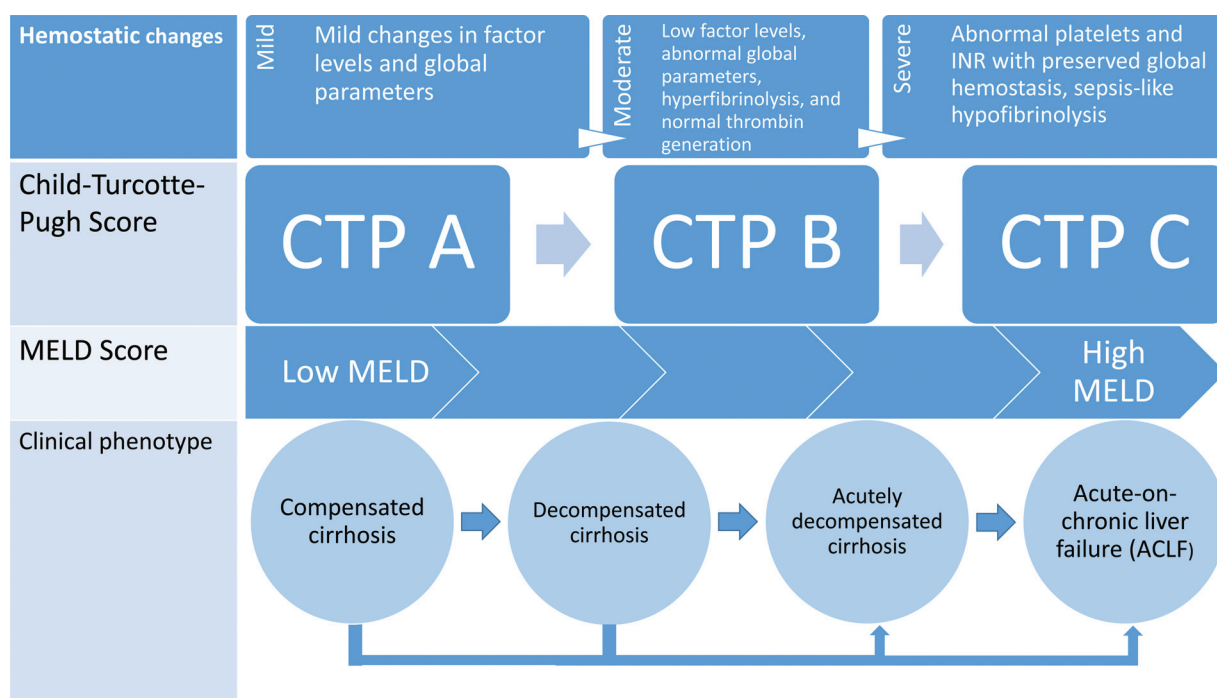**Fig. 1** Classification[Q5] systems showing progressive disease severity in patients with cirrhosis, ranging from CTP classes (A through C) to MELD score to specific clinical phenotypes of disease. Notably, several changes to hemostasis can be seen with worsening liver disease. ACLF, acute-on-chronic liver failure; CTP, Child–Turcotte–Pugh; INR, international normalized ratio; MELD, Model for End-Stage Liver Disease.

studies examining hemostasis and coagulopathy in liver disease have not always differentiated between compensated cirrhosis, AD, or ACLF. In this setting, a "one size fits all" approach has left clinicians with critical knowledge gaps in the understanding of hemostatic abnormalities in those with liver disease.

## Hemostasis According to Disease Severity

Previous studies examining hemostasis and coagulopathy in liver disease have included heterogeneous cohorts with varied methodology. Patients with liver disease can be grouped according to a wide variety of characteristics including disease etiology (e.g., alcohol vs. hepatitis C), acute and chronic comorbidities (e.g., active infection), patient setting (e.g., ambulatory vs. hospital), and disease severity (MELD or CTP class). With emerging evidence of clearly unique pathology underlying specific phenotypes of AD cirrhosis and ACLF, the importance of careful cohort selection is now paramount in study design consideration.

