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# The Nature of Changes in the Hemostatic System in Liver Cirrhosis

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**Abstract:** The nature of violations of the hemostatic system in liver cirrhosis is complex, often unpredictable and concerns all its links – vascular-platelet, coagulation and fibrinolysis. It is now well established that patients with cirrhosis may experience both bleeding and thrombosis. The mechanisms of blood clotting disorders in this case are very complex, since defects simultaneously occur both in the procoagulant system and in the anticoagulation system. Aim to study the factors and mechanism of the development of hemostasis imbalance in patients with liver cirrhosis based on the analysis of scientific literature, to determine the information content of existing laboratory tests for the study of hemostasis and the features of correction of hemostasis disorders depending on hyper- or hypocoagulation. It is generally accepted that cirrhosis results in a state of hypocoagulation with an increased tendency to bleeding. However, a number of publications do not support this opinion, and the interpretation of laboratory parameters is explained by the standard methodology, where the procoagulant and antifibrinolytic systems of hemostasis are insufficiently studied. Many researchers have established a state of hypercoagulability in liver cirrhosis, leading to intra- and extrahepatic thrombosis. The cause of bleeding, primarily from varicose veins of the esophagus and stomach, is not hypocoagulation as such, but rupture of varices due to hemodynamic disturbances with increased portal pressure, one of which is thrombosis. Accordingly, therapeutic tactics should be aimed, first of all, not at normalizing laboratory tests, but at eliminating the pathogenetic mechanisms of hemostatic imbalance that occur in liver cirrhosis. At the same time, drug correction should be directed not at individual links of the hemostasis system - pro or anticoagulant, but at the correction of hemostatic imbalance as a whole. Conclusions. To date questions about the nature of changes in the hemostasis system in liver cirrhosis, their relationship with hemorrhagic complications or thrombosis, the principles of drug correction remain open, requiring further research in this direction.

**Keywords:** Liver Cirrhosis, Hemostasis System, Bleeding, Thrombosis, Diagnosis, Treatment

## 1. Introduction

The nature of hemostatic system violations in liver cirrhosis (LC) is complex, often unpredictable and concerns all its links - vascular-platelet, coagulation and fibrinolysis. It is accompanied by an imbalance of the pro- and anticoagulant system. It is now well established that both bleeding and thrombosis are possible in patients with liver cirrhosis. It is generally accepted that with the liver cirrhosis there is a state of hypocoagulation with an increased tendency to bleeding. However, a number of publications do not support this opinion, and the interpretation of laboratory parameters is explained by the standard methodology, where the procoagulant and antifibrinolytic systems of hemostasis are insufficiently studied. Many researchers have established a state of hypercoagulability in liver cirrhosis, leading to intra- and extrahepatic. The cause of bleeding, primarily from varicose veins of the esophagus and stomach, is not hypocoagulation as such, but rupture of varices due to hemodynamic disturbances with increased portal pressure, one of which is thrombosis [1-8].

## 2. Aim

Based on the analysis of scientific literature, to study the

factors and mechanism of the development of hemostasis system imbalance in patients with liver cirrhosis, to determine the information content of existing laboratory tests for the study of hemostasis and the peculiarities of the correction of hemostasis disorders depending on hyper- or hypocoagulation.

# 3. Results

Primary thrombosis (portal and hepatic veins, intrahepatic portal and hepatic venules), which develops in the vessels of an initially healthy liver, and thrombosis in liver cirrhosis are distinguished. Whether there is a connection between primary thrombosis and liver pathology, whether thrombosis is a consequence of a decompensated course of liver cirrhosis or the cause of its decompensation with the development of specific complications - these questions remain unresolved today [1, 2, 4, 5, 8, 9]. In 2020, updates were issued to the American association for the Study of Liver Diseases practice guidelines on liver vascular disease, thrombosis, and bleeding in patients with liver pathology, where the generally accepted data on the pathophysiological and clinical features of hemostasis disorders in patients with cirrhosis were critically examined, which suggests further research in this direction [1, 4].

### *3.1. Primary Thrombosis*

Portal thrombosis, intra- and extrahepatic, is detected in approximately half of patients with the syndrome of portal hypertension of non-cirrhotic genesis [4]. Thrombosis of the hepatic veins (veno-occlusive disease, Budd-Chiari syndrome) is even more common. According to a number of researchers, extrahepatic thrombosis may be secondary to the primary lesion of the intrahepatic venous system [4, 11, 12].

Pathogenetically, thrombosis is caused by a combination of local and general factors.

Local factors include: cancer (any organ of the abdominal cavity); acute and chronic inflammatory diseases of the abdominal organs; damage of the portal system veins (splenectomy, liver transplantation, abdominal trauma); portocaval shunting (surgical, endovascular). Thrombogenic lesions of the portal tracts are possible with granulomatous diseases - schistosomiasis, sarcidosis, tuberculosis; autoimmune liver diseases - primary biliary cirrhosis, primary sclerosing cholangitis. The action of some toxic substances (captured by endothelial cells in the Disse space) leads to increased fibrinogenesis and obstruction of small branches of the portal vein [4, 11, 13].

Common factors include congenital and acquired abnormalities in the hemostatic system. Congenital ones include a deficiency of natural coagulation inhibitors (deficiency of antithrombin III), factors II and V (mutation of factor Leiden), mutation of the prothrombin gene. Acquired factors are myeloproliferative diseases, antiphospholipid syndrome, deficiency of proteins S and C, paroxysmal nocturnal hemoglobinuria, hyperhomocysteinemia, Behcet's disease, inflammatory and oncological diseases, the use of oral contraceptives, pregnancy, etc.

In portal vein thrombosis (PVT), local factors can be identified in about 30% of patients, and common factors in 70%. In hepatic vein thrombosis, common risk factors are found in 87% of patients. Local factors remain unidentified in more than 95% of patients, although the main factors may be the same as in PVT. A combination of several causative factors is found in approximately 25-44% of patients [4, 5, 12, 15-17].

In half of the patients, the direct cause of thrombosis cannot be established, however, most of them have various comorbidities - hypothyroidism, diabetes mellitus, dermatomyositis, rheumatoid arthritis, ulcerative colitis, Crohn's disease, obesity, metabolic syndrome, etc. [4, 13, 16].

*The course and prognosis of primary thrombosis*. It has been experimentally and clinically established that hypercoagulation is associated with an accelerated progression of liver fibrosis and the development of cirrhosis. Thrombin, in addition to its powerful procoagulant action, has many cellular effects through the activation of hepatic stellate cells responsible for pathological fibrosis. The degree of expression of the thrombin receptor is associated with the severity of liver disease [1, 17]. The development of fibrosis with $CCl_4$ intoxication is preceded by thrombosis with subsequent obliteration of the vessels of the necrotic areas and fibrous septa. The severity of viral hepatitis is associated with capillary thrombi, probably due to the induction of procoagulant systems in activated endothelial cells and macrophages. A decrease in the content of antithrombin, proteins C and S, an increase in the level of factor VIII in patients with viral hepatitis or non-alcoholic fatty hepatosis correlates with more severe stage of fibrosis and accelerated progression to cirrhosis. In such patients, cirrhosis of the liver developed, on average, after 18 years. In the absence of thrombotic complications, the average time of development of cirrhosis is 40 years [18, 19].

### *3.2. Thrombosis in Liver Cirrhosis*

It is now well established that patients with cirrhosis may experience both bleeding and thrombosis. Thrombotic complications include intrahepatic thrombosis, thrombosis of the portal veins, deep veins of the lower extremities, and pulmonary thromboembolism [4, 5, 20-23].

#### *3.2.1. Intrahepatic Thrombosis*

In a morphological study of cirrhotic liver removed during transplantation, intimate fibrosis due to thrombosis was detected in the intrahepatic portal and hepatic veins in 36% and 70% of cases, respectively. The defeat of the hepatic veins was focal and was largely confined to medium-sized veins. The lesion of the portal vessels was more evenly distributed throughout the liver. There was a relationship between thrombosis and regional changes in the size of cirrhotic nodes, recurrent bleeding, ascites or encephalopathy in history. It is assumed that intrahepatic thrombosis is frequent in cirrhosis; these thrombosis could cause the progression of the disease and contribute to the development of fatal complications [2, 7, 10, 16, 24].

