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REVIEW

Minimum platelet count threshold before invasive procedures in cirrhosis: Evolution of the guidelines

Marco Biolato, Federica Vitale, Tiziano Galasso, Antonio Gasbarrini, Antonio Grieco

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Abstract

Cirrhotic patients with severe thrombocytopenia are at increased risk of bleeding during invasive procedures. The need for preprocedural prophylaxis aimed at reducing the risk of bleeding in cirrhotic patients with thrombocytopenia who undergo scheduled procedures is assessed *via* the platelet count; however, establishing a minimum threshold considered safe is challenging. A platelet count ≥ 50000/μL is a frequent target, but levels vary by provider, procedure, and specific patient. Over the years, this value has changed several times according to the different guidelines proposed in the literature. According to the latest guidelines, many procedures can be performed at any level of platelet count, which should not necessarily be checked before the procedure. In this review, we aim to investigate and describe how the guidelines have evolved in recent years in the evaluation of the minimum platelet count threshold required to perform different invasive procedures, according to their bleeding risk.

Key Words: Liver disease; Thrombocytopenia; Avatrombopag; Lusutrombopag; Transfusion

Core Tip: There are several reviews in the literature that deals with the management of thrombocytopenia in patients with cirrhosis undergoing scheduled invasive procedures. However, this review is one of the few to provide a comparison between the main guidelines concerning the platelet-count reference threshold to consider safely performing the various types of procedures.

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INTRODUCTION

Thrombocytopenia, defined as any decrease in platelet count below the normal limit (< 150000/μL), is a very common hematological alteration in advanced liver disease, with an incidence of 77% to 85% in patients with cirrhosis[1,2].

Thrombocytopenia is classified as moderate when the platelet count falls into the range of 50000-100000/μL and severe if the platelet count is < 50000/μL, with an observed prevalence of 13% and 1% of patients with chronic liver disease (CLD), respectively[3]. Thrombocytopenia is the most common peripheral blood alteration with respect to anemia and leukopenia in patients with cirrhosis[4].

The development of thrombocytopenia in patients with cirrhosis can be determined by two major mechanisms, platelet sequestration and increased clearance in the spleen due to congestive splenomegaly induced by portal hypertension, a phenomenon called "hypersplenism"[5,6], and decreased production of the growth factor thrombopoietin (TPO) in the liver that regulates megakaryocyte and platelet production, whose circulating levels are lower in cirrhotic patients with thrombocytopenia than in cirrhotic patients with normal platelet counts[7-10].

Other factors, including bone marrow suppression by chronic viral infections, antiviral treatments and anticancer agents, and the development of antiplatelet antibodies, can be involved in the etiopathogenesis of thrombocytopenia.

Thrombocytopenia, which can be considered a useful early prognostic marker in cirrhotic patients [11], is associated with increased bleeding risk, thereby narrowing the available treatment options and impacting the timing and outcome of invasive procedures in this population of patients[12,13].

Even though clinically significant spontaneous bleeding does not usually occur when the platelet count is > 10-20000/μL, cirrhotic patients with severe thrombocytopenia are at increased risk of bleeding, and invasive therapeutic procedures can often be challenging to perform because of the elevated hemorrhagic risk they present[14-16].

In the past, the management of thrombocytopenia in cirrhotic patients included platelet transfusion, splenic artery embolization, splenectomy, and transjugular intrahepatic portosystemic stent shunting. Preprocedural platelet transfusion was the most common approach. However, the efficacy of platelet transfusion to reduce bleeding risks in patients with thrombocytopenia and liver disease undergoing a scheduled procedure is variable and generally does not exceed an increase in platelet count by 5000-10000/μL with a half-life of 2-4 d. Adverse effects of platelet transfusion can be associated with potentially fatal complications, such as the development of febrile nonhemolytic reactions, the transmission of infectious agents, and transfusion-related acute lung injury. Moreover, after repeated administration of platelets, refractoriness due to human leukocyte antigen alloimmunization can occur [17-21]. Finally, it should be remembered that platelet transfusion is a limited health resource, the use of which is fundamental in other clinical contexts (for example, the management of post-trauma hemorrhage in patients with a low platelet count).

