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Correction of Thrombocytopenia before Elective Surgery / Invasive Procedures in Patients with Liver Cirrhosis (Experts' Agreement)

Marina V. Maevskaya[1,§], Maria Yu. Nadinskaia[1,§,*], Elena N. Bessonova[2,3], Natalia I. Geyvandova[4,5], Maria S. Zharkova[1], Evgeniy A. Kitsenko[6], Natalia V. Korochanskaya[7,8], Irina A. Kurkina[1], Anait L. Melikyan[9], Viacheslav G. Morozov[10], Yury V. Khoronko[11], Tatiana A. Deeva[1], Kseniya A. Gulyaeva[1], Vladimir T. Ivashkin[1]

[1] *I. M. Sechenov First Moscow State Medical University (Sechenov University), Moscow, Russian Federation*
[2] *Ural State Medical University, Yekaterinburg, Russian Federation*
[3] *Sverdlovsk Regional Clinical Hospital No. 1, Yekaterinburg, Russian Federation*
[4] *Stavropol State Medical University, Stavropol, Russian Federation*
[5] *Stavropol Regional Clinical Hospital, Stavropol, Russian Federation*
[6] *Russian Scientific Center of Surgery named after Academician B.V. Petrovsky, Moscow, Russian Federation*
[7] *Kuban State Medical University, Krasnodar, Russian Federation*
[8] *Regional Clinical Hospital No. 2, Krasnodar, Russian Federation*
[9] *National Medical Research Center for Hematology, Moscow, Russian Federation*
[10] *Medical Company "Hepatologist", Samara, Russian Federation*
[11] *Rostov State Medical University, Rostov-on-Don, Russian Federation*

Introduction. As a result of portal hypertension (sequestration of platelets in an enlarged spleen) and liver failure (decreased production of thrombopoietin in the liver) in liver cirrhosis, thrombocytopenia develops, which is associated with the risk of periprocedural/perioperative bleeding complications. There are still unresolved questions regarding risk stratification of bleeding complications, the prognostic role of thrombocytopenia, as well as the need for treatment of thrombocytopenia and its methods.
Materials and methods. The Russian Scientific Liver Society selected a panel of experts in the field of therapeutic and surgical hepatology, hematology, transfusion medicine to make reasoned statements and recommendations on the issue of treatment of thrombocytopenia before elective surgery / invasive procedures in patients with liver cirrhosis.
Results. Relevant clinical issues were determined based on the PICO principle (patient or population, intervention, comparison, outcome). The Delphi panel made five questions and gave reasoned answers, framed as 'clinical practice recommendations and statements' with evidence-based comments. The questions and statements were based on the results of search and critical analysis of medical literature using keywords in English- and Russian-language databases. The formulated questions could be combined into four categories: bleeding risk stratification, the prognostic value of thrombocytopenia, the necessity and methods of thrombocytopenia drug correction, and bleeding risk reduction.
Conclusions. The results of experts' work are directly related to high-quality management of patients with liver cirrhosis and thrombocytopenia, who have scheduled invasive procedures/surgery. Thus, this recommendations and statements can be used in clinical practice.
Keywords: PICO, thrombocytopenia, hemostasis, bleeding complications, thrombosis, thrombocytopenia correction, thrombopoietin receptor agonists, TPO-RAs, eltrombopag, lusutrombopag, avatrombopag, romiplostim
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§ Marina V. Maevskaya and Maria Yu. Nadinskaia contributed equally to this work and should be considered first co-authors.

Коррекция тромбоцитопении у пациентов с циррозом печени перед плановыми хирургическими вмешательствами / инвазивными процедурами (соглашение специалистов)

М.В. Маевская[1, §], М.Ю. Надинская[1, §, *], Е.Н. Бессонова[2,3], Н.И. Гейвандова[4,5], М.С. Жаркова[1], Е.А. Киценко[6], Н.В. Корочанская[7,8], И.А. Куркина[1], А.Л. Меликян[9], В.Г. Морозов[10], Ю.В. Хоронько[11], Т.А. Деева[1], К.А. Гуляева[1], В.Т. Ивашкин[1]

[1] *ФГАОУ ВО «Первый Московский государственный медицинский университет им. И.М. Сеченова» Министерства здравоохранения Российской Федерации (Сеченовский университет), Москва, Российская Федерация*

[2] *ФГБОУ ВО «Уральский государственный медицинский университет» Министерства здравоохранения Российской Федерации, Екатеринбург, Российская Федерация*

[3] *ГАУЗ Свердловской области «Свердловская областная клиническая больница № 1», Екатеринбург, Российская Федерация*

[4] *ФГБОУ ВО «Ставропольский государственный медицинский университет» Министерства здравоохранения Российской Федерации, Ставрополь, Российская Федерация*

[5] *ГБУЗ Ставропольского края «Ставропольская краевая клиническая больница», Ставрополь, Российская Федерация*

[6] *ФГБНУ «Российский научный центр хирургии им. академика Б.В. Петровского», Москва, Российская Федерация*

[7] *ФГБОУ ВО «Кубанский государственный медицинский университет» Министерства здравоохранения Российской Федерации, Краснодар, Российская Федерация*

[8] *ГБУЗ «Краевая клиническая больница № 2», Краснодар, Российская Федерация*

[9] *ФГБУ «Национальный медицинский исследовательский центр гематологии» Министерства здравоохранения Российской Федерации, Москва, Российская Федерация*

[10] *Медицинская компания «Гепатолог», Самара, Российская Федерация*

[11] *ФГБОУ ВО «Ростовский государственный медицинский университет» Министерства здравоохранения Российской Федерации, Ростов-на-Дону, Российская Федерация*

Введение. В результате портальной гипертензии (секвестрация тромбоцитов в увеличенной селезенке) и печеночной недостаточности (снижение синтеза тромбопоэтина в печени) при циррозе печени развивается тромбоцитопения, которая ассоциирована с риском перипроцедурных/периоперационных геморрагических осложнений. На сегодняшний день остаются вопросы по стратификации риска геморрагических осложнений, роли прогностического значения тромбоцитопении, а также необходимости и методам медикаментозной коррекции тромбоцитопении.

Материалы и методы. Российское общество по изучению печени объединило экспертов в области терапевтической и хирургической гепатологии, гематологии, трансфузиологии для вынесения аргументированных рекомендаций и положений по проблеме «Коррекция тромбоцитопении у пациентов с циррозом печени перед плановыми хирургическими вмешательствами / инвазивными процедурами».

Результаты. Формулировка актуальных клинических вопросов осуществлялась по принципу PICO (patient or population; intervention; comparison; outcome). Эксперты работали по упрощенному дельфийскому методу, сформулировали пять вопросов и дали на них аргументированные ответы, оформленные как «рекомендации и положения для клинической практики» с комментариями на основе принципов доказательной медицины. В основу формулировки вопросов, рекомендаций и положений лег критический анализ медицинской литературы, найденной по ключевым словам в англоязычных и русскоязычных базах данных. Объединить сформулированные вопросы можно в четыре категории: стратификация риска геморрагических осложнений, прогностическое значение тромбоцитопении, необходимость и методы медикаментозной коррекции тромбоцитопении, снижение риска геморрагических осложнений.