## Early Translational Studies in Coagulopathy of Cirrhosis

An early seminal study explored the thrombin generation assay as a tool to assess the coagulation system in patients with cirrhosis.[25] Plasma was collected from 44 patients with cirrhosis (separated for comparison by CTP class), with a mean CTP score of 9 (class B) and a median MELD score of 9. Information regarding other disease characteristics such as patient location (ambulatory vs. hospitalized) was not reported. Analysis was performed by comparing healthy controls with the *entire* amalgamated cohort of patients with cirrhosis. While the patients in the cirrhosis cohort displayed abnormal conventional coagulation parameters, thrombin generation was preserved with the addition of thrombomodulin (which allows activation of protein C), demonstrating that thrombin generation remains intact in patients with cirrhosis compared with healthy controls. This observation was integral to the future of the field and established the underpinnings of the currently accepted paradigm of the rebalanced coagulation system in cirrhosis. Building on this study, another group examined the role of platelets and von Willebrand factor (VWF) in compensatory responses in the hemostatic system in cirrhosis, providing evidence for a rebalance in primary hemostasis.[26] This study examined 54 patients with cirrhosis (19 with CTP class A, 17 with CTP class B, 18 with CTP class C) but did not report other characteristics beyond disease etiology. Levels of VWF were elevated in all patients with cirrhosis, and this was highly and directly correlated with disease severity. The investigators then showed that the elevated VWF levels in plasma from patients with cirrhosis enhanced in vitro platelet adhesion compared with normal plasma when platelet count and hematocrit were adjusted to comparable levels. Similarly, a rebalanced fibrinolytic system was demonstrated in a similar cohort,[1] although the fibrinolytic status of patients with relatively stable disease remains controversial.[27]

The early recognition that changes in coagulation system depend directly on disease severity was essential to the development of our understanding of the coagulopathy of cirrhosis. Building upon these foundational studies, subsequent translational studies examining the role of platelets in thrombin generation,[28] the role of acquired protein C deficiency,[29] the VWF/platelet axis,[26] and the fibrinolytic system[1] have revealed a clear association between the degree of hepatic decompensation (as defined by CTP) and the severity of change in the coagulation and hemostatic system. However, investigators have often grouped patients together for global coagulation system analysis using thrombin generation assay or viscoelastic testing[30] to derive general conclusions about patients with cirrhosis as a whole. This approach is necessary due to the realities of research with limitations in resources and sample population. However, given our early understanding of differences related to disease severity coupled with more recent evidence (discussed in the next section) that patients with cirrhosis are a very complex and heterogeneous group, it is now clear that efforts to examine hemostasis in translational research require examination of more refined and homogenous cohorts.

## Clinical Examples of the Role of Disease Severity in Hemostasis

### Portal Vein Thrombosis

The relationship of portal vein thrombosis (PVT) with cirrhosis and portal hypertension has been long recognized and studied.[31] The development of thrombus in the portal vein and splanchnic system is relatively common in patients with cirrhosis, and its incidence increases with disease severity. Patients with cirrhosis likely have an increased risk of PVT secondary to reduced portal venous flow, which is a result of portal hypertension. Portal vein velocity correlates with the risk of portal vein thrombus, with lower velocity being a significant risk factor.[32] Patients with cirrhosis vary considerably and often have other risk factors that can contribute to PVT risk (e.g., hypercoagulability, endothelial damage). Therefore, studies on PVT need to account for not only disease severity but also other factors such as concurrent organ failure, the presence of infection, medications, and other characteristics.

Numerous studies have examined the prevalence and incidence of PVT in a wide variety of patient cohorts.[33,34] A systematic review of transplant patients reported a wide range of prevalence of PVT from 2 to 23%, reflecting the underlying heterogeneity of cohort selection across studies.[33] A multicenter prospective study from France followed patients with well-compensated CTP A and B cirrhosis and found an incidence rate of 5% at 1 year, 8% at 3 years, and 11% at 5 years.[35] In a population of patients with cirrhosis listed for transplantation (CTP B/C 74%), incidence of PVT was 7%.[36] In a more recent prospective trial of patients with CTP B/C, the incidence of PVT was 17% in 1 year.[37] Together, these data support the current understanding that the risk of PVT correlates directly with disease state and is higher in patients with more advanced cirrhosis. Consequently, studies examining PVT in cirrhosis,

whether epidemiological based, translational or therapeutic, require careful cohort selection to reduce bias.

