Section A -Research paper

Coagulopathy and Portal Vein Thrombosis in Cirrhotic Patients

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Abstract:

Liver cirrhosis is associated with number of hematological complications and coagulation disturbances. In view of various hemostatic abnormalities it is surprising that many patients do not bleed spontaneously. Severe coagulopathy of liver disease is more frequently seen in acute liver failure, but still remains important complication of liver cirrhosis and chronic liver failure. Decreased production of blood coagulation factors by the liver plays a key role in altered hemostasis in liver diseases. Altered fragile balance of blood coagulation proteins and infection are associated with both worsening coagulopathy and bleeding risk. Additional hemostatic abnormalities in patients with severe liver diseases are thrombocytopenia, disseminated intravascular coagulation, accelerated fibrinolysis, hypofibrinogenemia and dysfibrinogenemia. In this review we discuss a complicated issue of multiple coagulopathies in patients with advanced liver dysfunction.

Keywords: Coagulopathy, Portal Vein, Thrombosis, Cirrhotic Patients.

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Introduction:

Several pathophysiological changes occur in cirrhosis and put cirrhotic patients at increased risk of both bleeding and thrombosis. The liver synthesizes clotting factors,

anticoagulants, proteins involved in fibrinolysis, and the platelet production regulator "thrombopoietin" from megakaryocytes. Importantly, liver dysfunction disrupts the coagulation process ***(1, 2).***

The following Figure shows the coagulation cascade and associated pathophysiological changes that occur in cirrhosis.

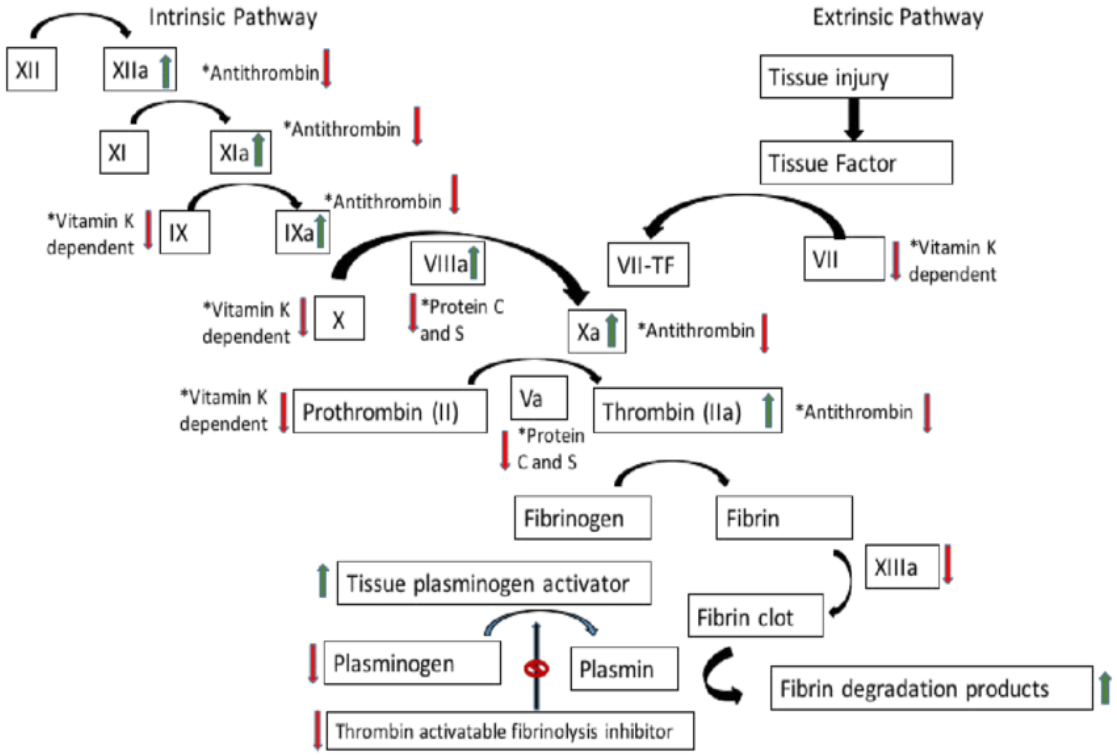

Figure 1: *The coagulation cascade and associated pathophysiological changes that occur in cirrhosis* **(3).**

There is decreased synthesis of vitamin K-dependent and independent clotting factors and anticoagulants, abnormalities in platelet production, and portal hypertension that causes hypersplenism and shunting of blood to the peripheral circulation, leading to consumptive coagulopathy and further aggravating thrombocytopenia ***(4).***