#### *3.2.2. Portal Vein Thrombosis*

Portal vein thrombosis is a recognized phenomenon in patients with liver cirrhosis, which makes it possible to consider liver cirrhosis as one of the main causes of its occurrence. There is a clear correlation between PVT and more severe portal hypertension [20, 23]. The prevalence of PVT increases with the progression of cirrhosis, being in less than 1% of patients with a compensated stage and more than 8-26% (up to 50%) in candidates for liver transplantation. At the same time, the development of portal vein thrombosis is a significant milestone in the natural course of liver cirrhosis and is associated with decompensation of hepatic function and the development of major complications. That is, the occurrence of PVT in patients with cirrhosis is an unfavorable prognostic factor [3-5, 20, 25, 26].

#### *3.2.3. Hepatic Vein Thrombosis*

According to statistics, more than 8% of patients with Budd-Chiari syndrome, the latter develops against the background of liver cirrhosis [4, 11, 13]. Although, according to some researchers, extrahepatic thrombosis is secondary to the primary lesion of the intrahepatic venous system [15].

#### *3.2.4. Visceral Thrombosis*

*Visceral Thrombosis* (thrombosis of the visceral veins). A number of studies indicate the presence of visceral vein thrombosis in 18% of patients with cirrhosis. In acute gastric bleeding, the presence of visceral venous thrombosis worsens the short-term prognosis [42].

#### *3.2.5. Deep Vein Thrombosis of the Lower Extremities and Venous Thromboembolism (VTE)*

It was statistically established that LC is a risk factor in which there is more than twofold increase in the number of peripheral vein thrombosis and thromboembolism compared to the general population [21, 23, 25, 26]. A number of studies have shown an increase in the percentage of thromboembolism due to venous thrombosis in patients with functional class C (8%) according to Child-Pugh compared with patients in class B (4.6%) and class A (4.2%). According to a nationwide study carried out in the United States, the presence of VTE ended with an increase in mortality in patients with liver cirrhosis, regardless of the presence or absence of decompensation of the disease [5, 25].

### *3.3. Pathogenesis of Thrombosis in LC*

The coagulation system is a dynamic process linking primary and secondary hemostasis with fibrinolysis. Changes in hemostasis that accompany liver pathology affect all levels of the coagulation system, leading to a hemostatic imbalance. At the same time, there are many factors that can disturb this balance in one direction or another and, accordingly, predispose the patient to bleeding or thrombosis. In clinical practice, a decrease in the procoagulant potential can be interpreted as a primary defect only when the indicators of the anticoagulant system are within the normal range, and vice versa [10, 17, 26].

There are three main pathophysiological mechanisms that affect the coagulation system in LC.

The first group includes extrahepatic mechanisms - hemodynamic disturbances of portal blood flow due to endothelial dysfunction, viremia, endotoxemia, renal dysfunction, etc., which often accompany liver cirrhosis, systemic inflammatory reactions, and diabetes mellitus. A low level of albumin can also be attributed to extrahepatic factors, which, according to some authors, is an independent risk factor for the development of extrahepatic thrombosis [4, 20, 25, 26, 28]. A decrease in the linear and volumetric velocity of portal blood flow in this case is the main factor leading to thrombosis. The level of PVT development was significantly higher in patients where the portal blood flow velocity did not exceed 10 cm/sec and the portal volumetric blood flow was less than 400 ml/min. Nonselective beta-blockers, which are widely used for primary and secondary prevention of bleeding from varicose veins of the esophagus, can significantly reduce the velocity of blood flow in the portal vein, increasing the risk of thrombosis in patients with LC by 4.62 times [1, 2, 4, 5, 11, 30].

The second group of reasons includes hemostatic imbalance caused, as in primary thrombosis, by congenital and acquired defects of the pro- and anticoagulant systems [17, 21]. With targeted examination of patients with LC, the percentage of detection of thrombogenic diseases significantly exceeds that in patients without LC. A number of studies report a thrombophilic genotype in 69% of patients with portal vein thrombosis on the background of LC. Among congenital diseases, the most common are deficiency of coagulation factors II and V; among acquired - antiphospholipid syndrome, deficiency of proteins S, C, antithrombin III (AT III), anti-Xa factor, thrombomodulin, paroxysmal nocturnal hemoglobinuria, Behcet's disease, myeloproliferative diseases and hyperhomocysteinemia. It is characteristic that patients with LC and hereditary thrombophilia have more rapid progression of the disease, in contrast to patients with LC and hemophilia. However, even in patients with compensated cirrhosis, the underlying thrombogenic disease is difficult to detect due to secondary changes in marker genes [5, 21, 22, 25, 27, 31].

The third group of mechanisms is associated with coagulopathy due to the natural course of liver cirrhosis. With LC, changes were noted in all phases of hemostasis caused by impaired liver synthetic function. The mechanisms of blood clotting disorders in this case are very complex, since defects simultaneously occur both in the procoagulant system and in the anticoagulation system. In the natural course of LC, the imbalance of pro- and anticoagulants is shifted towards hypercoagulation. The procoagulant link is characterized mainly by a decrease in the levels of protein C, S and AT III, metalloprotease ADAMTS-13 (together with other pro- and anticoagulants synthesized in the liver), in combination with an increase in the level of coagulation factor FVIII, Willenbrand factor, having extrahepatic origin, which is a typical feature in cirrhosis.

It has been shown that procoagulant imbalance is associated with more severe course of the disease, independently

predicting the development of ascites and varicose bleeding [1, 4, 5, 7, 22, 25, 32].

#### *3.3.1. Violation of Primary (Vascular-platelet) Hemostasis*

One of the most common signs of impaired primary hemostasis and often the first abnormality observed in patients with chronic liver disease is thrombocytopenia (TP) [4, 5, 33, 34]. The prevalence and severity of thrombocytopenia is determined by the degree of functional liver failure, the severity of fibrosis and, apparently, the etiology of liver damage. So, in patients with chronic liver diseases, it is detected in 6% of patients with mild and moderate fibrosis and in 64-76% of patients at the stage of liver cirrhosis. Thrombocytopenia is possible both with bleeding and thrombosis, but the mechanisms of this are not fully understood. At the same time, a number of studies indicate that thrombocytopenia in LC does not fundamentally affect hemostasis and a low platelet count in these patients cannot necessarily be considered a risk factor for bleeding.

And, on the contrary, paradoxically, thrombocytopenia in LC is an independent predisposition factor for portal vein thrombosis [4, 5, 23, 27, 34, 35].

The cause of thrombocytopenia in LC is multifactorial, including both increased platelet destruction and decreased platelet production.

*Increased destruction of platelets*

*Syndrome of hypersplenism in liver cirrhosis.* Increased sequestration and destruction of platelets in the spleen as a result of splenomegaly and hypersplenism, closely associated with portal hypertension, is considered the main cause of TP. In patients with the liver cirrhosis, up to 90% of platelets can be found in the spleen. However, even in these patients, the number of platelets in the peripheral blood decreases slightly. There is evidence of a shorter platelet half-life associated with hypersplenism. However, the lack of full recovery of platelet levels after shunting operations that reduce portal pressure, or after embolization of the splenic artery, which inhibits spleen function, questioned the importance of the spleen as the main mechanism in the development of thrombocytopenia [5, 34, 46].

*The presence of antiplatelet antibodies*. In chronic hepatitis, especially of autoimmune and viral nature, autoantibodies directed against platelet surface antigens are often detected. The binding of these antibodies to platelets promotes their absorption by the cells of the reticuloendothelial system in the spleen and liver. Antiplatelet antibodies were detected in 64% of cases. In chronic hepatitis C, the role of antibodies directed against neoantigens, the formation of which occurs due to the binding of the virus to platelet surface antigens, is assumed [5, 34].

*The presence of circulating immune complexes*. The destruction of platelets due to nonspecific binding to circulating immune complexes is another factor in the development of TP in patients with chronic liver disease. This mechanism of TP development has been described in HIV infection and in the administration of certain medications [36].

*Increased consumption in the vascular system*, in particular, in the case of disseminated intravascular coagulation (disseminated intravascular coagulation), which often accompanies LC. However, the presence of this syndrome in patients with cirrhosis is interpreted differently by different specialists [36].