Small orally bioavailable TPO receptor agonists, namely, avatrombopag and lusutrombopag, act selectively on the human TPO receptor and activate signal transduction pathways, thereby promoting the proliferation and differentiation of bone marrow cells into megakaryocytes and increasing the platelet levels. These drugs represent a promising emerging therapeutic option for the treatment of thrombocytopenia to prevent hemorrhagic events and raise the platelet count before scheduled procedures[22-24].

The phase 3, randomized, placebo-controlled, ADAPT-1 and ADAPT-2 studies demonstrated that avatrombopag was superior to placebo in reducing the need for platelet transfusions or rescue procedures for bleeding in patients with thrombocytopenia and CLD undergoing a scheduled procedure[25]. In the phase 3, randomized, double-blind, placebo-controlled study, L-PLUS 2, lusutrombopag was demonstrated to be superior to placebo in avoiding preprocedural platelet transfusion and rescue therapy for bleeding (64.8% of patients in the lusutrombopag group *vs* 29.0% in the placebo group) and in achieving a durable platelet count response in patients with thrombocytopenia and CLD undergoing invasive procedures, with a safety profile similar to placebo[26].

Similarly, a systematic meta-analysis performed by Orme *et al*[27] showed the efficacy and safety of treatment with lusutrombopag in this patient population. More patients treated with lusutrombopag (compared to placebo) required no platelet transfusion and no rescue therapy for bleeding for at least 7 days post-procedure (RR 3.42; 95%CI: 1.86, 6.26; $P = 0.0001$). Moreover, they had a lower risk of any bleeding event (RR 0.55; 95%CI: 0.32, 0.95; $P = 0.03$) but similar thrombosis event rates (RR 0.79; 95%CI: 0.19, 3.24; $P = 0.74$).

The effects of lusutrombopag on post-invasive procedural bleeding in thrombocytopenic patients with CLD were also investigated in a study by Yoshida *et al*[28]. There was a lower incidence of bleeding events in the lusutrombopag group than in the platelet transfusion group (3.7% *vs* 8.2%, $P < 0.001$) and lower average medical costs, supporting the effectiveness of this drug as a prophylactic treatment for bleeding prevention.

The need for these preprocedural treatments aimed at reducing the risk of bleeding in cirrhotic patients with thrombocytopenia who undergo scheduled procedures is assessed *via* the platelet count compared with the reference threshold considered safe. Over the years, this value has changed several times according to the different guidelines proposed in the literature. In this review, we aim to investigate and describe how the guidelines have evolved in recent years in the evaluation of the minimum platelet count threshold required to perform different invasive procedures, according to their bleeding risk.

BLEEDING RISK OF DIFFERENT PROCEDURES AND MAIN GUIDELINES

Procedures are divided into three groups by the original Society of Interventional Radiology (SIR) consensus guidelines: (1) Low risk when they are expected to rarely have hemorrhagic complications or are occurring in areas where bleeding is easy to diagnose and control (paracentesis, thoracentesis, dental extraction, diagnostic endoscopy, variceal band ligation, uncomplicated polypectomy, cardiac catheterization, central line placement); (2) Moderate risk [lumbar puncture, percutaneous or transjugular liver biopsy, transjugular intrahepatic portosystemic shunt, percutaneous gastrostomy placement, biliary sphincterotomy, percutaneous biopsy of extrahepatic organ or lesions, trans-arterial or percutaneous hepatocellular carcinoma (HCC) therapies]; and (3) High risk when they are expected to have hemorrhagic complications, occurring in areas where bleeding will be difficult to diagnose or treat or in sites where even minor amounts of bleeding may have devastating consequences (brain or spinal surgery, cardiac, intra-abdominal and orthopedic surgery, intracranial pressure catheter insertion, large polypectomy with endoscopic mucosal or submucosal resection)[29-31].

According to SIR guidelines, for patients with minimal risk factors for bleeding, screening coagulation laboratory testing is not routinely recommended for procedures with low bleeding risk, but it may be considered for patients receiving warfarin or low molecular weight heparin or those with an inherently higher risk of bleeding. Platelet transfusion should be considered for low-bleeding-risk procedures that require arterial access when the platelet count is < 20000/μL and for high bleeding risk procedures if the platelet count is < 50000/μL, obtaining an appropriate preprocedural coagulation testing[31].