Выводы. Результаты работы экспертов имеют прямое отношение к качественному ведению пациентов с циррозом печени и тромбоцитопенией перед плановыми инвазивными процедурами / хирургическими вмешательствами; сформулированные экспертами рекомендации и положения могут использоваться в клинической практике.

Ключевые слова: PICO, тромбоцитопения, гемостаз, геморрагические осложнения, тромбоз, коррекция тромбоцитопении, агонисты рецептора тромбопоэтина, аТПО-р, элтромбопаг, лусутромбопаг, аватромбопаг, ромиплостим

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Introduction

Liver cirrhosis (LC) is the final stage of chronic liver diseases that is characterized by the development of severe complications and is potentially associated with a high financial burden for the state. The LC complications are based on portal hypertension, which later becomes accompanied by liver failure [1–3].

Clinical manifestations of portal hypertension include splenomegaly and hypersplenism (a decrease in blood counts (particularly platelet counts) due to their sequestration and increased destruction in the spleen) [4, 5]. Another pathophysiological factor of thrombocytopenia in LC patients is a decrease in the production of thrombopoietin (TPO) with reduced liver synthetic function [6–8]. Such etiological factors of liver disease as hepatitis viruses [9, 10], alcohol [11], iron overload [12], as well as the administration of certain medications [13, 14] or the presence of an independent hematologic disorder [15], may contribute to the development of thrombocytopenia via a direct myelosuppressive effect.

Platelets are produced in the bone marrow from megakaryocytes. Thousands of platelets, which play a key role in primary hemostasis, emerge from each megakaryocyte as a result of fragmentation [16–18].

The major regulator of platelet production in the bone marrow, TPO, is mainly produced in the liver, and small amounts of it are produced in the kidney and bone marrow [19–23]. TPO stimulates megakaryocyte differentiation from progenitor cells, megakaryocyte proliferation and acts synergistically with other hematopoietic cytokines such as interleukin-3 (IL-3), IL-11 and stem cell factor (SCF) [24–26]. Experimental studies have shown that in the absence of TPO or its receptor (c-MPL), bone marrow continues platelet production, which indicated the role of other regulators in the thrombopoiesis [27, 28].

Thrombocytopenia is a decrease in peripheral blood platelet count $< 150 \times 10^9$/L. The frequency of LC-associated thrombocytopenia is 56–86 % [2, 29–31]. Thrombocytopenia may be mild (100 to 150 $\times 10^9$/L), moderate (50 to 100 $\times 10^9$/L), or severe ($< 50 \times 10^9$/L) [32–34]. The frequency of severe thrombocytopenia according to different studies ranges from 1 to 14 % [30, 31, 34, 35], increasing with LC decompensationbecomes more severe [31, 36–38].

Because of the extremely low risk of spontaneous bleeding, LC-associated thrombocytopenia usually does not require treatment until the platelet count fall below 20×10^9/L. The issue of thrombocytopenia treatment is considered when a patient with LC needs an invasive procedure/surgery. In these circumstances, the risk of periprocedural/perioperative bleeding complications should be assessed and, if necessary, platelet counts, and other blood coagulation factors should be corrected. Patients with LC and severe thrombocytopenia are often denied elective invasive procedure/surgeries due to the lack of unified guidelines on this issue.

This document discusses the prognostic role of thrombocytopenia in the assessment of bleeding risk in LC patients who undergo elective invasive procedures/surgeries, indications and efficacy criteria for different methods of thrombocytopenia treatment in this setting.

Materials and methods

To discuss relevant practical issues regarding "correction of thrombocytopenia before elective surgery/invasive procedures in LC patients" and the development of statements for clinical practitioners, the Russian Scientific Liver Society (RSLS) assigned a panel of experts that included leading specialists of the Russian Federation in the field of therapeutic and surgical hepatology, hematology, and transfusion medicine. A Delphi panel consisted of seven gastroenterologists/hepatologists (M.V. Mayevskaya, M.Yu. Nadinskaia, E.N. Bessonova, N.I. Geyvandova, M.S. Zharkova, N.V. Korochanskaya, V.G. Morozov); two surgeons specializing in portal hypertension surgery (E.A. Kitsenko, Yu.V. Khoronko); one leading hematologist (A.L. Melikyan); one leading transfusion medicine specialist (I.A. Kurkina). Another two certified gastrointestinal specialists worked with literature and prepared the manuscript (T.A. Deeva, K.A. Gulyaeva). Scientific management of the project was carried out by chief freelance specialist gastroenterologist of the Ministry of Health of the Russian Federation, President of the RSLS, Academician V.T. Ivashkin.

Before starting their work on the consensus, several experts met in person to discuss the relevance of thrombocytopenia in patients with cirrhosis in clinical practice and summarized their opinion in a publication [39] stating the need to develop a consensus statement on the correction of thrombocytopenia in LC patients before performing elective surgery/invasive procedures.

The experts had several tasks to accomplish while working on this agreement. Specifically, one of them was to stratify the risk of periprocedural (occurring during/after an invasive

procedure) and perioperative (occurring during/after a surgical procedure) bleeding complications in patients with LC based on the literature data and experts' own experience. The other one was to select the threshold platelet count for performing elective surgery/invasive procedures depending on the risk of hemorrhagic events.

The purpose of the question according to the PICO method is to highlight the problems of a patient or population ("patient or population"), any intervention or method ("intervention"), to carry out comparison, if applicable ("comparison") and to discuss the result ("outcome") [40].

Once the questions were formulated, the Delphi panel discussed them online. Some of the questions were modified. The answers to the questions were prepared in the form of recommendations and statements and substantiated. The experts used the simplified Delphi method. The following rules were applied to approve the formulated statements for clinical practitioners: if the statement was approved by less than 50 % of the experts, it was rewritten and resubmitted for discussion and voting according to the Delphi method; if a statement was approved by 50–75 % of the experts, it was improved, discussed, and adopted without a second vote; if a statement was approved by 75–90 % of the experts, it was adopted with comments; if a statement was approved by more than 95 % of the experts, it was adopted without amendments [41].

In total, the experts had four online meetings, three rounds of voting, as well as correspondence and other forms of remote communication (individual and group phone calls). As a result, the experts came to an agreement, i.e. all statements were discussed, adjusted and unanimously approved.

To substantiate the statements, the experts conducted an advanced literature search in the English language using the following keywords: "Procedural Bleeding" OR "Perioperative Bleeding" OR "Surgical risk" OR "Surgical procedures" OR "Haemostasis" OR "Hemostasis" OR "Correction of Haemostatic alterations" OR "Correction of Hemostatic alterations" OR "Invasive procedures" OR "Thrombocytopenia" OR "Correction of thrombocytopenia" OR "Correction of platelet count" OR "Thrombopoietin" AND "Liver Cirrhosis (LC)" and included all types of studies.