*Impaired platelet formation*

*Decrease in the level/activity of thrombopoietin in the liver*. Thrombopoietin is a cytokine that regulates the maturation of megakaryocytes and the formation of platelets in the bone marrow. Hepatocytes are the main site of thrombopoietin synthesis and constantly release it into the bloodstream. In patients with liver cirrhosis, due to a decrease in the functional activity of hepatocytes, there is a decrease in the production of thrombopoietin. That is, the platelet count reflects the functional state of the liver [5, 7, 34-46].

*Suppression of bone marrow hematopoiesis* (hepatitis viruses, alcohol, drugs). With viral etiology of LC, suppression of bone marrow hematopoiesis is possible, both as a result of the direct action of hepatitis viruses (in particular, hepatitis C), and as a result of antiviral treatment. In alcoholic LC, thrombocytopenia may be associated with autoimmune damage to platelets, the production of defective platelets due to a lack of folic acid, or the toxic effect of ethanol on megakaryocytes [5, 34-36].

The *compensatory* mechanism in thrombocytopenia is a significant increase in the level of Willebrand factor formed in the vascular endothelium, the main protein responsible for platelet adhesion, procoagulant proteins and a decrease in fibrinolysis inhibitors and anticoagulant proteins. It has been shown more than a tenfold increase in the concentration of Willebrand factor in LC, which at least partially can compensate for a decrease in the number of platelets with a possible impairment of their function. That is, an increased level of Willebrand factor is a characteristic feature of LC. Correlates with the degree of portal hypertension and can serve as a prognostic marker of "portal crisis", decompensation and mortality associated, in particular, with the development of thrombosis, being a negative prognostic factor [4, 7, 23, 25, 26, 31, 37].

*An increase in the number of platelets* in the blood (thrombocytosis), which can also occur with LC, is inconsistently observed in: myeloproliferative diseases (erythremia, chronic myeloid leukemia, osteomyelofibrosis, etc.); malignant neoplasms of various localization; after splenectomy. With splenomegaly in patients with LC and platelet counts of more than 200x109, it is necessary to bear in mind the presence of the above pathology [32].

#### *3.3.2. Violation of Secondary (Coagulation) Hemostasis*

The hepatocyte is the main site for the synthesis of all proteins of the coagulation system, as procoagulants (with the exception of Willebrand factor and factor VIII) - vitamin K-dependent coagulation factors II, V, VII, IX, X, XI, XII, fibrinogen and fibrin-stabilizing factor XIII, and coagulation inhibitors - AT III, proteins C, S, a2 -macroglobulin, α-antitrypsin, etc. Proteins C and S are also vitamin K-dependent. In liver failure, the amount of these proteins in

varying proportions decreases, which leads to a violation of the hemostatic balance in one direction or another and, accordingly, to the patient's predisposition to bleeding or thrombosis [2, 10, 17, 26, 31].

In this case, the decompensation of the disease (bleeding, ascites, encephalopathy) is accompanied by a deeper imbalance towards hypercoagulability associated with an increased risk of venous thrombosis [2, 7, 27]. A characteristic feature of LC is an increase in the level of extrahepatic coagulation factor FVIII against the background of a decrease in the levels of proteins C, S and AT III, which are anticoagulants. One of the reasons for the increase in the level of FVIII is considered to be its connection with the Willebrand factor. The latter binds FVIII in vivo and protects it from degradation by plasma proteases and premature clearance. That is, the level of FVIII, like that of Willebrand, can serve as a prognostic criterion for an unfavorable course of CP [2, 5, 9, 20, 31, 32].

#### *3.3.3. Violation of Fibrinolysis*

Both in the pro- and anticoagulation system, and between fibrinolysis and antifibrinolysis, there is a dynamic balance, which is disturbed in liver diseases. All proteins involved in fibrinolysis, with the exception of tissue plasminogen activator (t-PA) and tissue plasminogen activator-1 inhibitor (PAI-1), are also synthesized by the liver, and their level decreases in acute and chronic liver damage. However, the content of the activator profibrinolysin in the plasma remains normal due to the increased synthesis of its endothelium and/or decreased clearance of the diseased liver. The result of these changes in liver pathology has been classically described as hyperfibrinolysis.

Although a number of researchers believe that hyperfibrinolysis in liver cirrhosis is secondary and occurs as a consequence of thrombosis or disseminated intravascular coagulation syndrome against the background of hypercoagulability. There is no clear evidence that hyperfibrinolysis is associated with bleeding.

The level of tissue plasminogen activator inhibitor-1 also increases compensatory, but to a lesser extent. PAI-1 level is especially high in acute liver failure and cholestatic liver diseases, where hyperfibrinolysis is rare. With an increase in liver failure, the imbalance of pro- and anti-fibrinolysis activators shifts towards hypofibrinolysis [17, 23, 26, 31].

#### *3.3.4. Disseminated Intravascular Coagulation Syndrome (DIC-syndrome)*

The issue of disseminated intravascular coagulation in patients with liver cirrhosis, chronic hepatitis and acute hepatitis remains a subject of discussion. The results of the study of thrombin-antithrombin complexes, soluble fibrin, fibrin and fibrinogen degradation products suggest that mild DIC-syndrome is involved in the pathogenesis of coagulopathy in some patients with diffuse liver diseases.

Regardless of the initial state, patients with liver cirrhosis have a greater risk of developing advanced disseminated intravascular coagulation syndrome compared with patients where the liver is not affected, especially in the presence of endotoxemia, renal dysfunction, and arterial hypotension. In the study of ascitic fluid in decompensated patients with LC, fibrin monomers, its degradation products and a small amount of fibrinogen are determined, which indicates an active intraperitoneal coagulation process. With peritoneovenous shunting, intravenous infusion of ascitic fluid, fibrinolysis caused by the presence of plasminogen activators causes systemic coagulopathy with corresponding complications confirming the presence of disseminated intravascular coagulation syndrome in patients with LC [23].

### *3.4. Diagnostics*

#### *3.4.1. Instrumental*

For the diagnosis of thrombosis in the extrahepatic and large hepatic veins, Doppler ultrasound (Doppler ultrasound), spiral computed tomography (CT) or magnetic resonance imaging (MRI), which are recommended to be performed systematically, are optimal. Doppler ultrasound is more informative in detecting thrombosis of the portal vein and its intrahepatic branches. The presence of a cavernous transformation indicates a long-standing thrombosis in which the vein is unlikely to be completely recanalized. CT allows better assessment of the superior mesenteric vein, direct portosystemic shifts, renal veins, and inferior vena cava. Magnetic nuclear resonance imaging (MRI) is an alternative to CT in patients with reduced renal function. However, its informative value is lower, especially in patients with intense ascites [11, 20].

#### *3.4.2. Laboratory Diagnostics*

A big problem in clinical practice is the discrepancy between laboratory parameters assessing the hemostatic system with the development of bleeding or thrombosis. To date, there is no single test available that could accurately predict the risk of bleeding or thrombosis in patients with LC, which may lead to inappropriate treatment [22, 23]. Even in patients with compensated cirrhosis, routine tests do not reflect the true state of the coagulation-anticoagulant system and cannot be adequately interpreted. These patients may have normal coagulogram indices due to balancing the deficiency of procoagulants with a deficiency of anticoagulants (synthesis of both reflects liver function). So, for example, prolongation of prothrombin time (PT), international normalized ratio (INR), decrease in prothrombin index (PI), decrease in activated partially thrombosed time (APTT), which characterize hypocoagulation and are traditionally considered one of the unfavorable prognostic factors of the liver cirrhosis course, do not take into account the possible decrease in coagulation inhibitors in the same patients. As a result, integral hemostasis may remain normal due to balancing the deficiency of procoagulants with a deficiency of anticoagulants, and the threat of hemorrhagic complications is exaggerated. The American Association for the Study of Liver Diseases guidelines note that there is no defined PT-INR level that objectively predicts the risk of bleeding during or after a liver biopsy. In addition, there is a high variability of INR values in different laboratories in patients with LC. As a

measure of hemostasis in cirrhosis, INR has so many disadvantages that it is recommended to abandon it in this regard [1, 2, 4-6].

