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HEMOSTATIC ABNORMALITIES IN PATIENT WITH LIVER CIRRHOSIS: A REVIEW

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ABSTRACT

Liver cirrhosis is one of Indonesia's most common liver diseases, where the incidence is 38 – 52.8% of all liver diseases.[1] Liver cirrhosis refers to a late-stage pathological lesion caused by the accumulation of extracellular matrix in the liver parenchyma. Liver cirrhosis is caused by chronic injury to the liver due to viral infections, autoimmune, toxins, cholestasis, metabolic diseases, and other diseases.[2] Patients with cirrhosis, especially decompensated liver cirrhosis, often have a variety of comorbidities. One of the complications that occur is a disturbance in the hemostasis system. Disorders of hemostasis in these patients can occur at the stage of primary hemostasis, secondary, or fibrinolysis. This literature review discusses disorders of hemostasis in patients with liver cirrhosis accompanied by diagnosis and treatment. This review was conducted by searching, reviewing, and collecting from various studies. The result of various studies shows many patients with liver cirrhosis are at risk of developing thrombotic and/or coagulation disorders.

Keywords: *Cirrhosis, Coagulation, Hemostatic, Thrombotic.*

INTRODUCTION

Hemostasis is a biological process in which platelets are activated as the major effector and originator of the coagulation process.[3] The word hemostasis originates from *hemo* (blood) and stasis (maintenance). Therefore, hemostasis can be stated as a process of stopping bleeding from a broken blood vessel.[4]

Primary and secondary hemostasis are two types of primary hemostasis. Platelet aggregation and plug production are the first steps in primary hemostasis. Secondary hemostasis is a process that begins with the deposition of insoluble fibrin and ends with the formation of a mesh around the previously produced platelet plug.[5] The third step (fibrinolysis) usually begins after the primary and secondary phases of the procedure have been completed. The plasma anticoagulant protein begins to break down the fibrin mesh that has developed.[6]

Patients with liver cirrhosis, especially decompensated stage, are accompanied by various co-morbidities. One of the co-morbidity that occurs is a disturbance of the hemostasis system. The incidence of hemostatic disorders in patients with liver cirrhosis is around 78,57%.

METHODS

The method of this review were searching various articles and books using online databases, including PubMed, Google scholar, and science direct with the keywords: "liver cirrhosis" and "hemostatic disorder". The articles will be selected according to inclusion and exclusion criteria. The inclusion criteria were accredited articles and books, while the exclusion criteria are incomplete articles.

RESULTS

Primary Hemostatic Changes

1. Thrombocytopenia

Thrombocytopenia affects nearly one-third of patients with chronic liver disease. Mild thrombocytopenia (platelet count less than 150 x 10^9/L) affects 78% of all patients with liver cirrhosis. In 13% of cirrhotic individuals, moderate thrombocytopenia (platelets 50-75 x 109/L) develops. Meanwhile, severe thrombocytopenia (platelets 50 x 109/L) affects 1% to 2% of patients with liver cirrhosis.[7]

Thrombocytopenia can be caused by various factors, including decreased platelet synthesis, increased platelet clearance and destruction, or other disorders. Due to reduced *thrombopoietin* (TPO) and suppression of bone marrow, the primary regulator of platelet formation, which is generated by hepatocytes, platelet synthesis is reduced. Patients with cirrhosis have hepatocyte cell destruction, which decreases the Ashwell-Morell receptors (AMrs) and the stimulus to release TPO mRNA, resulting in decreased functional TPO.[7,8]

Increased platelet clearance leads to thrombocytopenia through hypersplenism, increased antiplatelet antibodies (platelet-associated immunoglobulin G, PAIgG), and coagulation

cascade activation. Hypersplenism is a disorder characterized by a decrease in red blood cells due to sequestrants or destruction in the spleen.[7,9]

2. Thrombocytopathy

Thrombocytopathy refers to platelet abnormalities.[10] Patients with cirrhosis of the liver develop thrombocytopathy due to platelet aggregation and elimination of circulating platelets. It results in aberrant intracellular signaling, a decrease in thromboxane A2 metabolism, and a deficiency in the storage pool. The unusual intracellular signal decreases phospholipase A1/C while increasing cAMP/cGMP.[7]

3. ADAMTS13 Reduction

ADAMTS13, a protease predominantly generated by the liver, serves as a von Willebrand factor detachment enzyme at the injury site.[11] ADAMTS13 plays a vital function in hemostasis due to its antithrombotic properties. A decrease in ADAMTS13 in patients with cirrhosis leads to an increase in von Willebrand factor and thrombocytopenia.[7]