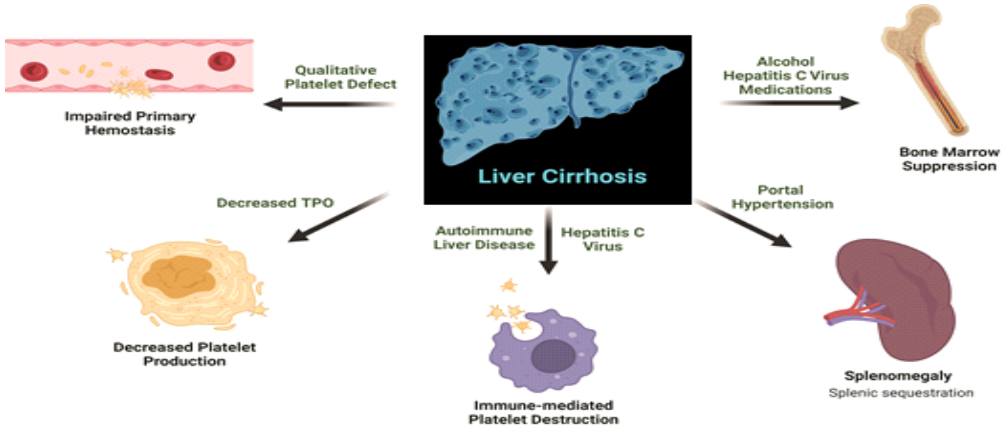

Figure 2: *Multifactorial hematologic abnormality seen in liver disease* **(6).**

Thrombocytopenia in Cirrhosis:

Thrombocytopenia in liver cirrhosis is multifactorial due to increased consumption from the spleen and decreased platelet production. Thrombopoietin is a key regulator of platelet production (5).

Inappropriately low thrombopoietin (TPO) plays a significant role in thrombocytopenia of liver disease. Thrombopoietin, which is primarily produced by the liver, promotes megakaryopoiesis and thrombopoiesis by binding to the c-MPL receptor on platelet progenitors. Circulating TPO levels are regulated through the binding of TPO to mature platelets and their subsequent clearance. Circulating TPO levels rise because there are fewer platelets for TPO to bind, therefore encouraging thrombopoiesis ***(7).***

Treatment of underlying etiologies of cirrhosis can be complicated by significant medication-related bone marrow suppression e.g. Azathioprine, a common treatment for autoimmune hepatitis. Only a small subset of patients on azathioprine develop thrombocytopenia, but it may exacerbate baseline thrombocytopenia in advanced liver disease patients ***(8).***

Exposure to other common medications, such as β-lactam and fluoroquinolone antibiotics, frequently used to treat infectious complications such as subacute bacterial peritonitis, may be another potential cause of thrombocytopenia due to bone marrow suppression or drug-induced immune thrombocytopenia ***(9).***

Immune-mediated thrombocytopenia (ITP) may be seen in patients with autoimmune liver diseases, such as autoimmune hepatitis and primary biliary cirrhosis ***(10)*** chronic hepatitis C with or without cirrhosis is also a well-known predisposing condition associated with secondary ITP which frequently improves with viral eradication and also responds to conventional ITP therapy ***(11).***

Fibrolysis in cirrhosis:

Hyper fibrinolysis or premature thrombolysis is a bleeding pattern in cirrhotic patients, clinically characterized by diffuse mucosal bleeding often in critically ill decompensated patients

(12). Almost all body cavities such as oral, biliary, urinary, and peritoneal are fibrinolytic, which is favorable for inappropriate clot formation and clot remodeling. Recent literature also suggests that ascites is a potential factor in this process ***(13).***

Plasminogen and tissue plasminogen activator (t-PA) contribute to the breakdown of blood clots. Plasmin degrades factor VIII, factor V, von Willebrand factor (vWF), and factor XIII to prevent clotting, and dissolves fibrin to produce degradation products such as D-dimer, a marker for fibrin turnover and inflammation. Tissue plasminogen activator is inhibited by plasminogen activator type 1 inhibitor (PAI-1), which is produced by endothelial cells. Thrombin activetable fibrinolysis inhibitors (TAFI), an enzyme produced in the liver that blocks plasminogen binding and activation, thereby inhibiting fibrinolysis ***(1).***