Thromboelastography (TEG) seems to be a more accurate tool for the evaluation of coagulation derangement than classical tests, such as the international normalized ratio (INR) and platelet count. The reaction time (r) and maximum amplitude (MA) of TEG are able to predict the need for blood transfusion in thrombocytopenic patients undergoing invasive procedures. In a recent controlled trial on 60 patients undergoing invasive procedures, significant savings of transfusion units (both fresh frozen plasma and platelets) were observed with the use of TEG parameters compared to INR and platelets with the same bleeding complication level[32]. Unfortunately, this study was criticized because of the transfusion thresholds employed in the control arm, which were considered too extensive and not consistent with what is routinely made in clinical practice. However, in the following years, other studies and randomized clinical trials will be able to confirm the role of TEG-based transfusion in guiding and restricting transfusion both in cirrhotic patients with acute variceal bleeding and in patients undergoing invasive procedures, such as percutaneous liver biopsy, transjugular intrahepatic portosystemic shunt, percutaneous acetic acid injection and transarterial chemoembolization, without compromising hemostasis or increasing the risk of bleeding[33-36].

The main recommendations for prophylactic platelet transfusion before invasive procedures reported in the British Committee for Standards in Hematology guidelines of 2016 are about central venous line placement (> 20000/μL), lumbar puncture (> 40000/μL), surgery or percutaneous liver biopsy (> 50000/μL), insertion or removal of epidural catheters (> 80000/μL) and neurosurgery or ophthalmic surgery (> 100000/μL).

No platelet transfusions are routinely recommended before bone marrow aspirate or biopsy, peripherally inserted central catheters, traction removal of tunneled central venous catheters (CVC), and cataract surgery[37].

A consideration of platelet transfusion before high-risk procedures or when active bleeding is encountered is recommended by current guidelines and expert opinions for patients with platelet

counts below 50000/mL[38]. A relationship between platelet levels < 75000/μL and procedure-related bleeding was demonstrated in one study among patients undergoing liver transplant evaluations[39], and platelet levels < 30000/μL were also an independent predictor of major bleeding among critically ill cirrhosis patients in the intensive care unit setting[40]. However, in another prospective study, there were no predictions of postprocedural bleeding in cirrhosis by baseline platelet levels[41].

According to the Italian Association for the Study of Liver Diseases and the Italian Society of Internal Medicine consensus conference of 2016, platelet counts ≥ 50000/μL are considered to ensure normal primary hemostasis, with a recommendation to perform platelet transfusion when counts are < 50000/μL that is supported only by biological plausibility[42].

An important statement about prophylactic platelet transfusions is reported by the National Institute for Health and Care Excellence guidelines of 2015 that suggest an increase in platelet count above 50000/μL in all the patients undergoing invasive procedures or surgery; a threshold of 50-75000/μL and > 100000/μL should be taken into consideration respectively for high risk of bleeding and surgery at critical sites[43].

The American Gastroenterology Association guidelines of 2019[44] and the American College of Gastroenterology guidelines of 2021[45] do not recommend coagulation assessment and prophylactic platelet transfusions before common procedures such as diagnostic and therapeutic paracentesis, thoracentesis, upper endoscopy to screen for and band esophageal varices, and diagnostic (but not therapeutic) colonoscopy, outside of significant renal dysfunction or sepsis, suggesting that higher platelet levels may be more appropriate for high-risk procedures such as the removal of large polyps and major surgery.

According to the International Society on Thrombosis and Hemostasis guidelines of 2019[46] and the American Association for the Study of Liver Diseases (AASLD) guidelines of 2020[47] there is not a strong recommendation to correct the platelet count prior to low- and high-risk procedures.

According to the American Gastroenterology Association guidelines of 2021[48], a specific value of platelets that identifies patients at an increased bleeding risk is not defined, suggesting against preprocedural testing. Similarly, the European Association for the Study of the Liver guidelines of 2022[49] does not recommend a laboratory evaluation of hemostasis to predict postprocedural bleeding in patients with cirrhosis undergoing invasive procedures, among cases with both low and high risk of bleeding, although such analysis may serve to provide a baseline status of the patient in case of bleeding events in high-risk procedures.

Liver biopsy

Liver biopsy is performed in some cases to clarify the etiology of CLD[50], but thrombocytopenia is often considered a relative contraindication to this procedure because of an elevated risk of bleeding, especially in patients with platelet counts ≤ 60000/μL[51,52].

