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REVIEW

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Procedure-related bleeding risk in patients with cirrhosis and severe thrombocytopenia

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Abstract

Background: Gaps of knowledge still exist about the potential association between severe thrombocytopenia and increased risk of procedure-associated bleeding in patients with liver disease.

Methods: In this narrative review, we aimed at examining the association between procedure-related bleeding risk and platelet count in patients with cirrhosis and severe thrombocytopenia in various settings. We updated to 2020 a previously conducted literature search using MEDLINE/PubMed and EMBASE. The search string included clinical studies, adult patients with chronic liver disease and thrombocytopenia undergoing invasive procedures, any interventions and comparators, and haemorrhagic events of any severity as outcome.

Results: The literature search identified 1276 unique publications, and 15 studies met the inclusion criteria and were analysed together with those identified by the previous search. Most of the new studies included in our analysis did not assess the association between post-procedural bleeding risk and platelet count alone in patients with chronic liver disease. Furthermore, some results could have been biased by prophylactic platelet transfusions. A few studies found that severe thrombocytopenia may be predictive of bleeding following percutaneous liver biopsy, dental extractions, percutaneous ablation of liver tumours and endoscopic polypectomy.

Conclusions: Currently available literature cannot support definitive conclusions about the appropriate target platelet counts to improve the risk of bleeding in cirrhotic patients who underwent invasive procedures; moreover, it showed enormous variability in the use of prophylactic platelet transfusions.

KEYWORDS

biopsy, liver cirrhosis, platelet count, platelet transfusions, thrombocytopenia

1 | INTRODUCTION

Thrombocytopenia is a very common complication of chronic liver disease.[1] However, severity of the underlying liver disease and differences in definition criteria of low platelet count cut-off makes the prevalence of thrombocytopenia widely variable.[2,3] Available data show a prevalence of thrombocytopenia (i.e. platelet count $< 150 \times 10^9$/L) ranging from 6% to 78%, with lower percentages in non-cirrhotic patients, which become progressively greater in patients with compensated and decompensated cirrhosis.[1,4,5] Also, moderate (i.e. platelet count between 50 and 75×10^9/L) and severe ($<50 \times 10^9$/L) thrombocytopenia has been reported in 13% and 1% of patients with cirrhosis, respectively.[6]

Despite the possible coexistence of coagulopathy, mild-to-moderate thrombocytopenia (i.e. platelet count between 50 and 150×10^9/L) rarely represents a critical condition in patients without complication of liver disease (e.g. infections and renal failure). On the contrary, a platelet count $< 50 \times 10^9$/L could have a negative impact on the clinical management of patients with advanced liver disease, since it may lead to postponement or cancellation of invasive procedures and may be associated with an increased risk of procedure-associated bleeding.[6-8]

De Pietri et al[9] categorized procedures based on the associated bleeding risk: procedures were defined at high or low risk if associated with a bleeding risk > 3% (variceal band ligation, hepatic resection, abdominal surgery, endoscopic polypectomy, radio-frequency ablation, liver biopsy, biopsy of sites other than liver, abdominal drainage and endoscopic retrograde cholangiopancreatography with sphincterotomy or thoracotomy) or <3% (paracentesis, thoracentesis, central vein cannulation and transjugular intrahepatic portosystemic shunts), respectively.

Literature analysis conducted by the working group of the Position Paper of the Italian Association for the Study of Liver Diseases (AISF) and the Italian Society of Internal Medicine (SIMI)[8] found that the bleeding risk in cirrhotic patients was low (3%) following paracentesis, thoracentesis, and percutaneous or transjugular liver biopsy, and moderate (<10%) following endoscopic variceal ligation, endoscopic polypectomy and minor abdominal surgery (i.e. cholecystectomy and hernioplasty). The Position Paper concluded that, despite the limitations of the studies analysed, a platelet count $< 50\text{-}60 \times 10^9$/L may be predictive of procedure-associated bleeding.[8]

The aim of this narrative review was to update the literature search conducted by the AISF/SIMI working group and examine the association between procedure-related bleeding risk and the platelet count in patients with cirrhosis and severe thrombocytopenia in different settings.

2 | LITERATURE SEARCH

Starting from the literature search conducted by the working group of the Position Paper AISF/SIMI, which covered relevant evidence on 'Risk of bleeding following invasive procedures or surgery' until 2014,[8] we conducted a new search using MEDLINE/PubMed and EMBASE with the aim to update data from 2014 to 2020 (last accessed on 4 March 2020). The search string has been designed on the basis of the PICOS scheme and included clinical (RCT and observational) studies conducted on adult patients with chronic liver disease and thrombocytopenia undergoing invasive procedures, with any interventions and comparators, that had haemorrhagic events of any severity as outcome.

Two independent investigators conducted the literature search; the revision and the selection of the studies were performed by the working group based on title/abstract and subsequently on full text. Study screening flow diagram is reported in Figure 1.

Since in the Position Paper AISF/SIMI selection criteria were not specified, we assumed they were the same ones we applied in our literature search. Therefore, the 15 studies, which met the inclusion criteria,[9-23] were analysed together with those identified by the working group AISF/SIMI.[24-68]

3 | PROCEDURE-RELATED BLEEDING RISK IN DIFFERENT SETTINGS

Table 1 summarizes the studies included in the analysis.