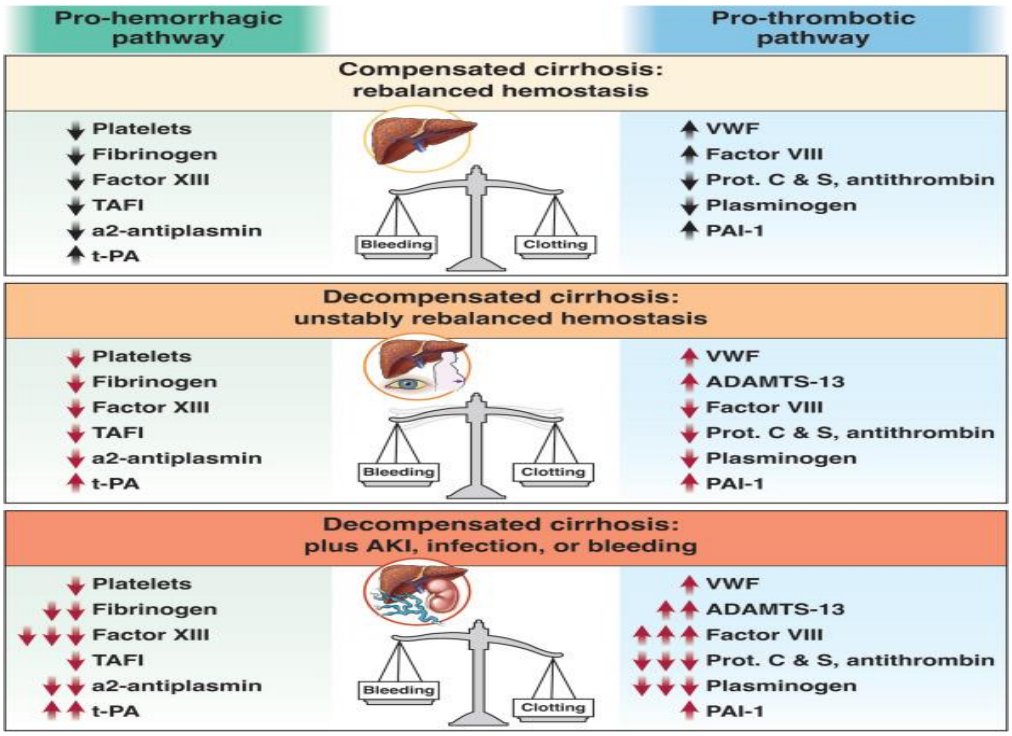

Figure 3: *Reassessment between pro-hemostatic and hemostatic drivers in LC* * **(14).** * Hemostatic balance in patients with compensated cirrhosis, decompensated cirrhosis, or decompensated cirrhosis with complications (acute kidney injury, infection, bleeding). In compensated cirrhosis, the parallel changes in both pro- and antihemostatic pathways result in a rebalanced hemostatic state. With advancing disease severity, the ratio of pro **vs.** anticoagulant drivers increases progressively, resulting in higher hemostatic imbalance, tipping toward hypercoagulability, and a more fragile rebalanced state. This is further worsened by clinical events like AKI, bleeding, or infection. These relative changes are discussed in greater detail in the narrative. ADAMTS-13, a disintegrin and metalloprotease with thrombospondin-1 domain, member 13; PAI-1, plasminogen activator inhibitor-1; t-PA, tissue plasminogen activator; TAFI, thrombin activatable fibrinolysis inhibitor.

In compensated cirrhosis there is a vulnerable balance between coagulopathic and thrombophilic tendencies. Various precipitating factors can tip this balance one way or the other leading to distinct complications. Advancing liver disease is associated with a higher tendency for hypercoagulability. The decreased levels of most coagulation factors, except factor VIII and vWF, are characteristic hallmarks of hemostasis in cirrhosis **(15).**

Comorbidities such as sepsis, malnutrition, and other comorbidities can lead to endothelial dysfunction and metabolic disturbances which can further disrupt hemostatic and clotting responses ***(4).*** More recent studies have shown that systemic infections can exacerbate hypercoagulability and hypocoagulability through opposing effects on clotting factors vs. platelet aggregation ***(16).***

Prevalence and Incidence of Thrombotic Complications in cirrhosis

The prevalence of deep venous thrombosis (DVT) and pulmonary embolism (PE) varies in different series. There is considerable agreement that the adjusted risk ratio is higher than in the general population, ranging from 1.7 to 2, particularly in younger patients (< 45 years of age), and that the risk increases with the severity of the disease. Like DVT, PVT is strongly influenced by the severity of liver disease ***(17).***

As regard to arterial thrombosis, the risk of ischemic stroke is reported to be higher in cirrhotic patients. The risk of myocardial infarction, despite the higher incidence of coronary atherosclerosis in patients with cirrhosis, is increased only in decompensated patients ***(18).***

Coagulation Assessment in Cirrhosis for Different Procedures

Common procedures do not require a routine coagulation assessment in cirrhotic patients including diagnostic and therapeutic paracentesis, thoracentesis, upper endoscopy to screen for and band esophageal varices, and diagnostic (not therapeutic) colonoscopy ***(19).***

The need for prophylactic measures depends on procedure risk assessment. In general, minor procedures like paracentesis/thoracentesis and upper endoscopy with banding do not require prophylaxis, although the authors recognize that risk assessment will vary in the clinical context **(20).**

Table 1: *Examples of commonly performed procedures in patients with cirrhosis and their associated bleeding risk* *** (21).**

	Low bleeding risk	**High bleeding risk**
Endoscopic	Diagnostic procedures Endoscopic variceal ligation Transoesopheageal echocardiogram	Bronchoscopy with biopsy Colonoscopy with polypectomy Endoscopic retrograde cholangiopancreatography with sphincterotomy
Percutaneous	Paracentesis Thoracocentesis	Percutaneous liver biopsy Tunnelled ascitic/pleural drain placement Cranial/spinal surgery
Vascular	Peripheral/central venous catheterization Transjugular liver biopsy	Transjugular intrahepatic portosystemic shunt Transcatheter arterial chemoembolization
Other	Dental procedures including extractions Skin biopsy	Intraocular procedures[b]

*Classification based on major bleeding >1.5% or where minor bleeding associated with high risk of significant organ damage/death.

