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

Domenico Alvaro1 | Nicola Caporaso2 | Edoardo Giovanni Giannini3 | Angelo Iacobellis4 | Mariacristina Morelli5 | Pierluigi Toniutto6 | Francesco Violi7 | The PReBRiC (Procedure-Related Bleeding Risk in Cirrhosis) group

1Department of Translational and Precision Medicine, Sapienza University of Rome, Rome, Italy
2Department of Clinical Medicine and Surgery, University of Naples 'Federico II', Naples, Italy
3Gastroenterology Unit, Department of Internal Medicine, University of Genoa, IRCCS-Ospedale Policlinico San Martino, Genoa, Italy
4Division of Gastroenterology, Fondazione IRCCS Casa Sollievo della Sofferenza, Foggia, Italy
5IRCCS Azienda Ospedaliero-Universitaria di Bologna, Bologna, Italy
6Hepatology and Liver Transplantation Unit, Azienda Sanitaria Universitaria Integrata, Academic Hospital, Udine, Italy
7I Clinica Medica, Sapienza University of Rome, Rome, Italy

Correspondence
Edoardo Giovanni Giannini, Gastroenterology Unit, Department of Internal Medicine, University of Genoa, IRCCS-Ospedale Policlinico San Martino, Viale Benedetto XV, no. 6 – 16132, Genoa, Italy.
Email: egiannini@unige.it

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Shionogi srl

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
INTRODUCTION

Thrombocytopenia is a very common complication of chronic liver disease. 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. Available data show a prevalence of thrombocytopenia (i.e. platelet count < 150 × 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. Also, moderate (i.e. platelet count between 50 and 75 × 10^9/L) and severe (<50 × 10^9/L) thrombocytopenia has been reported in 13% and 1% of patients with cirrhosis, respectively.

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 × 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.

De Pietri et al 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.

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

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, 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, were analysed together with those identified by the working group AISF/SIMI.

PROCEDURE-RELATED BLEEDING RISK IN DIFFERENT SETTINGS

Table 1 summarizes the studies included in the analysis.

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. Even in the most numerous samples with a clear evaluation of platelet count, no bleeding was recorded in paracentesis performed with platelet count < 50 × 10^9/L.