The risk of bleeding in patients with CLD after a liver biopsy was first investigated in the Hepatitis C Antiviral Long-Term treatment against cirrhosis (HALT-C) trial, between 2000 and 2006, in a cohort of 2740 patients with advanced chronic hepatitis C[53] and platelets ≥ 50000/μL[51], evaluating the safety and efficacy of long-term, low-dose maintenance therapy with peginterferon alfa-2a and identifying a significant difference in bleeding risk according to the platelet count (0.2% with platelets ≥ 150000/μL, from 0.6% to 0.7% for platelets between 61-150000/μL and 5.3% for platelet ≤ 60000/μL).

Another study retrospectively reported a bleeding rate of 23% in patients with platelet counts < 60 000/μL compared with no episodes of bleeding with platelet counts above this range[54]. These results were similarly reported in another small retrospective study[55]. On the other hand, certain studies did not show any correlation between bleeding risk and coagulation tests[56].

In addition, an absolute platelet count threshold does not take into account platelet function; *in vitro* data proved that platelet-related thrombin production is shown to be adequate in cirrhotic patients with a platelet count of at least 56.000/mm^3 but *in vivo*, there is no evidence that this threshold can be considered a target for pre-procedure platelet count[57].

In 2009, the pivotal AASLD guidelines dedicated to liver biopsy recommended a platelet count of at least 50-60000/μL as the safety minimum threshold of platelets to perform a liver biopsy. In the case of a high risk of complications with percutaneous liver biopsy, a transjugular approach was suggested: in a series of 51 biopsies, a threshold count of 30000/μL was identified to be safe[58].

As shown by Potretzke *et al*[59], bleeding rates after subcapsular mass biopsy (0.86%) are not significantly different from those noted after non subcapsular (0.66%) or site biopsy (0.65%), suggesting that biopsy of subcapsular lesions should no longer be considered contraindicated.

In a different setting, evaluating the safety of percutaneous liver biopsy performed with a Klatskin needle, Takyar *et al*[60] identified platelets ≤ 100000/μL and aPTT > 35 as independent risk factors for post-biopsy bleeding and suggested a higher risk of major complications in certain acutely ill subjects and those with systemic illnesses, underlining the importance of considering risk/benefit balance of liver biopsy in these patients while alternative approaches are viable.

Among the invasive procedures performed in cirrhotic patients, liver biopsy is the one for which the most solid evidence is available. Despite this fact, the guidelines have evolved considerably in the following years. This evolution concerns both the minimum platelet threshold and the perception of the bleeding risk associated with the procedure. The evolution of the guidelines regarding the minimum

threshold for the platelet count before the percutaneous liver biopsy is shown in Table 1. According to the latest guidelines, liver biopsy is considered a low-risk procedure and can be performed at any platelet count level, which should not necessarily be checked before the procedure[30,31,42-49].

Endoscopy

Routine pre-endoscopy platelet assessment in patients with a high risk for thrombocytopenia is supported by current American Society for Gastrointestinal Endoscopy (ASGE) guidelines, but there is not a determined minimum platelet count necessary for safely performing endoscopic procedures[61].

A strict threshold for an upper endoscopy is not specified, so endoscopists act based on their preference. In 2012, ASGE guidelines suggested safe platelet levels ≥ 20000/μL for diagnostic upper endoscopy and a platelet count ≥ 50000/μL for endoscopic biopsies and variceal banding[62].

Similarly, no specific platelet guidelines exist for lower endoscopy and other endoscopic procedures. Even though they are categorized by the ASGE into high and low risk for bleeding, this risk cannot be applied specifically to patients with advanced liver disease, so the strategies are often individualized. Commonly, a platelet count ≥ 50000/μL is considered for higher-risk procedures, such as large polypectomy, endoscopic treatment of hemorrhage, endoscopic retrograde cholangiopancreatography with sphincterotomy, or endoscopic ultrasound with fine needle aspiration[63,64].

Only the study by Soh *et al*[65] identified a correlation between postprocedural bleeding and platelet count (bleeding rate 27.5% with platelets ≤ 50000/μL *vs* 7.5%-relative risk 6), showing that Child-Pugh B or C cirrhosis (P = 0.011), a platelet count < 50000/μL (P < 0.001), 3 or more polyps (P = 0.017), endoscopic mucosal resection or submucosal dissection (P < 0.001), and polypectomy performed by trainees (P < 0.001) were independent risk factors for immediate post polypectomy bleeding.

