Mistakes in coagulation in liver disease and how to avoid them

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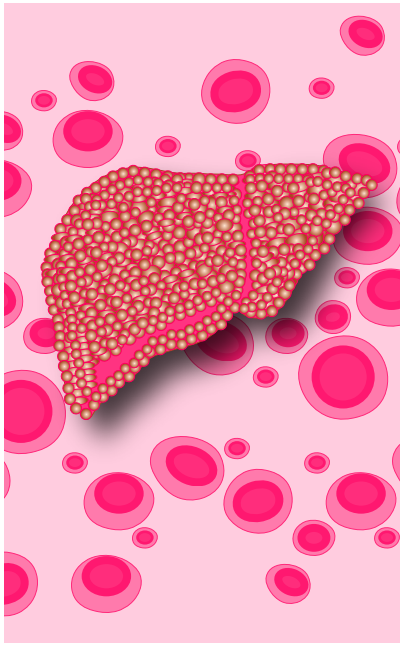

Alteration of common coagulation tests and thrombocytopenia represent an integral part of the clinical picture of patients with advanced chronic liver disease.[1] As such, the International Normalised Ratio for prothrombin time is part of the Model for End-stage Liver Disease score, which is commonly used to assess prognosis and the need for liver transplantation in patients with cirrhosis.[2] Thrombocytopenia—being mainly related to hypersplenism and decreased synthesis of thrombopoietin by the liver—can also be used to identify the presence of portal hypertension and decreased liver function in patients with chronic liver disease.[3]

In patients who have liver disease, altered coagulation parameters and thrombocytopenia have long been considered a hallmark of an increased risk of bleeding and such patients are generally believed to be 'anticoagulated'. However, recent advances in our understanding actually suggest this belief is not correct.[4–6] Indeed, there is evidence of an increased risk of thrombotic events in these patients, despite the presence of a deranged International Normalised Ratio and severe thrombocytopenia.[7–9] Overall, the findings from several studies indicate that anti- and procoagulant tendencies are still balanced in patients who have advanced liver disease, though less robustly than in healthy individuals, and that they can be unbalanced in either direction by perturbing events, such as infections or acute kidney injury.[10–12] In these patients, bleeding is generally portal-pressure-driven while inappropriate clotting is made evident by peripheral venous thrombosis and especially by portal-mesenteric thrombosis.

Here we discuss some of the mistakes frequently made when managing patients who have liver disease and findings of altered coagulation or thrombocytopenia. The discussion is based on the best level of evidence available in the literature and expert consensus.

Mistake 1 Assuming spontaneous bleeding is always associated with altered coagulation parameters

Oesophageal variceal bleeding is one of the most dreaded complications in patients with advanced chronic liver disease, as it is associated with substantial morbidity and an increased risk of death.[13] In patients with cirrhosis, thrombocytopenia or an altered prothrombin time can be used to noninvasively predict the presence of varices, due to their association with portal hypertension and decreased liver function.[14,15] These findings have often led to the misconception that a decreased platelet count or elevated International Normalised Ratio (INR), per se, can be a cause of oesophageal variceal bleeding, rather than representing a proxy for more advanced liver disease and increased portal pressure, thus pinpointing patients at increased risk of bleeding. The main parameters associated with risk of bleeding from varices are, in fact, variceal size, the presence of red signs on varices, and decompensation of liver disease, while altered coagulation has no direct correlation with this clinical event.[16]

Moreover, apart from bleeding events being a direct complication of the underlying liver disease, the occurrence of spontaneous bleeding in patients with cirrhosis is rare.[17] In the largest study to evaluate this issue in patients with cirrhosis, any major or clinically relevant non-major bleeding event—defined as having a symptomatic presentation or requiring prompt medical intervention—were uncommon, with a reported annual significant bleeding rate of 5.5%.[17] In this study, which also included patients on anticoagulants, the annual rate of major bleeding events was 3.6%, with more than 90% being portal-hypertension-related, while the annual rate of minor bleeding events was 1.9%, with the vast majority originating from the gastrointestinal tract.[17] Interestingly, no association was identified between the occurrence of bleeding events and platelet counts or INR, but these events were rather related to features of portosystemic shunting and increased portal pressure, such as hepatic encephalopathy and previous gastrointestinal bleeding.[17]

All in all, it is important to emphasize that portal-hypertension-related bleeding represents the preponderance of major bleeding events in patients with cirrhosis. Alteration of common coagulation parameters may be used to identify those with more advanced liver disease in whom bleeding prophylaxis—either with nonselective beta-blockers or endoscopic treatment—is crucial to improve survival independently of any alteration in coagulation parameters.[13]