3.1 | Paracentesis

In clinical practice, paracentesis is usually performed in cirrhotic patients with significant portal hypertension and thrombocytopenia. However, according to the literature, the incidence of post-paracentesis haemorrhagic events was extremely low, and since the presence of portal hypertension is associated with bleeding regardless of platelet count, it was probably related to the patient clinical condition rather than the platelet count.[10,24-28] Even in the most numerous samples with a clear evaluation of platelet count, no bleeding was recorded in paracentesis performed with platelet count $< 50 \times 10^9$/L.[10,25]

3.2 | Liver biopsy

Bleeding risk associated with percutaneous liver biopsy was about 0.6% in different studies including numerous sample

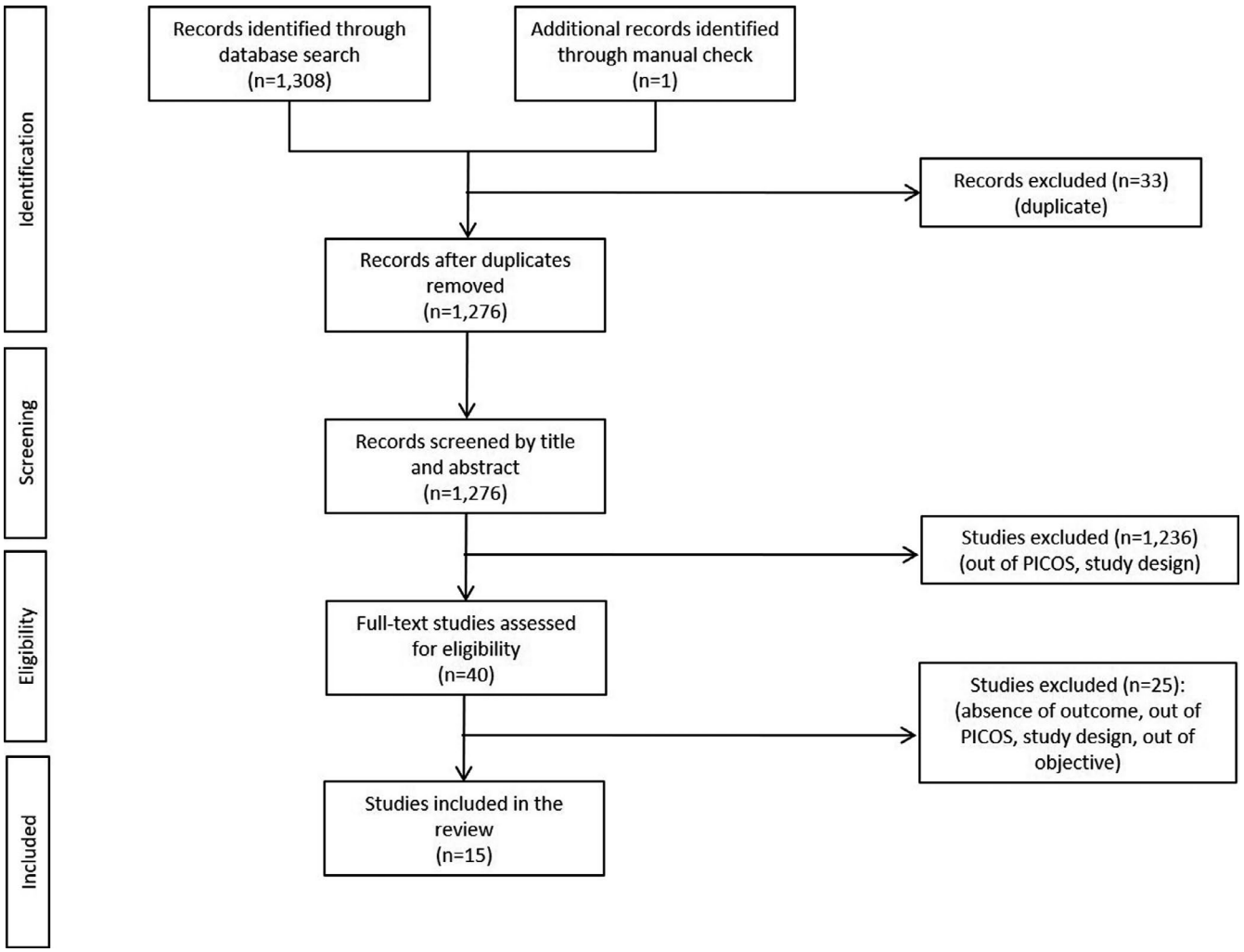

FIGURE 1 Study screening flow diagram

sizes, but also very heterogeneous populations in terms of stage of liver disease.[11,12,32,33] Due to the fact that the presence of severe thrombocytopenia proxies advanced liver disease, thus obviating the need for histological confirmation of the presence of cirrhosis, and to the perceived potential bleeding risk, in clinical practice percutaneous liver biopsy is usually performed in patients without portal hypertension and platelet count $> 50 \times 10^9$/L. The HALT-C trial[33] represented the largest sample of patients with advanced liver disease who underwent percutaneous liver biopsy. Even if the bleeding complications were rare (overall haemorrhagic rate = 0.6%), the study highlighted an increased risk of post-procedural bleeding in patients with platelet count $\leq 60 \times 10^9$/L (4/76; 5.3%) compared to patients with a platelet count $> 60 \times 10^9$/L (11/2578; 0.4%), even though in this study a platelet count $< 50 \times 10^9$/L was an exclusion criterion.

Transjugular liver biopsy is a procedure related to the operator expertise and in clinical practice is usually performed in patients with advanced liver disease, portal hypertension and thrombocytopenia. In spite of this, bleeding rate from studies was <2% and was mainly represented by the occurrence of haematoma at the site of insertion.[34-37] None of the studies evaluated the association between platelet count and post-procedural bleeding rate.