An advanced literature search to include all types of publications was carried out in Russian databases RusMed and eLibrary in the Russian language using the same keywords.

The search of clinical guidelines by keywords was carried out on the electronic resource "Clinical Guidelines Classifier of the Ministry of Health of the Russian Federation". Two documents were found — "Liver cirrhosis and fibrosis" (ID 715[1]) and "Immune thrombocytopenia" (ID 699[2]).

The experts unanimously agreed to use the platelet count thresholds for LC patients that had been developed for patients with immune thrombocytopenia for elective invasive procedures/surgeries in selected clinical situations [42].

The level of evidence was determined based on the criteria of the Oxford Center for Evidence-Based Medicine[3] (Tables 1 and 2).

The issues of diagnostics and correction of plasma hemostasis are not covered in this consensus; they are discussed in relevant publications [43–45] as well as federal and local regulatory documents[4,5].

Questions and statements, recommendations

How do we stratify the bleeding risk when performing elective surgery / invasive procedures in LC patients?

Statement. Elective surgery/invasive procedures in patients with LC are stratified as low (≤ 1.5 %) and high (> 1.5 %) bleeding risk.
(LOE — 3, 100 % consensus)

When performing elective surgery/invasive procedures in any patient cohort, the bleeding risk is assessed depending on the type of the

[1] Clinical guidelines: Liver cirrhosis and fibrosis. 2021. Approved by the Research and Practical Council of the Ministry of Health of the Russian Federation. URL: https://cr.minzdrav.gov.ru/schema/715_1 (date of access: October 27, 2023).
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Table 1. Level of evidence based on the Oxford Centre for Evidence-based Medicine

LoE	Criteria	Simple model for high, intermediate and low evidence
1	Systematic reviews (with homogeneity) of randomized controlled trials	Further research is unlikely to change our confidence in the estimate of benefit and risk.
2	Randomized controlled trials or observational studies with dramatic effects; systematic reviews of lower quality studies (i.e. non-randomized, retrospective)	
3	Non-randomized controlled cohort/follow-up study/control arm of randomized trial (systematic review is generally better than individual study)	Further research (if performed) is likely to have an impact on our confidence in the estimate of benefit and risk and may change the estimate.
4	Case-series, case-control, or historically controlled studies (systematic review is generally better than an individual study)	
5	Expert opinion (mechanism-based reasoning)	Any estimate of effect is uncertain.

Note: LoE — level of evidence.

Таблица 2. Grades of recommendation

Grade	Wording	Criteria
Strong	Must, shall, should, is recommended Shall not, should not, is not recommended	Evidence, consistency of studies, risk-benefit ratio, patient
Weak or open	Can, may, is suggested May not, is not suggested	Preferences, ethical obligations, feasibility

procedure, technique, operator's experience, number of procedures, presence of congenital coagulation disorders, the influence of systemic factors (anemia, infections, kidney disease, malignancy), medications affecting the hemostasis system, and the ability to control active bleeding if it occurs [44, 46–49].

In patients with LC, the bleeding risk is significantly affected by additional liver disease factors: in particular, impaired synthetic liver function leading to decreased production of procoagulants and anticoagulants; thrombocytopenia; portal hypertension; decompensation of cirrhosis and acute-on-chronic liver failure (ACLF) [45, 48, 50–53].

Although the contribution of liver disease-related and non-liver disease-related factors to the risk of periprocedural bleeding is different in each patient with LC, international guidelines and expert opinion classify this risk as low or high (as in patients without LC) [45–48, 54].

Low-risk procedures constitute all procedures whereby major bleeding is expected to occur in ≤ 1.5 % of cases and/or, if it occurs, can be easily controlled. Conversely, high-risk procedures have increased risk of bleeding (> 1.5 %) and/or, if bleeding occurs, it may be difficult to manage or result in catastrophic consequences, even if small (e.g., central nervous system bleeding) [45–48, 55] (Tables 3 and 4).

What is the prognostic value of thrombocytopenia in assessing bleeding risk in LC patients during elective surgery/invasive procedures?

Statement. Thrombocytopenia may be one of the bleeding risk factors during elective surgery/invasive procedures in LC patients.
(LOE — 3, 100 % consensus)

To date, considerable experience has been accumulated in assessing the bleeding risk in LC patients undergoing invasive procedures, and its association with the severity of thrombocytopenia has been studied.

A number of studies have demonstrated that blood platelet counts in patients with LC do not play a significant role in predicting the bleeding risk during the most common hepatic procedures such as abdominal paracentesis [56–59], thoracentesis [60, 61], hepatic venous pressure gradient measurement [62]; esophageal band ligation [63, 64]; transjugular, percutaneous or laparoscopic liver biopsy [61, 65–69].

A study by D.R. Kitchin et al. [70] has shown that during percutaneous liver biopsy the blood platelet count ≥ 25 × 10^9/L and the international normalized ratio (INR) ≤ 2 did not result in increased rates of hemorrhagic complication but did result in a significant decrease in use of fresh frozen plasma and platelet transfusion.

In patients with LC, no association between platelet counts, INR, and the risk of periprocedural bleeding during other procedures has been found either: central lines insertion [61, 71], colonoscopy with polypectomy, endoscopic retrograde cholangiopancreatography and papillosphincterotomy [72, 73], dental extraction with the possibility of local hemostatic measures [74], multiple dental extractions (10 or more) during preparation for liver transplantation [75].

Similar data were obtained in the recently published large multicenter international prospective study ROC-BLeeD [76]. Platelet counts did not affect the risk of hemorrhagic events in 3006 most common endoscopic, percutaneous, vascular, and dental procedures of low and high risk of hemorrhage in 1187 patients with LC, of whom 57.1 % had Child — Pugh Class C [76].

However, other studies have reported an increased risk of periprocedural bleeding in patients with LC and severe thrombocytopenia. Thus, in one of the largest studies — HALT-C [49] during which 2740 percutaneous liver biopsies were performed in patients with severe fibrosis/compensated LC (Child — Pugh score ≤ 7), thrombocytopenia (50 to 60 × 10^9/L) was a risk factor for periprocedural bleeding (hemoperitoneum, subcapsular hematoma, hemobilia, hemothorax).

In two other studies, a platelet counts < 50 × 10^9/L was a risk factor for hemoperitoneum in patients with LC and hepatocellular carcinoma (HCC) after radiofrequency ablation (RFA) [77, 78] and intestinal bleeding after colon polypectomy [72].

In a study by N. Cocero et al. [79], severe thrombocytopenia (≤ 40 × 10^9/L) and INR > 2.5 were found to be risk factors for bleeding after oral surgery. In another study by J.B. Medina et al. [80], intraoperative bleeding during dental extraction in patients with LC was associated with thrombocytopenia (p = 0.026), but patients with platelet counts > 16 × 10^9/L and INR < 3 needed no previous blood transfusion, with local measures being enough to manage haemorrhagic events.

A study by S.A. McCluskey et al. [81] identified seven independent predictors of massive transfusions for liver transplantation, including platelet counts ≤ 70 × 10^9/L.