## Anticoagulation in Patients with Cirrhosis

Patients with cirrhosis have been excluded from large clinical trials examining the safety and efficacy of anticoagulation for the treatment of venous thromboembolism (VTE) and for thromboprophylaxis in the setting of atrial fibrillation.[38] Therefore, our current understanding of the pharmacology of anticoagulation medications (vitamin K antagonists, low-molecular-weight heparin [LMWH], and direct oral anticoagulants [DOACs]) in patients with cirrhosis remains understudied and severely limited. DOACs are generally restricted to well-compensated cirrhosis (CTP A) according to package insert guidance in the United States. Importantly, in vitro studies examining the effect of anticoagulation on thrombin generation have been performed in patients with varying degrees of cirrhosis.[39,40] These studies reveal significant differences between patients with compensated (CTP A) and more decompensated disease (CTP B and C). Notably, dabigatran showed a stepwise increase in anticoagulant potency when comparing healthy controls with patients with CTP A, B, and C cirrhosis. These data clearly illustrate the notion that coagulopathy in liver disease is highly dependent on disease state and further emphasize the need for studies in more advanced disease phenotypes of cirrhosis.

The majority of clinical studies examining the safety and efficacy of anticoagulation in cirrhosis have been performed in patients with well-compensated cirrhosis undergoing treatment for PVT.[31] A systematic review analyzing six studies in PVT and cirrhosis concluded that anticoagulation was safe and effective in promoting recanalization of the portal vein.[34] However, as randomized controlled trials are lacking, these studies suffer from significant selection bias, and cohorts are highly selected with predominantly patients with well-compensated disease. Therefore, the generalizability of these studies remains questionable, and caution is advised when extrapolating to different populations of cirrhosis with more severe disease including decompensated cirrhosis or ACLF. Anticoagulation for thromboprophylaxis in atrial fibrillation is an area of emerging study in patients with cirrhosis.[41,42] However, studies are generally derived from population databases and therefore lack descriptive granularity regarding the degree of hepatic decompensation and other important characteristics in patients with cirrhosis.[43–46] In studies where disease severity is reported and analyzed, cohorts consist mainly of CTP A patients, with some studies enrolling CTP B patients as well.[47–49] Similar to studies on patients with PVT, these studies are limited by selection bias and have limited generalizability, particularly in patients with more severe liver disease. Clinical data examining the efficacy and safety of all types of anticoagulation therefore remain sparse in decompensated cirrhosis, and current knowledge likely reflects the behavior of these medications in patients with well-compensated disease. As translational studies have shown, the coagulation system can vary considerably across disease states and therefore it is imperative to focus future research on specific cohorts for which data are currently lacking.

## Hemostasis with Procedures in Patients with Cirrhosis

Patients with AD cirrhosis or ACLF are often hospitalized and undergo numerous invasive procedures. Consistent with the current paradigm in coagulopathy of liver disease as rebalanced, bleeding from these nonsurgical procedures in patients with cirrhosis is rare.[50] It is challenging to compare reported incidence or prevalence of bleeding events in studies on procedural bleeding in cirrhosis as they did not adhere to uniform bleeding definitions and were conducted in patients with varying degrees of hepatic decompensation in the outpatient and/or inpatient settings. Bleeding from procedures depends on the specific risk of the procedure and is likely not uniform. Studies examining the safety of specific procedures in cirrhosis report generally low rates of associated bleeding. It should be noted, however, that the majority of these studies are retrospective, with highly variable cohorts, do not control for prohemostatic prophylaxis, and lack uniform outcome definitions.