Assessment of the thrombin level in plasma by methods reflecting the content of pro- and anticoagulants shows that it does not differ in patients with LC from healthy subjects.

Bleeding time, traditionally assessing platelet function, was considered a predictor of the risk of hemorrhagic complications in patients with LC. However, as a result of a number of studies, this test has lost its significance due to its low sensitivity. In LC, there is no direct correlation between platelet count and bleeding time. The bleeding time does not differ between healthy and patients with LC. It has been experimentally shown that the platelet level 50-60 × 109/L is relatively safe, and its increase above 100 × 109/L has no additional benefit compared to the control groups [1, 4-6, 8, 9, 31, 36].

Prognostic marker for determining the level of fibrinogen also lost its significance as a prognostic marker for determining the level of fibrinogen, which is significantly reduced in patients with LC in the presence of disseminated intravascular coagulation syndrome due to decompensation of the disease [23, 27, 33].

Hemodilution and hypersplenism (as a consequence of portal hypertension in LC) decrease the peripheral indices of blood cells and, thus, mask the peripheral features of the blood in various coagulopathies. In addition, a number of diseases that contribute to thrombosis are difficult to interpret as a cause or consequence of LC decompensation [16, 17, 35]. Therefore, some authors attribute patients with liver cirrhosis and normal coagulation parameters to a specific risk group for thrombogenic complications and recommend regular ultrasound Doppler ultrasonography of the hepatic vessels [24]. In the future, tests should be developed and implemented to improve the diagnosis of thrombogenic diseases - an increase in the levels of Willenbrand factors and FVIII, a deficiency of proteins C and S, antithrombin, a decrease in the activity of ADAMTS1 (cleaves von Willebrand factor), the presence of antiphospholipid syndrome, etc. [2, 9, 22, 23, 27].

#### *3.4.3. Thromboelastography (TEG)/Thromboelastometry*

One of the most valuable and accessible general assessment tests is thromboelastography, on the basis of which it is possible to judge integrally the functioning of the procoagulant, platelet links, the fibrinolytic system and the anticoagulant link of the hemostasis system. In addition, TEG makes it possible to differentiate between subacute and acute forms of disseminated intravascular coagulation, thrombocytopenia and thrombocytopathy, and to assess the adequacy of thrombolytic and hemostatic therapy. The method is based on the graphical registration of changes in the viscosity and elastic-elastic properties of blood during the formation of a fibrin clot. A number of studies have found a high degree of positive correlation of TEG parameters with standard coagulation tests. Comparative studies of INR and TEG indices in patients with manifestations of acute hepatic failure have shown that with an average INR of 3.4 (range from 1.5 to 9.6), which is considered as hypocoagulation, only 20% of TEG parameters corresponded to hypocoagulation, in 45% of all TEG parameters were normal, and 35% had a state of hypercoagulability [1, 4-6, 23, 26, 39].

### *3.5. Treatment of Coagulopathies in Patients with Liver Cirrhosis*

#### *3.5.1. Procoagulants*

Pharmaceuticals commonly used to correct coagulopathy in patients with liver diseases and hemorrhagic complications include blood products (erythrocyte mass, fresh frozen plasma, platelet concentrate), prothrombin complex concentrate, recombinant clotting factor FVIIa, antifibrinolytics (ε-aminocaproic acid), tranexamic acid, vitamin K (vicasol). The attitude to the clinical efficacy, risk/benefit of many drugs, respectively, to the indications for their appointment is changing [4, 23].

*Fresh frozen plasma* (FFP) and *blood transfusion*. With prolonged prothrombin time, fresh frozen plasma is often prescribed nowadays. However, the effectiveness of its use with LC is questioned. FFP transfusion in patients with liver cirrhosis only slightly improves the performance of coagulation tests in a limited number of patients and worsens them in a third of cases, that is, it has an unpredictable effect. In addition, plasma transfusion can be accompanied by side effects, such as an increase in the volume of circulating blood and an increase in the level of portal hypertension with recurrent bleeding, the risk of developing acute pulmonary edema, and infectious complications. For every 100 ml of rapid increase in blood volume with the introduction of FFP, the portal pressure increases by 1 mm Hg. Therefore, according to the latest guidelines for transfusion of blood and blood substitutes, an increase in PT in patients with liver pathology is not an indication for prophylactic transfusion of FFP. Restriction is also recommended for compensated patients undergoing various invasive procedures. Even liver transplantation can be performed without prescribing FFP, despite an increase in INR values. The American Association for the Study of Liver Diseases does not recommend prescribing FFP to correct PI or INR and, as a preventive measure before surgery, in patients with LC [4-6, 27].

Similarly, more stringent indications for patients with LC are set for blood transfusion. Transfusing blood to prevent or treat bleeding can lead to unavoidable risks and costs without clear benefits. In acute liver failure, blood transfusion leads to the development of disseminated intravascular coagulation syndrome with ensuing multiple organ dysfunctions. The critical hemoglobin level for prescribing blood transfusion is considered to be 70 g/l [15, 19].

*Platelet concentrate*. Platelet transfusion is a common practice for thrombocytopenia, which has its positive and negative aspects. The American Association of Hepatologists recommends platelet transfusion before medical and diagnostic procedures (liver biopsy, laparocentesis), when the platelet count is below 50-60 × 109 /l. In addition, there is agreement that platelet counts should not be allowed to fall below 50 × 109/l in patients with acute bleeding [4, 5, 19].

However, there are several problems associated with the administration of platelets. According to in vitro laboratory data, a platelet count of more than 55 × 109 /l improves hemostasis in patients with LC, however, these data assess only the procoagulant activity of platelets and do not take into account in vivo compensatory responses due to Willebrand factor and other components of the endothelium. An elevated PT can be corrected by transfusing platelet concentrate. However, as with the use of FFP, the clinical significance of the normalization of prothrombin time remains questionable. In addition, a number of studies have found increased platelet activation in cirrhosis, which leads to thrombogenic complications. Therefore, there are no clinically proven, clear, safe platelet thresholds for various procedures. As well as there is no convincing data on the significance of thrombocytopenia in varicose bleeding and the therapeutic efficacy of increasing platelet levels in this case. In patients who received thrombocyte concentrate before medical and diagnostic procedures, paradoxically, signs of bleeding occurred more often.

Prophylactic platelet transfusions have a short-term effect, leading to a slight improvement in platelet count only, but thrombin formation and TEG parameters are not normalized. Finally, frequent platelet transfusions can lead to transfusion reactions, to refractoriness of platelets with the inability to achieve the desired number of platelets in subsequent transfusions [4, 8, 10, 15, 19, 22, 23, 27, 34].

*Stimulants of thrombocytopoiesis*. They are being developed as an alternative to thrombocyte concentrate with the elimination of its negative effects.

*Thrombopoietin, romiplostim* (synthetic analogue of thrombopoietin). Experimental studies have shown that the use of thrombopoietin reduces liver fibrosis and stimulates regeneration after liver resection, which is associated with increased platelet accumulation in the rest of the liver. As one of the side effects of an increase in platelet count in LC, some authors indicate their stimulation of carcinogenesis, in particular, hepatocellular carcinoma. Other authors report that there is no connection between the appointment of thrombopoietin and the development of carcinoma either in experiment or in vivo, and therefore recommend that patients with cirrhosis in thrombocytopenia have thrombocytopenia. Against the background of romiplostim in patients with thrombocytopenia receiving antiviral therapy, there was an increase in the number of platelets in 33 of 35 patients with a maximum rise between the second and third weeks, starting with the first peptide injection [40].