Liver biopsy

Bleeding risk associated with percutaneous liver biopsy was about 0.6% in different studies including numerous sample
sizes, but also very heterogeneous populations in terms of stage of liver disease.\textsuperscript{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\textsuperscript{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.\textsuperscript{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.\textsuperscript{14,38,39} Furthermore, the study of Ward et al.\textsuperscript{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.,\textsuperscript{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   | Retrospective      | 179 outpatients          | Not specified            | 4 haemorrhagic complications in patients with PLT > 80 × 10^9/L                                                                         |
| Grabau et al, 2004    | 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     | 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       | Prospective        | 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 × 10^9/L |
| De Gottardi et al, 2009 | Prospective        | 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    | 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 | 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 | 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     | Retrospective      | 835 pts                  | Not specified            | Overall rate of major haemorrhagic events: 0.12%. Association between bleeding and PLT not evaluated                                        |
| West et al, 2010      | 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     | Retrospective      | 2740 percutaneous biopsies | Pts with PLT < 50 × 10^9/L were excluded | Overall haemorrhagic rate: 0.6%. Pts with PLT = 30-60 × 10^9/L was significantly higher than pts with PLT > 60 × 10^9/L (5.3% vs 0.4%). |
| Kalambokis et al, 2007 | 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 | Retrospective    | 306 transjugular biopsies | Not specified            | No major complications. No association between bleeding rate and PLT count                                                               |
| Mammen et al, 2008    | 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  | Prospective        | 75 transjugular biopsies | Not specified            | Haemorrhagic rate = 1.3%. No association with PLT count                                                                                |
| Takyar et al, 2017    | 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)
| Author, year              | Study design         | Procedures/patients (n.) | PLT count or PLT cut-off | Findings                                                                 |
|--------------------------|----------------------|--------------------------|--------------------------|---------------------------------------------------------------------------|
| Potretzke et al, 2018     | Retrospective        | 1876 percutaneous biopsies in 1732 pts | Cut-off $70 \times 10^9$/L | Haemorrhagic rate = 0.69%. No association with PLT count |
| Dentistry                |                      |                          |                          | No association between PLT count and prolonged postoperative bleeding.    |
| Ward et al, 2006         | Retrospective        | 35 procedures in 30 pts | Cut-off 35-50 $\times 10^9$/L (depending on the risk group) | 1 postoperative bleeding (2.9%) in pts with PLT = 50 $\times 10^9$/L. No haemorrhagic complication during procedures (n = 12) with PLT = 30-49 $\times 10^9$/L. |
| Perdigao et al, 2012     | Prospective observational | 35 procedures in 23 pts | PLT $< 50 \times 10^9$/L in 34% of pts | Haemorrhagic rate: 0.4% in pts with PLT $> 40 \times 10^9$/L and INR < 2.5; 5.88% in pts with PLT $\leq 40 \times 10^9$/L. Overall haemorrhagic rate: 6.3%. Intraoperative bleeding was associated with low count of platelets. However, this counting could explain only 16% of the cases of bleeding. |
| Cocero et al, 2017       | Retrospective        | 1,183 extractions in 381 pts | Cut-off PLT $\leq 40 \times 10^9$/L in 96.3% of pts |                                    |
| Medina et al, 2018       | Retrospective        | 190 extractions          | PLT $< 150 \times 10^9$/L in 96.3% of pts |                                    |
| Endoscopic variceal ligation |                  |                          |                          |                                                                                      |
| Vieira da Rocha et al, 2009 | Prospective observational | 150 pts               | PLT $< 50 \times 10^9$/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 | 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         | 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          | 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          | Retrospective        | 1267 patients            | Cut-off $50 \times 10^9$/L | Haemorrhagic rate (immediate + delayed): 7.5%. PLT $< 50 \times 10^9$/L significantly associated with immediate post-procedural bleeding (rate: 27.5%; OR = 6.6) |
| Percutaneous ablation     |                      |                          |                          |                                                                                      |
| Cammà et al, 2005        | Retrospective        | 202 pts                  | $\geq 40 \times 10^9$/L in all pts | Haemorrhagic rate: 0.50%. Association between bleeding and PLT not evaluated |
| Livraghi et al, 2008     | Retrospective        | 218 pts                  | $\geq 40 \times 10^9$/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                                                                             |
| Elmat Gamal et al, 2012\(^{50}\) | Prospective observational | 286 pts                   | Not specified            | No significant association between PLT count and bleeding 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 pts                   | Not specified            | Haemorrhagic complications in 2.62% of pts. PLT count < 100 × 10\(^9\)/L was independently correlated with postoperative morbidity and hospital mortality |
| 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\(^39\) | 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\(^39\) | 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                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      |
international normalized ratio (INR) <2.5, and 5.88% in patients with platelet count ≤ 40 × 10^9/L. Finally, in the only prospective study 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 × 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 Vanniervliet 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 al15 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 al16 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 al16 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 \(150 \times 10^9/L\)) 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 ≥ 1.5 and/or platelet count ≤ \(50 \times 10^9/L\)) 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.\textsuperscript{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,\textsuperscript{11,33} dental extractions,\textsuperscript{13,14} percutaneous ablation of liver tumours\textsuperscript{16,46} and endoscopic polypectomy.\textsuperscript{15} Noteworthy, none of the prospective studies included in this review highlighted a significant correlation between post-procedural haemorrhagic rate and platelet count.\textsuperscript{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,\textsuperscript{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.\textsuperscript{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.\textsuperscript{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 × 10^9/L who are scheduled to undergo invasive procedures.\textsuperscript{8,71-74} In these patients, although there is no solid evidence of its efficacy on raising and maintaining an adequate platelet count level,\textsuperscript{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.\textsuperscript{79} In this context, in cirrhotic patients with high risk of bleeding, thrombopoietin receptor agonists (TPO-RAs) may represent an advantageous therapeutic alternative.\textsuperscript{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

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**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
the risk of postponement or cancellation of procedures due to an inadequate increase in platelet count, as is often observed with platelet transfusions.\textsuperscript{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.\textsuperscript{75} More in detail, as reported by Loffredo et al,\textsuperscript{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,\textsuperscript{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.\textsuperscript{85} Lusutrombopag showed efficacy in reducing the need for platelet transfusion, raising the platelet count > 50 × 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.\textsuperscript{80,81,85} 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).\textsuperscript{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.\textsuperscript{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).\textsuperscript{80,84}

In the ADAPT-1 and ADAPT-2, pivotal studies on avatrombopag patients with low (<40 × 10\(^9\)/L) and high (40-50 × 10\(^9\)/L) baseline platelet count received avatrombopag 40 and 60 mg, respectively.\textsuperscript{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 × 10\(^9\)/L.\textsuperscript{82}
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. 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.