Table 2: *Key prophylactic measures in bleeding prophylaxis before procedures* **(22).**

Bleeding prophylaxis	Comment
Platelets ≥50,000 by infusion or with TPO agonist if elective	Whether or not to recheck platelets is debated but recommended when bleeding risk is greater than minimal.
Fibrinogen ≥120 mg/dL	Best achieved with cryoprecipitate. Weight-based dose usually raises fibrinogen level by 50 mg/dL.
Control infection	Active infection may cause release of endothelial-derived "heparinoids," which can have an anticoagulant effect.
Optimize renal function	Superimposed renal failure is associated with uremic platelet dysfunction, volume issues, and changes in hemostatic cascade.
Hematocrit of ≥25% is suggested	Improves platelet margination

Table 3: *Key prophylactic measures in active bleeding before procedures* **(*22*).**

Active bleeding	Comment
Portal hypertension–related	Anti-portal hypertension interventions, minimize volume expansion and blood product transfusions due to effects on portal pressure.
Wound or mucosal oozing suspicious for DIC or hyper fibrinolysis	Platelets to ≥50,000, fibrinogen ≥120 mg/dL, Consider anti-fibrinolytic agent (aminocaproic acid or tranexamic acid).
Control infection	Active infection may cause release of endothelial-derived heparinoids, which can have an anticoagulant effect.
Optimize renal function	Superimposed renal failure is associated with uremic platelet dysfunction, volume issues, and changes in hemostatic cascade.
Hematocrit of ≥24% is suggested	Improves platelet margination.

Benefits/Risks of interventions to correct thrombocytopenia in different procedures

- ***Platelet transfusion:***

From a clinical view, platelet transfusion is standard of care and often considered a routine pre-procedure for cirrhotic patients to improve platelet counts with no strong evidence basis. Recent randomized controlled trials in cirrhotic patients with intracerebral hemorrhage showed more deaths, bleeding, and poor neurological recovery with liberal platelet transfusion ***(23).***

Drolz et al. (24) Identified platelet count <30 × 109/L (and fibrinogen level <60 mg/dL and activated partial thromboplastin time (APTT) > 100 s) to be the strongest predictors for major bleeding in 211 cirrhotic patients among nearly 1500 patients in a critical care unit during one year**.**

Platelet counts less than 30 × 109/L is rare in cirrhosis and clinicians should look for causes other than liver dysfunction for the thrombocytopenia. It may be considered good practice to regularly check and exclude treatable causes of thrombocytopenia in cirrhosis including:

- Immune thrombocytopenia that may be related to HBV or HCV and autoimmune hepatitis.
- Revise drugs which may cause thrombocytopenia.
- Improving portal hypertension measures as splenic artery embolization and TIPSS placement, as these interventions may improve platelet count.
- Correct nutritional deficiencies that can cause cytopenias **(21).**

- ***Thrombopoietin receptor agonists:***

Thrombopoietin receptor agonists are considered alternative to platelet transfusions, three thrombopoitin receptor agonists (TPO-RAs) have been tested in patients with liver disease with thrombocytopenia: eltrombopag, avatrombopag, and lusutrombopag. Of these, the last two were approved for use in chronic liver disease patients undergoing invasive procedures ***(25).***

Afdhal, et al. Studied the use of eltrombopag in patients with cirrhosis and thrombocytopenia who were scheduled for an elective procedure and found that a large number of patients (104 out of 145) taking eltrombopag avoided platelet transfusion, compared with only 28 of these 147 patients receiving placebo ($p<0.001$). Although there was no difference in bleeding rates (17% for eltrombopag vs. 23% for placebo), there was a difference in the rate of developing portal vein thrombosis (6 for eltrombopag vs. 1 in the placebo group) ***(26).***

In patients with platelet counts <50 × 109/L, avatrombopag and lusutrombopag increased the platelet counts adequately and reduced the frequency of platelet transfusions ***(25, 27).*** Maximum platelet counts were achieved almost at 12 days from the first dose returning to patients' baseline levels ***(28).***

Two further systematic review and meta-analyses of trials which used TPO-RAs for procedures in CLD patients showed that these drugs are to be significantly more successful in raising the platelet count greater than 50 × 109/L thus reducing the need for platelet transfusions. The impact on the clinically important endpoint of periprocedural bleeding was not consistent

across the two analyses but the majority of bleeding events were mild to moderate, with both studies confirmed no rise in the rate of thrombosis ***(29).***