*Eltrombopag*. Eltrombopag is a low molecular weight non-protein selective agonist of the thrombopoietin receptor, which stimulates thrombocytopoiesis. In vitro studies have shown that eltrombopag induces proliferation and differentiation of the megakaryocytic lineage to the same extent as thrombopoietin. However, unlike the latter, eltrombopag does not enhance ADP-mediated platelet activation. In studies on healthy volunteers, it was found that oral administration of eltrombopag for 10 days led to a dose-dependent increase in the number of platelets, starting from the 8th day of therapy. The maximum level was observed by 16 days, and by 22 the number of platelets returned to the initial values. However, a number of studies that studied the results of prescribing eltrombopag for thrombocytopenia in patients with LC before invasive interventions (in order to reduce the need for blood clot transfusion) showed that eltrombopag reduced the need for platelet transfusions, but at the same time increased the risk of portal vein thrombosis compared with placebo that is a side effect of the drug. In addition, there was no difference in the incidence of episodes of gastrointestinal bleeding in both those who received and did not receive eltrombopag [10, 27, 35, 37]. Despite the increase in platelet counts above 100x109/ml in the group of patients taking the drug, there was no statistically significant decrease in the incidence of hemorrhagic complications. The study evaluating eltrombopag was terminated prematurely due to an increase in the incidence of PVT [4, 5, 8].

Recent randomized trials have evaluated the role of *avatrombopag* and *lusutrombopag*. These agents are superior to placebo in achieving a target platelet count of more than 50x109/l with no statistical difference in thrombogenic complications. In addition, patients treated with lusutrombopag experienced a sustained increase in platelet count over a longer period of time compared with platelet transfusion. At the same time, it should be noted that there are no statistical differences in the incidence of bleeding in the treatment group and placebo, therefore, the routine use of these agents for the prevention of bleeding against the background of thrombocytopenia is not recommended [4, 5, 8, 41].

*Prothrombin complex* (PCC) *concentrates* and *recombinant clotting factor* FVIIa were originally developed for the treatment of patients with hemophilia. PCC are available as three-factor (II, IX, X) and four-factor (II, IX, X, with the addition of VII) products. They additionally contain anti-coagulation factors - protein C, protein S, antithrombin III with or without heparin. However, randomized clinical trials have not shown a beneficial effect of these drugs in controlling bleeding from varicose veins of the esophagus in patients with LC, and no improvement in mortality rates has been demonstrated. In this case, there are indications of an increase in the number of thrombosis and thromboembolism [4, 5].

Thus, taking into account the emerging doubts about the causes of hemorrhagic complications in liver cirrhosis, therapeutic tactics should be aimed, first of all, not at normalizing laboratory tests, but at eliminating other pathogenetic mechanisms that occur in cirrhosis, which include thrombosis.

### *3.5.2. Anticoagulant Therapy for Liver Cirrhosis*

Numerous prospective studies have shown the effectiveness of anticoagulant therapy in primary hepatic thrombosis. Anticoagulant treatment significantly reduced the risk of recurrent thrombosis without increasing the risk of variceal bleeding in the esophagus and stomach [4, 16]. In fact, the risk of variceal bleeding tended to decrease when anticoagulant therapy was initiated. The severity of bleeding was

independent of whether anticoagulants were used or not. And there were no deaths due to bleeding directly related to the intake of anticoagulants. "Large varicose veins" or a history of gastrointestinal bleeding are not a contraindication for the appointment of long-term anticoagulant therapy, provided that hemodynamic disturbances and portal hypertension are adequately corrected [4, 5].

*In LC*, as mentioned above, questions remain unresolved whether thrombosis is a primary disease contributing to accelerated fibrosis and cirrhosis, a manifestation of disease decompensation, or the cause of decompensation. At the same time, anticoagulant therapy could probably be effective both in terms of preventing the development of cirrhosis and treating its complications, but the risk of bleeding dictates the need for preliminary correction of portal hypertension syndrome [2, 10, 17, 20, 42-44]. There are insufficient data on the practical use of anticoagulants in LC, and they are limited by experience in patients with portal vein thrombosis. It is believed that in patients with compensated cirrhosis of the liver, the development of portal vein thrombosis cannot be considered a simple consequence of it. Therefore, the examination and treatment of such patients should be the same as for patients with PVT without cirrhosis. Interestingly, anticoagulant therapy did not significantly affect blood loss and the duration of surgery for transplantation. Bleeding recurrence rates did not differ in those who received or did not receive anticoagulant therapy. But mortality was significantly lower in patients receiving anticoagulants [1, 5, 6, 29, 42, 43].

*Duration of anticoagulant therapy*. The optimal duration of anticoagulant therapy for thrombosis in patients with LC has not been determined. A group of international experts recommended anticoagulant therapy for acute thrombosis within 3 months, preferably within 6 months. Immediate therapy for up to 6 months was associated with complete lumen repair in 50% of patients, partial lumen repair in approximately 40% of patients, and no lumen repair in 10% of patients. In the presence of thrombogenic risk factors, which include LC, even after the clot disappears, continuous anticoagulant therapy is recommended. Thus, upon discontinuation of anticoagulant therapy, portal vein thrombosis re-emerged in 39% of patients. With residual thrombosis after discontinuation of treatment, the latter progressed in 71% of cases. This requires improved diagnosis of major thrombogenic diseases, improved methodology of anticoagulant therapy and the selection of appropriate drugs [4, 5, 34, 35, 38].

*Prevention of thrombosis*. If patients with chronic hepatitis have thrombogenic conditions, in the future, the question may arise about the advisability of prophylactic anticoagulant therapy. A number of experimental and clinical studies have shown that long-term use of anticoagulants can prevent or stabilize the development of fibrosis. The mechanism of the anti-fibrotic effect of anticoagulants may partly be related to blocking ERK (kinase) and AP 1 (activator protein) signaling in activated hepatic stellate cells; inactivation of thrombin weakened the activity of hepatic stellate cells. Studies of the hemostatic system in patients before transplantation suggest the benefits of the prophylactic use of anticoagulants in order to reduce thromboembolic complications after transplantation. Long-term administration of anticoagulants in patients with compensated LC lengthens the development of decompensation, which is explained by the fact that microthrombi, causing ischemia, stimulate pathological processes. The use of thromboprophylaxis in hospitalized patients with cirrhosis is not associated with high rates of gastrointestinal bleeding or death. At the same time, the scope of application of anticoagulants should be expanded to patients where transplantation is not indicated [1, 35].

#### *3.5.3. Choice of Anticoagulant Therapy*

To date, there is no agreement on the choice of anticoagulants in patients with LC. Standard anticoagulant therapy protocols include antiplatelet agents, low molecular weight and unfractionated heparins, vitamin K antagonists, and direct oral anticoagulants, which have been successfully used to restore the lumen of a thrombosed vessel in patients without cirrhosis [4, 44].

*Disaggregants.* The drugs of choice are P2Y12 receptor inhibitors, which irreversibly block ADF-induced platelet accumulation (*ticlopidine, clopidogrel*). The negative point is that the drugs are metabolized by the liver, which can result in their unpredictable pharmacokinetics in LC. *Dipyridomol* has fewer side effects. The positive effect of the drug on the course of chronic diffuse liver diseases and the degree of portal hypertension has been experimentally proven. However, dipyridomol has been shown to impair renal function in patients with ascites, which limits its use in LC. LC is traditionally a contraindication for *aspirin*, as a representative of non-steroidal anti-inflammatory drugs, due to the risk of gastrointestinal bleeding. In addition, taking aspirin in patients with ascites can lead to renal failure, hyponatremia, and resistant ascites. Disaggregants do not require strict laboratory control to select a dosage. In this case, the use of antiplatelet agents can be complicated by thrombocytopenia or functional platelet defects [4, 21].

*Anticoagulants.* Anticoagulants include various groups of drugs according to the mechanism of action - indirect and direct, and the route of administration - parenteral and oral.

*Indirect anticoagulants* for parenteral administration include heparin, low molecular weight (LMWH) and unfractionated heparins (UFH), fondaparinux, and for oral administration, vitamin K antagonists.

*Heparin* chemical structure is a mixture of mucopolysaccharides with an average molecular weight of 12,000 - 16,000 Da.

UFH is a glycosaminoglycan contained in almost all tissues and organs of the body and consisting of a mixture of polysaccharide fractions with a molecular weight ranging from 3,000 to 30,000 Da. LMWH - UFH fragments obtained by chemical or enzymatic depolymerization of ordinary heparin molecules with an average molecular weight of 4,000-8,000 daltons.

The anticoagulant role of heparins is AT III mediated anti-Xa activity. They interact (bind) with an inactive blood

protein - antithrombin III.

