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REVIEW

Clinical Implications of Thrombocytopenia for the Cirrhotic Patient

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Abstract: Thrombocytopenia is a frequent complication in patients with cirrhosis. As many as 84% of patients with cirrhosis have thrombocytopenia, and it is an independent variable indicative of advanced disease and poor prognosis. Although there is great concern that it may aggravate bleeding during surgical procedures, there is limited evidence to inform decisions regarding the treatment of cirrhotic patients with thrombocytopenia undergoing invasive procedures. Finally, there is evidence that platelets play a significant role in liver regeneration. In this report, the clinical implications of thrombocytopenia in cirrhotic patients are reviewed. The utility of platelet counts in the prognosis of cirrhosis and relationship to complications of advanced liver disease, including portal hypertension, esophageal varices, and hepatocellular carcinoma. The impact of low platelet counts on bleeding complications during invasive procedures is outlined. Finally, the role of platelets and potential adverse impact in liver regeneration is reviewed.

Keywords: thrombocytopenia, prognosis, invasive procedures, liver regeneration

Plain Language Summary

A low platelet count is common in patients with cirrhosis. It can indicate its presence, and it has an important impact on the patient's prognosis. It indicates a more serious and advanced nature of the condition and an increased risk of complications. Although many assume that thrombocytopenia increases the risk of bleeding at the time of a procedure that can cause bleeding, this is not necessary the case. Platelets also potentially help a liver regrow after injury, and the presence of a low platelet count may reduce its ability to regenerate.

Background

Thrombocytopenia, variably defined as a platelet count (PC) <100 or 150 X 10^9/L, is a common finding in patients with chronic liver disease.[1] Its pathogenesis is multifactorial and includes splenic sequestration of platelets secondary to portal hypertension, decreased production of thrombopoietin (TPO), myelosuppression, and increased destruction.[2] Although clinically significant spontaneous bleeding due to thrombocytopenia rarely occurs, its presence has important clinical implications.[1,3]

Thrombocytopenia is a marker of cirrhosis and a poor prognosis, and it frequently complicates the performance of invasive procedures.[1,4,5] Finally, it may adversely affect liver regeneration.[6] In a previous report, the pathophysiology of thrombocytopenia was reviewed.[2] This review provides an overview of the clinical implications of thrombocytopenia.

Prognosis of Cirrhosis

Thrombocytopenia is predictive of the presence and prognosis of cirrhosis, complications of portal hypertension, and the presence and prognosis of hepatocellular carcinoma.

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Predictor of Cirrhosis

While a liver biopsy is the gold standard test for cirrhosis diagnosis, significant interest exists for a non-invasive methods for its detection. Multiple simple tests have been developed that utilize readily available hematologic and biochemical tests to predict its presence. Validated models include APRI (aspartate aminotransferase to platelet ratio index), AAR, Fibrosis-4 (FIB-4), Lok, and Forns scores. A consistent feature among these tests is the platelet count as there an inverse relationship between thrombocytopenia and liver fibrosis.[7] Thrombocytopenia occurs with greater frequency and severity among patients with higher compared to lower fibrosis scores, and a platelet count of ≤150 X 10^9/L predicts the presence of cirrhosis.[8,9] A meta-analysis of studies of the APRI score indicates a moderate diagnostic utility in predicting fibrosis in HCV-infected patients (Table 1), with an APRI >1 having a sensitivity and specificity of 76% and 72%, respectively, for cirrhosis.[10] Reports of studies of the other indices for patients with chronic hepatitis B and C and fatty liver indicate similar results.[1]

Predictor of Survival for the Patient with Cirrhosis

Increasing thrombocytopenia is associated with cirrhosis severity and prognosis. Thrombocytopenia is the first cytopenia to develop and is followed by leukopenia and then anemia. The combination of thrombocytopenia and leukopenia predicts increased morbidity and mortality.[3] The PALBI grade, which incorporates the platelet count into the albumin-bilirubin (ALBI) grade, predicts survival in patients with decompensated cirrhosis.[4] Among 325 patients awaiting liver transplantation, it actually performed better than the Child-Turcotte-Pugh score.