3.3 | Dentistry

Most of the evidence on this topic is provided by retrospective studies in which bleeding risk seemed to be inherently related to the procedure, or the number of teeth extraction, rather than to platelet count.[14,38,39] Furthermore, the study of Ward et al[38] was severely biased by massive transfusions before the procedure, thus making unfeasible any interpretation of the results in regard to the potential association between bleeding and severe thrombocytopenia. An association between platelet count and post-procedural bleeding was found in the study of Cocero et al,[13] in which the haemorrhagic rate was 0.4% for patients with platelet count $> 40 \times 10^9$/L and

TABLE 1 Summary of the studies included in the analysis

Author, year	Study design	Procedures/ patients (n.)	PLT count or PLT cut-off	Findings
Paracentesis				
Webster et al, 1996[24]	Retrospective	179 outpatients	Not specified	4 haemorrhagic complications in patients with PLT > 80×10^9/L
Grabau et al, 2004[25]	Retrospective	1100 in 628 pts	PLT < 50×10^9/L in 55.64% of procedures	No bleedings in procedures performed with PLT < 50×10^9/L
Pache et al, 2005[26]	Retrospective	4729 paracenteses	Not specified	Severe haemorrhagic complications (6 haemoperitoneum, 3 abdominal wall haematoma) in 0.2% of procedures without association with PLT count
Lin et al, 2005[27]	Prospective observational	410 in 163 pts	PLT < 50×10^9/L in 13% of procedures	Minor bleeding rate (1 local ecchymosis, 1 cutaneous bleeding) in 0.5% of procedures in patients with PLT = 50-100 $\times 10^9$/L
De Gottardi et al, 2009[28]	Prospective observational	515 in 171 pts	PLT < 50×10^9/L in 10% and PLT < 100×10^9/L in 40% of pts	Association between PLT < 50×10^9/L and increased risk of overall complications (P =.07). Association with bleeding risk not reported
Rowley et al, 2019[10]	Retrospective	3116 in 123 pts	PLT < 50×10^9/L in 12% of pts	Overall bleeding rate: 0.2%. No bleeding with PLT < 50×10^9/L
Liver biopsy				
Piccinino et al, 1986[29]	Retrospective	68 276 percutaneous biopsies	PLT > 50×10^9/L in all biopsies	Overall rate of major haemorrhagic events: 0.06%. Association between bleeding and PLT not evaluated
Caturelli et al, 1996[30]	Retrospective	NR (only abstract available)	Not specified	Overall rate of haemorrhagic complications: 0.13%. Association between bleeding and PLT not evaluated
Actis et al, 2007[31]	Retrospective	835 pts	Not specified	Overall rate of major haemorrhagic events: 0.12%. Association between bleeding and PLT not evaluated
West et al, 2010[32]	Retrospective	61 187 pts	Not specified	Overall rate of major haemorrhagic events: 0.65%. Association between bleeding and PLT not evaluated
Seeff et al, 2010[33]	Retrospective	2740 percutaneous biopsies	Pts with PLT < 50×10^9/L were excluded	Overall haemorrhagic rate: 0.6%. Pts with PLT = 50-60 $\times 10^9$/L was significantly higher than pts with PLT > 60×10^9/L (5.3% vs 0.4%).
Kalambokis et al, 2007[34]	Review	7649 transjugular biopsies in 7189 pts	Cut-off 60×10^9/L	Haemorrhagic rate < 2% (minor bleeding). No association with PLT count
Alessandria et al, 2008[35]	Retrospective	306 transjugular biopsies	Not specified	No major complications. No association between bleeding rate and PLT count
Mammen et al, 2008[36]	Retrospective	601 transjugular biopsies	PLT < 60×10^9/L in 20.3% of pts	Haemorrhagic rate = 0.9%. No association with PLT count
Procopet et al, 2012[37]	Prospective	75 transjugular biopsies	Not specified	Haemorrhagic rate = 1.3%. No association with PLT count
Takyar et al, 2017[11]	Retrospective	3357 percutaneous biopsies	Cut-off 100×10^9/L	Haemorrhagic rate: 0.69% (fatal in 0.09%). PLT < 100×10^9/L was an independent risk factors for post-biopsy bleeding, but % pts with PLT < 60×10^9/L were not different between groups

(Continues)

TABLE 1 (Continued)

Author, year	Study design	Procedures/ patients (n.)	PLT count or PLT cut-off	Findings
Potretzke et al, 2018[12]	Retrospective	1876 percutaneous biopsies in 1732 pts	Cut-off 70 × 10^9/L	Haemorrhagic rate = 0.69%. No association with PLT count
Dentistry				
Ward et al, 2006[38]	Retrospective	35 procedures in 30 pts	Cut-off 35-50 × 10^9/L (depending on the risk group)	No association between PLT count and prolonged postoperative bleeding
Perdigao et al, 2012[39]	Prospective observational	35 procedures in 23 pts	PLT < 50 × 10^9/L in 34% of pts	1 postoperative bleeding (2.9%) in pts with PLT = 50 × 10^9/L. No haemorrhagic complication during procedures (n = 12) with PLT = 30-49 × 10^9/L
Cocero et al, 2017[13]	Retrospective	1,183 extractions in 381 pts	Cut-off PLT ≤ 40 × 10^9/L	Haemorrhagic rate: 0.4% in pts with PLT > 40x10^9/L and INR < 2.5; 5.88% in pts with PLT ≤ 40 × 10^9/L
Medina et al, 2018[14]	Retrospective	190 extractions	PLT < 150 × 10^9/L in 96.3% of pts	Overall haemorrhagic rate: 6.3%. Intra-operative bleeding was associated with low count of platelets. However, this counting could explain only 16% of the cases of bleeding.
Endoscopic variceal ligation				
Vieira da Rocha et al, 2009[40]	Prospective observational	150 pts	PLT < 50 × 10^9/L in 12% of pts	Severe post-procedural ulcer bleeding in 7.33% of pts. Risk of bleeding was not associated with PLT count.
Vanbiervliet et al, 2010[41]	Retrospective	837 ligations in 605 pts	Not specified	Post-procedural bleeding rate: 2.75%. No association between PLT count and bleeding but high platelet ratio index was an independent predictive factor of bleeding
Endoscopic polypectomy				
Jeon et al, 2012[42]	Retrospective	66 in 30 pts	Not specified	Post-procedural bleeding in 3% of procedures. No association between bleeding and PLT count
Lee et al, 2014[43]	Retrospective	89 pts w/ liver cirrhosis + 348 w/o liver disease	Not specified	Post-procedural bleeding in 14.61% of pts. Association between bleeding and PLT not evaluated
Soh et al, 2020[15]	Retrospective	1267 patients	Cut-off 50 × 10^9/L	Haemorrhagic rate (immediate + delayed): 7.5%. PLT < 50 × 10^9/L significantly associated with immediate post-procedural bleeding (rate: 27.5%; OR = 6.6)
Percutaneous ablation				
Cammà et al, 2005[44]	Retrospective	202 pts	≥40 × 10^9/L in all pts	Haemorrhagic rate: 0.50%. Association between bleeding and PLT not evaluated
Livraghi et al, 2008[45]	Retrospective	218 pts	≥40 × 10^9/L in all pts	Haemorrhagic rate: 0.92%. Association between bleeding and PLT not evaluated