Endoscopic band ligation of esophageal varices is a common procedure in cirrhotic patients. For patients undergoing this procedure, the risk of post banding ulcer bleeding has been variably reported, ranging from 2.8%[66] to 7.3%[67], but in both studies, the platelet count was not associated with bleeding risk. Other observational studies confirmed that platelet count is not a predictor of post ligation bleeding and six-week mortality in patients with rebleeding, but only lower fibrinogen levels have a significant correlation with them[68,69]. According to AASLD Practice Guidelines for the management of variceal bleeding, a recommendation about platelet transfusion in patients with variceal hemorrhage is not provided[70]. In contrast, other guidelines consider a platelet count of 50000/μL as a minimum threshold to perform the endoscopy procedure[71].

The guidelines for the minimum platelet count threshold before esophageal variceal band ligation are shown in Table 2. Additionally, in this case, the revision of the guidelines has gone toward the abolition of a minimum safety threshold of the platelet count to be obtained before the procedure. It should be noted that the perception of the risk of bleeding is very different between the various guidelines, depending on which of the few studies available were included in the bleeding risk calculation and what their relative weight was[30,42-49,61,70,71].

Even though transfusion of blood products in CLD has the apparent clinical benefits of correcting thrombocytopenia and deranging INR, many studies have shown its association with several risks, such as rising portal pressure and predisposition to a vicious cycle of rebleeding, extended hospital stays, and poorer outcomes[72-74].

Similarly, Biswas *et al*[75] investigated how platelet counts, platelet transfusions, and fresh frozen plasma transfusions affect the outcomes of acute variceal bleeding in cirrhosis patients in terms of bleeding control, rebleeding, and mortality. In a cohort of 913 patients stratified into three different groups according to platelet count (< 20000/μL, 20000/μL-50000/μL, > 50000/μL), thrombocytopenia did not affect rebleeding rates on days 5 and 42 (13%, 6.5%, and 4.7%, respectively, on day 5; and 21.7%, 17.3%, and 14.4%, respectively, on day 42) and mortality rates (13.0%, 23.2%, and 17.2%, respectively) that were similar between the three platelet groups. However, platelet transfusion increased rebleeding on day 5 (14.6% *vs* 4.5%; P = 0.039) and day 42 (32.6% *vs* 15.7%; P = 0.014) compared to patients who did not receive it, with a higher but nonsignificant effect on mortality (25.8% *vs* 23.6%)[75].

These studies support the view that a restrictive transfusion strategy is beneficial compared to a more liberal one and that the correction of coagulopathy is often a futile target in the management and control of acute variceal bleeding.

Paracentesis and thoracentesis

Data on patients with abnormal coagulation profiles (INR > 1.5 and/or platelet counts < 50000/μL) indicate that paracentesis[15,76,77] and thoracentesis[78-81] pose a very low risk for major bleeding.

Patients with advanced CLD usually need to undergo therapeutic large-volume paracentesis for the management of tense or recurrent ascites. It is an important routine diagnostic and therapeutic procedure used to evaluate the etiology of ascites and the presence of spontaneous bacterial peritonitis. Rarely, the procedure could be complicated by potential abdominal wall hematoma and hemoperitoneum after a puncture of abdominal wall collateral under high portal pressure[82].

However, the safety of this procedure in the setting of thrombocytopenia is demonstrated in real-world experiences, showing minimal bleeding complications (< 0.02%) in a platelet count range from 19000/μL to 341000/μL. In these two studies, risk factors for severe bleeding were only higher model for end-stage liver disease (MELD) scores and renal failure[83,84]. Rowley *et al*[85] confirmed that

Table 1 Threshold of platelet count before percutaneous liver biopsy: evolution of the guidelines