Table 1 Formulas of Different Prediction Scores

Score	Formulas
APRI	[(AST/ULN) × 100]/PLT
AAR	AST/ALT
FIB-4	(age×AST)/(PLT×*$ALT^{1/2}$)
FI	8-0.01×PLT−ALB
King	Age×AST×INR/PLT
Lok	−5.56–0.0089×PLT+1.26×AST/ALT+5.27×INR
Forns	7.811–3.131×ln(PLT)+0.781×ln(GGT) +3.467×ln(age) −0.014×(cholesterol)
Fibro Index	1.738–0.064×PLT+0.005×AST+0.463×gamma globulin

Abbreviations: AAR, AST-to-ALT ratio; ALB, albumin; ALT, alanine aminotransferase; APRI, AST to platelets ratio index; AST, aspartate aminotransferase; FI, fibrosis index; FIB-4, fibrosis 4 index; GGT, gamma glutamyl transpeptidase; INR, international normalized ratio; PLT, platelet count; ULN, upper limit of normal.

Portal Hypertension

Increasing portal hypertension is associated with increasing splenomegaly. A low platelet count is the most common laboratory sign of portal hypertension and correlates slightly with hepatic venous pressure gradient (HVPG) and the presence of gastroesophageal varices.[11]

Presence of Esophageal Varices and High-Risk Varices

A low platelet count is an independent risk factor for the presence of varices.[12] Variceal bleeding is the most common bleeding event in patients with cirrhosis and carries a 15% to 20% six-week mortality rate.[13] Although bleeding risk is most closely associated with large variceal size, appearance (red wale marks) and advanced liver disease (Child-Pugh class B or C), thrombocytopenia is also an independent risk factor for bleeding.[13] In a Cochrane analysis of the diagnosis of varices at high risk of bleeding, the platelet count at a value of 150,000 showed sensitivity of 0.80 (95% CI 0.73 to 0.85) and specificity of 0.68 (95% CI 0.57 to 0.77).[14] In addition, thrombocytopenia also predicts recurrence of varices. Among 218 consecutive cirrhotic patients undergoing sclerotherapy for variceal bleeding, a level ≤ 80,000/μL was associated with recurrent bleeding.[15]

Identification of patients at risk for variceal bleeding is an important aspect of management of patients with cirrhosis. Until recently, screening endoscopy was recommended for all cirrhotic patients with prophylactic treatment upon detection of high-risk varices with either non-selective beta-blocker (NSBB) therapy or endoscopic band ligation (EBL). Due to expense and invasive nature, compliance with screening endoscopy was limited. As a result, numerous studies have evaluated the ability of the various non-invasive scores to identify patients at risk for clinically significant varices.[16–18]

Although thrombocytopenia is associated with large esophageal varices, the level of sensitivity is not adequate to be employed clinically. Likewise, meta-analyses of the various non-invasive scores that include the platelet count have low to moderate accuracy.[7] Other approaches that have been evaluated include the combination of a low platelet count and Child-Pugh classification and the platelet count/spleen diameter ratio.[19] However, both measures lack the sensitivity to be employed clinically. Recently, it has been shown that a combination of liver stiffness as

measured by transient elastography and platelet count identifies a population with a very low (<5%) probability of having clinically significant varices. Current guidelines recommend the use of these tests to triage patients for screening endoscopy; endoscopy can be avoided in patients with compensated cirrhosis with a liver stiffness <20 kPa and a platelet count >150,000/μL (Baveno VI guidelines).[20,21] A low baseline platelet count is also predictive of progression to medium or large varices.[22] Finally, patients who have experienced a variceal bleed are at high risk of recurrent bleeding.[11] Factors predictive of recurrent bleeding include peptic esophagitis, a high platelet ratio index score (APRI), and low prothrombin index.[23]

Ascites and Risk of SBP

Ascites occurs in 5% to 10% of cirrhotic patients each year. Large volume ascites carries a significant risk for spontaneous bacterial peritonitis (SBP) which may only be diagnosed with paracentesis in the early stages. Among 392 patients with ascites undergoing paracentesis, the presence of thrombocytopenia was found to be an independent predictor of SBP.[24] Patients with refractory ascites requiring serial large volume paracenteses have markedly diminished survival that can be improved following control with insertion of a transjugular portal systemic shunt (TIPS).[25] Although the MELD and Na-MELD scores are mostly commonly employed to determine suitability for TIPS, the combination of serum bilirubin concentration and platelet count also predicts survival, and EASL guidelines caution against the use of TIPS in patients with a platelet count lower than 75 x 10^9/L.[25]

Hepatocellular Carcinoma

The presence of thrombocytopenia is an independent risk factor the development of hepatocellular carcinoma (HCC) in patients with viral hepatitis and non-alcoholic fatty liver disease.[26,27] Patients with tumors of small diameters, interestingly, have lower platelet levels and higher bilirubin levels compared to those with tumors of large diameter.[28,29] In contrast, large HCC are frequently associated with normal platelet counts. In a series of 1047 patients with HCC, thrombocytopenia occurred in 40.7% of patients with smaller tumors (≤ 4.4cm) but only in 11.3% of patients with larger tumors (≥ 9.7cm).[28]

Predictor of Hepatic Decompensation After Liver Resection and Impaired Post-Transplant Outcomes

Thrombocytopenia has prognostic implications following liver resection and transplantation.