(Continues)

TABLE 1 (Continued)

Author, year	Study design	Procedures/ patients (n.)	PLT count or PLT cut-off	Findings
Goto et al, 2010[46]	Retrospective	4133 in 2154 pts	Mean PLT count = 125 ± 33 × 10^9/L (50-669)	Haemorrhagic complications rate: 1.5%. Low PLT count was a significant risk factor for haemoperitoneum (PLT ≥ 50 × 10^9/L was an inclusion criteria)
Park et al, 2017[16]	Retrospective	1843 in 1211 patients	Mean PLT count = 140 ± 85 × 10^9/L	Post-procedural bleeding rate was 0.6%, and the risk was significantly greater in patients with PLT < 50 × 10^9/L (OR = 8.79)
Liver transplantation				
McCluskey et al, 2006[47]	Retrospective	460 pts	Not specified	Incidence of massive blood transfusion: 42%. PLT < 70 × 10^9/L was an independent predictor of massive blood transfusion (+32% vs PLT > 70 × 10^9/L)
Massicotte et al, 2008[48]	Prospective + retrospective	200 pts	<50 × 10^9/L in 18% of pts; <30 × 10^9/L in 4% of pts	No association between PLT count and transfusion rate
Massicotte et al, 2012[49]	Retrospective	503 pts	Not specified	No significant association between PLT count and blood loss
Esmat Gamil et al, 2012[50]	Prospective observational	286 pts	Not specified	No significant association between PLT count and blood loss
Li et al, 2014[17]	Retrospective	241 pts	Not specified	Postoperative bleeding in 4.98% of pts. No significant association between PLT count and bleeding risk
Akamatsu et al, 2015[18]	Retrospective	403 pts	Mean PLT count 86 ± 70 × 10^9/L	Haemorrhagic episodes in 8.68% of pts. No significant association between PLT count and blood loss
Eghbal et al, 2019[19]	Retrospective	754 pts	Not specified	PLT count was inversely correlated with total bleeding
Liver surgery				
Wei et al, 2003[51]	Retrospective	155 pts	Median PLT count 205 × 10^9/L (82-473)	Postoperative intra-abdominal haemorrhage in 5% of patients. Association between bleeding and PLT not evaluated
Kubo et al, 2007[52]	Retrospective	100 pts	Not specified	Postoperative bleeding in 4% of patients. Association between bleeding and PLT not evaluated
Palavecino et al, 2009[53]	Retrospective	1557 resections in 1477 pts	Median PLT count 232 × 10^9/L (64.0-775.0)	PLT < 100 × 10^9/L (1% of pts) was an independent risk factors for blood transfusion (OR = 8.8)
Hsu et al, 2009[54]	Retrospective	1027 resections	Not specified	PLT < 100 × 10^9/L was correlated with perioperative mortality in the univariate analysis but not in the multivariate one
Cockbain et al, 2010[55]	Retrospective	589 pts	Cut-off 150 × 10^9/L	No association between PLT > 150 × 10^9/L and lower transfusion rate
Yang et al, 2011[56]	Retrospective	305	Not specified	Haemorrhagic complications in 2.62% of pts. PLT count < 100 × 10^9/L was independently correlated with postoperative morbidity and hospital mortality

(Continues)

TABLE 1 (Continued)

Author, year	Study design	Procedures/ patients (n.)	PLT count or PLT cut-off	Findings
Vascular catheter insertion				
Fisher et al, 1999[57]	Retrospective	658 cannulations in 283 pts	PLT < 50×10^9/L in ~ 25% pts	1 haemothorax in pts with PLT = 68×10^9/L. PLT ≤ 10×10^9/L significantly associated with superficial haematoma vs PLT > 50×10^9/L (4,8% vs. 1,6%, respectively)
Estcourt et al, 2015[20]	Systematic review	-	Not specified	No evidence from RCTs to determine whether PLT transfusions are required prior to central line insertion in patients with thrombocytopenia, and, if a PLT transfusion is required, what is the correct threshold.
HVPG measurement				
Bosch et al 2009[58]	Review + single-centre experience	12 000 measurement	Not reported	Major complications have been limited to local injury at the puncture site and include leakage, haematoma and rarely fistulae or Horner syndrome
Woolfson et al, 2013[59]	Retrospective	52 HVPG measurements in 49 children	PLT < 100×10^9/L in 28 pts	Variceal bleeding and variceal bleeding + ascites occurred each in 1/7 patients with cirrhosis. Association between bleeding and PLT not evaluated
Cholecystectomy				
Sleeman et al, 1998[60]	Retrospective	25 pts	PLT < 100×10^9/L in 36%	Association between bleeding and PLT not evaluated
Da Silveira et al 2006[61]	Retrospective	99 pts	Not reported	Association between bleeding and PLT not evaluated
Delis et al, 2010[62]	Retrospective	220 procedures	Transfusion when PLT < 50×10^9/L	Intra-operative bleeding rate: 8%. Association between bleeding and PLT not evaluated
Herniotomy				
Carbonell et al, 2005[63]	Retrospective	32 033 procedures	Not reported	Association between bleeding and PLT not evaluated.
Ammar et al, 2010[64]	Prospective	80 pts	Not reported	Association between bleeding and PLT not evaluated
Thoracentesis				
Castellote et al, 2001[65]	Retrospective	245 thoracentesis in 69 cirrhotic pts	Not reported	Haemorrhagic rate: 2%. Association between bleeding and PLT not evaluated
Xiol et al, 2001[66]	Retrospective	215 thoracenteses in 60 cirrhotic pts	Not reported	Association between bleeding and PLT not evaluated
Urological surgery				
Nielsen et al, 2001[67]	Retrospective	180 pts	Not reported	Association between bleeding and PLT not evaluated
Lund et al, 2003[68]	Retrospective	611	Not reported	Association between bleeding and PLT not evaluated