Mistake 2 Believing an altered INR is associated with an increased risk of procedure-related bleeding

The prothrombin time (PT)-derived INR is commonly used in clinical practice to determine the adequacy of vitamin K antagonist (VKA) treatment.[18] Due to the nature of the test, which includes calibration of the PT measuring system with PT values of patients on VKA, its application in any other setting is not appropriate.[19]

Patients with advanced liver disease, and hence decreased liver synthetic capacity, produce less procoagulant factors, as reflected by an

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increased INR. As such, this alteration has been identified as a hallmark of dismal prognosis and of bleeding risk in patients with liver cirrhosis. However, this extrapolation does not take into account several limitations of the test, including that it does not account for the concomitant decrease in anticoagulant factors that are synthesized by the liver, such as protein C and protein S, and antithrombin. It also ignores the fact that there is significant interlaboratory variation — as high as 47% — in the reporting of its results due to the use of various thromboplastin reagents.[20]

Nevertheless, the INR is generally used in clinical practice to assess the risk of bleeding in patients with liver disease, either spontaneous or following invasive procedures, and fresh frozen plasma (FFP) is often administered to correct INR alterations. However, even the most recent guidelines from Interventional Radiology Societies acknowledge the lack of evidence supporting the use of FFP before invasive procedures in patients with liver disease.[21]

To put things in perspective, a wealth of studies have repeatedly demonstrated that PT or INR prolongation have no association with the risk of bleeding in patients with liver disease either following liver biopsy, paracentesis, endoscopic oesophageal varices ligation, or a range of other invasive procedures including ablation of hepatocellular carcinoma (HCC).[22–25] Indeed, in patients undergoing these procedures, bleeding occurred independently of an altered INR, and was not more prevalent in patients who had an INR >1.5, which is the threshold commonly used in guidelines to indicate the need for its correction. Despite this overwhelming evidence, until quite recently approximately 90% of hepatologists reported correcting modest INR alterations (i.e. 1.2–1.6) in liver disease patients undergoing invasive procedures at moderate risk of bleeding.[26] In a UK survey, 24% of physicians transfused FFP to correct INR despite the absence of actual bleeding or any planned procedure, while 22% of patients who underwent a high-risk procedure received FFP transfusions despite having an INR <1.5.[27]

Besides not being evidence based, the practice of transfusing patients who have advanced liver disease with FFP to correct an altered INR may do harm. Sudden increases in circulating volume in patients with portal hypertension, such as those that occur following the transfusion of several FFP units in a short period of time in preparation for a procedure, may indeed exacerbate portal pressure, and eventually cause bleeding.[28] Moreover, transfusing FFP was shown, at least in vitro, to be unable to increase the actual coagulation potential of patients with cirrhosis, due to the transfusion of both pro- and anticoagulant factors in similar amounts, and of being unable to improve thrombin generation regardless of the ability to numerically improve INR values.[29,30] In fact, administration of large quantities of FFP to patients with cirrhosis to decrease bleeding risk before procedures or to treat bleeding, resulted in decreased thrombin generation in 34% of patients.[31]

In summary, INR cannot be regarded as a guide to assess the bleeding risk of patients with liver disease undergoing procedures, and its correction via FFP administration may result, in the majority of cases, in useless numerical improvement in coagulation, and could even cause harm to patients.

Mistake 3 Failing to correct thrombocytopenia prophylactically to decrease the risk of procedure-related bleeding

There are several factors that can cause thrombocytopenia in patients who have chronic liver disease. Those factors most frequently involved in determining severe thrombocytopenia — commonly defined as a platelet count below $50x10^9$/L—are splenic sequestration of platelets due to portal hypertension and decreased thrombopoietin synthesis in a failing liver.[32]

Despite a low platelet count being a fairly frequent finding in patients who have cirrhosis, severe thrombocytopenia is observed in ≤1% of patients, normally those with more advanced stages of liver disease, such as Child–Pugh class C patients.[33] Besides a reduction in platelet number, there is evidence of altered platelet function in patients with liver disease. However, it needs to be emphasized that whether there is a clear functional platelet defect in terms of hypoaggregability is debated, and the evidence supporting this finding is controversial, mainly because the in vitro studies that have explored this issue lacked standardization (e.g. not under flow conditions, using adjusted platelet count, etc.).[34]