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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ORCID
Edoardo Giovanni Giannini https://orcid.org/0000-0001-8526-837X
35. Alessandria C, Debernardi-Venon W, Rizzetto M, Marzano A. Transjugular liver biopsy: a relatively simple procedure with an indefinite past and an expected brilliant future. J Hepatol. 2008;48(1):171-173.

36. Mammen T, Keshava SN, Eapen CE, et al. Transjugular liver biopsy: a retrospective analysis of 601 cases. J Vasc Interv Radiol. 2008;19(3):351-358.

37. Procopet B, Bureau C, Métivier S, et al. Tolerance of liver biopsy in a tertiary care center: comparison of the percutaneous and the transvenous route in 143 prospectively followed patients. Eur J Gastroenterol Hepatol. 2012;24(10):1209-1213.

38. Ward BB, Weideman EM. Long-term postoperative bleeding after dentoalveolar surgery in the pretransplant failure patient. J Oral Maxillofac Surg. 2006;64(10):1469-1474.

39. Vieira da Rocha EC, D'Amico EA, Caldwell SH, et al. A prospective study of conventional and expanded coagulation indices in predicting ulcer bleeding after variceal band ligation. Clin Gastroenterol Hepatol. 2009;7(9):989-993.

40. Vanbiervliet G, Giudicelli-Bornard S, Piche T, et al. Predictive factors of bleeding related to post-banding ulcer following endoscopic variceal ligation in cirrhotic patients: a case-control study. Aliment Pharmacol Ther. 2010;32(2):225-232.

41. Jeon JW, Shin HP, Lee JI, et al. The risk of postpolypectomy bleeding during colonoscopy in patients with early liver cirrhosis. Surg Endosc. 2012;26(11):3258-3263.

42. Lee S, Park SJ, Cheon JH, et al. Child-Pugh score is an independent risk factor for immediate bleeding after colonoscopy polypectomy in liver cirrhosis. Yonsei Med J. 2014;55(5):1281-1288.

43. Cammà C, Di Marco V, Orlando A, et al. Treatment of hepatocellular carcinoma in compensated cirrhosis with radio-frequency thermal ablation (RFTA): a prospective study. J Hepatol. 2005;42(4):535-540.

44. Livraghi T, Meloni F, Di Stasi M, et al. Sustained complete response and complications rates after radiofrequency ablation of very early hepatocellular carcinoma in cirrhosis: is resection still the treatment of choice? Hepatology. 2008;47(1):82-89.

45. Goto E, Tateishi R, Shinya S, et al. Hemorrhagic complications of percutaneous radiofrequency ablation for liver tumors. J Clin Gastroenterol. 2010;44(5):374-380.

46. McCluskey SA, Karkouti K, Wijeysundera DN, et al. Derivation of a risk index for the prediction of massive blood transfusion in liver transplantation. Liver Transpl. 2006;12(11):1584-1593.

47. Massicotte L, Beaulieu D, Thibeault L, et al. Coagulation defects do not predict blood product requirements during liver transplantation. Transplantation. 2008;85(7):956-962.

48. Massicotte L, Denault AY, Beaulieu D, et al. Transfusion rate for 500 consecutive liver transplantations: experience of one liver transplantation center. Transplantation. 2012;93(12):1276-1281.

49. Esfand Mari M, Pierrene J, Van Malestein H, et al. Risk factors for bleeding and clinical implications in patients undergoing liver transplantation. Transplant Proc. 2012;44(9):2857-2860.