(Continues)

TABLE 1 (Continued)

Author, year	Study design	Procedures/ patients (n.)	PLT count or PLT cut-off	Findings
Miscellaneous				
Shah et al, 2015[21]	Prospective observational	380 pts	Cut-off 50×10^9/L	Clinically significant bleeding following high-risk procedures occurred in 3 patients with significant coagulopathy and 0 patients without significant coagulopathy (P =.061)
De Pietri et al, 2016[9]	RCT open-label ITT	60 pts	Cut-off 50×10^9/L	Bleeding occurred in 1.7% of patients (1/60) following paracentesis (PLT = 111×10^9/L)
Napolitano et al, 2017[22]	Prospective observational	852 procedures in 363 pts	Cut-off 50×10^9/L	Overall bleeding complication rate: 2.75%. No bleeding in 90 procedures with PLT count < 50×10^9 L and no association were identified between PLT count and bleeding risk
Vuyyuru et al, 2020[23]	RCT open-label	60 pts	Cut-off 50×10^9/L	No bleeding in 58 procedures with PLT count < 50×10^9 L

Abbreviations: HVPG, hepatic venous pressure gradient; INR, international normalized ratio; OR, odds ratio; PLT, platelet; pts, patients.

international normalized ratio (INR) <2.5, and 5.88% in patients with platelet count ≤ 40×10^9/L. Finally, in the only prospective study[39] postoperative bleeding occurred in only one procedure (2.9%) performed in a patient with liver cirrhosis, INR = 2.50 and platelet count = 50×10^9/L, whereas no bleeding occurred in procedures performed in patients with platelets = 30-49 $\times 10^9$/L.

3.4 | Endoscopic variceal ligation

In the two studies analysed, the post-procedural bleeding rate ranged from 2.75% in the case-control study of Vanbiervliet et al,[41] to 7.33% in the prospective study of Viera da Rocha et al[40] In both cases, there was no association between bleeding risk and platelet count. In general, post-ligation bleeding was related to technical problem occurred during the procedure, late bleeding or portal hypertension.

3.5 | Endoscopic polypectomy

All the studies identified were retrospective and potentially biased by the heterogeneity of the investigated population including both cirrhotic and noncirrhotic patients.[15,42,43] Only the study by Soh et al[15] identified a correlation between post-procedural bleeding and platelet count: while the overall haemorrhagic rate was 7.5%, in patients with platelets <50×10^9/L, the immediate post-procedural bleeding rate was 27.5% with a relative risk of about 6.

3.6 | Percutaneous radio-frequency ablation of hepatocellular carcinoma

In clinical practice, percutaneous radio-frequency ablation of hepatocellular carcinoma (HCC) is rarely performed in patients with platelets <50×10^9/L and is usually preceded by platelet transfusions and a close monitoring of platelet count. Therefore, the rate of bleeding following the radio-frequency ablation of HCC was lower than 1.[16,44,45] Only the study of Park et al[16] found a correlation between a platelet count < 50×10^9/L and an increased risk of post-procedural bleeding rate (OR = 8.79). However, the study was biased by prophylactic platelet transfusion in patients with platelets <50×10^9/L. Finally, the study of Goto et al[46] showed a haemorrhagic complication rate of 1.5% in 4133 radio-frequency ablations (not only HCC), and thrombocytopenia was identified as significant risk factor for hemoperitoneum, even though patients with severe thrombocytopenia (platelets <50×10^9/L) were not included in the study.

3.7 | Liver transplantation

The risk and extent of bleeding during liver transplantation were difficult to quantify and were generally reported only as indirect evidence (i.e. number of transfused blood products or amount of blood loss). None of the studies showed an association between platelet count and intra- or post-transplantation bleeding.[17-19,47-50] Indeed, in this setting, the bleeding risk cannot be evaluated on the basis of blood

coagulation parameters, since it may be influenced by other recipient's conditions, technical difficulties and portal hypertension control. Besides improvements in surgical experience and techniques in liver transplantation, strategies to reduce the use of blood products termed 'patient blood management' are increasingly adopted. For monitoring of haemostasis disturbances, thromboelastography (TEG) or thromboelastometry (TEM) is indicated as the best blood tests that can guide the application of plasma components, platelets and antifibrinolytics.[69]

3.8 | Liver surgery

In liver surgery, portal hypertension is the main determinant of outcome; in a large series published in 2011, even mild thrombocytopenia (platelet count of less than 150×10^9/L) predicted major postoperative complications and mortality after resection of HCC independently of functional scores such as Child-Pugh or MELD score.[70]

However, in this setting, bleeding rate and risk factors were very difficult to identify due to heterogeneous populations (i.e. inclusion of cirrhotic and noncirrhotic patients). All the studies were retrospective, and none evaluated the association between platelet count and bleeding risk in liver surgery.[51-56] This was probably due to the fact that in clinical practice moderate-to-severe thrombocytopenia is often considered a contraindication to liver surgery and patients are treated with pre- or intra-operative platelet transfusions.