In patients with liver disease, the most clinically-evident platelet alteration, that is a decrease in their number, is a slow and progressive process, and increased von Willebrand Factor (vWF) levels tend to compensate for thrombocytopenia.[35] In more detail, endothelial perturbation and both reduced activity and levels of the cleaving protease ADAMTS13 are responsible for elevated vWF levels in patients with cirrhosis, and there is compelling evidence that this phenomenon supports adequate platelet adhesion despite their reduced numbers.[35] In addition, this finding may also be responsible for the apparently paradoxical prothrombotic tendency that can be observed in severely thrombocytopenic patients with cirrhosis under some conditions, such as systemic inflammation, when further reduced ADAMTS13 activity may tip the coagulation balance towards a prothrombotic state.[36]

This complex picture should be framed in the clinical context of a patient with advanced liver disease who needs an invasive procedure, where platelet transfusion is often recommended due to the perceived risk of procedure-associated bleeding secondary to thrombocytopenia. Overall, the aforementioned findings support this notion, further backed by practical evidence, that significant bleeding as a consequence of an invasive procedure is a rare event in patients with cirrhosis. In fact, some common clinical procedures in patients with advanced liver disease, such as paracentesis or thoracentesis, do not require platelet transfusion even in patients with severe thrombocytopenia, as there is evidence of a lack of increased bleeding risk in these patients unless there is an inadvertent vessel puncture.

These suggestions are reinforced by a study that included a large series of paracenteses (n=1,100) carried out by trained nurses, where 54.4% of patients had severe thrombocytopenia, and where no bleeding episodes occurred even in the absence of prophylactic platelet transfusion.[23] Furthermore, in a series of 9,320 thoracenteses the rate of bleeding complications was 0.18%, with no bleeding episodes observed in patients who had a platelet count below $50x10^9$/L.[37] Lastly, other procedures frequently carried out in patients with cirrhosis, such as dental extractions or prophylactic oesophageal banding ligation, have a low incidence of significant bleeding complications—2.9% and approximately 5%, respectively—that are unrelated to platelet count.[24,38,39] Furthermore, in the only prospective study in which dental extractions were performed without administration of blood products and where 34.4% of the procedures were performed in patients with platelet counts of $30–50x10^9$/L, application of local pressure with a gauze achieved adequate haemostasis.[24] Moreover, bleeding following oesophageal banding ligation has often been described as a late event associated with banding dislodgment.[38,39]

However, there are some clinical procedures—such as liver biopsy or ablation of liver tumours—where bleeding seems more closely associated with severe thrombocytopenia. Indeed, there is a reported thrombocytopenia incidence of 5.3% following liver biopsy in patients with platelet counts of $50–60x10^9$/L, and of 0.8% in those with platelet counts $>60x10^9$/L, while in patients undergoing percutaneous ablation of HCC a platelet count $<50x10^9$/L increased the risk of bleeding by nearly ninefold.[40,41]

What are the concrete implications that can be gathered from this evidence and that may help us avoid pitfalls when managing these patients in clinical practice? The $50x10^9$/L platelet count limit is still considered the 'magic threshold' below which even experts in coagulation in liver disease and society recommendations agree that platelet counts should be raised, either by platelet transfusion or by means of thrombopoietin

receptor agonists, in order to decrease the likelihood of bleeding in the case of high-risk procedures.[6,42–44] The results of pragmatic studies designed to identify whether proactively increasing platelet counts, by any means, before a procedure might be associated with an actual decrease in the risk of bleeding, compared with a reactive wait-and-see strategy that involves blood product administration only in the case of bleeding, are eagerly awaited. In the meantime, the recommendation to maintain a platelet count above 50x10^9/L still holds true in patients undergoing high-risk procedures, or low-risk procedures if the occurence of bleeding may be catastrophic (e.g. intercranial) or cannot be managed by local haemostasis.

Mistake 4 Assuming that altered coagulation parameters in patients with cirrhosis have the same clinical relevance regardless of whether they have stable disease or acute-on-chronic liver failure.