50. Wei AC, Tung-Ping Poon R, Fan ST, Wong J. Risk factors for perioperative morbidity and mortality after extended hepatectomy for hepatocellular carcinoma. Br J Surg. 2003;90(1):33-41. https://doi.org/10.1002/bjs.4018

51. Kubo S, Takemura S, Yamamoto S, et al. Risk factors for massive blood loss during liver resection for hepatocellular carcinoma in patients with cirrhosis. Hepatogastroenterology. 2007;54(75):830-833.

52. Palavecino M, Kishi Y, Chun YS, et al. Two-surgeon technique of parenchymal transection contributes to reduced transfusion rate in patients undergoing major hepatectomy: analysis of 1,557 consecutive liver resections. Surgery. 2010;147(1):40-48.

53. Hsu KY, Chau GY, Lui WY, Tsay SH, King KL, Wu CW. Predicting morbidity and mortality after hepatic resection in patients with hepatocellular carcinoma: the role of Model for End-Stage Liver Disease score. World J Surg. 2009;33(11):2412-2419.

54. Cockbain AJ, Masudi T, Lodge JP, Toogood GJ, Prasad KR. Predictors of blood transfusion requirement in elective liver resection. HPB (Oxford). 2010;12(1):50-55.

55. Yang T, Zhang J, Lu JH, Yang GS, Wu MC, Yu WF. Risk factors influencing postoperative outcomes of major hepatic resection of hepatocellular carcinoma for patients with underlying liver diseases. World J Surg. 2011;35(9):2073-2082.

56. Fisher NC, Mutimer DJ. Central venous cannulation in patients with liver disease and coagulopathy—a prospective audit. Intensive Care Med. 1999;25(5):481-485.

57. Bosch J, Abraldes JG, Berzigotti A, García-Pagan JC. The clinical use of HVPG measurements in chronic liver disease. Nat Rev Gastroenterol Hepatol. 2009;6(10):573-582.

58. Woolfson J, John P, Kamath B, Ng VL, Ling SC. Measurement of hepatic venous pressure gradient is feasible and safe in children. J Pediatr Gastroenterol Nutr. 2013;57(5):634-637.

59. Sleeman D, Namias N, Levi D, et al. Laparoscopic cholecystectomy in cirrhotic patients. J Am Coll Surg. 1998;187(4):400-403.

60. da Silveira EB. Outcome of cirrhotic patients undergoing cholecystectomy: applying Bayesian analysis in gastroenterology. J Gastroenterol Hepatol. 2006;21(6):958-962.

61. Delis S, Bakoyiannis A, Madariaga J, Bramis J, Tassopoulos N, Dervenis C. Laparoscopic cholecystectomy in cirrhotic patients: the value of MELD score and Child-Pugh classification in predicting outcome. Surg Endosc. 2010;24(2):407-412.

62. Carbonell AM, Wolfe LG, DeMaria EJ. Poor outcomes in cirrhosis-associated hernia repair: a nationwide cohort study of 32,033 patients. Hernia. 2005;9(4):353-357.

63. Ammar SA. Management of complicated umbilical hernias in cirrhotic patients using permanent mesh: randomized clinical trial. Hernia. 2010;14(1):35-38.

64. Castellote J, Xiol X, Cortés-Beut R, Tremosa G, Rodríguez E, Vázquez S. Complications of thoracentesis in cirrhotic patients with pleural effusion. Rev Esp Enferm Dig. 2001;93(9):566-575.

65. Xiol X, Castellote J, Cortés-Beut R, Delgado M, Guàrdiola J, Sesé E. Usefulness and complications of thoracentesis in cirrhotic patients. Am J Med. 2001;111(1):67-69.

66. Nielsen SS, Thulstrup AM, Jepsen P, Vilstrup H, Sørensen HT. Postoperative mortality in patients with liver cirrhosis undergoing transurethral resection of the prostate: a Danish nationwide cohort study. BJU Int. 2001;87(3):183-186.

67. Lund L, Jepsen P, Vilstrup H, Sørensen HT. Thirty-day case fatality after nephrectomy in patients with liver cirrhosis—a Danish population-based cohort study. Scand J Urol Nephrol. 2003;37(5):433-436. https://doi.org/10.1080/00365590310006219

68. Tobin JM, Tanaka KA, Smith CE. Factor concentrates in trauma. Curr Opin Anaesthesiol. 2015;28(2):217-226.

69. Maithel SK, Kneuerz PJ, Kooby DA, et al. Importance of low preoperative platelet count in selecting patients for resection of
hepatocellular carcinoma: a multi-institutional analysis. J Am Coll Surg. 2011;212(4):638–650.