Society	Year	Bleeding risk	Platelet count threshold (/μL)	Ref.
National Institute for Health and Care Excellence	2015	Not classified	50000	National Clinical Guideline Centre (UK)[43]
British Committee for Standards in Haematology	2016	Not classified	50000	Estcourt *et al*[37]
Italian Association for the Study of Liver Diseases and the Italian Society of Internal Medicine	2016	Low	50000 "this recommendation is supported only by biological plausibility"	Under the auspices of the Italian Association for the Study of Liver Diseases (AISF) and the Italian Society of Internal Medicine (SIMI)[42]
International Coagulation in Liver Disease	2017	Intermediate	"Generally not recommended"	Intagliata *et al*[30]
American Gastroenterological Association	2019	Intermediate	50000	O'Leary *et al*[44]
Society of Interventional Radiology	2019	High	50000 (20000 for transjugular liver biopsy)	Patel *et al*[31]
American Association for the Study of Liver Diseases	2020	High	"Suggest individualized approaches"	Northup *et al*[47]
American College of Gastroenterology	2020	Not classified	Correction not recommended	Simonetto *et al*[45]
International Society on Thrombosis and Haemostasis	2021	High	Do not correct	Roberts *et al*[46]
American Gastroenterological Association	2021	High	"Suggests against the prepro-cedural testing"	O'Shea *et al*[48]
European Association for the Study of the Liver	2022	Low	"Cannot be generally indicated"	European Association for the Study of the Liver [49]

postprocedural hemorrhage is very rare (0.19%) when paracentesis is performed with real-time ultrasound guidance by radiologists, without correction of coagulation abnormalities with prophylactic blood product transfusion. In this setting, the incidence of hemorrhagic events is probably related to the patient's clinical condition rather than the platelet count since the presence of portal hypertension is associated with bleeding regardless of platelet count.

Other retrospective reviews on thoracentesis suggest similar results, reporting 17 bleeding-related complications after thoracentesis in 9320 patients (0.18%), all of which occurred in patients with platelet counts > 50000/μL[86].

Hence, no prophylactic blood product transfusions before paracentesis and thoracentesis are recommended by national and international consensus guidelines in the setting of thrombocytopenia and coagulopathy because of this very low risk of bleeding[85,87,88].

Central venous line

Insertion of a CVC for the management of gastrointestinal bleeding in the setting of intensive care treatment is commonly required in cirrhotic patients. Studies in the literature describe only a very low incidence of bleeding, such as mild oozing and hematomas controlled with local pressure, as a complication of this procedure in patients with thrombocytopenia, showing no association between platelet count and bleeding complications[89-91].

Only one study reported a high rate of non-severe bleeding (32%) in patients with platelet counts below 20000/μL[91]. Similarly, another study identified a platelet count of < 30000/μL as a cut-off for hematoma formation and ooze[92]. Stecker *et al*[93] observed a prolonged time of hemostasis in cirrhotic patients with tunneled cuffed CVC at the moment of removal but did not report a relevant relationship with the platelet count.

A 2015 Cochrane review highlighted that no randomized controlled trials about the platelet count minimum threshold to safely perform a CVC insertion were available[94], with an enormous variation of the reference recommended according to the different countries considered, from 50000/μL in the United Kingdom[95] to 30000/μL and 20000/μL respectively in Belgium[96] and the United States[97], and only 10000/μL in Germany.

Presently, non-randomized studies are available concerning the safety of invasive procedures in cirrhotic patients with thrombocytopenia without prophylactic platelet transfusions[98-100]. A guideline updated by the American Association of Blood Banks based on 8 observational studies asserts that a recommendation is given if the platelet count is < 20000/μL for patients undergoing elective CVC placement, and this is also supported by the American Society of Clinical Oncology, which states that "certain procedures, such as bone marrow aspirations and biopsies, and insertion or removal of CVCs, can be performed safely at counts > 20000/μL"[101].

Table 2 Threshold of platelet count before esophageal variceal band ligation: evolution of the guidelines

Society	Year	Bleeding risk	Platelet count threshold (/μL)	Ref.
American Society for Gastrointestinal Endoscopy	2014	Not classified	"Not recommended"	ASGE Standards of Practice Committee *et al* [61]
National Institute for Health and Care Excellence	2015	Not classified	50000	National Clinical Guideline Centre (UK)[43]
American Association for the Study of Liver Diseases	2016	Not classified	"Not provided a recommendation"	Garcia-Tsao *et al*[70]
Italian Association for the Study of Liver Diseases and the Italian Society of Internal Medicine	2016	Moderate	50000 "this recommendation is supported only by biological plausibility"	Under the auspices of the Italian Association for the Study of Liver Diseases (AISF) and the Italian Society of Internal Medicine (SIMI)[42]
Austrian Society of Gastroenterology and Hepatology and the Austrian Society of Interventional Radiology	2017	Not classified	50000	Reiberger *et al*[71]
International Coagulation in Liver Disease	2017	Low	"Generally not recommended"	Intagliata *et al*[30]
American Gastroenterological Association	2019	Low	"Prophylaxis not required, although the authors recognize that risk assessment will vary in the clinical context"	O'Leary *et al*[44]
American Association for the Study of Liver Diseases	2020	Low	"Suggest individualized approaches"	Northup *et al*[47]
American College of Gastroenterology	2020	Not classified	Correction not recommended	Simonetto *et al*[45]
International Society on Thrombosis and Haemostasis	2021	Low	Do not correct	Roberts *et al*[46]
American Gastroenterological Association	2021	Low	"Suggests against the preprocedural testing"	O'Shea *et al*[48]
European Association for the Study of the Liver	2022	High	"Generally not indicated"	European Association for the Study of the Liver[49]