Benefits/Risks of interventions to correct coagulation in different procedures

- ***Cryoprecipitate and fibrinogen concentrates:***

There are few studies on the effects of concentrated sources of fibrinogen (cryoprecipitate or concentrates) on hemostasis in cirrhotic patients ***(30)*** There is a considerable interest in fibrinogen as a predictor of mortality in patients with major bleeding, for example postpartum hemorrhage (PPH) or trauma, with similar analyses in cirrhosis ***(31).*** In another cohort study for disease severity, there was no independent association between fibrinogen level and mortality. Also, using of cryoprecipitate did not influence bleeding rates or survival ***(32).***

- ***Prothrombin complex concentrate and recombinant activated factor VII:***

Prothrombin complex concentrate (PCC) may be an attractive alternative for coagulation factor replacement for the smaller volume required. But, there is no evidence to support correcting PT/INR and limited data on PCC ***(33).***

- ***Fresh frozen plasma:***

Fresh frozen plasma (FFP) has often been utilized in the periprocedural setting in a trial to correct prolonged INR ***(34).*** However, INR is a measure of disease severity and does not reflect the hemostatic balance in cirrhosis. There is a good evidence that it does not predict procedural bleeding and no evidence that correction reduces the bleeding risk during procedures. Also, FFP carries the potential risk of transfusion-related acute lung injury, and the volume required for a therapeutic dose may lead to transfusion-associated circulatory overload ***(35).***

There are many guidances from expert societies recommending the non-prophylactic use of FFP in the periprocedural setting regardless of the procedural bleeding risk in table 4 ***(36).***

Table 4: *Guidances from expert societies in the periprocedural setting regardless of the procedural bleeding risk* **(21).**

	ISTH 2021	AASLD 2021	AGA 2021	ACG 2020	SIR 2019
PT/INR	Do not evaluate routinely	Do not correct	Do not evaluate routinely	Do not correct	INR>2.5
Platelet count	Do not correct	Do not correct	Do not evaluate routinely	$>50\times10^9$/L	$>30\times10^9$/L
Fibrinogen	Do not evaluate routinely	Do not correct	Do not evaluate routinely	No specific recommendation	>1 g/L
VHA	Do not use routinely	Do not use routinely	No recommendation	May be useful	No specific recommendation

Abbreviations: AASLD, American Association for the Study of Liver Diseases; ACG, American College of Gastroenterology; AGA, American Gastroenterology Association; INR, international normalized ratio; ISTH, International Society on Thrombosis and Hemostasis; PCC, prothrombin complex concentrate; PT, prothrombin time; SIR, Society of Interventional Radiology; VHA, viscoelastic hemostatic assay.

- ***Tranexamic acid:***

Antifibrinolytics have an established role in reducing bleeding in other clinical settings, for example, trauma and PPH ***(37).*** However, there was no benefit seen in reducing gastrointestinal bleeding with evidence of increased thrombosis in those with cirrhosis ***(38).*** There are no studies evaluating its role in patients with cirrhosis in the periprocedural setting ***(22).***

- ***Vitamin K:***

Vitamin K deficiency can predispose to bleeding but is rare in patients with stable cirrhosis. Replacement of vitamin K may partially correct a prolonged INR in cirrhotic patients admitted to hospital with acute illness in cases of prolonged antibiotic use, malnutrition, or cholestasis. A single dose of 10 mg may be considered; if there is no change in INR at 12–24 h, repeated dosing is not recommended ***(22).***

Prevention and treatment of venous thromboembolism in liver cirrhosis:

The risk assessments and prophylactic strategies are often underutilized and as a result, the available data on DVT/PE prophylaxis are generally retrospective. However, available evidence indicates that thromboprophylaxis with low molecular weight heparin (LMWH) or with direct oral anticoagulants (DOACs) in hospitalized patients (Child-Pugh A and B) has an acceptable safety profile ***(39).***

Prevention and treatment of venous thromboembolism in liver cirrhosis is a major complex issue in clinical practice. In general, the available data are not yet sufficient to support broad application of prophylactic anticoagulation; however, the Baveno VII workshop has recently revised the previous negative indications, suggesting that anticoagulation should not be discouraged as anticoagulants may reduce liver-related side effects and improve overall survival ***(40).***

Few studies have been performed on the prevention of thrombotic complications in chronic liver disease, possibly due to concerns about bleeding events, a concept that has only recently been disproved. Despite that cirrhotic patients at risk for DVT/PE can be identified using predictive scores such as the ***Padua score*** (validated in cirrhotic patients) as shown in Figure 4 ***(41).***

Items	Score
Active cancer (metastases and/or chemoradiotherapy in the previous 6 months)	3
Previous VTE (with the exclusion of superficial vein thrombosis)	3
Bedrest for ≥3 days	3
Thrombophilia	3
Recent (≤1 month) trauma and/or surgery	2
Elderly age (≥70 years)	1
Heart and/or respiratory failure	1
Acute myocardial infarction or ischemic stroke	1
Acute infection and/or rheumatologic disorder	1
Obesity (BMI ≥30 kg/m^2)	1
Ongoing hormonal treatment	1

High risk of VTE: ≥4 points. VTE: Venous thromboembolism; BMI: Body mass index.