In general surgery, the most common procedure is cholecystectomy. The risk of gallstone in LC patients is 2–4 times higher than the population risk and increases and increases with decompensation of cirrhosis [82–84]. A study by L. Perkins et al. [85] has shown that platelet counts < 150 × 10^9/L and INR > 1.2 were associated with an increased risk of complications after cholecystectomy, including anemia, coagulopathy and use of blood products. These same complications were more likely to develop in patients with Model for End-Stage Liver Disease (MELD) score > 8 [85]. Similar data were obtained in a study by G. Currò et al. [86]: perioperative hemorrhagic events during laparoscopic cholecystectomy were more frequently observed in patients with decompensated LC (Child — Pugh Class C). The data of these and other studies [87–90] indicate a significant influence of the degree of LC decompensation on the risk of perioperative hemorrhagic events.

A recently published narrative review by The Italian Association for the Study of the Liver (AISF) and The Italian Society of Internal Medicine (SIMI) [91] studied the relationship between severe thrombocytopenia and the risk of periprocedural bleeding in LC patients during elective surgery/invasive procedures such as liver biopsy, abdominal paracentesis, invasive endoscopic procedures, thermal tumor ablation, and liver surgery. The authors of the review concluded that it is difficult to determine a target platelet count that can be a reliable risk factor of periprocedural bleeding risk [91].

How can we determine the true blood platelet count in patients with LC and severe thrombocytopenia using an automated hematology analyzer?

Recommendation. To exclude pseudothrombocytopenia in patients with LC and severe thrombocytopenia (< 50 × 10^9/L), according to the study of a complete blood count on an automated hematology analyzer, a blood sample should be taken into the sodium citrate tube and the platelet count should be evaluated again using an automated hematology analyzer.
(LOE — 3, strong recommendation, 100 % consensus)

In clinical practice, the clinician may encounter false thrombocytopenia or pseudothrombocytopenia when using an automated hematology analyzer. This phenomenon occurs *in vitro* and is

characterized by platelet clumping due to naturally occurring antiplatelet antibodies that is exposed by the ethylenediaminetetraacetic acid (EDTA) anticoagulant used for routine blood sample collections [42, 92].

The use of sodium citrate tube prevents this event and helps determine the true platelet count on an automated hematology analyzer; other blood cells are not evaluated in this case.

It is not appropriate to study platelets' function tests (aggregation or adhesion) in patients with LC in routine clinical practice, whereas the results are distorted due to thrombocytopenia and do not predict the risk of bleeding and/or thrombosis. It should be noted that even severe thrombocytopenia may be accompanied by a change in their properties toward increased prothrombotic potential due to elevated level of von Willebrand factor and reduced level of ADAMTS13 (A disintegrin-like and metalloproteinase with thrombospondin-like domains, member 13) in patients with LC [93, 94].

How do clinical outcomes change when severe thrombocytopenia (< 50 × 10^9/L) is corrected before elective surgery / invasive procedures in patients with LC?

Statement. The use of thrombopoietin receptor agonists (TPO-RAs) (in the Russian Federation, avatrombopag is approved for use) in patients with LC and severe (< 50 × 10^9/L) thrombocytopenia before performing elective surgery/invasive procedures increase platelet counts, decrease periprocedural/perioperative bleeding and the need for platelet transfusion for these complications with a safety comparable to placebo.
(LoE — 1, 100 % consensus)

For many years, thrombocytopenia could only be corrected before invasive procedures/surgery by platelet transfusion.

Current guidelines of international professional organizations that are based on the analysis of a large number of clinical studies, specify that platelet transfusion before invasive procedures/surgery no effect on the risk of periprocedural bleeding [44, 48, 70, 76, 95]. Furthermore, the PROC-BLeeD study found that prophylactic platelet transfusion (more often for patients with severe thrombocytopenia) increased the risk of periprocedural bleeding in patients with LC undergoing various invasive procedures compared with those who had not received transfusions (6.5 % vs. 2.2 %; $p = 0.024$) [76]. In the same study, prophylactic plasma transfusion had a similar effect: patients with LC had a high risk of periprocedural bleeding (9.7 % vs. 2.1 %; $p < 0.001$) [76], and similar findings have been reported elsewhere [95–97].

Undoubtedly, platelet transfusion remains a salvage procedure in patients with LC and severe thrombocytopenia if emergency procedures are required or in case of perioperative bleeding [43]. It should be taken into account, that transfused platelets have a short life span (3–4 days), which becomes even shorter in patients with LC due to sequestration of transfused platelets by their enlarged spleen [8, 34, 43, 98, 99]. Blood transfusion can be complicated by severe reactions such as acute lung injury [100–103], circulatory overload [100–103], allergic and anaphylactic transfusion reactions [104–105], acute hemolytic transfusion reactions [104, 106], and septic transfusion reactions [104, 107, 108].

Currently, TPO-RAs are used as an alternative option to correct severe (< 50 × 10^9/L) thrombocytopenia before elective surgery/invasive procedures. These drugs were originally developed to treat patients with immune thrombocytopenia [109]. In patients with chronic liver diseases, TPO-RAs produce a replacement effect in the setting of decreased TPO production [110].

Binding of a ligand (TPO or TPO-RA) to the TPO receptor (c-MPL) on the megakaryocyte causes a conformational change of the receptor, resulting in downstream activation of various signaling pathways, including JAK2/STAT5 (Janus kinase 2/Signal transducers and activators of transcription 5), PI3K/AKT (Phosphatidylinositol-3 kinase/Serine-threonine protein kinase also known as protein kinase B), ERK (Extracellular signal-regulated kinase). This leads to increased maturation rate, and increased number, size, and ploidy of megakaryocytes, as well as decreased apoptosis, and ultimately increased platelet production [109, 111, 112].

Several recently published randomized placebo-controlled trials (RCTs) have evaluated the efficacy of second-generation non-peptide TPO-RAs for the correction of thrombocytopenia in patients with LC before elective surgery/invasive procedures: eltrombopag, avatrombopag, and lusutrombopag [113–119].

The results of the ELEVATE study [119] demonstrated the efficacy of eltrombopag in elective surgery/invasive procedures: the proportion of patients not requiring perioperative platelet transfusion was 72 % in the eltrombopag group in comparison with 19 % in the placebo group

($p < 0.001$); no differences in the incidence of perioperative bleeding were observed between the groups. However, serious adverse events were reported during the study: six patients in the eltrombopag group developed portal vein thrombosis (versus one in the placebo group), which led to premature termination of the study. This resulted in refusal of marketing authorization for eltrombopag for the treatment of severe thrombocytopenia in LC patients [119].

The efficacy of avatrombopag in the correction of thrombocytopenia in patients with chronic liver disease before performing elective surgery/invasive procedures was evaluated in an international multicenter ADAPT program, which combined similarly designed phase 3 RCTs ADAPT-1 and ADAPT-2 [113, 114]. Adult patients with chronic liver disease (MELD ≤ 24) and severe thrombocytopenia were stratified into two groups: the first included patients with platelet counts < 40 × 10^9/L, and the second included patients with platelet counts between 40 and 50 × 10^9/L. The dose of avatrombopag in Group 1 and Group 2 was 60 mg/day and 40 mg/day, respectively, and the duration of treatment was 5 days. Elective surgery/invasive procedures were scheduled 5–8 days after the last dose of the study drug or placebo.