Patients with colorectal carcinoma liver metastases subjected to portal vein embolization for major liver resection have decreased liver hypertrophy if platelet counts are decreased due to pre-procedural chemotherapy,[30] and postoperative low platelet counts are associated with poor outcome after resection for hepatocellular carcinoma.[31] In a cohort of 565 consecutive hepatitis B-related HCC patients who underwent major liver resection, those with low immediate postoperative platelet count < 100 X 10^9/L had more high grade complications and higher rates of postoperative liver failure and mortality compared with those with platelet counts ≥ 100 X 10^9/L.[32]

Patients with thrombocytopenia (100 x 10^9/L or 150 x 10^9/L) undergoing liver transplantation have increased morbidity and mortality.[33,34] In a cohort of 234 consecutive adult-to-adult living donor liver transplantation recipients, patients with an immediate postoperative low platelet level α≤ 68 X 10^3/μL had higher rates of early allograft dysfunction (22.6% vs. 7.0%) and severe complications (22.6% vs. 10.9%) compared to those with a platelet level > 68 X 10^3/μL.[34] One-, three-, and five-year patient survival and graft survival rates of patients with platelet counts < 60 X 10^9/L on postoperative day 5 are lower than for patients with platelet counts ≥ 60 X 10^9/L.[35] As such, the "60–5 criteria" of a platelet count of < 60 X 10^3/μL on postoperative day 5 predicts severe postoperative complications, early graft failure, and early patient mortality. Finally, six-month survival following liver transplantation is significantly lower (61%) in patients with low platelet counts (<100) on postoperative day 14 compared with patients with high platelet counts (>100, 93%).[36]

Bleeding Risk

Stable cirrhotic patients seldom have spontaneous bleeding episodes. Clinically significant bleeding does not usually occur until the platelet count is less than 10 X 10^9/L.[5] Although historically viewed as a hypocoagulable state, the situation is more complex as there are both hypocoagulable as well as hypercoagulable features. Important considerations in determining bleeding risk in patients with cirrhosis and thrombocytopenia include platelet dysfunction, assessment of risk, potential for excessive

bleeding, and interference with the performance of invasive procedures.

Platelet Dysfunction

Bleeding time, a crude measure of platelet function, is abnormal in up to 42% of patients with liver disease but correlates poorly with the severity of thrombocytopenia, suggesting the presence of underlying qualitative platelet abnormalities.[37] Potential sources of defective platelet function include immaturity, size, and aggregation. To compensate for thrombocytopenia, patients frequently have increased numbers of immature platelets and a larger mean platelet volume, both of which have been associated with dysfunction.[38–40] Platelets play a critical role in facilitating fibrin mesh formation by exposing activated clotting factors on the cell surface.[41] In vitro studies suggest that platelets adhere less tightly to damaged endothelial surfaces in cirrhosis.[41] Molecular mechanisms that have been proposed to account for decreased aggregability include reduced transmembrane signaling and cytosolic calcium after thrombin-induced platelet stimulation, decreased levels of arachidonic acid, and activation of intrinsic inhibitory pathways with upregulation of cAMP and cGMP. Concentrations of circulating plasma factors (HDL apolipoprotein E, fibrin degradation products, bile salts) that inhibit platelet aggregation are also increased. Agonist-stimulated platelet surface expression of P-selectin and activated GPIIb-IIIa is reduced in thrombocytopenic CLD patients compared to healthy controls with the same degree of thrombocytopenia.[42] Platelet function is further compromised by defective thromboxane A2 synthesis, storage pool deficiency, and abnormalities of the platelet glycoprotein Ib. Counteracting these changes are pro-thrombotic changes. Elevated levels of von Willebrand factor and multimers due to reduced clearance resulting from diminished levels of its cleaver, ADAMTS13, are present and parallel the severity of cirrhosis.[43,44] Among 102 cirrhotic patients with thrombocytopenia, high vWF-Ag levels and FVIII-to-PC ratios were the most prominent hemostatic disorder.[44]