Figure 4: *Padua score* **(6).**

Regardless some limitations in mind, there is a general agreement that all class of drugs (LMWH, Vitamin K antagonists (VKA), DOACs) are safe ***(42)*** and treatment was shown to be generally effective in preventing recurrence of major events such as VTE or ischemic stroke. According to EASL Guidelines on prevention and management of bleeding and thrombosis in

patients with cirrhosis, VKA, LMWH, and DOACs can be recommended for Child-Pugh A patients. In Child-Pugh B and C patients, LMWH is the drug of choice, while unfractionated heparin is the treatment of choice in case of renal failure ***(21).***

Although the role of anticoagulation is expanding in the management of Chronic liver disease patients, the risk of bleeding needs to be assessed at treatment initiation and also reconsidered in case of a new clinical event. Assessment should include not only history of non–portal hypertensive–related bleeding, but also the risk in patients prone to encephalopathy or in those who have an excessive alcohol consumption. Superadded conditions including infections and renal impairment should also be considered ***(43).***

Table 5 describes the mechanism of the anticoagulant medications described below

Table 5: *The mechanism of the anticoagulant medications* ***(44).***

Anticoagulant	**Mechanism of action**
Unfractionated heparin	Potentiates antithrombin III to inactivate thrombin; prevents conversion of fibrinogen to fibrin
Low molecular weight heparin	Potentiates antithrombin III to inactivate thrombin; inhibits factor Xa
Vitamin K antagonists	Inhibits vitamin K epoxide reductase complex 1
Direct thrombin inhibitors	Inactivate circulating and clot-bound thrombin
Direct factor Xa inhibitors	Inactivate circulating and clot-bound factor Xa

1. **Vitamin K antagonists:**

Vitamin K antagonists, such as warfarin, can be used to treat DVT in cirrhotic patients. Warfarin is effective in preventing progression of thrombosis and improving revascularization rates. However, there is no evidence that it improves the rate of liver decompensation or provides a benefit in mortality ***(45).***

One warning that arises in cirrhotic patients is the high INR, which makes it difficult to calculate warfarin dose. A four-point scale was developed to identify cirrhotic patients at high risk for warfarin use. Patients receive 1 point if their albumin is between 2.5 and 3.49 g/dL or if their creatinine is between 1 and 1.99 mg/day and 2 points if their albumin is below 2.5 g/dL or if

creatinine is greater than or equal to 2 mg/dL. Those with a score of 0 were found to have a lower treatment time without more bleeding. However, people with cirrhosis and a score of 4 had poorer INR control and a higher risk of bleeding. For this, it is advisable to start with 1 mg and aim for an INR of 2-3 ***(46).***

2. Low molecular weight heparin:

LMWH treatment can lead to complete recanalization in 45% of patients and a lower rate of clot progression**.** Use of LMWH for prevention and treatment of PVT is not associated with higher bleeding rates, but treatment with unfractionated heparin is possible ***(44).***

Some studies reported an increased risk of minor bleeding with thromboprophylaxis in cirrhotic patients, but did not increase major bleeding or affect mortality. The patients in these studies were older and had longer hospital stays ***(47).***

3. Direct oral anticoagulants:

Although the recent decade has provided evidence for the usefulness and safety of DOACs, evidence for the use of DOACS in cirrhosis is lacking. One study compared apixaban and rivaroxaban to traditional anticoagulants with warfarin and LMWH, and found no significant differences in rates of major bleeding or time until occurring bleeding (p=0.9). This study included only Child-Pugh patients A and B, and was small with only 39 cases examined ***(39).*** A recent randomized clinical trial showed that rivaroxaban 15 mg/d reduced the incidence of VTE without increasing the risk of major bleeding ***(48).***

References:

1. Tripodi A. (2015): Hemostasis abnormalities in cirrhosis. Curr Opin Hematol; 22:406–412.
2. Muciño-Bermejo J, Carrillo-Esper R, Méndez-Sánchez N et al. (2015): Thrombosis and hemorrhage in the critically ill cirrhotic patients: Five years retrospective prevalence study. Ann Hepatol; 14:93.
3. Flores, B., Trivedi, H. D., Robson et al. (2017). Hemostasis, bleeding and thrombosis in liver disease. Journal of translational science, 3(3).
4. Kurokawa T, Zheng YW, Ohkohchi N. (2016): Novel functions of platelets in the liver. J Gastroenterol Hepatol. ; 31:745–751.
5. Giannini EG, Savarino V. (2008): Thrombocytopenia in liver disease. Curr Opin Hematol; 15:473–480.
6. Lim, H. I., & Cuker, A. (2022). Thrombocytopenia and liver disease: pathophysiology and periprocedural management. Hematology, 2022(1), 296-302.