As a result, AT III goes into an active state and, in turn, binds to the active centers of blood coagulation factors II, IXa, Xa, XIa and XIIa, which entails the suppression of their activity. In addition, heparin inhibits the proteolytic activity of thrombin and clotting factor XIII, and thereby blocks the transition of fibrinogen to fibrin.

UFH for medical use is available in the form of sodium and calcium salts. UFH acts quickly, but is short-lived. When administered by infusion, the effect develops immediately and is maintained continuously at the required level. When the introduction is stopped or its speed is reduced, the effect of UFH quickly fades away. With a bolus intravenous injection, the effect of the drug lasts 4-5 hours. After subcutaneous injection, the effect develops in 40-60 minutes and lasts 8-12 hours. The anticoagulant effect of UFH is monitored using partially activated thrombin time (APTT), which is recommended to be increased by 1.5-2.5 times. The determination of APTT should be carried out every 6 hours with the correction of the rate of heparin administration until two subsequent measurements correspond to the target values, and the patient's condition is not stable.

LMWH (Fraxiparin, Clexane, Nadroparin, Flenox, Cibor, Fragmin, Enoxaparin) has the basic properties of heparin, but unlike it, low molecular weight heparins preferentially inhibit FX activity, having little effect on the activity of factor FII. As a result, this group has a more pronounced antithrombotic effect and less anticoagulant and, therefore, they do not have a significant effect on blood coagulation time, which reduces the risk of hemorrhages. LMWH has a more convenient mode of administration (twice a day subcutaneously, Fraxiparin Forte - once a day), when using them there is no need for laboratory monitoring.

Preliminary data indicate that enoxyparin over a long period (12 months) is able to significantly reduce PVT and venous thrombosis compared with placebo, without corresponding side effects in patients with LC.

At the same time, a decrease in the incidence of hepatic decompensation was noted. A number of experimental studies have demonstrated a significant decrease in portal pressure when using enoxyparin, which is associated with a decrease in intrahepatic resistance due to inhibition of the activation of hepatic stellate cells and a decrease in the formation of microthrombi (fibrin) in the liver. Individual cases of thrombocytopenia, portal gastropathy are not directly related to the intake of an anticoagulant, being a consequence of a decrease in hepatic function. LMWH are currently the anticoagulants of choice in the treatment and prevention of thrombosis in patients with LC.

The main disadvantage of heparins is that the manifestation of their anticoagulant activity is possible only with a sufficient level of AT. In the case of a decrease in the concentration of the latter in the blood, the administration of heparins is useless. The level of AT III in patients with liver cirrhosis is 10–23% lower than in healthy people, which complicates the use of heparins in patients with cirrhosis. The side effects of heparins include possible hemorrhagic complications, the development of heparin-induced thrombocytopenia (HIT). Another disadvantage of using heparins is the need for injections. In addition, with renal dysfunction, the problem of dosage of the anticoagulant arises.

*Fondaparinux* (Arixtra) by its chemical structure belongs to the group of synthetic pentasaccharides, the mechanism of action of which is to inhibit the activity of F Xa by binding to AT III. Unlike heparins, pentasaccharides do not conjugate with other proteins, including platelet factor IV, and therefore are unable to provoke HIT. Pentasaccharides also do not inactivate thrombin. Like LMWH, fondaparinux can be administered subcutaneously once or twice a day without the need for routine monitoring of the blood coagulation system [4, 20, 27, 42, 44].

*Vitamin K antagonists* (AVK) - syncumar, phenylin, warfarin. Vitamin K antagonists inhibit the synthesis of blood coagulation factors without directly interfering with the coagulation process. The advantage of AVK is the possibility of oral administration, which makes them convenient for long-term use. Their advantage is also the absence of the need to interact with AT for the manifestation of a hypocoagulant effect; therefore, the use of AVK is possible against the background of AT deficiency. At the same time, data on the efficacy and safety of AVK are ambiguous from different authors. The criterion for the control and effectiveness of AVK is considered to be an increase in the INR level within 2-3.

However, with initially high INR values (more than 2), it is difficult to control the AVK dosage, which guarantees adequate anticoagulation and the absence of hemorrhagic complications. A number of studies indicate an increased risk of hemorrhagic complications when using AVK in patients with LC. Thus, the use of AVK in patients with LC is associated with an unfavorable risk/benefit ratio, especially with a high INR prior to drug initiation. To stop bleeding in patients receiving warfarin, vitamin K, prothrombin complex concentrates and fresh frozen plasma can be used [6, 10, 20, 21, 44].

On the other hand, it is assumed that if one of the causes of procoagulant imbalance is a decrease in the levels of proteins C, S, antithrombin - vitamin-K dependent anticoagulant factors, in combination with an extrahepatic increase in the level of coagulation factor FVIII, then the use of AVK is in principle inappropriate. The action of AVK reduces the synthesis in the liver of vitamin K-dependent blood coagulation factors, both pro and anticoagulant, which are already reduced due to the inhibition of the synthetic function of the liver in cirrhosis. Therefore, it cannot be ruled out that the use of conventional anticoagulants for LC, especially if they are used in high dosages, may, paradoxically, increase the procoagulant imbalance due to an increase in the level of vitamin K independent plasma coagulation factor FVIII, increasing the risk of thrombosis [9, 17, 21, 25. 27].

*Parenteral direct anticoagulants* selectively inhibit only one coagulation factor - FIIa (hirudin, bivalirudin, argatroban) or FXa (otamixaban) - *direct thrombin inhibitors*. In addition, these drugs, in contrast to heparins and fondaparinux, do not need to form a complex with antithrombin for the anticoagulant effect.

They do not bind to FIV (platelet factor), they are not antigens, and they do not cause immune thrombocytopenia.

The data on the use of direct parenteral anticoagulants in hepatology are ambiguous. In patients with acute coronary syndromes, representatives of this drug class, contrary to expectations, do not significantly affect the results of therapy and prognosis in comparison with heparins. A significant decrease in the incidence of adverse outcomes during therapy with direct thrombin inhibitors is observed only in the early phase and practically does not extend to the period after the cessation of drug administration. Thus, direct anticoagulants for parenteral administration have not yet found widespread use in clinical practice.

*Direct oral anticoagulants* (DOACs). Like parenteral, DOACs selectively inhibit only one coagulation factor - either FIIa (dabigatran etexilate - "Pradaxa"), or FXa (apixaban, rivaroxaban - "Xarelto", edoxaban), regardless of antithrombin. The possibility of their use in wide clinical practice is a breakthrough in modern medicine, since for the first time in many decades a real alternative to warfarin has appeared. At the same time, DOACs have a number of advantages over vitamin K-dependent anticoagulants in patients with LC, because they do not reduce the level of proteins C and S. In addition, unlike AVK and heparins, new drugs do not require laboratory monitoring and diet, demonstrate limited the number of interactions with other drugs. However, the effectiveness and safety of new antithrombotic drugs in cirrhosis require adequate clinical studies [4, 6, 10, 21, 44].

Direct use of antithrombin III may become one of the essential, safe and effective methods of treating patients with thrombosis. Especially in cases with a low level of it, that occurs in patients with LC. In single studies, AT III has shown safety and efficacy in patients with diffuse liver diseases complicated by PVT, reaching full or partial recanalization in 55.6% of patients [13].

Certain hopes are pinned on the introduction of new methods of anticoagulant therapy based on the use of anticoagulant peptides, antiplatelet agents (monoclonal antibodies to platelets, RGD peptides), pentosans, glycosaminoglycans, etc. However, the effectiveness and safety of new antithrombotic drugs in liver cirrhosis require adequate clinical trials.

*Vitamin K* (vicasol). The role of vitamin K deficiency has not been assessed in both hypo- and hypercoagulation. Moreover, with LC, the synthesis and balance of vitamin-K dependent pro- and anticoagulant factors are disturbed. Vitamin K deficiency is commonly seen in cases of liver cirrhosis decompensation and is associated with hypocoagulation. At the same time, as a result of taking vikasol (a synthetic analogue of vitamin K), the indicators of both the procoagulant system - an increase in PI, and the anticoagulant system - an increase in the level of protein C. That is, vitamin K eliminates the procoagulant imbalance and can be recommended for patients with LC in both bleeding and thrombosis. Vicasol has an injectable and tablet form, it is recommended and should be prescribed to all patients with decompensated liver cirrhosis [4, 45, 46].