Acute-on-chronic liver failure (AoCLF) is a complex syndrome that can develop in patients who have cirrhosis, with acute liver disease decompensation and concomitant failure of different organs.[45] AoCLF can develop in both compensated and previously decompensated cirrhotic patients, and can be triggered by various superimposed factors, among which the most common precipitating factor, at least in Western countries, is bacterial infection.[46] In particular, the CANONIC study showed that spontaneous bacterial peritonitis was by far the most frequent precipitating infectious trigger for the development of AoCLF.[47] Moreover, AoCLF is characterized by the development of an intense systemic inflammatory response and a marked increase in proinflammatory cytokines that are deemed responsible for both liver disease derangement and the several extrahepatic manifestations of the disease.[48]

AoCLF is a clinically demanding complication, with a substantially increased risk of death, and patients often have a profoundly altered and highly unstable coagulation balance, with a greater risk of either spontaneous or procedure-related bleeding, as well as development of macro- and microvascular thrombosis.[49–51] Indeed, patients with AoCLF may have a profound perturbation in the fibrinolytic equilibrium, and a variable tendency towards profibrinolytic activity or hypofibrinolysis has been described, which may lead to bleeding or thrombosis in the individual patient.[50,51] All in all, these patients tend to have abnormal clot formation with a varied clot lysis time, and are characterized by marked hypofibrinogenaemia, suggesting bleeding diathesis. Moreover, despite often having a prolonged INR, patients have elevated factor VIII and decreased antithrombin III levels, which potentially account for a procoagulant balance.[52] On the clinical side, the net result of such altered coagulation is represented by the occurrence of bleeding, observed in up to 67% of AoCLF patients, or the formation of intraparenchymal microthrombi that can contribute to liver dysfunction and other organ failures, or even macrovascular thrombosis that might precipitate or follow AoCLF.[53,54]

A retrospective study showed that patients with AoCLF have a threefold higher incidence of bleeding after paracentesis compared with controls. In addition, when AoCLF patients were propensity score-matched for severity of liver disease with patients who had decompensated cirrhosis, no differences were observed in platelet counts and INR between those who experienced post-procedural bleeding and those who did not. The only parameter predictive of haemorrhagic complications after paracentesis in AoCLF patients was hypofibrinogenaemia.[55] On the other hand, another study observed that the plasma levels of individual fibrinolytic proteins were unable to identify those patients who exhibited a hypo- or hyperfibrinolytic tendency, with patients showing marked variability in clot lysis times; patients with AoCLF and sepsis had the highest clot lysis time and plasminogen activator inhibitor type 1 levels, with non-survivors having significantly higher clot lysis times.[51] This last finding encourages speculation that such coagulation alterations might be involved in the development of intraorgan microthrombosis, leading to organ dysfunction and liver parenchymal extinction with organ atrophy.

From a practical point of view, patients with AoCLF are a heterogeneous group and common coagulation test results are not a solid reflection of their coagulative status, or of potential responses when the coagulation process is challenged, for instance, after invasive procedures. Despite identifying an hypocoagulable profile, global coagulation assays results in AoCLF patients have been described not to associate with bleeding episodes related or unrelated to portal hypertension, although these results are not consistent with those of another study in which deranged thromboelastograhy results were predictive of bleeding.[50,53]

Thus, these findings emphasize once again how unreliable common coagulation tests are in this complex population, and how their alteration may not portray the actual bleeding or thrombotic risk in these patients. In clinical practice, the use of global coagulation assays, such as viscoelastic tests (e.g. ROTEM® [Instrumentation Laboratory] or TEG® [Haemonetics Corporation]), may be indicated to assess the coagulation balance and the need for blood product supplementation, or of anticoagulation, in the individual patient, despite some shortcomings when used to predict outcome in the AoCLF population as a whole.

Mistake 5 Treating portal vein thrombosis in patients with cirrhosis too conservatively

Portal vein thrombosis (PVT) is a common finding in patients with chronic liver disease. As cancer-related PVT and PVT in non-cirrhotic patients are distinct enough from benign PVT in cirrhosis to warrant separate consideration, the following discussion focuses on non-HCC-related PVT in patients with cirrhosis.[56,57]

PVT in cirrhosis is often discovered incidentally, but it can be symptomatic in ~50% of patients, manifesting as pain, exacerbation of fluid retention and sometimes with portal hypertensive bleeding.[56,57] PVT may further be described based on the extent of the thrombus, in terms of whether the thrombus is occlusive, partial or mural and whether it extends into portal vein branches and the mesenteric and/or splenic veins.[57]

Deciding whether to treat a patient with anticoagulants or to observe them is challenging and depends on multiple individual considerations. If symptoms are present and suspected to be related to the PVT, this obviously favours therapy. On the other hand, the decision to treat has to be balanced against the bleeding risk (usually assessed endoscopically and potentially managed by prophylactic banding of varices) and, perhaps more importantly, against the fall risk, which may be difficult to assess but is probably related, at least in part, to the patient's frailty.[58] One of the clearest indications to treat PVT is among patients awaiting liver transplantation, as a patent portal vein allows for avoidance of complicated vascular anastomoses.[59]