The integrated analysis of pooled data from two studies (ADAPT) showed that platelet counts on procedure day were ≥ 50 × 10^9/L in the majority of patients (77.6 %) treated with avatrombopag vs. 15.8 % in the placebo group ($p < 0.0001$) [114]. The maximum platelet count was reached by days 5–8 at the end of avatrombopag administration and returned to baseline values within a month. Avatrombopag was significantly more effective than placebo in reducing the need for platelet transfusions: 75.8 % vs. 31.7 % ($p < 0.0001$) [114].

Subgroup analysis showed that avatrombopag was equally effective in both low and high bleeding risk of invasive procedures/surgeries. The ADAPT program assessed the risk of bleeding during the following procedures: abdominal paracentesis; thoracocentesis; esophagogastroduodenoscopy (EGD) with a biopsy, variceal banding, or sclerotherapy; colonoscopy with a biopsy, polypectomy; bronchoscopy with a biopsy; liver, kidney biopsy; treatment of HCC (ethanol ablation, RFA, chemoembolization); vascular procedures (catheterization, transjugular intrahepatic portosystemic shunt); biliary interventions; nephrostomy tube placement; laparoscopic interventions; dental procedures [113, 114].

The efficacy of avatrombopag was not affected by the patient's sex, age, race, disease etiology, MELD score, and Child — Pugh class [113, 114]. The safety was similar to that of placebo: the overall incidence of serious treatment-emergent adverse events was 7.3 % in the avatrombopag group and 9 % in the placebo group ($p > 0.05$) [114].

The efficacy of avatrombopag in patients with chronic liver diseases/LC before performing elective surgery/invasive procedures (EGD with a biopsy, variceal banding; colonoscopy with a biopsy, polypectomy; liver biopsy; sigmoidoscopy; inguinal or umbilical hernia repairs; abdominal paracentesis; RFA for HCC; vascular catheterization; cervical epidural injection; endometrial curette; LIII–LIV microdiscectomy; dental procedures) was assessed in a phase 4 observational cohort study [115]. In real-world clinical practice, the administration of avatrombopag according to the regimen described in the ADAPT program was well tolerated and resulted in an increased platelet count, with a mean change in platelet count from baseline to procedure day of 41.1 × 10^9/L, and was characterized by a high proportion of patients (98 %) who did not require platelet transfusion after baseline and up to 7 days following procedure; no tromboembolic events or deaths were reported [115].

The data demonstrating the efficacy and safety of lusutrombopag (which is not approved for use in the Russian Federation) in patients with LC and severe thrombocytopenia before elective surgery/invasive procedures were obtained during two multinational multicenter phase 3 RCTs L-PLUS 1 and L-PLUS 2 (the profile of procedures was similar to that in the ADAPT program) [116, 117]. In these studies, adult patients with chronic liver disease and severe thrombocytopenia (< 50 × 10^9/L) were randomized to receive lusutrombopag 3 mg or placebo once daily for 4–7 days; invasive procedures/surgeries were performed 2–5 days after the end of treatment. Another multicenter phase 2b RCT evaluated the efficacy of lusutrombopag for bleeding prophylaxis in patients with chronic liver disease, HCC, and platelet counts < 50 × 10^9/L prior to percutaneous RFA [120].

The data of these three studies are combined in a systematic review and meta-analysis by M.E. Orme et al. [121]. Patients treated with lusutrombopag were significantly more likely to respond to treatment compared with the placebo group (risk ratio (RR) of an increase in platelet counts on the procedure day ≥ 50 × 10^9/L and

platelet counts ≥ 20 × 10^9/L from baseline at any time during the study was 6.39; 95 % confidence interval (95 % CI): 3.69–11.07; $p < 0.0001$). The proportion of patients who did not require platelet transfusion and rescue therapy for bleeding for up to 7 days after the procedure was greater in the group of patients receiving lusutrombopag than in the placebo group (RR — 3.42; 95 % CI: 1.86–6.26; $p = 0.0001$). The risk of a bleeding event of any type was significantly lower for lusutrombopag compared to placebo (RR — 0.55; 95 % CI: 0.32–0.95; $p = 0.03$); no significant differences in the rates of thrombosis were observed between lusutrombopag and placebo (RR — 0.79; 95 % CI: 0.19–3.24; $p = 0.74$) [121].

In a systematic review and a meta-analysis by P.D. Rose a pooled data on the efficacy of all three above mentioned TPO-RAs (eltrombopag, avatrombopag, and lusutrombopag) has been conducted [122]. This study included six RCTs conducted in a total of 1,229 patients with LC and severe thrombocytopenia who underwent elective surgery/invasive procedures. The use of TPO-RAs was associated with a statistically significant increase in platelet counts: the weighted mean difference in platelet counts between the baseline level and the maximum level before the procedure was 35.6 × 10^9/L (95 % CI: 28.6–42.7) and was statistically significantly higher in the TPO-RA group ($p < 0.01$); and an 88 % decrease in the risk of platelet transfusion in the periprocedural period: the odds ratio (OR) was 0.12 (95 % CI: 0.08–0.17; $p < 0.001$). The safety of TPO-RAs was similar to that in the placebo group in terms of the number of adverse events (OR — 0.87; 95 % CI: 0.47–1.62; $p = 0.66$) including thrombotic events [122]. This is important for clinical practice given the twofold increase in the risk of venous thromboembolism in hospitalized patients with chronic liver disease compared with patients without liver disease [123].

In the Russian Federation, the second-generation peptide TPO-RA (romiplostim) is approved for use only for the treatment of immune thrombocytopenia. Several small, single-center, non-comparative studies have been published in which this product was used to treat thrombocytopenia in patients with chronic liver disease/LC. Subcutaneous administration of romiplostim at an average dose of 2–2.5 mg/kg once weekly resulted in an increase in platelet counts (with the change from 39 × 10^9/L to 117 × 10^9/L) 12 to 18 days, on average, after the first dosing and was characterized by a high proportion of patients who did not require platelet transfusion. No significant thromboembolic events were reported in these studies [124–126].

Further research is needed to evaluate the effect of TPO-RAs prior to major surgeries (head and neck surgery, open thoracic surgery, laparotomy, organ resection/removal/transplantation) to assess the effect on the number of clinically significant bleeding events, hospital and long-term mortality rates, length of hospital stay, and quality of life.

What platelet counts are associated with lower risks of hemorrhagic events when performing elective surgery / invasive procedures in LC patients?