# 4. Conclusions

Changes in hemostasis in liver cirrhosis affect all levels of the coagulation system, leading to hemostatic imbalance. At the same time, there are many factors that can upset this balance in one direction or another. In clinical practice, a decrease in the procoagulant potential can be interpreted as a primary defect only when the indicators of the anticoagulant system are within normal limits, and vice versa.

In compensated patients with liver cirrhosis, the state of hemostasis is characterized by an imbalance towards hypercoagulation with a predisposition to intra- and extrahepatic thrombosis. In decompensated patients, disseminated intravascular coagulation (DIC) occurs in varying degrees of severity, which clinically determines hemorrhagic complications.

Therapeutic tactics for hemostatic imbalance should be aimed, first of all, not at normalizing laboratory tests, but at eliminating the pathogenetic mechanisms of hemostatic imbalance characteristic of the natural course of liver cirrhosis. At the same time, medical correction should be directed not at individual links of the hemostasis system, but at correcting the hemostatic imbalance as a whole. The choice of the drug should take into account the functional disorders of the liver in cirrhosis - an imbalance in the synthesis of pro- and anticoagulants.

Thus, to date, questions about the nature of changes in the hemostasis system in liver cirrhosis, their relationship with hemorrhagic complications or thrombosis, the principles of drug correction remain open, requiring further research in this direction.

# Conflicts of Interest

The authors declare that they have no competing interests.

# References

[1] Caldwell, S., & Carlini, L. E. (2020). Coagulation Homeostasis in Liver Disease. *Clinical liver disease*, *16* (4), 137–141. https://doi.org/10.1002/cld.935.

[2] Driever, E. G., Stravitz, R. T., Zhang, J., Adelmeijer, J., Durkalski, V., Lee, W. M., & Lisman, T. (2021). VWF/ADAMTS13 Imbalance, But Not Global Coagulation or Fibrinolysis, Is Associated With Outcome and Bleeding in Acute Liver Failure. *Hepatology (Baltimore, Md.)*, *73* (5), 1882–1891. https://doi.org/10.1002/hep.31507.

[3] Kodali, S., & Singal, A. K. (2020). Portal and Mesenteric Venous Thrombosis. *Clinical liver disease*, *16* (4), 142–145. https://doi.org/10.1002/cld.938.

[4] Northup, P. G., Garcia-Pagan, J. C., Garcia-Tsao, G., Intagliata, N. M., Superina, R. A., Roberts, L. N., Lisman, T., & Valla, D. C. (2021). 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 (Baltimore, Md.)*, *73* (1), 366–413. https://doi.org/10.1002/hep.31646.

[5] Premkumar, M., & Sarin, S. K. (2020). Current Concepts in Coagulation Profile in Cirrhosis and Acute-on-Chronic Liver Failure. *Clinical liver disease*, *16* (4), 158–167. https://doi.org/10.1002/cld.976.

[6] Shenoy, A., Jarava, D., Stotts, M. J., Intagliata, N. M. (2021). Anticoagulation Management in Patients with Atrial Fibrillation and Cirrhosis. *Clinical Liver Disease*, 17 (4), 277-281. https://doi.org/10.1002/cld.1048.

[7] Shah, N. L., & Caldwell, S. H. (2016). Assessing the risk of bleeding and clotting in cirrhosis. *Clinical liver disease*, *7* (2), 26–28. https://doi.org/10.1002/cld.528.

[8] Singh, A. D., & Shalimar (2020). Use of Blood Products and Drugs Before Procedures in Patients With Cirrhosis. *Clinical liver disease*, *16* (4), 153–157. https://doi.org/10.1002/cld.906.

[9] Tugushev, A. S, Vakulenko, V. V., Cherkovskaya, O. S., Mihantev, D. I., Neshta, V. V., Potapenko, P. I. (2015). Harakter izmenenij sistemy gemostaza u bolnyh cirrozom pecheni [Character of changes hemostasis system in patients with cirrhosis]. *Science Rise – Science Rise*, 5/4 (10), 28-32 [in Russian]. DOI: 10.15587/2313-8416.2015.43105.

[10] Kumar, M., Ahmad, J., Maiwall, R., Choudhury, A., Bajpai, M., Mitra, L. G., Saluja, V., Mohan Agarwal, P., Bihari, C., Shasthry, S. M., Jindal, A., Bhardwaj, A., Kumar, G., & Sarin, S. K. (2020). Thromboelastography-Guided Blood Component Use in Patients With Cirrhosis With Nonvariceal Bleeding: A Randomized Controlled Trial. *Hepatology (Baltimore, Md.)*, *71* (1), 235–246. https://doi.org/10.1002/hep.30794.

[11] European Association for the Study of the Liver. Electronic address: easloffice@easloffice.eu (2016). EASL Clinical Practice Guidelines: Vascular diseases of the liver. *Journal of hepatology*, *64* (1), 179–202. https://doi.org/10.1016/j.jhep.2015.07.040

[12] Young, K., & Wong, R. (2018). Evaluation and management of acute and chronic portal vein thrombosis in patients with cirrhosis. *Clinical liver disease*, *10* (6), 152–156. https://doi.org/10.1002/cld.679.

[13] Hidaka, H., Kokubu, S., Sato, T., Katsushima, S., Izumi, N., Igura, T., Asahara, S., Notsumata, K., Osaki, Y., Tsuji, K., Kawanaka, H., Akahoshi, T., Hirota, S., Matsutani, S., & NPB-06 study group (2018). Antithrombin III for portal vein thrombosis in patients with liver disease: A randomized, double-blind, controlled trial. *Hepatology research: the official journal of the Japan Society of Hepatology*, *48* (3), E107–E116. https://doi.org/10.1111/hepr.12934.

[14] Kurokawa, T., Zheng, Y. W., & Ohkohchi, N. (2016). Novel functions of platelets in the liver. *Journal of gastroenterology and hepatology*, *31* (4), 745–751. https://doi.org/10.1111/jgh.13244.

[15] Rassi, A. B., d'Amico, E. A., Tripodi, A., da Rocha, T., Migita, B. Y., Ferreira, C. M., Carrilho, F. J., & Farias, A. Q. (2020). Fresh frozen plasma transfusion in patients with cirrhosis and coagulopathy: Effect on conventional coagulation tests and thrombomodulin-modified thrombin generation. *Journal of hepatology*, *72* (1), 85–94. https://doi.org/10.1016/j.jhep.2019.09.008.

[16] Nowatari, T., Murata, S., Fukunaga, K., & Ohkohchi, N. (2014). Role of platelets in chronic liver disease and acute liver injury. *Hepatology research: the official journal of the Japan Society of Hepatology*, *44* (2), 165–172. https://doi.org/10.1111/hepr.12205.

[17] Wannhoff, A., Friedrich, K., & Gotthardt, D. N. (2017). Reduced influence of procoagulant changes on survival in patients with advanced cirrhosis. *Journal of hepatology*, *66* (2), 454–455. https://doi.org/10.1016/j.jhep.2016.08.025.

[18] Olson J. C. (2019). Thromboelastography-Guided Blood Product Use Before Invasive Procedures in Cirrhosis With Severe Coagulopathy: A Randomized Controlled Trial. *Clinical liver disease*, *13* (4), 102–105. https://doi.org/10.1002/cld.749.

[19] Stravitz R. T. (2017). Thrombosis and coagulopathy in the liver transplant candidate and recipient. *Clinical liver disease*, *9* (1), 11–17. https://doi.org/10.1002/cld.606.

[20] Intagliata, N. M., Ferreira, C. N., & Caldwell, S. H. (2016). Anticoagulation for portal vein thrombosis in cirrhosis. *Clinical liver disease*, *7* (6), 126–131. https://doi.org/10.1002/cld.552.

[21] La Mura, V., Tripodi, A., Tosetti, G., Cavallaro, F., Chantarangkul, V., Colombo, M., & Primignani, M. (2016). Resistance to thrombomodulin is associated with de novo portal vein thrombosis and low survival in patients with cirrhosis. *Liver international: official journal of the International Association for the Study of the Liver*, *36* (9), 1322–1330. https://doi.org/10.1111/liv.13087.