4. Decrease of von Willebrand Factor

Antigen or activity of von Willebrand factor can rise in liver cirrhosis patients with elevated von Willebrand factor levels. Increased production of endothelial cells, endothelial cell malfunction (e.g., due to bacterial infection), and impaired hepatic clearance as in individuals with liver cirrhosis are the causes causing this syndrome.[7] In addition to producing clotting factors, the liver also functions to clean activating substances and procoagulants in the blood. Due to excessive activator substances, this causes plasminogen activation to plasmin and causes fibrinolysis. If the procoagulant circulating in the circulation exceeds the liver clearance capacity, this procoagulant activates the coagulation system and disseminates intravascular coagulation.[12]

Coagulation Changes

1. Coagulation Factor

Hepatocytes generate all coagulation factors and natural anticoagulants, except F VIII, which is formed by sinusoidal endothelial cells:[12]

a. Depending on Vitamin K

Vitamin K acts as a coenzyme in the carboxylation phase of gamma glutamic acid from F II, F VII, F IX, and F X.[12] In patients with liver cirrhosis, the liver cannot synthesize clotting factors due to hepatic tissue dysfunction and portal hypertension.[3] In addition, patients with liver cirrhosis often receive antibiotics in the long term (more than 14 days). It can affect the disruption of the synthesis of vitamin K by the intestine. Reduced synthesis of vitamin K results in the formation of imperfect clotting factors and can act like anticoagulants.[12]

b. Fibrinogen group

F V, F VIII, and F XIII are classified as fibrinogen because their mass is >300,000 *daltons*, and they do not require vitamin K for their synthesis.[12] Due to excessive fibrinogenolysis, decreased fibrinogen synthesis, or abnormal formation. In contrast to other coagulation factors, decreased fibrinogen levels only occur in patients with advanced liver cirrhosis. Changes in the amount and structure of fibrinogen in cirrhotic patients lead to clot formation and fibrinolysis, which puts the patient in a prothrombotic state.[7]

c. Contact clotting factor

F XI and F XII are the contact clotting factors. Contact clotting factors cannot assess whether hepatic cirrhosis in a patient is stable or unstable. Decreased levels of F XII can also coincide with a decrease in serum albumin levels.[12]

2. Factor VIII, Proteins C, and S

In patients with liver cirrhosis, coagulopathy is mainly brought on by a decrease in protein C and S and an increase in F VIII. It occurs since the portal circulation has more significant levels of F VIII and lower levels of C and S proteins than the peripheral circulation. It results in a prothrombotic solid condition in the portal circulation, as well as elevated levels of D-dimer and prothrombin fragments 1 and 2.[7]

3. Other anticoagulants

Antithrombin and other anticoagulants are lowered in patients with liver cirrhosis. The reduction was the suppression result of the tissue factor (TF) inhibitor complex TF/VIIa system route, which is strongly dependent on the S and F Xa proteins. Because protein S and F Xa are diminished in cirrhotic patients, it impacts the synthesis of antithrombin.[7]

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4. Procoagulant Microparticles

Procoagulant microparticles are small membrane vesicles released by various cells through plasma membrane exocytosis in response to activated cellular responses or apoptotic processes. Microparticles secrete a variety of procoagulant phospholipids.[13] In patients with liver cirrhosis, tissue factors containing procoagulant microparticles (TF-MP) are elevated. Platelets *leukoendothelial* cells, lymphocytes, erythrocytes, hepatocytes, and hepatocytes account for most of the TF-MP rise. The TF-MP plays a role in hypercoagulability conditions.[7]

Changes in Fibrinolysis

Fibrinolysis is a complex process that is disrupted in liver cirrhosis patients. Starting the fibrinolysis process is the activation of plasminogen to plasmin, which breaks the fibrin clot. The tissue-plasminogen activator (tPA) produced by endothelial cells activates most plasminogen, which then activates plasmin when it binds to fibrin. tPA is rendered inactive by plasminogen activator inhibitor-1 (PAI-1), an inhibitor released by endothelial cells and platelets, and can be induced by inflammatory cytokines. Patients with cirrhosis of the liver are susceptible to hyperfibrinolysis, resulting in bleeding.[7]

Table 1. Fibrinolytic changes in liver cirrhosis

Fibrinolytic	Explanation	Level
Plasminogen	Activity	Decrease
tPA	Activity	Increase
PAI-1	Antigen	Stable or increase
	Activity	Decrease or stable
TAFI	Antigen	Decrease
α2AP	Antigen	Decrease

Types of Hemostatic Disorders in Patients with Liver Cirrhosis

1. Bleeding Episodes

a. Variceal bleeding

Variceal bleeding was caused by portal hypertension and mostly occurs in the veins of the gastrointestinal tract, particularly the esophagus and stomach. The bleeding occurs in 20-30% of patients with liver cirrhosis, with 50% of patients with decompensated liver cirrhosis experiencing it as their primary coagulopathy problem.