3.9 | Abdominal surgery and other invasive procedures

The vascular catheter insertion and the hepatic venous pressure gradient measurement are procedures related to the operator expertise and are usually performed in patients at high risk of bleeding due to advanced liver disease, portal hypertension and thrombocytopenia. However, the available studies were not sufficient to determine a relationship between platelet count and bleeding risk following these two procedures.[20,57-59]

Regarding cholecystectomy and herniotomy, the wide heterogeneity in the management of blood coagulation parameters in the pre-procedural phases made the relationship between thrombocytopenia and haemorrhagic risk not evaluable. Furthermore, the available studies did not evaluate this association.[60-64] Finally, also the available evidence related to thoracentesis[65,66] and urological surgery[67,68] was not sufficient to assess the association between platelet count and post-procedural bleeding risk.

3.10 | Miscellaneous

Some studies evaluated the overall risk of bleeding in cirrhotic patients submitted to different procedures and the association with platelet count and/or coagulopathy.[9,13,15,23] In the open-label, intention-to-treat trial of De Pietri et al[9] cirrhosis and significant coagulopathy (defined as INR > 1.8 and/or platelet count $< 50 \times 10^9$/L) did not expose to an increased procedure-related bleeding risk, regardless of the procedure (i.e. high- or low-risk procedures), although the cohort included was small (i.e. 30 patients per arm) and all patients with severe thrombocytopenia in the standard of care arm received prophylactic platelet transfusions.

Similarly, the prospective case series of Napolitano et al[15] did not identify any association between platelet count and post-procedural bleeding risk, not even in patients with a platelet count $< 50 \times 10^9$/L. In this case, the only parameter associated with the risk of bleeding was the number of invasive procedures sequentially performed in each single patient: 3 events following 598 single procedures (bleeding rate: 0.5%) and 7 events following multiple procedures (1.5%).[15]

Also, in the randomized controlled trial of Vuyyuru et al[23] no bleeding complications occurred following 58 procedures in cirrhotic patients with platelet count $< 50 \times 10^9$/L, whereas in the prospective multicentre study of Shah et al,[13] in which none of the patients received peri-procedural correction of abnormal coagulation parameters, the occurrence of clinically significant bleeding following high-risk procedures (i.e. cholecystectomy, splenectomy, chemoembolization, central vein cannulation, percutaneous liver biopsy and endoscopic polypectomy) tended to be greater in patients with significant coagulopathy (defined as INR $\geq$ 1.5 and/or platelet count $\leq 50 \times 10^9$/L) as compared to patients without significant coagulopathy (3 vs 0, $P = .061$), although it was not possible to single out the role played by thrombocytopenia alone on the bleeding risk in this study.

4 | INTERPRETATION OF THE RESULTS AND POTENTIAL CLINICAL IMPLICATIONS

Despite the lack of solid evidence identified in the previous consensus conference and the call for prospective studies to address the issue of procedure-related bleeding risk in patients with liver disease, even most of the new studies included in our analysis had the limitation of not adequately assessing the association between post-procedural bleeding risk and platelet count in patients with chronic liver disease. We also found other limitations of the available literature. The first is that the majority of studies that investigated the role of platelet count were retrospective and heterogeneous in terms

of population (i.e. inclusion of cirrhotic and noncirrhotic patients). Also, it is important to note that in clinical practice moderate-to-severe thrombocytopenia is often considered a contraindication to some procedures (e.g. percutaneous radio-frequency ablation of HCC, liver biopsy and liver surgery) and that patients are frequently treated with plasma and pre- or intra-operative platelet transfusion in order to mitigate the risk of bleeding.[8,71-74] Therefore, it could be possible that some results were biased by these prophylactic interventions.

Only a few studies, among those who assessed the risk of bleeding in relation to platelet count, found that thrombocytopenia may be predictive of bleeding following percutaneous liver biopsy,[11,33] dental extractions,[13,14] percutaneous ablation of liver tumours[16,46] and endoscopic polypectomy.[15] Noteworthy, none of the prospective studies included in this review highlighted a significant correlation between post-procedural haemorrhagic rate and platelet count.[9,21-23]

Despite the above limitations, that would require the conduction of prospective studies properly designed to evaluate the bleeding risk in patients with chronic liver disease undergoing invasive procedures, according to platelet count, the available literature highlighted that severe thrombocytopenia is one of the most frequent issues to exclude cirrhotic patients to invasive procedures, which could be, in some cases, life-saving, such as percutaneous radio-frequency ablation in malignant lesions. However, available evidence had also the strength to confirm that there is no platelet count threshold at which bleeding is predictable, as other factors contribute to bleeding risk.

Indeed, it has been shown that in patients with chronic liver disease, even at an advanced stage, platelet count alone cannot be considered the only predictor of increased risk of bleeding,[75,76] while platelet count should be properly considered in the presence of other risk factors such as sepsis and acute kidney injury, in order to provide a more accurate estimate of the bleeding risk of the patients.[21,77]

In addition, in cirrhotic patients the aetiology and severity of the disease can influence the haemostatic balance and comorbidities could alter the feeble haemostatic equilibrium in patients with advanced liver disease.[8,77]

Despite the limited evidence available, several Position Papers and Guidelines of Scientific Societies recommend the correction of thrombocytopenia in patients with chronic liver disease and platelet count $< 50 \times 10^9$/L who are scheduled to undergo invasive procedures.[8,71-74] In these patients, although there is no solid evidence of its efficacy on raising and maintaining an adequate platelet count level,[22,78] the standard of care is platelet transfusion. On the contrary, in patients with advanced liver disease there is evidence that prophylactic blood products transfusions, and the resultant volume expansion in a short timeframe, may aggravate portal hypertension and therefore paradoxically determine an increase in bleeding risk.[79] In this context, in cirrhotic patients with high risk of bleeding, thrombopoietin receptor agonists (TPO-RAs) may represent an advantageous therapeutic alternative.[80-82] TPO-RAs may improve patient clinical management as they are able to increase patient's platelet counts in a predictable fashion, thus allowing to plan invasive procedures and avoiding