Thromboembolic Risk

Patients with cirrhosis have a rebalanced system of hemostasis and are prone to both haemorrhage and thrombosis. Abnormal routine laboratory testing results present in decompensated cirrhosis (elevated INR, thrombocytopenia) frequently lead a clinician to believe that the patient is "auto-anticoagulated."[41] Although data are limited to retrospective studies, there is considerable evidence that, in fact, the contrary may be true; individuals with cirrhosis may actually be at an increased risk of thrombosis despite these laboratory abnormalities. In a large retrospective case-control study utilizing a Danish case registry, patients with cirrhosis had a relative risk of 2.06 to develop unprovoked venous thromboembolism (VTE) compared to non-cirrhotic controls.[45] Cirrhotic patients under 45 years of age had a 25% increased risk of venous thrombotic events, and those over the age of 45 years had a risk similar to that seen in patients without cirrhosis, and a meta-analysis reported that patients with cirrhosis were 1.68 times more likely to have unprovoked VTE.[46] Although one report indicated that patients with mild liver disease was correlated with higher rates of VTE but moderate-severe liver disease was actually protective, less than 1% of the patients in the moderate-severe liver disease group had coagulopathy based on ICD codes.[47] Finally, it has been reported that the incidence of VTE is lower than that in those with chronic medical illnesses such as chronic kidney disease, heart failure and cancer but similar to those without significant co-morbidities despite an elevated INR and low platelet count.[48]

The severity of the coagulation abnormality (INR and platelet count) is for the most part not predictive of VTE. Among patients with cirrhosis, there was no difference in incidence of VTE stratified by INR levels.[49] Concerning the impact of thrombocytopenia, one report indicated that thrombocytopenia was associated with decreased risk, but most studies have not identified a relationship.[50,51] Rather, the presence of thrombocytopenia is strongly associated with the development of portal vein thrombosis.[52] Given the underlying perception that patients with decompensated cirrhosis are coagulopathic, there is often suboptimal use of pharmacologic VTE prophylaxis, likely due to misconceptions about bleeding risk.[53]

Assessment of Bleeding Risk

Thrombocytopenia and platelet dysfunction are only two of the multiple disturbances in hemostasis that are present in cirrhosis.[54] Because the prothrombin time and INR only assess pro-coagulants, these tests are of much less value in patients with cirrhosis because anti-coagulants (proteins C and S, anti-thrombin) are equally reduced. As a result, it overstates the degree of coagulopathy.[41] In addition, the procoagulant factor VIII is increased in parallel with cirrhosis severity.[43] Increased expression of plasminogen activator inhibitor (PAI-1) and elevated tissue plasminogen

activator due to reduced hepatic clearance leads to a hyperfibrinolytic state, resulting in reduced levels of plasminogen and antiplasmin (α 2-antiplasmin) and thrombin-activatable fibrinolysis inhibitor (TAFI).[43] The abnormalities tend to offset each other. However, the equilibrium is tenuous. Minor perturbances caused by infection, bleeding, or hypovolemia, can disturb it, predisposing the patient to either hemorrhage or thrombosis.[41] Because of the complex interplay of thrombocytopenia with altered pro- and anticoagulant factors, routine laboratory tests do not reliably predict the bleeding risk.[41] Viscoelastic testing, including thromboelastometry and rotational thrombelastography, are adjunctive tests that can elucidate bleeding and clotting risk more accurately. By utilizing the rotation of a pin in a sample of blood, the resulting elastic forces are measured during clot formation, yielding a read-out of the overall kinetics of thrombus formation and stability which can determine whether thrombocytopenia, coagulation disorders, or hyperfibrinolysis is driving hemostatic abnormalities.[54,55]

Potential for Excessive Bleeding

The platelet count does not predict unprovoked major or minor bleeding in cirrhotic patients. In aprospective study of 280 cirrhotic patients in which the annual rate of any significant bleeding was 5.45%/year (3.57%/year and 1.89%/year for major and minor bleeding, respectively), platelet counts were similar in patients with or without major or minor bleeding: aplatelet count $\leq 50 \times 10^3/\mu L$ was detected in three (6%) patients with and in 20 (9%) patients without any bleeding event.[3] Although the platelet count may not predict unprovoked major bleeding in the cirrhotic patient, patients with cirrhosis clearly experience bleeding complications similar to patients with thrombocytopenia of other causes in addition to those related to portal hypertension.