Recommendation. When preparing for elective surgery/invasive procedures in LC patients, the recommended platelet count depends on the risk and the type of the procedure (Tables 3, 4). **(LOE — 3, weak recommendation, 100 % consensus)**

Severe thrombocytopenia in patients with LC is one of the risk factors for hemorrhagic complications when performing surgery/invasive procedures, and treatment with TPO-RAs is associated with higher platelet counts, lower risk of periprocedural bleeding, and lower need for platelet transfusions for the treatment of periprocedural hemorrhagic events. Therefore, there is the question whether severe thrombocytopenia should be treated for the achievement of the required platelet count before performing elective surgery/invasive procedures. This should be decided on a case-by-case basis, taking into account patient characteristics and all factors that influence the procedure-related bleeding risk.

According to the guidelines of the American Gastroenterological Association (AGA) [102] and the American College of Gastroenterology (ACG) [127], the All-Russian Public Organization "Federation of Anesthesiologists and Reanimatologists" (FAR), the National Association of experts on thrombosis, clinical hemostasiology and hemorheology (NATH) [43], correction of thrombocytopenia in patients with LC and/or hepatic failure to prevent periprocedural bleeding is recommended if the platelet count is < 50 × 10^9/L before elective surgery/invasive procedures associated with a high risk of bleeding.

Prophylactic platelet transfusion to LC patients may be considered only if no other options for the treatment of severe thrombocytopenia

(< 50 × 10^9/L) are available to prevent periprocedural bleeding during the procedures associated with a high risk of hemorrhagic events [102, 128].

In a study by R. Rai et al. [129], it was recommended to evaluate the platelet counts in patients with LC preparing for elective procedures, and to use prophylactic platelet transfusion directly before the surgery in the following cases: when performing procedures with an intermediate risk of bleeding in patients with a platelet count of < 50 × 10^9/L and when performing procedures with a high risk of bleeding in patients with a platelet count of < 100 × 10^9/L.

In routine cases, when preparing patients with severe (< 50 × 10^9/L) thrombocytopenia for elective surgery/invasive procedures associated with a high risk of bleeding (> 1.5 %), prophylactic platelet transfusion should be replaced with the use of second-generation TPO-RAs (avatrombopag in the Russian Federation) as these drugs are superior over platelet transfusion for the following reasons: they are administered orally; they do not require the patient to be in a medical facility; they increase platelet counts in the patient's blood for a longer period of time compared to platelet transfusions; they have a good safety profile (the number of adverse events is comparable to the placebo group) and are not associated with an increased risk of thrombotic events [113, 114, 130].

Based on the results of the literature review and their own experience, the experts prepared Tables 3 and 4, which define the recommended threshold platelet count for each intervention according to the stratified risk (low, high) of hemorrhagic events during elective surgery/invasive procedures in patients with LC.

Conclusion

The statements and recommendations in this document have been prepared by experts in the management of patients with LC and its major complications in clinical practice. The experts are experienced in research of thrombocytopenia and its role in the development of hemorrhagic complications in LC patients and are qualified in evaluating the respective diagnostic tests and therapeutic options. The statements have been approved by the chief freelance gastroenterologist of the Ministry of Health of the Russian Federation, President of the Russian Scientific Liver Society and can be recommended for use by a wide range of clinical practitioners.

Table 3. Recommended minimum threshold platelet concentration during elective surgery in patients with cirrhosis depending on the risk of bleeding

Anatomical region	Examples of surgeries		Minimum threshold platelet concentration, $\times 10^9$/л
	High risk of bleeding (> 1,5 %)		
Head and neck	• Surgeries on the central nervous system and brain • Thyroid surgeries • All variants of cervical lymph node dissection • Tonsillectomy	• Maxillotomy • Septoplasty • Reposition of nasal bones • Submucosal vasotomy of the inferior turbinates • Open ophthalmic surgeries	≥ 100
Thorax	• Thymectomy • Lung surgeries • Surgeries for mediastinal tumors	• Video-assisted mediastinal lymphadenectomy	
Abdomen, retroperitoneum, rectum	• All types of interventions on the liver, gall bladder, bile ducts • Gastric resection/gastrostomy • Resection of the small/large intestine; enterostomy/colostomy • Pancreatic resection • Splenectomy	• Surgical treatment of inguinal, femoral and other hernias • Low anterior rectal resection • Rectal extirpation • Hemorrhoidectomy • Surgeries on the adrenal gland	
Kidneys, urinary tract, pelvic organs	• Nephrotomy/nephrectomy/ nephrostomy • Bladder resection/cystectomy • Salpingectomy/salpingoophorectomy • Caesarean section	• Cystostomy • Removal of ovarian cyst • Artificial termination of pregnancy (abortion)	
Musculoskeletal system	• Endoprosthetics of intervertebral discs; hip, knee and other joints	• Osteosynthesis with titanium plate	
Maxillofacial region	• Osteosynthesis of the upper/lower jaw • Complex tooth extraction • Surgeries on the temporomandibular joint	• Dental implantation with osteoplasty (bone grafting, sinus lift, bone augmentation)	
Low risk of bleeding (≤ 1,5 %)			
Abdomen, rectum, perianal area	• Ligation of hemorrhoids • Operations for rectal fissures	• Operations for rectal fistulas • Excision of the epithelial coccygeal duct	≥ 80
Musculoskeletal system	• Arthroscopic plastic surgery of the knee ligaments		
Maxillofacial region	• Simple tooth extraction and other minor dental surgeries		≥ 50

Table 4. Recommended minimum threshold platelet concentration for elective invasive procedures in patients with cirrhosis depending on the risk of bleeding

Procedure	Examples of invasive procedures		Minimum threshold platelet concentration, $\times 10^9$/л
	High risk of bleeding (> 1,5 %)		
Percutaneous/ Vascular	• Neuraxial methods of analgesia/ anesthesia (catheterization of the epidural space, regional epidural or spinal anesthesia and others)		≥ 100
Percutaneous/ Vascular	• Intraperitoneal needle biopsy of solid organs (including liver) • Laparoscopic biopsy • Ultrasound-guided prostate biopsy • Intrathoracic organ biopsy • Intraocular procedures/injections • Intra-articular injections	• Puncture decompression of intervertebral discs • Drainage of abscesses of various locations • Radiofrequency catheter/ percutaneous ablation	≥ 80
Percutaneous/ Vascular	• Transjugular intrahepatic portosystemic shun • Angiography/coronary angiography/ venography with intervention	• Transhepatic arterial chemoembolization or radioembolization	≥ 50
Endoscopic	• Endoscopic removal of polyps from the intestine, female genital organs (> 2 polyps, size ≥ 1 cm) • Endoscopic retrograde cholangiopancreatography with papillosphincterotomy • Endoscopic ultrasound with fine needle aspiration	• Balloon enteroscopy • Therapeutic bronchoscopy • Endoscopic dilatation of stricture or mucosal resection • Percutaneous endoscopic gastrostomy placemen • Cystogastrostomy • Endoscopic sclerotherapy	≥ 80
Low risk of bleeding (≤ 1,5 %)			
Percutaneous/ Vascular	• Lumbar puncture • Skin biopsy / removal of skin tumors • Installation/removal of central catheter	• Transjugular measurement of hepatic venous pressure gradient (with liver biopsy) • Diagnostic coronary angiography and right heart catheterization	≥ 50
Endoscopic	• Diagnostic endoscopy and standard ligation of varicose veins of the esophagus and stomach • Colonoscopy (with mucosal biopsy, 1 polyp <1 cm in diameter) • Enteroscopy • Capsule endoscopy	• Endoscopic retrograde cholangiopancreatography without papillosphincterotomy • Endoscopic ultrasound examination • Transesophageal echocardiography	
Percutaneous/ Vascular	• Laparocentesis • Thoracentesis • Drainage of the pleural, abdominal cavity • Replacement of drainage catheter	• Catheterization of the ureter • Installation of a vena cava filter • Diagnostic venography	≥ 30
Dental	• Local anesthesia	• Sanitation of the oral cavity (treatment of caries, removal of plaque, deep cleaning of teeth and other therapeutic procedures)	