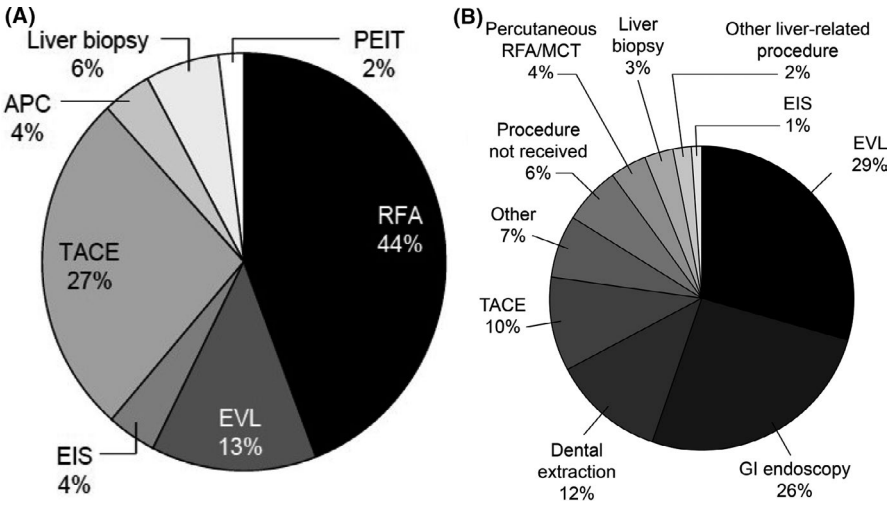

FIGURE 2 Invasive procedures performed in the lusutrombopag group during the (A) L-PLUS 1 and (B) L-PLUS 2 studies. APC = argon plasma coagulation; EIS = endoscopic injection sclerosis; EVL = endoscopic variceal ligation; GI = gastrointestinal; MCT = microwave coagulation therapy; PEIT = percutaneous ethanol injection therapy; RFA = radio-frequency ablation; TACE = transcatheter arterial chemoembolization. (A) From: Hidaka H et al. Lusutrombopag Reduces Need for Platelet Transfusion in Patients With Thrombocytopenia Undergoing Invasive Procedures. Clin Gastroenterol Hepatol. 2019;17(6):1192-1200 (B) Elaborated from: Peck-Radosavljevic et al Lusutrombopag for the Treatment of Thrombocytopenia in Patients With Chronic Liver Disease Undergoing Invasive Procedures (L-PLUS 2). Hepatology. 2019;70(4):1336-1348

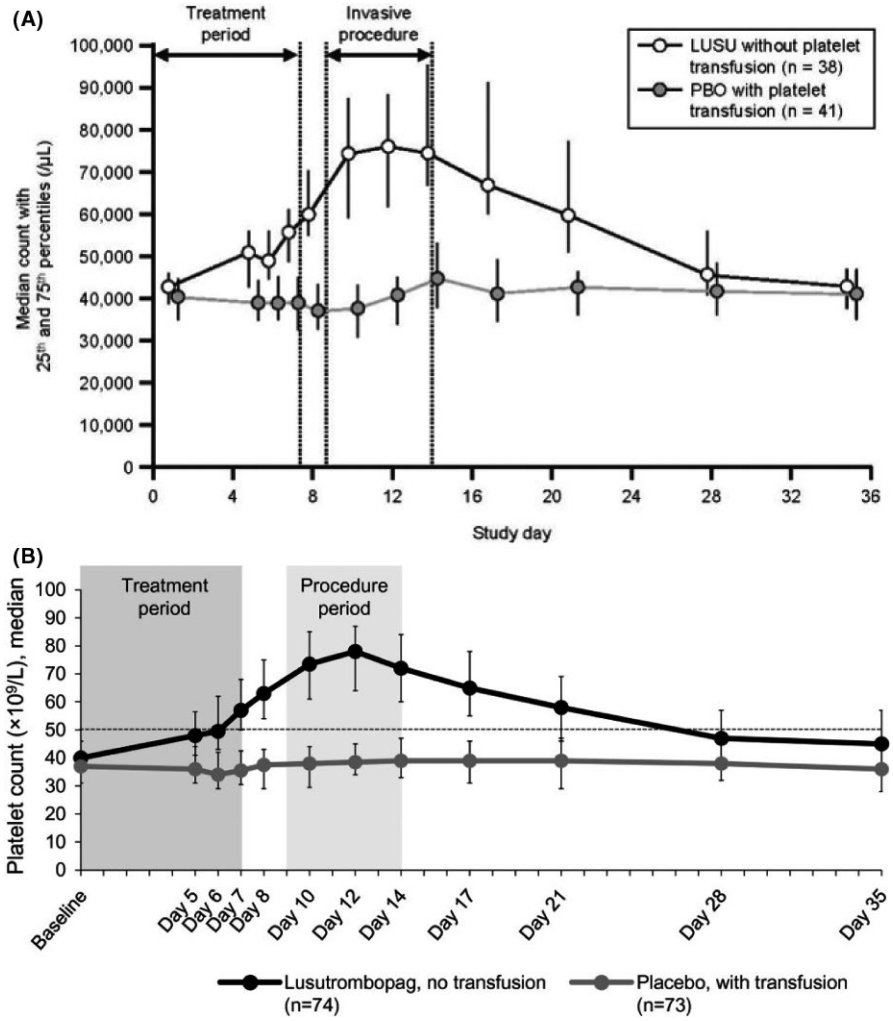

FIGURE 3 Median PCs over time for patients treated with lusutrombopag (without platelet transfusion) or placebo (with platelet transfusion) in the (A) PLUS-1 and (B) PLUS-2 studies. From: (A) Hidaka H et al's Lusutrombopag Reduces Need for Platelet Transfusion in Patients With Thrombocytopenia Undergoing Invasive Procedures. Clin Gastroenterol Hepatol. 2019;17(6):1192-1200 (B) Peck-Radosavljevic et al Lusutrombopag for the Treatment of Thrombocytopenia in Patients With Chronic Liver Disease Undergoing Invasive Procedures (L-PLUS 2). Hepatology. 2019;70(4):1336-1348

the risk of postponement or cancellation of procedures due to an inadequate increase in platelet count, as is often observed with platelet transfusions.[80-82] However, the use of TPO-RAs has been associated with venous thromboembolism in patients with chronic liver disease, probably because of too high a rise in the platelet count and platelet hyperactivity in liver cirrhosis patients.[75] More in detail, as reported by Loffredo et al,[83] a statistically significant association between thrombotic risk and TPO-RAs use was observed only in patients treated with eltrombopag.