Dental extractions

Dental extractions are frequently performed in cirrhotic patients to remove sources of systemic infection or before they are listed for liver transplantation (LT). Cocero *et al*[102] showed in their retrospective analysis of 1183 extractions in 318 patients that the bleeding rate was 0.4% in those with platelet count > 40000/μL and INR < 2.5 and that the rate increased with both platelet count < 40000/μL and INR > 2.5. In a study of 190 visits for the extraction of 333 teeth in cirrhotic patients with platelet counts 16-216000/μL, 12 patients (6%) had hemorrhagic complications that were controlled with local measures [103]. Similarly, in 23 patients with platelet counts > 30000/μL, postoperative bleeding was observed in only 2.9% (one patient) of procedures and was treated using only local hemostatic measures without the need for transfusion[104]. Overall, the data suggest that local hemostatic techniques or intranasal desmopressin can be employed instead of platelet transfusion, which is not necessary.

Lumbar puncture

Generally, platelet goals of 50000/μL are widely recommended for many procedures[101]. Devastating neurological consequences could potentially occur in cases of bleeding within the central nervous system. For this reason, procedures such as vertebral augmentation and procedures with a risk of epidural bleeding are usually classified as associated with high bleeding risk[105].

A platelet count of 50000/μL is recommended as the threshold for lumbar puncture by the American Association of Blood Banks[97]. Moreover, it is supported by the Canadian C17 guidelines committee [106], considering platelet transfusions for diagnostic lumbar puncture for newly diagnosed pediatric patients with leukemia when platelets are < 50000/μL and a threshold for transfusion of 20000/μL for pediatric patients in a stable condition requiring lumbar puncture.

However, Chung *et al*[107] recently conducted a study of oncology patients and compared the incidence of lumbar puncture-related complications for groups above and below the minimum platelet threshold (50000/μL). The results revealed that patients with platelet count less than 50000/μL did not have a higher incidence of clinically significant postlumbar puncture complications (P = 0.29). This evidence, although the study did not specifically involve patients with CLD, underlines the low-quality evidence of the minimum preprocedural platelet threshold of 50000/μL for transfusion, adding strength to the concept that further studies are necessary to clarify this assumption.

Neurological surgery and vascular procedures

For non-neurological surgery, a count of 50000/μL is considered acceptable, but higher platelet goals (closer to 100000/μL) are recommended in patients with neurosurgical needs[105,106,108]. Similarly, a correlation between a platelet count < 100000/μL and a higher incidence of post-angiographic hematoma in patients undergoing femoral arterial puncture for a diagnostic or therapeutic vascular procedure has been demonstrated[109].

Transarterial chemoembolization

There is very little evidence in the literature regarding transarterial chemoembolization. Several guidelines from 2017 to 2022 classified this type of procedure as posing intermediate or high risks of bleeding, but no recommended correction of the platelet count before the procedure was made[30,46,47,49].

The evolution of the guidelines regarding the minimum threshold of the platelet count before transarterial chemoembolization is shown in Table 3[30,43,46,47,49]. Additionally, in this case, the scarcity of evidence available in the literature is the basis of the evident inhomogeneity of the guidelines.

Regarding radiofrequency ablation, a correlation between a platelet count < 50000/μL and an increased risk of postprocedural bleeding (OR = 8.79) was found only by Park *et al*[110], but the study was biased by prophylactic platelet transfusion in patients with platelets < 50000/μL.