The optimal duration of therapy is also unclear as recurrence after stopping therapy appears to be common. Indeed, recurrence can be as high as 38.5% following discontinuation of anticoagulants in patients with previously known PVT who had achieved complete recanalization.[60,61] This probably reflects persistence of the underlying risks for PVT associated with cirrhosis—endothelial injury from the underlying liver disease, slow venous flow in liver fibrosis and cirrhosis-related hypercoagulability.[4] The persistent constellation of risks for PVT in cirrhosis represents the key elements of Virchow's triad—stasis, endothelial injury and hypercoagulable blood.

One final consideration is the possible role of prophylactic anticoagulation in the setting of these significant risk factors. In a provocative study, which has yet to be confirmed or refuted, Villa et al. demonstrated a decreased incidence of PVT, a remarkable reduction in decompensation and improved survival in patients with compensated cirrhosis who received a trial of prophylactic low-molecular-weight heparin (LMWH) that was conducted over 2 years (1 year of active therapy).[62] The study was controlled but small and unblinded, but

nonetheless it raises interesting questions regarding the potential role of haemostatic mechanisms in fibrosis and cirrhosis progression.[63–65]

Mistake 6 Believing all portal vein thrombosis warrants anticoagulant therapy

The decision to treat PVT in cirrhosis requires careful analysis of the risks versus the benefits. In the absence of strong prospective studies, the decision is generally very difficult and individualized. One of the clearest indications to avoid anticoagulation therapy of PVT is incidentally discovered, non-occlusive thrombi as they often spontaneously regress as a result of clot remodelling. In fact, non-occlusive PVT disappeared without intervention in up to 45–70% of patients in prospective studies, and its progression did not seem to be associated with clinical worsening.[66,67] When therapy is administered, the optimal approach remains unclear. Most published studies have reported on warfarin and LMWH treatment, with the successful use of direct-acting oral anticoagulants (DOACs) being increasingly reported.[68,69]

One potential approach is to begin therapy with subcutaneously administered LMWH, provided its co-factor—liver synthesized anti-thrombin—is adequate, and then transition, if possible, to a DOAC after ~6 weeks. This approach provides a test period with an easily reversible agent to assess the patient's stability on therapy. One of the main factors associated with a greater likelihood of portal vein recanalization in patients who have acute or subacute thrombosis, or progression of a pre-existent thrombosis, is early initiation of anticoagulants, with an overall recanalization rate averaging 60%.[61,70] However, it must be taken into consideration that the re-thrombosis rate after discontinuation of anticoagulants can be as high as 38.5%, and that ~10% of patients may experience bleeding events, which tend to be more common when anticoagulation is performed with VKAs.[61,71]

Altogether, the risk of bleeding while on anticoagulation in patients with cirrhosis may be non-negligible. While risk scores exist for anticoagulation therapy in patients with conditions such as atrial fibrillation, risk assessment in cirrhosis remains remarkably subjective. Notably, the 'HAS-BLED' score used in patients with atrial fibrillation actually includes liver disease as a variable, and therefore applying this score to patients with PVT and underlying liver disease is obviously problematic.[72]

Although gastrointestinal bleeding risk can be fairly easily assessed and addressed endoscopically, the fall risk with potentially severe central nervous system bleeding remains an important concern. While we suspect that 'frailty scores' may have a role in this respect to better triage patients, prospective data are lacking.[1,73] From a pragmatic point of view, our current practice is to avoid anticoagulation therapy in patients who have advanced Model for End-Stage Liver Disease (MELD) scores and/or those with high frailty scores in the presence of what we suspect are high fall risks.

Mistake 7 Failing to recognize the limitations of heparin anticoagulation in cirrhosis

Clearly the decision to undertake anticoagulation therapy in liver disease patients is not simple and requires careful consideration of the risks versus benefits, generally in the absence of well-controlled evidence-based decision trees. If heparin therapy is undertaken, the provider must also recognize that heparin activity is largely dependent on the liver-derived activity of the heparin cofactor antithrombin, which is also known as antithrombin III. Antithrombin is a liver-derived proteinase inhibitor of thrombin and several other haemostatic factors, and it serves as an essential cofactor for the anticoagulant effects of heparin.