Members of the Expert Group

Bessonova E.N., Geyvandova N.I., Zharkova M.S., Kitsenko E.A., Korochanskaya N.V., Kurkina I.A., Maev-skaya M.V., Melikyan A.L., Morozov V.G., Nadinskaia M.Yu., Khoronko Yu.V.

Work with literature sources and text

Gulyaeva K.A., Deeva T.A.

Scientific Project Director

Ivashkin V.T.

Состав экспертной группы

Бессонова Е.Н., Гейвандова Н.И., Жаркова М.С., Киценко Е.А., Корочанская Н.В., Куркина И.А., Маевская М.В., Меликян А.Л., Морозов В.Г., Надинская М.Ю., Хоронько Ю.В.

Работа с литературой и текстом

Гуляева К.А., Деева Т.А.

Научный руководитель проекта

Ивашкин В.Т.

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Information about the authors

Marina V. Maevskaya — Dr. Sci. (Med.), Professor, Consultant at the Diagnostic and Treatment Department of the University Clinical Hospital No. 2, I.M. Sechenov First Moscow State Medical University (Sechenov University).
Contact information: mvmaevskaya@me.com;
119048, Moscow, Trubetskaya str., 8/2.
ORCID: https://orcid.org/0000-0001-8913-140X

Maria Yu. Nadinskaia* — Cand. Sci. (Med.), Associate Professor at the Department of Propaedeutics of Internal Diseases, Gastroenterology and Hepatology, I.M. Sechenov First Moscow State Medical University (Sechenov University).
Contact information: nadinskaya_m_yu@staff.sechenov.ru;
119048, Moscow, Trubetskaya str., 8/2.
ORCID: https://orcid.org/0000-0002-1210-2528

Сведения об авторах

Маевская Марина Викторовна — доктор медицинских наук, профессор, консультант лечебно-диагностического отделения Университетской клинической больницы № 2, ФГАОУ ВО «Первый Московский государственный медицинский университет им. И.М. Сеченова» Министерства здравоохранения Российской Федерации (Сеченовский Университет).
Контактная информация: mvmaevskaya@me.com;
119048, г. Москва, ул. Трубецкая, 8, стр. 2.
ORCID: https://orcid.org/0000-0001-8913-140X

Надинская Мария Юрьевна* — кандидат медицинских наук, доцент кафедры пропедевтики внутренних болезней, гастроэнтерологии и гепатологии, ФГАОУ ВО «Первый Московский государственный медицинский университет им. И.М. Сеченова» Министерства здравоохранения Российской Федерации (Сеченовский Университет).
Контактная информация: nadinskaya_m_yu@staff.sechenov.ru;
119048, г. Москва, ул. Трубецкая, 8, стр. 2.
ORCID: https://orcid.org/0000-0002-1210-2528

* Corresponding author / Автор, ответственный за переписку

Elena N. Bessonova — Dr. Sci. (Med.), Associate Professor at the Department of Polyclinic Therapy, Ural State Medical University; Chief Freelance Gastroenterologist of the Ministry of Health of the Sverdlovsk Region, Head of the Sverdlovsk Regional Hepatological Center, Sverdlovsk Regional Clinical Hospital No. 1.
Contact information: benbessonova@yandex.ru;
620102, Yekaterinburg, Volgogradskaya str., 185.
ORCID: https://orcid.org/0000-0002-4223-3473

Бессонова Елена Николаевна — доктор медицинских наук, доцент кафедры поликлинической терапии, ФГБОУ ВО «Уральский государственный медицинский университет» Министерства здравоохранения Российской Федерации; главный внештатный гастроэнтеролог Министерства здравоохранения Свердловской области; руководитель Свердловского областного гепатологического центра, ГАУЗ Свердловской области «Свердловская областная клиническая больница № 1».
Контактная информация: benbessonova@yandex.ru;
620102, г. Екатеринбург, ул. Волгоградская, 185.
ORCID: https://orcid.org/0000-0002-4223-3473

Natalia I. Geyvandova — Dr. Sci. (Med.), Professor of the Department of Hospital Therapy, Stavropol State Medical University; Consultant, Gastroenterology Department, Stavropol Regional Clinical Hospital.
Contact information: ngeyvandova@yandex.ru;
355017, Stavropol, Mira str., 310.
ORCID: https://orcid.org/0000-0001-5920-5703

Гейвандова Наталья Иогановна — доктор медицинских наук, профессор кафедры госпитальной терапии, ФГБОУ ВО «Ставропольский государственный медицинский университет» Министерства здравоохранения Российской Федерации; консультант гастроэнтерологического отделения, ГБУЗ Ставропольского края «Ставропольская краевая клиническая больница».
Контактная информация: ngeyvandova@yandex.ru;
355017, г. Ставрополь, ул. Мира, 310.
ORCID: https://orcid.org/0000-0001-5920-5703

Maria S. Zharkova — Cand. Sci. (Med.), Head of the Hepatology Department, V. Kh. Vasilenko Clinic of Internal Disease Propaedeutics, Gastroenterology and Hepatology, I.M. Sechenov First Moscow State Medical University (Sechenov University).
Contact information: zharkova_m_s@staff.sechenov.ru;
119048, Moscow, Trubetskaya str., 8/2.
ORCID: https://orcid.org/0000-0001-5939-1032

Жаркова Мария Сергеевна — кандидат медицинских наук, заведующая отделением гепатологии Клиники пропедевтики внутренних болезней, гастроэнтерологии, гепатологии им. В.Х. Василенко, ФГАОУ ВО «Первый Московский государственный университет им. И.М. Сеченова» Министерства здравоохранения Российской Федерации (Сеченовский Университет).
Контактная информация: zharkova_m_s@staff.sechenov.ru;
119048, г. Москва, ул. Трубецкая, 8, стр. 2.
ORCID: https://orcid.org/0000-0001-5939-1032

Evgeniy A. Kitsenko — Dr. Sci. (Med.), Professor, Leading Researcher, Russian Scientific Center of Surgery named after Academician B.V. Petrovsky.
Contact information: kitsenko-surgeon@mail.ru;
119991, Moscow, Abrikosovsky lane, 2.
ORCID: https://orcid.org/0000-0002-8268-3129