7. Van Dievoet MA, Eeckhoudt S, Stephenne X. (2020): Primary hemostasis in chronic liver disease and cirrhosis: what did we learn over the past decade? Int J Mol Sci; 21(9):3294. Doi: 10.3390/ijms21093294.
8. Josefsdottir KS, Baldridge MT, Kadmon CS et al. (2017): Antibiotics impair murine hematopoiesis by depleting the intestinal microbiota. Blood; 129(6):729-739.
9. Bakchoul T, Marini I. (2018): Drug-associated thrombocytopenia. Hematology Am Soc Hematol Educ Program. (1):576-583. Doi:10.1182/asheducation-2018.1.576.
10. Fukuda H, Takata K, Kitaguchi T et al., (2018): Autoimmune hepatitis with concomitant idiopathic thrombocytopenic purpura diagnosed by transjugular liver biopsy. Case Reports Hepatol. (December):5305691. Doi:10.1155/2018/5305691.
11. Van der Meer AJ, Maan R, Veldt BJ et al., (2016): Improvement of platelets after SVR among patients with chronic HCV infection and advanced hepatic fibrosis. J Gastroenterol Hepatol; 31(6):1168-1176. Doi:10.1111/jgh.13252.
12. D.C. Rijken, E.L. Kock, A.H. Guimaraes et al., (2012): Evidence for an enhanced fibrinolytic capacity in cirrhosis as measured with two different global fibrinolysis tests. J Thromb Haemost, 10, pp. 2116-2122.
13. Thaler J, Lisman T, Quehenberger P et al., (2022): Intraperitoneal activation of coagulation and fibrinolysis in patients with cirrhosis and ascites. Thromb Haemost; 122: 353-362.
14. Rautou, P. E., Caldwell, S. H et al. (2023). Bleeding and Thrombotic Complications in Patients with Cirrhosis: A State of the Art Appraisal. Clinical Gastroenterology and Hepatology.
15. Tripodi A, Primignani M et al., (2010): Detection of the imbalance of procoagulant versus anticoagulant factors in cirrhosis by a simple laboratory method. Hepatol; 52(1), 249-255.
16. Zanetto A, Campello E, Bulato C et al. (2022): Global hemostatic profiling in patients with decompensated cirrhosis and bacterial infections. JHEP Rep; 4100493.
17. Pan J, Wang L, Gao F et al. (2022): Epidemiology of portal vein thrombosis in liver cirrhosis: a systematic review and meta-analysis. Eur J Intern Med; 104: 21-32.
18. A.J. Kovalic, C.N. Majeed, N.S. Samji et al. (2020): Systematic review with meta-analysis: abnormalities in the international normalised ratio do not correlate with periprocedural

bleeding events among patients with cirrhosis. Aliment Pharmacol Ther, 52, pp. 1298-1310.

19. Garcia-Tsao G., Abraldes J.G., Berzigotti A et al. (2017). Portal hypertensive bleeding in cirrhosis: risk stratification, diagnosis, and management: 2016 practice guidance by the American Association for the Study of Liver Diseases. Hepatology; 65:310–335.
20. Intagliata NM, Argo CK, Stine JG et al. (2018): Concepts and controversies in haemostasis and thrombosis associated with liver disease: proceedings of the 7th International Coagulation in Liver Disease Conference. Thromb Haemost; 118(8):1491-1506.
21. Roberts L.N, Hernandez-Gea V, Magnusson M et al. (2022): Thromboprophylaxis for venous thromboembolism prevention in hospitalized patients with cirrhosis: guidance from the SSC of the ISTH. J Thromb Haemost; 20: 2237-2245.
22. O'Leary J.G., Greenberg C.S., Patton H.M et al. (2019): AGA clinical practice update: coagulation in cirrhosis.Gastroenterology, 157, pp. 34-43.e1.
23. Baharoglu M.I., Cordonnier C., Salman R.-.S et al. (2016): Platelet transfusion versus standard care after acute stroke due to spontaneous cerebral haemorrhage associated with antiplatelet therapy (PATCH): a randomised, open-label, phase 3 trial. Lancet, 387, pp. 2605-2613.
24. Drolz A., Horvatits T., Roedl K, et al., (2016): Coagulation parameters and major bleeding in critically ill patients with cirrhosis. Hepatology, 64, pp. 556-568.
25. Khemichian S., Terrault N.A. (2020): Thrombopoietin receptor agonists in patients with chronic liver disease. Semin Thromb Hemost, 46, pp. 682-692
26. Afdhal NH, Giannini EG, Tayyab G et al. (2012): Eltrombopag before procedures in patients with cirrhosis and thrombocytopenia. N Engl J Med; 367:716–724.
27. Nilles K.M., Flamm S.L. (2020): Thrombocytopenia in chronic liver disease: new management strategies. Clin Liver Dis, 24, pp. 437-451.
28. Miller J.B., Figueroa E.J., Haug R.M et al. (2019): Thrombocytopenia in chronic liver disease and the role of thrombopoietin agonists. Gastroenterol Hepatol, 15, pp. 326-332.
29. Rose P.D., Au M., Woodman R.J et al. (2021): Pre-procedural use of thrombopoietin-receptor agonists in cirrhosis and severe thrombocytopenia: a systematic review and meta-analysis Dig Liver Dis.