Therefore, after the early termination of the clinical trial of eltrombopag, due to the increased thrombotic risk,[84] lusutrombopag was the first oral drug approved by EMA for the treatment of severe thrombocytopenia in patients with chronic liver disease undergoing invasive procedures.[85] Lusutrombopag showed efficacy in reducing the need for platelet transfusion, raising the platelet count $> 50 \times 10^9$/L at the time of procedures and maintaining an adequate platelet level following the procedures, thus granting a safe lingering effect that may theoretically protect from delayed bleeding or allow to perform repeated invasive procedures.[80,81] In the pivotal studies L-PLUS 1 and L-PLUS 2, in fact, lusutrombopag allowed to reach the platelet threshold of 50×10^9/L in about 9 days, to maintain it for a median of 20.9 days, and safely performed invasive procedures (Figures 2 and 3).[80,81]

Furthermore, the aggregated data showed that the use of lusutrombopag was associated with a numerical lower rate of post-procedural bleeding (6.7% vs 10.6%) without increased risk of thrombosis.[80,81,85] Platelet increase with lusutrombopag was in fact more moderate than with other TPO-RAs (median highest platelet count eltrombopag vs lusutrombopag: 140×10^9/L vs 80×10^9/L).[80,84]

In the ADAPT-1 and ADAPT-2, pivotal studies on avatrombopag patients with low ($<40 \times 10^9$/L) and high ($40\text{-}50 \times 10^9$/L) baseline platelet count received avatrombopag 40 and 60 mg, respectively.[82] In both cohorts, the proportion of patients who did not require a platelet transfusion after randomization and up to 7 days after the procedure was higher in those who received avatrombopag, compared with placebo. Moreover, in both avatrombopag treatment groups, platelet count increase was observed from day 4, reaching a maximum at days 10-13. The mean platelet count remained at or above 50×10^9/L at day 17, and only 3 patients reach platelet count $> 200 \times 10^9$/L.[82]

5 | CONCLUSIONS AND FUTURE DIRECTIONS

Despite several studies were conducted in the past, there is still a lack of adequate and solid data depicting the risk of bleeding following invasive procedures in patients with advanced liver disease, and its potential association with decreased platelet count. This notwithstanding, the best evidence currently available points to an association between severe thrombocytopenia and an increased risk of bleeding in patients with advanced cirrhosis undergoing procedures, in particular in subjects who undergo 'closed procedures' such as biopsies of parenchymal organs or liver tumour ablations. In this regard, international guidelines suggest that severe thrombocytopenia should be corrected before procedures in these patients, nevertheless, due to the lack of literature to support definitive conclusions about the appropriate target platelet counts to improve the risk of bleeding, there is an enormous variability in the use of prophylactic platelet transfusions.[86] It is, however, well established that the prophylactic use of platelet transfusions for these patients is of unpredictable efficacy and biased by potential adverse events including transfusion reactions, sepsis, refractoriness to further platelet transfusions, prolonged hospitalization and increased costs. Specifically, refractoriness to further platelet transfusions may add complexity to the management of these patients and reduce treatment options for bleeding associated with invasive procedures and/or surgery including liver transplant.

For all the above, research for therapeutic options alternative to platelet transfusion is welcome and TPO-RAs seem to represent a valid option given the safety and efficacy, simplifying the clinical management of these patients. It is important to underline that, unlike platelet transfusion, the use of TPO-RAs represents the only strategy capable of obtaining a real significant increase in the platelet count. Furthermore, the use of TPO-RAs may be associated with the improvement in global healthcare resource utilisation, as blood product transfusions—and in particular platelets—are quite often used in clinical practice to increase platelets in patients undergoing procedures, and therefore, in this setting a treatment alternative may increase platelet availability for other clinical purposes.[86,87]

In this context, still to be detailed is for which invasive procedure TPO-RA prescription can be allocated and if some liver-related disease complication may question the therapeutic efficacy. Despite a clear indication of the use of platelet growth factor in cirrhotic patients undergoing procedures at particular risk of bleeding, a valid therapeutic address to be considered is in liver transplant candidates, although in advanced stage of Child-Pugh score the safety of TPO-RAs has not yet been assessed. Routine procedures such as dental extraction, endoscopic polypectomy, ligation of oesophageal varices, transjugular intrahepatic portosystemic shunt (TIPS) and HCC transarterial chemoembolization (TACE) could benefit from a single period of drug therapy with the maximum result in terms of lower flow overload (compared with platelet transfusion), fewer days of hospitalization (due to ineffective increase platelet with transfusions) and lower risk of bleeding due to the achievement of a more adequate level of platelets in the plasma by using platelet growth factors.

In the next future, well-designed studies may disclose whether the use of TPO-RAs may actually be associated with a decreased risk of bleeding following procedures in patients with liver disease as compared to platelet transfusions, although planning such studies may represent a difficult task due to the variability of clinical situations, the vast array of potential procedures and their different risk of bleeding, and the overall low risk of bleeding that should call for the enrolment of very large cohorts of patients. Furthermore, real-life data could add important information on the effectiveness and safety of TPO-RAs in the management of invasive procedures in cirrhotic patients at high risk of bleeding, thus providing the basis of a potential new standard of care.

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AUTHOR CONTRIBUTIONS

The review topic was proposed by all authors. Literature selection and analysis of data were undertaken by all authors. Critical revisions of the manuscript were conducted by all authors. Final approval for the version to be published was obtained from all authors. All authors read and approved the final manuscript.

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