De Pietri et al conducted a randomized control trial of patients undergoing procedures with decompensated cirrhosis.[51] There was one (1.7%) bleeding event (major bleed, defined by the World Health Organization [WHO] bleeding score) out of 60 patients. Another study including advanced cirrhotic patients listed for liver transplantation reported a higher prevalence of procedural related bleeding of 20% (10/50 patients).[52] A retrospective study in a large cohort of mainly patients with compensated cirrhosis (278/363 [77%] CTP A or B) found a low prevalence of bleeding events (defined by the WHO bleeding score), with only 10 postprocedural bleeding events or 2.8% of the cohort.[53] One study examined a cohort of 600 hospitalized patients with cirrhosis (MELD range: 13–16) who did or did not receive VTE prophylaxis and found an overall incidence of inhospital procedure-related bleeding of 2.3% (14/600).[54] More recently, two large multicenter randomized controlled trials investigated the efficacy and safety of thrombopoietin agonists to improve thrombocytopenia for planned procedures in patients with cirrhosis.[55,56] Both studies were conducted in patients with primarily compensated cirrhosis (CTP A) and included mainly low-risk procedures. The range of incident bleeding events (minor and major as defined by the WHO bleeding score) in these studies was 2.6 to 5.6%. Other studies have reported varying rates of inhospital bleeding in patients with decompensated cirrhosis. Drolz et al studied 211 patients in the intensive care unit with decompensated cirrhosis (CTP C) and ACLF.[57] While reported bleeding complications included both bleed events attributed to portal hypertension bleeds from other causes, 6.7% of patients developed bleeding (ISTH definition of bleeding) unrelated to portal hypertension, with the majority of these (10/14) related to procedures or surgical interventions.

Patients with cirrhosis have dynamic and complex physiology. Therefore, categorizing patients into groups for the purposes of research will always be artificial and biased. Previous studies often merged cohorts of compensated and decompensated patients with cirrhosis together to draw general conclusions for all patients with cirrhosis. While classification systems such as CTP and MELD are well-established and useful for categorizing patients in research, numerous other factors

**Table 1** Classification of liver disease

| Classification systems for patients with cirrhosis | | |
|---|---|---|
| **Clinical phenotype** | **Characteristics** | **Median survival** |
| Compensated cirrhosis | The presence of cirrhosis without any decompensations of liver disease (see below). These individuals are often asymptomatic and many may remain undiagnosed. In general, these patients are thought to have low levels of underlying inflammation and a "balanced" hemostatic system. | ~9–12 y |
| Acutely decompensated cirrhosis | The presence of cirrhosis with symptomatic decompensations such as ascites, variceal hemorrhage, jaundice, and hepatic encephalopathy. In general, these patients have varying degrees of underlying inflammation and a much more precarious yet rebalanced hemostatic system. | ~2 y |
| Acute-on-chronic liver failure | A syndrome in which a patient with chronic liver disease has an acute insult (often infection or circulatory failure) that leads to a rapid deterioration in liver function. While data are limited, these patients have severe underlying levels of inflammation and are likely at higher risk of bleeding and thrombotic complications that contribute to short-term mortality. | Days to weeks (depending on the definition used and underlying severity) |
| **Scoring system** | **Characteristics** | **Median survival** |
| MELD score | Calculated from three commonly obtained laboratory parameters (serum creatinine, serum bilirubin, INR). Uses objective data and validated in a variety of clinical settings to predict mortality in patients with cirrhosis. The MELD score provides values of disease severity along a continuous spectrum but generally requires access to a MELD calculator. | Varies depending on score |
| CTP score | Calculated from five parameters (serum albumin, serum bilirubin, prothrombin time, grade of encephalopathy, and severity of ascites). Relies on both subjective and objective data and validated in a variety of clinical settings to predict mortality in patients with cirrhosis. Limited ability to differentiate those with progressively worsening liver dysfunction (groups patients into three classes based on a combined score). | Varies depending on score |

Abbreviations: CTP, Child–Turcotte–Pugh; INR, international normalized ratio; MELD, Model for End-Stage Liver Disease.

such as systemic inflammation, infection, acute kidney injury, and other organ dysfunctions contribute to hemostatic alterations (►**Table 1**). Thus, the field of hemostasis in liver disease is rapidly changing, and studies in this important population are now emerging.