Nearly 30% of first bleeding is deadly, and 70% of patients will experience recurrent bleeding within two weeks following the original bleed. Patients with a high Child's-Pugh classification, red wale symptoms on endoscopic examination, and the dilatation of blood vessels are known to enhance the risk of bleeding. Laboratory tests will reveal elevated D-dimer and t-PA concentrations.[14]

b. Intracerebral bleeding

In patients being treated for cirrhosis of the liver, spontaneous intracerebral bleeding is uncommon; roughly 80.3% of these episodes are linked to a virus as the cause of cirrhosis, and 1.8% to alcohol.[14]

2. Thrombosis episodes

a. Venous thromboembolism

Patients with liver cirrhosis are 1.65 to 1.74 times more likely to develop venous thromboembolism. Independent predictors of venous thromboembolic events, specifically a shortened APTT and a low blood albumin concentration.[14]

b. Portal venous thromboembolism and emboli pulmonary

The incidence of portal vein thrombosis ranges between 7.4 and 11% in patients with liver cirrhosis.[14] The two types of portal vein thrombosis are acute and chronic. Acute portal vein thrombosis is defined by the abrupt blockage of the portal vein due to a thrombus. Abdominal discomfort, variceal bleeding, and intestinal infarction are common clinical symptoms; however, in some cases, these symptoms are absent (asymptomatic). Chronic portal vein thrombosis is an acute form of portal vein thrombosis that does not improve, resulting in the establishment of a collateral circulation that flows blood around the obstruction in this patient (cavernous transformation).[15]

The prevalence of pulmonary embolism in cirrhotic patients is around 19.5%. Protein C and S insufficiency, antithrombin III deficiency, and individuals with other comorbidities are all risk factors (myeloproliferative disease, hepatocellular carcinoma, mutations in prothrombin or F V Leiden, history of sclerotherapy, history of abdominal surgery).[14]

Laboratory diagnosis

One of the supporting examinations that can be done to assess hemostatic function in patients with liver cirrhosis is laboratory examination. Several examinations included:[3,7,8]

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Table 2. Laboratory examination

	Hasil
INR, PT	Prolonged
APTT	Normal or prolonged
Platelet count	Normal or decreased
Bleeding time	Prolonged
vWF	Increase
Fibrinogen	Normal or decrease: a. Decrease fibrinogen in serum mean hyperfibrinolytic stage. b. Fibrinogen >100 mg/dL shows adequate fibrinogen to start coagulation process.
Coagulant factors	a. Decrease of factor II, V, VII, IX, X, XI b. Increase of factor VIII .
Procoagulant microparticle	Increase

Treatment

1. Bleeding Episode

The therapeutic objectives for patients with liver cirrhosis who encounter bouts of bleeding are to stop the bleeding and restore blood volume. The treatments that can be administered were:[12]

a. Blood transfusion

Blood and fresh frozen plasma transfusions are the first-line treatment for bleeding.[12] Patients should be administered blood or blood components with prudence since excessive administration might result in fluid overload and transfusion-related acute lung damage. TRALI). Because each 100 mL of increased blood volume administered rapidly can induce a 1 mmHg increase in portal pressure, it can also result in portal collateral bleeding. Blood is typically administered at 15-30 mL/kg/IV. Moreover, other blood components such as prothrombin complex concentrate (PCC), recombinant F VIIa (rFVIIa), and cryoprecipitate are utilized.[6]

PCC is a component of blood that contains coagulation factors. PCC is currently separated into two formulations: PCC with three elements (F II, F IX, and F X) and PCC with four elements (II, IX, X, VII). PCC also includes proteins C and S, antithrombin III with or without heparin, and antithrombin III. Only patients administered a vitamin K antagonist are allowed to utilize PCC, and the dose is changed according to body weight, INR, or F IX number. The standard dose administered is 25-30 units/kg/IV. The blood component cryoprecipitate contains vWF, fibrinogen, and fibronectin.[6]

Cryoprecipitate has the benefit of not requiring cross-matching before injection. The dose is 10 to 20 mL of intravenous plasma. Patients with hepatic cirrhosis and thrombocytopenia can be transfused with platelets at 8,000 to 12,000 cells/IV unit.[6]

b. Anti-fibrinolysis

Tranexamic acid is an example of an anti-fibrinolysis medication that can be administered if fibrinolysis is detected. [12] The mechanism of action of the drug is to inhibit the interaction between plasminogen/plasmin and fibrin, preventing blood clot lysis. The dosage of 500 mg/6 hours can be administered IV or orally. E-aminocaproic acid (EACA) is another example of a medication that inhibits fibrinolysis by preventing the binding of plasminogen to fibrin. 4-5 g IV/PO is administered within the first hour, followed by a maintenance dosage of 1-4 g IV/PO every 4-8 hours.[6]

c. Beta-blocker

Propranolol is one of the beta-blockers used, and this medication reduces pressure in the portal vein. The drop in portal venous pressure decreases the blood flow in these blood arteries, decreasing the gastric mucosa's fibrinolytic activity.[12]

d. Sclerotherapy

Sclerotherapy is an injection-based treatment for variceal bleeding. The action can be applied as a long-term treatment to reduce bleeding.[12]

e. Tamponade balloon (Sengstaken-Blackmore Tube, SB Tube)