Non-Variceal Gastrointestinal Bleeding

Peptic Ulcer Disease

Peptic ulcer disease (PUD) is the most frequent cause of non-variceal bleeding. It is more frequent than in the general population with prevalence rates ranging from 6% to 15%.[56] PUD bleeding is associated with substantial morbidity and mortality.[57] In a prospective, 10-year study 14.8% of patients hospitalized for non-variceal upper gastrointestinal (UGI) bleeding were cirrhotic.[58] In a 10-year retrospective cohort study among patients hospitalized for peptic ulcer bleeding, patients with cirrhosis were 3.19 times more likely to have recurrent peptic ulcer bleeding.[57] Although variceal bleeding is associated with higher rebleeding rates than PUD, the mortality risk at 45 days is similar amongst the groups (19% v 17%, p=0.48).[59]

Proposed factors that contribute to increased rebleeding in cirrhosis include impaired mucosal defense, coagulopathy, endovascular dysfunction, and in hyperdynamic circulation. Relatively little information is available on the impact of thrombocytopenia. In a prospective analysis of risk factors for in-hospital and delayed mortality after UGI bleeding, patients who died had lower platelet counts on presentation and cirrhosis.[60] In a retrospective study on inpatients who underwent endoscopy for overt gastrointestinal bleeding (GIB) with a platelet count of 20 to $<50 \times 10^3$/mL compared to inpatients without cirrhosis, there were no differences in recurrent bleeding rates between the groups. An increased international normalized ratio (INR) >2, however, was a predictor of recurrent bleeding.[61]

Portal Hypertensive Gastropathy

Portal hypertensive gastropathy (PHG) is common among patients with cirrhosis and is the second most common cause of non-variceal GI bleeding. Its prevalence has been reported to range from 11% to 98%.[62] However, bleeding is relatively less common, with 10.8% of patients having chronic bleeding and only 2.5% acute bleeding.[63]

Platelet counts are lower in patients with PHG. The diagnostic accuracy of platelet count to spleen diameter ratio in 111 cirrhotic patients for sensitivity, specificity, PPV, NPV, and accuracy of PSR were 87.23%, 5.88%, 83.67%, 7.69%, and 74.7%, respectively.[62] The right liver lobe-diameter-to-albumin ratio and platelet-count-to-spleen-diameter ratio are noninvasive predictors of the presence and severity of portal hypertensive gastropathy.[62] There are no reports on the impact of thrombocytopenia on bleeding from PHG.

Epistaxis

Epistaxis in cirrhotic patients may be initially misdiagnosed as upper gastrointestinal bleeding (UGIB). A significant amount of blood can be swallowed, and the patient subsequently presents with hematemesis or melena.[64] In an observational study of 1249 patients admitted for presumed severe UGIB, 36.9% were cirrhotic, and 20 (4.3%) actually had epistaxis as the source of hemorrhage.[64] Although thrombocytopenia is frequently present in cirrhotic patients with epistaxis, its exact relationship has not been well studied. In a retrospective study

assessing the risk factors for recurrent epistaxis among 653 patients of all causes, thrombocytopenia was associated with late recurrent admission.[65]

Blood loss from epistaxis in cirrhosis can be associated with significant morbidity and mortality. In a retrospective case series of 39 patients with cirrhosis presenting with epistaxis (median platelet count 89,000), the swallowed blood precipitated an episode of hepatic encephalopathy in 10 (26%), and two patients required ICU admission due to the bleeding.[66] Mortality is as high as 63% in those admitted with severe epistaxis and lower platelet levels (54,000/mm^3 versus 76,000/mm^3).[64] In patients with thrombocytopenia, the insertion of an nasogastric tube can have significant bleeding complications.[66]

Abnormal Uterine Bleeding

Women with cirrhosis have a high risk of abnormal uterine bleeding.[67] Potential factors attributed to abnormal bleeding include endometrial hypertrophy stimulated by excessive estrogen due to decreased clearance, portal hypertension, coagulopathy, and thrombocytopenia. Excessive menstrual bleeding may be observed in patients with cirrhosis.[68] Although excessive menstrual bleeding is common in other conditions characterized by thrombocytopenia such as idiopathic thrombocytopenia purpura, information regarding the impact of thrombocytopenia on menstrual bleeding in cirrhosis is limited to case reports describing large volume vaginal hemorrhage.[69,70] Potential explanations for the lack of data include the post-menopausal state of most women due to age and amenorrhea due to hypothalamic-pituitary dysregulation.[71] Symptomatic anemia may be associated with severe menorrhea in women with cirrhosis, and large volume vaginal bleeding has been reported to precipitate hepatic decompensation, including hepatic encephalopathy, hepatorenal syndrome, and multi-organ failure.[68]