30. Nguyen-Buckley, C., Gao, W., Agopian, V., Wray, C., Steadman, R. H., & Xia, V. W. (2021). Major thromboembolic complications in liver transplantation: the role of rotational thromboelastometry and cryoprecipitate transfusion. Transplantation, 105(8), 1771-1777.
31. Desborough M.J., Kahan B.C., Stanworth S.J et al. (2017): Fibrinogen as an independent predictor of mortality in decompensated cirrhosis and bleeding. Hepatology, 65, pp. 1079-1080.
32. Budnick I.M., Davis J.P.E., Sundararaghavan A et al. (2021): Transfusion with cryoprecipitate for very low fibrinogen levels does not affect bleeding or survival in critically Ill cirrhosis patients. Thromb Haemost, 121, pp. 1317-1325.
33. Hartmann M., Walde C., Dirkmann D et al. (2019): Safety of coagulation factor concentrates guided by ROTEM-analyses in liver transplantation: results from 372 procedures.BMC Anesthesiol, 19, p. 97.
34. Desborough M.J.R., Hockley B et al., (2016): Patterns of blood component use in cirrhosis: a nationwide study. Liver International, 36, pp. 522-529.
35. Green L., Bolton et al., (2018): British Society of Haematology Guidelines on the spectrum of fresh frozen plasma and cryoprecipitate products: their handling and use in various patient groups in the absence of major bleeding. Br J Haematol, 181, pp. 54-67.
36. Northup P.G., Garcia-Pagan J.C et al., (2020): Vascular liver disorders, portal vein thrombosis, and procedural bleeding in patients with liver disease: 2020 practice guidance by the American Association for the Study of Liver Diseases, Hepatology. 31646.
37. H. Shakur, I. Roberts, B. Fawole et al. (2017): WOMAN trial collaborators. Effect of early tranexamic acid administration on mortality, hysterectomy, and other morbidities in women with post-partum haemorrhage (WOMAN): an international, randomised, double-blind, placebo-controlled trial.The Lancet, 389(10084), 2105-2116.
38. Roberts I, Shakur-Still H, Afolabi A et al. (2020): HALT-IT Trial Collaborators. Effects of a high-dose 24-h infusion of tranexamic acid on death and thromboembolic events in patients with acute gastrointestinal bleeding (HALT-IT): an international randomised, double-blind, placebo-controlled trial. Lancet; 395:1927-1936.

39. Intagliata N.M, Henry Z.H et al., (2016): Direct oral anticoagulants in cirrhosis patients pose similar risks of bleeding when compared to traditional anticoagulation. Dig Dis Sci; 61: 1721-1727.
40. De Franchis R., Bosch J., Garcia-Tsao G et al. (2022). Faculty Baveno VII – renewing consensus in portal hypertension. J Hepatol; 76:959–974.
41. Moorehead K.J, Jeffres M.N, Mueller S.W. (2017): A retrospective cohort analysis of pharmacologic VTE prophylaxis and Padua prediction score in hospitalized patients with chronic liver disease. J Pharm Pract; 30: 58-63.
42. Hoolwerf E.W, Kraaijpoel N, Buller H.R et al. (2018): Direct oral anticoagulants in patients with liver cirrhosis: a systematic review. Thromb Res; 170: 102-108.
43. Intagliata N.M, Caldwell S.H, Tripodi A. (2019): Diagnosis, development, and treatment of portal vein thrombosis in patients with and without cirrhosis. Gastroenterology; 156: 1582-1599.e1.
44. Shatzel J, Dulai PS, Harbin D et al. (2015): Safety and efficacy of pharmacological thromboprophylaxis for hospitalized patients with cirrhosis: A single-center retrospective cohort study. J ThrombHaemost; 13:1245–1253.
45. Chen H, Liu L, Qi X et al. (2016): Efficacy and safety of anticoagulation in more advanced portal vein thrombosis in patients with liver cirrhosis. Eur J Gastroenterol Hepatol; 28:82–89.
46. Witt DM, Clark NP, Kaatz S et al. (2016): Guidance for the practical management of warfarin therapy in the treatment of venous thromboembolism. J Thromb Thrombolysis; 41:187–205.
47. Reichert JA, Hlavinka PF, Stolzfus JC. (2014): Risk of hemorrhage in patients with chronic liver disease and coagulopathy receiving pharmacologic venous thromboembolism prophylaxis. Pharmacotherapy; 34:1043–1049.
48. Plessier A, Goria O, Cervoni J.P et al. (2022): Rivaroxaban prophylaxis in noncirrhotic portal vein thrombosis. NEJM Evid; 1EVIDoa2200104.