## Studies Examining Hemostasis in AD Cirrhosis and ACLF

Recent studies have highlighted an increasing interest in hemostasis in ACLF and AD cirrhosis, with findings that include a variety of abnormal coagulation parameters and varying associations with clinical outcomes. Factor XIII (FXIII) levels were shown to be lower in those with AD cirrhosis compared with healthy controls in a prospective study of hospitalized patients.[58] Among the AD cirrhosis group, FXIII levels were significantly lower in those with acute kidney injury (AKI) compared with those without, and FXIII levels had a positive correlation with maximal clot firmness and a negative correlation with clot formation time in rotational thromboelastometry (ROTEM). In a prospective cohort of healthy controls ($n = 35$) and patients with stable cirrhosis ($n = 8$), AD cirrhosis ($n = 44$), and ACLF ($n = 17$), Fisher et al demonstrated progressive changes in a variety of hemostatic parameters, including an increase in INR, factor VIII, and VWF levels along with a decrease in antithrombin, ADAMTS-13 (a disintegrin and

metalloproteinase with a thrombospondin type 1 motif, member 13), fibrinogen, and thrombin generation.[2] Blasi et al evaluated blood samples using ROTEM at admission and 72 hours after in consecutive patients with ACLF ($n = 36$) and AD cirrhosis ($n = 24$), finding that patients with ACLF showed prolonged time to initial fibrin formation and clot formation time, as well as a reduced maximum clot formation and α-angle values. They found that patients with more hypocoagulable ROTEM parameters had a higher short-term mortality but no higher risk of bleeding or need for transfusions. Conversely, Premkumar et al studied thromboelastography (TEG) and specific factor assays among consecutive patients with ACLF and found associations with derangements in hemostasis with both bleeding and mortality.[22] In another study using TEG in ACLF and AD, Goyal et al noted decreased clot strength and increased fibrinolysis in ACLF compared with HC, although most of those with ACLF had normal TEG parameters.[59]

Despite low platelets and coagulation factor levels, some studies suggest that coagulation remains relatively balanced and may even by hyperactivated in ACLF. Thrombin-antithrombin complexes and D-dimers, markers of activation of coagulation and coagulation with subsequent fibrinolysis, respectively, have been noted to be significantly increased in patients with ACLF, and D-dimer levels have been shown to be associated with an increased 28-day mortality in this group.[60,61] A separate study by Blasi et al assessed the plasma

fibrinolytic potential in a cohort of consecutively admitted patients with AD cirrhosis ($n = 52$) and ACLF ($n = 58$) compared with healthy controls ($n = 40$).[62] They found that median CLTs were shorter in those with AD cirrhosis compared with the other groups, but there was significant variability in CLTs among the AD cirrhosis and ACLF cohorts, with a proportion in each group having either prolonged or shortened CLTs. They also noted that baseline CLTs were significantly longer in those who died within 30 days of admission, potentially suggesting that thrombotic complications including intrahepatic microthrombosis could contribute to organ failure and short-term mortality.

In addition, a recent study assessed the in vitro effects of the addition of clinically relevant doses of a variety of pro- and anticoagulant agents in plasma from healthy patients ($n = 30$) compared with those with compensated cirrhosis ($n = 18$), AD cirrhosis ($n = 18$), and ACLF ($n = 10$).[63] Increases in thrombin generation were significantly different depending on which procoagulant agent was used, with only modest increases with the use of fresh frozen plasma and recombinant factor VIIa compared with more significant increases with prothrombin complex concentrate. In addition, the in vitro efficacy of the anticoagulants LMWH and dabigatran increased with progressive disease severity, whereas the efficacy of rivaroxaban was not proportional to the severity of disease.

The aforementioned studies highlight the potential clinical relevance of stratifying patients by disease severity when studying hemostasis in cirrhosis. Taken together, abnormalities in coagulation parameters can depend on disease severity and may be directly associated with clinical outcomes, including bleeding, thrombosis, and mortality. In addition, there may be important differences in the efficacy of anticoagulant agents in these groups, a finding that would have significant clinical relevance.

## Conclusions and Future Studies

Many of the studies examining hemostatic abnormalities in liver disease have included heterogeneous cohorts, without clearly differentiating compensated cirrhosis from decompensated cirrhosis and ACLF. However, emerging evidence suggests that ACLF represents a unique syndrome. Given the differences in underlying systemic inflammation, the profound disruption of coagulation and fibrinolysis that occurs, and the differences in short-term mortality, it is paramount that future studies account for these different phenotypes of liver disease. Only then will we be able to address the many critical knowledge gaps in this field, including determining which populations may benefit or be harmed by initiating anticoagulation and developing improved testing strategies to guide clinical decisions.

### Conflict of Interest
Dr. Intagliata reports other fees from Dova, outside the submitted work. All the other authors report no conflict of interest.

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