Interference with Performance of Invasive Procedures

There is frequent concern that severe thrombocytopenia (<50 X 10^9/L) can increase the bleeding risk of invasive procedures.[5] Moderate thrombocytopenia can also prevent patients from undergoing needed procedures.

Liver Biopsy

Random biopsy of liver parenchyma is commonly performed for diagnosis etiology of chronic liver disease, determining prognosis, and/or guiding therapy.[72] Biopsy of liver lesions is often employed to establish the diagnosis of malignancy. Thrombocytopenia is often considered a relative contraindication to biopsy owing to a concern about an elevated risk of bleeding, especially in patients with a platelet count ≤60,000/mm^3.[73] In a series of 2740 patients, bleeding risk was 5.3% below this level compared with 0.2% when the platelet count was >150,000/mm^3. Another early study reported a bleeding rate of 23% in patients with platelet counts <60,000/mm^3 compared with no episodes of bleeding with platelet count above this range.[74] In patients with high risk of complications with percutaneous liver biopsy, transjugular liver biopsy (TJLB) is a safe alternative.[75] In a series of 51 biopsies, a threshold count of 30 X 10^9/L was identified for safe TJLB.[76] In this study, no bleeding complications were observed using ultrasound guidance for venous access. AASLD guidelines recommend platelet transfusions when platelet levels are less than 50,000–60,000/$mm^3$for either transcutaneous or transvenous biopsies.[72]

Band Ligation or Sclerotherapy

Esophageal variceal band ligation (EVBL) is the initial treatment for patients with bleeding EVs and it is commonly employed for both primary and secondary prophylaxis of hemorrhage.[77] Rebleeding rates after EVBL can be as great as 20% and are associated with high mortality.[78] Due to the strong association of thrombocytopenia and large varices, a common concern is the performance of band ligation in patients with uncorrected thrombocytopenia. To evaluate factors predictive of post-endoscopic variceal band ligation bleeding, common coagulation parameters were assessed in 109 patients undergoing EVBL for primary variceal bleeding prophylaxis. In this series, incidence of post-EVBL bleeding was 5.5%.[79] INR and platelet counts were not predictors of post-EVBL bleeding. Rather, patients who bled had significantly lower fibrinogen levels.[79] In patients with cirrhosis undergoing band ligation for variceal bleeding, the platelet count does not have predictive value for six-week mortality in patients with rebleeding.[80] Risk factors for rebleeding from ligation sites include emergent versus elective procedures, bacterial infection, and severity of disease (ie, Child Class C) but not platelet counts.[81] The AASLD Practice Guidelines for the management of variceal bleeding do not provide a recommendation regarding platelet transfusion in patients with variceal hemorrhage. Other guidelines allow it as a consideration for patients with severe thrombocytopenia (platelet count <50 G/L).[11,82]

Paracentesis

Abdominal paracentesis is a routine diagnostic and therapeutic procedure. Diagnostic paracentesis is recommended for patients with new-onset ascites and all hospitalized patients with cirrhosis and ascites to establish the etiology and exclude the presence of spontaneous bacterial peritonitis.[83] Therapeutic large-volume paracentesis is indicated for the management of tense or recurrent ascites. Rare but potential bleeding complications of paracentesis include abdominal wall hematoma and hemoperitoneum that results from puncture of an abdominal wall collateral under high portal pressure.