This procedure is performed in patients with massive variceal bleeding. The way the tamponade balloon works is by pressing directly on the vessel.[12]

f. Surgery

Surgery is performed to stop or prevent recurrent bleeding. The actions taken were splenorenal shunt and esophageal transection.[12]

2. Thrombotic episodes

Patients with liver cirrhosis are at risk for thromboembolism, both systemic and in organs such as the portal and pulmonary veins. Treatment for thrombosis includes:[15]

a. Heparin

Heparin is an anticoagulant that is used in liver disease was unfractionated heparin and low molecular weight heparin (LMWH). The way heparin works are by inactivating F Xa and thrombin, thereby preventing the conversion of fibrinogen to fibrin.[6,15]

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b. Vitamin K antagonist

Warfarin is one of the vitamin K antagonists used in the treatment of portal vein thrombosis. The way it works is by inhibiting vitamin K epoxide reductase complex-1, and preventing thrombus progression.[15]

c. Surgery

The action can be done by transjugular intrahepatic portal shunt.

CONCLUSION

Hemostasis disorders are one of the complications that often occur in patients with liver cirrhosis. Impaired hemostasis can occur in primary, secondary hemostasis, or in the process of fibrinolysis. This disorder can occur due to changes in the physiology of the liver due to the formation of late-stage fibrotic tissue in hepatocyte cells. Impaired hemostasis puts patients with liver cirrhosis at risk for bleeding or thrombosis. Establishing a diagnosis of hemostatic disorders in patients with cirrhosis can be done by assessing clinical symptoms and supporting investigations in the form of laboratory tests. Management of patients with hemostatic disorders must be adjusted to the clinical condition of the patient. Where several treatments can be done including the use of medication and/or surgery.

CONFLICTS OF INTEREST

The authors declare no conflict of interest in this article.

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REFERENCES

1. Tambunan, K. L. Gangguan hemostasis pada sirosis hati dan saran penatalaksanaannya di Indonesia: ringkasan. (Universitas Indonesia, 1992).
2. Rockey, Don. C. Hepatic Fibrosis and Cirrhosis. in *Yamada's* Textbook *of Gastroenterology* (Wiley-Blackwell, 2016).
3. Northup, P. G. & Caldwell, S. H. Coagulation in Liver Disease: A Guide for the Clinician. *Clinical Gastroenterology and Hepatology* **11**, 1064–1074 (2013).
4. Sherwood, L. *Fisiologi Manusia dari Sistem ke Sel*. (EGC, 2012).
5. Gale, A. J. Current Understanding of Hemostasis. *Toxicol Pathol* **39**, 273–80 (2011).
6. Premkumar, M. & Sarin, S. K. Current Concepts in Coagulation Profile in Cirrhosis and Acute-on-Chronic Liver Failure. *Clin Liver Dis (Hoboken)* **16**, 158–167 (2020).
7. Zermatten, M. G. *et al.* Hemostatic Alterations in Patients With Cirrhosis: From Primary Hemostasis to Fibrinolysis. *Hepatology* **71**, 2135–2148 (2020).
8. Kujovich, J. L. Hemostatic defects in end stage liver disease. *Crit* Care *Clin* **21**, 563–87 (2005).
9. Lisman, T. & Leebeek, F. W. G. Hemostatic Alterations in Liver Disease: A Review on Pathophysiology, Clinical Consequences, and Treatment. *Digestive Surgery* **24**, 250–258 (2007).
10. Drogies, T., Braunert, L., Thiery, J. & Brügel, M. Thrombocytopathy: an update. *LaboratoriumsMedizin* **35**, 67–74 (2011).
11. Zheng, X. L. ADAMTS13 and von Willebrand factor in thrombotic thrombocytopenic purpura. *Annu Rev Med* **66**, 211–25 (2015).
12. Setiati, S. *et al. Buku Ajar Ilmu Penyakit Dalam*. (InternaPublishing, 2014).
13. Nomura, S. & Shimizu, M. Clinical significance of procoagulant microparticles. *J Intensive Care* **3**, 2 (2015).
14. Muciño-Bermejo, J., Carrillo-Esper, R., Uribe, M. & Méndez-Sánchez, N. Coagulation abnormalities in the cirrhotic patient. *Ann Hepatol* **12**, 713–24 (2013).
15. Flores, B., Trivedi, H. D., Robson, S. C. & Bonder, A. Hemostasis, bleeding and thrombosis in liver disease. *J Transl Sci* **3**, (2017).