Киценко Евгений Александрович — доктор медицинских наук, профессор, ведущий научный сотрудник, ФГБНУ «Российский научный центр хирургии им. академика Б.В. Петровского».
Контактная информация: kitsenko-surgeon@mail.ru;
119991, г. Москва, Абрикосовский пер., 2.
ORCID: https://orcid.org/0000-0002-8268-3129

Natalia V. Korochanskaya — Dr. Sci. (Med.), Professor of the Department of Surgery No. 3, Kuban State Medical University; Head of the Gastroenterological Center, Regional Clinical Hospital No. 2
Contact information: nvk-gastro@mail.ru;
350063, Krasnodar, Sedina str., 4.
ORCID: https://orcid.org/0000-0002-5538-9418

Корочанская Наталья Всеволодовна — доктор медицинских наук, профессор кафедры хирургии № 3, ФГБОУ ВО «Кубанский государственный медицинский университет» Министерства здравоохранения Российской Федерации; руководитель гастроэнтерологического центра, ГБУЗ «Краевая клиническая больница № 2».
Контактная информация: nvk-gastro@mail.ru;
350063, г. Краснодар, ул. Седина, 4.
ORCID: https://orcid.org/0000-0002-5538-9418

Irina A. Kurkina — Transfusiologist of the Highest Category, Head of the Department of Clinical Transfusiology, I.M. Sechenov First Moscow State Medical University (Sechenov University).
Contact information: kyrkinaia@rambler.ru;
119048, Moscow, Trubetskaya str., 8/2.
ORCID: https://orcid.org/0000-0003-1762-4760

Куркина Ирина Александровна — врач-трансфузиолог высшей категории, заведующая отделением клинической трансфузиологии, ФГАОУ ВО «Первый Московский государственный университет им. И.М. Сеченова» Министерства здравоохранения Российской Федерации (Сеченовский Университет).
Контактная информация: kyrkinaia@rambler.ru;
119048, г. Москва, ул. Трубецкая, 8, стр. 2.
ORCID: https://orcid.org/0000-0003-1762-4760

Anait L. Melikyan — Dr. Sci. (Med.), Head of the Department of Standardization of Treatment Methods for Hematological Diseases, National Medical Research Center for Hematology.
Contact information: anoblood@mail.ru;
125167, Moscow, Novy Zykovsky dr., 4.
ORCID: https://orcid.org/0000-0002-2119-3775

Меликян Анаит Левоновна — доктор медицинских наук, заведующая отделением стандартизации методов лечения гематологических заболеваний, ФГБУ «Национальный медицинский исследовательский центр гематологии» Министерства здравоохранения Российской Федерации.
Контактная информация: anoblood@mail.ru;
125167, г. Москва, Новый Зыковский пр., 4.
ORCID: https://orcid.org/0000-0002-2119-3775

Viacheslav G. Morozov — Dr. Sci. (Med.), Professor, Director, Medical Company "Hepatologist".
Contact information: viacheslavmorozov@yandex.ru;
443063, Samara, Serdobskaya str., 36A.
ORCID: https://orcid.org/0000-0002-4451-7891

Yury V. Khoronko — Dr. Sci. (Med.), Professor, Head of the Department of Operative Surgery and Topographic Anatomy, Rostov State Medical University.
Contact information: khoronko507@gmail.com;
344022, Rostov-on-Don, Nakhichevansky lane, 29.
ORCID: https://orcid.org/0000-0002-3752-3193

Tatiana A. Deeva — Cand. Sci. (Med.), Associate Professor at the Department of Biological Chemistry, I.M. Sechenov First Moscow State Medical University (Sechenov University).
Contact information: deeva_t_a@staff.sechenov.ru;
119048, Moscow, Trubetskaya str., 8/2.
ORCID: https://orcid.org/0000-0002-3126-141X

Kseniya A. Gulyaeva — Postgraduate, Department of Propaedeutics of Internal Diseases, Gastroenterology and Hepatology, I.M. Sechenov First Moscow State Medical University (Sechenov University).
Contact information: xen59@mail.ru;
119048, Moscow, Trubetskaya str., 8/2.
ORCID: https://orcid.org/0000-0002-3462-0123

Vladimir T. Ivashkin — Dr. Sci. (Med.), Academician of the Russian Academy of Sciences, Professor, Head of the Department of Propaedeutics of Internal Diseases, I.M. Sechenov First Moscow State Medical University (Sechenov University); Chief Gastroenterologist of the Ministry of Health of the Russian Federation; President of the Russian Scientific Liver Society.
Contact information: ivashkin_v_t@staff.sechenov.ru;
119048, Moscow, Trubetskaya str., 8/2.
ORCID: https://orcid.org/0000-0002-6815-6015

Морозов Вячеслав Геннадиевич — доктор медицинских наук, профессор, директор, Медицинская компания «Гепатолог».
Контактная информация: viacheslavmorozov@yandex.ru;
443063, г. Самара, ул. Сердобская, 36А.
ORCID: https://orcid.org/0000-0002-4451-7891

Хоронько Юрий Владиленович — доктор медицинских наук, профессор, заведующий кафедрой оперативной хирургии и топографической анатомии, ФГБОУ ВО «Ростовский государственный медицинский университет» Министерства здравоохранения Российской Федерации.
Контактная информация: khoronko507@gmail.com;
344022, г. Ростов-на-Дону, Нахичеванский пер., 29.
ORCID: https://orcid.org/0000-0002-3752-3193

Деева Татьяна Андреевна — кандидат медицинских наук, доцент кафедры биологической химии, ФГАОУ ВО «Первый Московский государственный медицинский университет им. И.М. Сеченова» Министерства здравоохранения Российской Федерации (Сеченовский Университет).
Контактная информация: deeva_t_a@staff.sechenov.ru;
119048, г. Москва, ул. Трубецкая, 8, стр. 2.
ORCID: https://orcid.org/0000-0002-3126-141X

Гуляева Ксения Александровна — аспирант кафедры пропедевтики внутренних болезней, гастроэнтерологии и гепатологии, ФГАОУ ВО «Первый Московский государственный медицинский университет им. И.М. Сеченова» Министерства здравоохранения Российской Федерации (Сеченовский Университет).
Контактная информация: xen59@mail.ru;
119048, Москва, ул. Трубецкая, 8, стр. 2.
ORCID: https://orcid.org/0000-0002-3462-0123

Ивашкин Владимир Трофимович — доктор медицинских наук, академик РАН, профессор, заведующий кафедрой пропедевтики внутренних болезней, гастроэнтерологии и гепатологии, ФГАОУ ВО «Первый Московский государственный медицинский университет им. И.М. Сеченова» Министерства здравоохранения Российской Федерации (Сеченовский Университет); главный внештатный специалист гастроэнтеролог МЗ РФ, президент Российского общества по изучению печени (РОПИП).
Контактная информация: ivashkin_v_t@staff.sechenov.ru;
119048, г. Москва, ул. Трубецкая, 8, стр. 2.

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