SIGNIFICANT LIMITATIONS AND FUTURE PERSPECTIVES

One of the limitations in this field is that currently in the literature, there are no studies with solid data relating to the risk of bleeding and the minimum platelet threshold considered safe for performing surgery either by laparotomy or laparoscopy.

Regarding urological surgery[111,112], cholecystectomy, and herniotomy[113-117], the available evidence is not enough to assess the association between platelet count and postprocedural bleeding risk because of the wide heterogeneity in the management of blood coagulation parameters in the preprocedural phases of surgical interventions.

Similarly, in LT, the risk and extent of bleeding are difficult to quantify, and in liver surgery, none of the studies available in the literature evaluate the association between platelet count and bleeding risk [118-123]. This is probably because moderate-to-severe thrombocytopenia is often considered a contraindication to liver surgery, and patients are treated with pre- or intraoperative platelet transfusions. Regarding this topic, Maithel *et al*[124] showed that even mild thrombocytopenia (platelet count < 150000/μL) was predictive of major postoperative complications and mortality after resection of HCC independent of functional scores.

Although Chai *et al*[125] reported successful combined coronary artery bypass grafting (CABG) and LT in a patient with a baseline platelet count of 50000/μL, the minimum threshold of platelets before CABG is > 50000/μL for the safe administration of heparin intraoperatively and dual antiplatelet therapy post-CABG. However, platelet transfusion during coronary artery bypass graft surgery was demonstrated by Spiess *et al*[126] to be associated with prolonged hospital stays, longer surgeries, more bleeding, reoperation for bleeding, more red blood cell transfusions, infections, vasopressor use, respiratory medication use, stroke, and death. In this scenario, a case report by Almalki *et al*[127] described the off-label, successful use of avatrombopag in a patient with a platelet count of 18000/μL and thromboembolic risks who was a candidate for combined coronary artery bypass grafting and LT, allowing him to proceed with 2 life-saving procedures.

Other areas that need further investigation include elderly patients, for whom there are currently no data collected in the literature, and the possible use of TEG to drive platelet transfusion before scheduled procedures. In this regard, more attention should be given to the inclusion criteria of patients and controls and the definition of a clear primary end-point (namely, procedural bleeding).

CONCLUSION

Thrombocytopenia is common in patients with advanced liver disease and can adversely affect treatments, limiting the ability to administer therapy and delaying planned surgical or diagnostic procedures because of an increased risk of bleeding. A platelet count ≥ 50000/μL is a frequent target in the literature, but levels vary by provider, procedure, and specific patient[3,128,129].

As we have presented in this review, the position of the guidelines has changed over the years, moving toward abolishing the concept of a minimum safety threshold of the platelet count to perform various procedures, with the need to individually evaluate each case according to a precision medicine strategy. However, this evolution has not been supported by new studies documenting the bleeding risk of the various invasive procedures in cirrhotic patients. In our opinion, that position reflects a methodological critique by the scientific community about TPO agonist trials. All trials on avatrombopag and

Table 3 Threshold of platelet count before trans-arterial chemoembolization: Evolution of the guidelines

Society	Year	Bleeding risk	Platelet count threshold (/μL)	Ref.
National Institute for Health and Care Excellence	2015	Not classified	50000	National Clinical Guideline Centre (UK)[43]
International Coagulation in Liver Disease	2017	Intermediate	"Generally not recommended"	Intagliata *et al*[30]
American Association for the Study of Liver Diseases	2020	High	"Suggest individualized approaches"	Northup *et al*[47]
International Society on Thrombosis and Haemostasis	2021	High	Do not correct	Roberts *et al*[46]
European Association for the Study of the Liver	2022	Low	"Cannot be generally indicated"	European Association for the Study of the Liver[49]

lusutrombopag were designed using the 50000/μL platelet threshold, choosing as the primary endpoint the number of platelet transfusions avoided and using a control arm in which all patients underwent platelet transfusions, assuming it was the standard of care. The criticisms were centered on the absence of a control arm without bleeding prophylaxis (which would have allowed a true estimate of the risk) and the decision not to choose bleeding as the primary endpoint.

To overcome this situation of open controversy between hepatologists and specialists of the various disciplines who practice invasive procedures on cirrhotic patients, more good quality evidence is needed to accurately define the bleeding risk of the various invasive procedures and their relationship with the platelet count, and studies of better methodological quality need to be carried out to support such decision-making.

FOOTNOTES

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