Clinical trial and real-world experience confirm the safety of paracentesis in the setting of thrombocytopenia. In a study of 628 patients with thrombocytopenia undergoing therapeutic paracentesis (platelet count range: 19 x 10^3/μL – 341 x 10^3/μL), no significant procedure-related bleeding complications were observed.[84] In a study of 4729 patients the rate of severe bleeding was exceedingly low at <0.02% of patients.[85] Risk factors for severe bleeding included more severe liver disease (higher MELD scores) and renal failure. Thrombocytopenia was not a risk factor. In another large study of patients undergoing both thoracentesis and paracentesis in thrombocytopenic patients, there was no significant difference in bleeding risk between patients with different degrees of thrombocytopenia.[86] Approximately 64% of patients with thrombocytopenia (< 100 x 10^3/μL) also had elevated PT/PTT. This subgroup of patients with both thrombocytopenia and abnormal coagulation tests did not have elevated rates of hemorrhagic complications. Similar to prior studies, renal failure was associated with higher rates of bleeding. These studies were conducted before the widespread use of bedside ultrasound-guided paracentesis. Using ultrasound guidance, an already low 0.8% rate of bleeding was further reduced by 68%.[87] In a retrospective study of 3116 ultrasound-guided paracenteses, post-procedure hemorrhage occurred in only 0.19% of procedures, none of which occurred in the 368 patients with a platelet level less than 50 x 10^3/μL. In a study of 4792 patients undergoing paracentesis, severe bleeding occurred in <0.02% and was unrelated to platelet count.[88] Only one study of 171 patients undergoing a total of 515 abdominal paracenteses (91% therapeutic) showed a correlation.[83] Thrombocytopenia below 50 X 10^9/L was present in 10.7% of cases. Major complications were seen in 1.6% of cases. Complications due to therapeutic procedures were associated with platelet counts < 50 X 10^9/L, but the differences were not statistically significant. As a result, national and international consensus guidelines consider paracentesis to be a safe procedure in the setting of thrombocytopenia and coagulopathy and do not recommend prophylactic blood product transfusions prior to paracentesis.[88,89]

Dental Extractions

Patients with advanced cirrhosis frequently require dental extractions to remove sources of systemic infection. While thrombocytopenia has been associated with postoperative bleeding in small studies of patients, coagulopathy appears to be a more important factor.[90] In a retrospective analysis of 1183 extractions in 318 patients, the three patients with both platelet counts below 40 x 10^3/μL and INR of 2.5 or more bled, whereas the bleeding rate was 0.4% in those with platelet counts above 40 x 10^3/μL and an INR less than 2.5.[91] In those with only one bleeding tendency, an elevated INR greater than 2.5 more accurately predict bleeding risk than thrombocytopenia. In a study of 190 visits for extraction of 333 teeth in cirrhotic patients with an INR less than 3 and platelet counts 16–216 x 10^3/μL,[78] 12 patients (6%) had hemorrhagic complications that were controlled with local measures.[92] Similarly, in 23 patients with INR of 3 or less and platelet counts of 30 x 10^3 or more, postoperative bleeding was observed in only 2.9% (one patient) of procedures and treated using only local hemostatic measures without the need for transfusion.[93]

Central Venous Line

Early studies involving patients with various coagulopathies indicated a very low incidence of bleeding, most of which were not severe such as mild oozing and a hematoma that were controlled with local pressure.[94] Non-randomized studies have reported that it is safe to perform invasive procedures without clinically significant bleeding in patients with thrombocytopenia without receiving prophylactic platelet transfusions.[95] A study using an ultrasound guidance approach in patients with hemostasis disorders reported minimal bleeding complications that consisted of oozing (6%) small hematomas (1.5%), or both (<1%).[96] The study found no association between platelet count and bleeding complications. In a study of 600 central venous catheters (CVCs) placements in patients with acute leukemia in which there were no severe bleeding incidences and nonsevere bleeding occurred in 32% of patients, only platelet counts below

20 X 10^9/L were associated with a high risk of nonsevere bleeding.[97]

Cirrhotic patients commonly require insertion of a central venous line for management of gastrointestinal bleeding and intensive care admissions. In a study of 380 cirrhotic patients undergoing invasive procedures (14% central line placement) without correction of a coagulopathy, the presence of a platelet count ≤50,000 was not predictive of bleeding complications.[98] Similarly, no difference in bleeding was noted among patients with platelet counts <50,000, 50–100,000, and >100,000, but those with <50,000 received a platelet transfusion prior to the procedure.[99] A platelet count of < 30,000/mL has identified as cutoff for hematoma formation and ooze.[100] In a prospective study using thromboelastogram (TEG), a CTP score ≥10 and the TEG were predictive of post-procedural bleeding after central venous cannulation.[101]