Cirrhosis acts as an acquired form of antithrombin deficiency and hence of potential heparin resistance. Critical antithrombin levels for heparin resistance in cirrhosis are not well studied, but mild deficiencies (i.e. levels that are 60–70% of normal) have been associated with thromboembolic problems in other forms of acquired antithrombin deficiency, such as sepsis and severe burns.[74] In a large retrospective study of patients with cirrhosis and mostly partial PVT, Rodriguez-Castro et al. showed that factors independently associated with PVT resolution after body-weight dose-adjusted LMWH treatment (40% dose reduction in patients with platelet count $\leq 50\times10^9$/L and in those with serum creatinine clearance ≤50 mL/min) were severity of liver disease, complete versus partial PVT, thrombus age and a time interval of <6 months from the beginning of treatment.[70] Of note, median antithrombin III levels in this study were well above 60% and not significantly different between patients who achieved recanalization of the portal vein and those who did not.[70]

Anecdotally, we have used the heparinase channel of the ROTEM® whole blood haemostatic test (HEPTEM) to demonstrate poor heparin effect and antithrombin activity of approximately 40% of normal in a patient with cirrhosis and acute PVT and distal extension with secondary mesenteric ischemia. In that situation, we successfully achieved portal decompression by means of a transjugular intrahepatic portosystemic shunt (TIPS) and transition from systemic heparin to bivalirudin, which is a direct thrombin inhibitor that does not depend on antithrombin levels. It is also worth noting that the role of anti-Xa monitoring as an index of heparin effect in cirrhosis needs further study and its use warrants some caution.[75]

Mistake 8 Missing hyperfibrinolysis in patients with diffuse mucosal, puncture wound and cutaneous oozing

Profusely bleeding patients with cirrhosis have left an indelible mark on generations of practitioners around the world since the dawn of modern medicine. The prolonged INR in these patients has led to the inappropriate but enduring reaction to transfuse FFP without consideration of modern conflicting findings. Bleeding in this setting can be generally divided into one of two things. The first is an acquired disorder of plasmin metabolism leading to premature clot dissolution called AICF (accelerated intravascular coagulation and fibrinolysis), which is probably the oldest described haemostatic disorder in liver disease. The second is portal-pressure-driven bleeding, which has very little to do with haemostatic pathways but, like a burst pipe, has everything to do with volume and pressure, which may be exacerbated with plasma infusion.[28,76–78] Unlike pressure-driven bleeding, AICF, which is characterised by diffuse mucosal bleeding/oozing, persistent puncture wound bleeding at intravenous sites and late post-procedure bleeding, has everything to do with disturbed haemostatic mechanisms. Pressure-driven bleeding is best addressed in society guidelines on variceal bleeding, so here we focus a few comments on AICF.[79,80]

The most important clinical points to recall about AICF or 'hyperfibrinolysis' are that it remains a clinical diagnosis but is one that has a potentially effective therapy in either epsilon aminocaproic acid ('amicar') or tranexamic acid, both of which inhibit dissolution of the fibrin clot. Neither agent is thought to have inherent hypercoagulable risks, with the exception of a pre-existing pathological thrombus such as PVT.[43,81] Confirmation of this condition by laboratory testing remains problematic as conventional testing, even with standard viscoelastic tests such as TEG® or ROTEM®, often fail to support the very obvious clinical diagnosis and response to antifibrinolytic therapy. A modification of the conventional TEG® that uses no clot stimulators and has a long run time, known as the 'Native TEG' from the Burroughs group at the Royal Free Hospital in London, UK, has consistently demonstrated these changes in past studies and clearly warrants further study as a standard for the detection of this condition in liver disease patients.[82,83]

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Your coagulation in liver disease briefing

UEG Week

- 'Complications of liver cirrhosis' session at UEG Week 2019 [https://ueg.eu/library/session/complications-of-liver-cirrhosis/156/2146].
- 'Hepatology from bench to bedside' session at UEG Week 2019 [https://ueg.eu/library/session/hepatology-from-bench-to-bedside/156/2557].
- 'Crash course: When the liver starts talking' session at UEG Week 2018 [https://ueg.eu/library/session/crash-course-when-the-liver-starts-talking/153/2040].
- 'Advances in the management of cirrhosis' session at UEG Week 2018 [https://ueg.eu/library/session/advances-in-the-management-of-cirrhosis/153/2070].
- 'Complications of liver cirrhosis' session at UEG Week 2015 [https://ueg.eu/library/session/complications-of-liver-cirrhosis/109/1372].

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