71. Cinnella G, Pavesi M, De Gasperi A, et al. Standards clinici per il Patient Blood Management e per il management della coagulazione e dell’emostasi nel perioperatorio Position paper della Società Italiana di Anestesia, Analgesia, Rianimazione e Terapia Intensiva (SIAARTI). 2018. http://www.siaarti.it/SiteAssets/Ricerca/Standards-clinici-per-il-Patient-Blood-Management/SIAARTI%20standard%20PBM.pdf. Accessed October 5, 2020

72. Intagliata NM, Argo CK, Stine JG, Lisman T, Caldwell SH, Violi F. Concepts and Controversies in haemostasis and thrombosis associated with liver disease: proceedings of the 7th international coagulation in liver disease conference. Thromb Haemost. 2018;118(08):1491-1506. https://doi.org/10.1055/s-0038-1666861

73. Liumbruno G, Bennardello F, Lattanzio A, Piccoli P, Rossetti G. Raccomandazioni SIMTI sul corretto utilizzo degli emocomponenti e dei plasmaderivati. Edizioni SIMTI; 2018.

74. British Committee for Standards in Haematology, Blood Transfusion Task Force. Guidelines for the use of platelet transfusions. Br J Haematol. 2003;122(1):10-23.

75. Violi F, Basili S, Raparelli V, Chowdary P, Gatt A, Burroughs AK. Patients with liver cirrhosis suffer from primary haemostatic defects? Fact or fiction? J Hepatol. 2011;55(6):1415-1427.

76. Basili S, Raparelli V, Napoleone L, et al. Platelet count does not predict bleeding in cirrhotic patients: results from the PRO-LIVER study. Am J Gastroenterol. 2018;113(3):368-375.

77. Hung A, Garcia-Tsao G. Acute kidney injury, but not sepsis, is associated with higher procedure-related bleeding in patients with decompensated cirrhosis. Liver Int. 2018;38(8):1437-1441.

78. Tripodi A, Primignani M, Chantarangkul V, et al. Global hemostasis tests in patients with cirrhosis before and after prophylactic platelet transfusion. Liver Int. 2013;33(3):362-367.

79. Giannini EG, Stravitz RT, Caldwell SH. Correction of hemostatic abnormalities and portal pressure variations in patients with cirrhosis. Hepatology. 2014;60(4):1442.

80. Hidaka H, Kuroskki M, Tanaka H, et al. Lusutrombopag reduces need for platelet transfusion in patients with thrombocytopenia undergoing invasive procedures. Clin Gastroenterol Hepatol. 2019;17(6):1192-1200.

81. Peck-Radosavljevic M, Simon K, Iacobellis A, 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.

82. Terraria N, Chen YC, Izumi N, et al. Avatrombopag before procedures reduces need for platelet transfusion in patients with chronic liver disease and thrombocytopenia. Gastroenterology. 2018;155(3):705-718.

83. Loffredo L, Violi F. Thrombopoietin receptor agonists and risk of portal vein thrombosis in patients with liver disease and thrombocytopenia: a meta-analysis. Dig Liver Dis. 2019;51(1):24-27.

84. Afzhal NH, Giannini EG, Tayyab G, et al. Eltrombopag before procedures in patients with cirrhosis and thrombocytopenia. N Engl J Med. 2012;367(8):716-724.

85. Committee for Medicinal Products for Human Use (CHMP). Assessment report – Lusutrombopag Shionogi. EMA/CHMP/817852/2018. https://www.ema.europa.eu/en/documents/assessment-report/lusutrombopag-shionogi-epar-public-assessment-report_en.pdf. Accessed October 5, 2020

86. Fortea JI, Puente Á, Ezcurra I, et al. Management of haemostatic alterations and associated disorders in cirrhosis in Spain: a national survey. Dig Liver Dis. 2019;51(1):95-103.

87. Desborough MJ, Hockley B, Sekhar M, et al. Patterns of blood component use in cirrhosis: a nationwide study. Liver Int. 2016;36(4):522-529.

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