Impaired Liver Regeneration

Experimental and clinical studies indicate that platelets play an important role in liver regeneration.[102] Platelets infused via the portal vein promote liver regeneration in rats after 70% hepatectomy, and thrombocytosis-induced splenectomy accelerates liver regeneration after partial hepatectomy in mice.[103,104] Mechanisms by which platelets promote regeneration include a direct effect on hepatocytes and a cooperative effect with liver sinusoidal endothelial cells (LSECs) and Kupffer cells.[105] The postoperative profile of circulating platelet-derived factors, especially serotonin, correlates with the ability of the remnant liver to regenerate.[106] Thrombocytosis after hepatectomy in mice activate the Akt and STAT3 signaling pathways which are associated with earlier and significantly overexpressed cell cycle, signaling pathways, metabolism and transport genes.[107] Following liver injury, platelets are recruited to and trapped within the liver, where they adhere to the endothelium. Subsequent platelet activation results in the release of platelet granules which activate liver sinusoidal endothelial cells, leading to the secretion of growth factors, such as interleukin-6.[108] Adhesion of platelets through thromboxane A_2 receptor signaling also facilitates liver repair during acute chemical-induced hepatotoxicity through HGF release from platelets adhering to the sinusoids.[109] Activated platelets deploy SDF-1 and VEGF-A to stimulate $CXCR7^+$ liver sinusoidal endothelial cells (LSEC) and $VEGFR1^+$ myeloid cells to promote hepatic regeneration.[110] Human platelets promote liver regeneration with Kupffer cells in SCID mice through release of VEGF.[111] Clinically, low postoperative plasma fibrinogen levels are associated with liver dysfunction and mortality in patients undergoing liver resection. Increased intrahepatic fibrin(ogen) deposition is present in livers of patients after liver resection but absent in patients displaying post-resection hepatic dysfunction.[112]

Experimental and clinical studies support the importance of platelets on regeneration in cirrhosis. Pre-treatment of cirrhotic rats with thrombopoietin prior to partial hepatectomy is associated with accumulation of platelets within the liver and correction of the impaired regeneration that is otherwise observed.[113] Although administration of the thrombopoietin receptor agonist eltrombopag for six months did not result in the improvement of liver function or increase in liver volume in a study of 5 patients with mild to moderate cirrhosis (Child-Pugh scores 8 or less) and thrombocytopenia, administration of 10 units of platelet concentrate once a week for 12 weeks in a series of 10 patients with cirrhosis and thrombocytopenia was associated with significant improvement of serum albumin.[105,114]

Platelets play an important role clinically in liver regeneration following living-donor liver transplantation. Among 87 patients undergoing right liver graft, adult-to-adult living-donor liver transplantation, the total amount of platelets transfused is associated with graft regeneration.[115] In a series of 32 recipients undergoing living-donor liver transplantation, serotonin levels were positively correlated with platelet counts, and allogeneic platelet transfusion significantly increased platelet counts and increased serum serotonin levels.[116] Among 379 patients undergoing living-donor liver transplantation, graft regeneration increased in relation to a graded increase in the number of transfused platelets and higher postreperfusion platelet counts during surgery.[117] Platelet transfusion was identified as the sole independent anesthetic factor contributing to graft regeneration. Platelet concentrate transfusion of one to six units vs. none was correlated with a 6.5% increase in graft regeneration. Platelet concentrate transfusion of more than six units vs. none was further correlated with an 18.4% increase in regeneration. In the subgroup of recipients without intraoperative platelet transfusion, mean platelet count measured during the intraoperative reperfusion phase was positively associated with graft regeneration.

Discussion and Conclusion

Thrombocytopenia is one of the most common and early findings in patients with chronic liver disease and has

important implications in terms of prognosis, bleeding concerns, and regeneration. Thrombocytopenia carries important prognostic information in terms of the presence of cirrhosis, portal hypertensive complications, hepatocellular carcinoma, post-liver resection and transplant course. Although frequently viewed as a hypocoagulable state, the condition is much more complex, and the patient is potentially at risk for both bleeding and thrombosis. Only limited information is available concerning its contribution to both physiologic and pathologic bleeding. Although there is a frequent significant clinical concern for excessive bleeding at the time of an elective, invasive procedure, evidence for a role in platelet transfusions is limited. Guidelines do not recommend platelet transfusions for treatment of variceal bleeding and prior to paracentesis. Finally, preliminary data support a role in liver regeneration with important implications after hepatic resection and liver transplantation.

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Author Contributions

All authors made substantial contributions to conception and design, acquisition of data, and analysis; took part in drafting the article; gave final approval of the version to be published; and agree to be accountable for all aspects of the work. Biocentric, Inc assisted with acquisition of data and technical support.

Disclosure

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