[22] Moore A. H. (2019). Thrombocytopenia in Cirrhosis: A Review of Pathophysiology and Management Options. *Clinical liver disease*, *14* (5), 183–186. https://doi.org/10.1002/cld.860.

[23] Nephew, L. D., & Goldberg, D. S. (2016). Impact of Anticoagulation on Upper Gastrointestinal Bleeding in Cirrhosis. *Gastroenterology*, *150* (5), 1239–1241. https://doi.org/10.1053/j.gastro.2016.03.024.

[24] Kalambokis, G. N., Oikonomou, A., Baltayiannis, G., Christou, L., Kolaitis, N. I., & Tsianos, E. V. (2016). Thrombin generation measured as thrombin-antithrombin complexes predicts clinical outcomes in patients with cirrhosis. *Hepatology research: the official journal of the Japan Society of Hepatology*, *46* (3), E36–E44. https://doi.org/10.1111/hepr.12520.

[25] Loffredo, L., Pastori, D., Farcomeni, A., & Violi, F. (2017). Effects of Anticoagulants in Patients with Cirrhosis and Portal Vein Thrombosis: A Systematic Review and Meta-analysis. *Gastroenterology*, *153* (2), 480–487. e1. https://doi.org/10.1053/j.gastro.2017.04.042.

[26] Bishnu, S., Ahammed, S. M., Sarkar, A., Hembram, J., Chatterjee, S., Das, K., Dhali, G. K., Chowdhury, A., & Das, K. (2018). Effects of atorvastatin on portal hemodynamics and clinical outcomes in patients with cirrhosis with portal hypertension: a proof-of-concept study. *European journal of gastroenterology & hepatology*, *30* (1), 54–59. https://doi.org/10.1097/MEG.0000000000001006.

[27] Tang, W., Wang, Y., Zhao, X., Wang, X., Zhang, T., Ou, X., Shou, W., You, H., & Jia, J. (2015). Procoagulant imbalance aggravated with falling liver function reserve, but not associated with the presence of portal vein thrombosis in cirrhosis. *European journal of gastroenterology & hepatology*, *27* (6), 672–678. https://doi.org/10.1097/MEG.0000000000000352.

[28] Balaphas, A., Meyer, J., Sadoul, K., Fontana, P., Morel, P., Gonelle-Gispert, C., & Bühler, L. H. (2019). Platelets and Platelet-Derived Extracellular Vesicles in Liver Physiology and Disease. *Hepatology communications*, *3* (7), 855–866. https://doi.org/10.1002/hep4.1358.

[29] La Mura, V., Braham, S., Tosetti, G., Branchi, F., Bitto, N., Moia, M., Fracanzani, A. L., Colombo, M., Tripodi, A., & Primignani, M. (2018). Harmful and Beneficial Effects of Anticoagulants in Patients with Cirrhosis and Portal Vein Thrombosis. *Clinical gastroenterology and hepatology: the official clinical practice journal of the American Gastroenterological Association*, *16* (7), 1146–1152. e4. https://doi.org/10.1016/j.cgh.2017.10.016.

[30] Xu, X., Guo, X., De Stefano, V., Silva-Junior, G., Goyal, H., Bai, Z., Zhao, Q., & Qi, X. (2019). Nonselective beta-blockers and development of portal vein thrombosis in liver cirrhosis: a systematic review and meta-analysis. *Hepatology international*, *13* (4), 468–481. https://doi.org/10.1007/s12072-019-09951-6.

[31] Zermatten, M. G., Fraga, M., Moradpour, D., Bertaggia Calderara, D., Aliotta, A., Stirnimann, G., De Gottardi, A., & Alberio, L. (2020). Hemostatic Alterations in Patients With Cirrhosis: From Primary Hemostasis to Fibrinolysis. *Hepatology (Baltimore, Md.)*, *71* (6), 2135–2148. https://doi.org/10.1002/hep.31201.

[32] Sherlock Sh., Dooley J. (2002). Diseases of the liver and biliary tract: a practical guide/Transl. From English; Edited by Z. G. Aprosina, N. A. Mukhina.- M.: GEOTAR-MED.- 864.

[33] Stravitz R. T. (2018). Algorithms for managing coagulation disorders in liver disease. *Hepatology International*, 12 (5), 390–401. https://doi.org/10.1007/s12072-018-9886-6.

[34] Intagliata, N. M., & Caldwell, S. H. (2014). Management of disordered hemostasis and coagulation in patients with cirrhosis. *Clinical liver disease*, *3* (6), 114–117. https://doi.org/10.1002/cld.333.

[35] Rank, K. M., & Lake, J. (2018). CON: Anticoagulation for Portal Vein Thrombosis in Advanced Cirrhosis. Clinical liver disease, 12 (3), 80–82. https://doi.org/10.1002/cld.713.

[36] Blasi, A., Patel, V. C., Adelmeijer, J., Azarian, S., Hernandez Tejero, M., Calvo, A., Fernández, J., Bernal, W., & Lisman, T. (2020). Mixed Fibrinolytic Phenotypes in Decompensated Cirrhosis and Acute-on-Chronic Liver Failure with Hypofibrinolysis in Those with Complications and Poor Survival. *Hepatology (Baltimore, Md.)*, *71* (4), 1381–1390. https://doi.org/10.1002/hep.30915.

[37] Intagliata, N. M., & Caldwell, S. H. (2017). Changes in hemostasis in liver disease. *Journal of hepatology*, *67* (6), 1332–1333. https://doi.org/10.1016/j.jhep.2017.07.001.

[38] To, U. K., & Garcia-Tsao, G. (2018). PRO: Patients with Advanced Cirrhosis and Portal Vein Thrombosis Should Receive Anticoagulation. *Clinical liver disease*, *12* (3), 74–79. https://doi.org/10.1002/cld.717.

[39] Shenoy, A., & Intagliata, N. M. (2020). Thromboelastography and Utility in Hepatology Practice. *Clinical liver disease*, *16* (4), 149–152. https://doi.org/10.1002/cld.947.

[40] Primignani, M., & La Mura, V. (2014). Diagnosis of thrombophilia/prothrombotic conditions in patients with liver disease. *Clinical liver disease*, *3* (6), 126–128. https://doi.org/10.1002/cld.342.

[41] Furuichi, Y., Takeuchi, H., Yoshimasu, Y., Kasai, Y., Abe, M., & Itoi, T. (2020). Thrombopoietin receptor agonist is more effective than platelet transfusion for chronic liver disease with thrombocytopenia, shown by propensity score matching. *Hepatology research: the official journal of the Japan Society of Hepatology*, *50* (9), 1062–1070. https://doi.org/10.1111/hepr.13530.

[42] Mancuso A. (2016). Management of portal vein thrombosis in cirrhosis: an update. *European journal of gastroenterology & hepatology*, *28* (7), 739–743. https://doi.org/10.1097/MEG.0000000000000633.

[43] Peck-Radosavljevic M. (2017). Thrombocytopenia in chronic liver disease. *Liver international: official journal of the International Association for the Study of the Liver*, *37* (6), 778–793. https://doi.org/10.1111/liv.13317.

[44] Ahmed, Z., Singal, A. K., & Kamath, P. S. (2020). Anticoagulants and Their Monitoring. *Clinical liver disease*, *16* (4), 146–148. https://doi.org/10.1002/cld.946.

[45] Tugushev, A. S., Mihantev, D. I., Neshta, V. V., Cherkovskaya, O. S., Ryazanova, E. D. (2015). Korrekciya sistemy gemostaza u bolnyh cirrozom pecheni [Correction of the hemostasis system in patients with liver cirrhosis]. Zaporizkij medichnij zhurnal – *Zaporozhye medical journal*, 5 (92), 45-48 [in Russian]. https://doi.org/10.14739/2310-1210.2015.5.53772.

[46] Stine, J. G., Wang, J., Shah, P. M., Argo, C. K., Intagliata, N., Uflacker, A., Caldwell, S. H., & Northup, P. G. (2018). Decreased portal vein velocity is predictive of the development of portal vein thrombosis: A matched case-control study. *Liver international: official journal of the International Association for the Study of the Liver*, *38* (1), 94–101. https://doi.org/10.1111/liv.13500.