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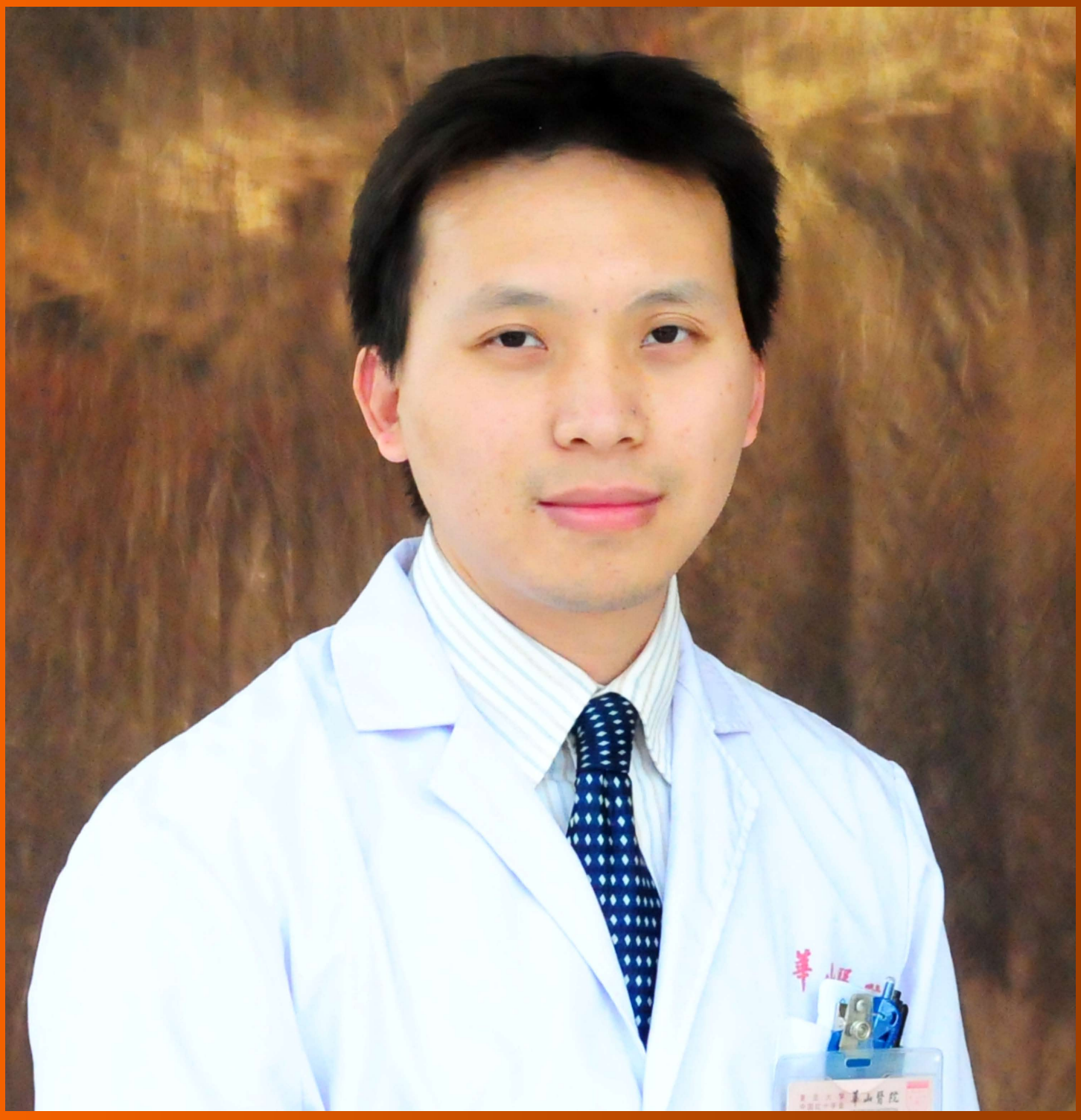

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ABOUT COVER

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MINIREVIEWS

Thrombocytopenia after liver transplantation: Should we care?

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Abstract

Transient thrombocytopenia is a common phenomenon after liver transplantation. After liver transplantation (LT), platelet count decreases and reaches a nadir on postoperative days 3-5, with an average reduction in platelet counts of 60%; platelet count recovers to preoperative levels approximately two weeks after LT. The putative mechanisms include haemodilution, decreased platelet production, increased sequestration, medications, infections, thrombosis, or combination of these processes. However, the precise mechanisms remain unclear. The role of platelets in liver transplantation has been highlighted in recent years, and particular attention has been given to their effects beyond hemostasis and thrombosis. Previous studies have demonstrated that perioperative thrombocytopenia causes poor graft regeneration, increases the incidence of postoperative morbidity, and deteriorates the graft and decreases patient survival in both the short and long term after liver transplantation. Platelet therapies to increase perioperative platelet counts, such as thrombopoietin, thrombopoietin receptor agonist, platelet transfusion, splenectomy, and intravenous immunoglobulin treatment might have a potential for improving graft survival, however clinical trials are lacking. Further studies are warranted to detect direct evidence on whether thrombocytopenia is the cause or result of poor-graft function and postoperative complications, and to determine who needs platelet therapies in order to prevent postoperative complications and thus improve post-transplant outcomes.

Key words: Thrombocytopenia; Liver regeneration; Platelet therapy; Platelet; Thrombopoietin receptor agonist; Intravenous immunoglobulin treatment; Liver transplantation

Core tip: Transient thrombocytopenia is commonly seen after liver transplantation, and many studies have demonstrated that perioperative thrombocytopenia is associated with deterioration of the graft and decreased patient survival after liver transplantation. The role of platelets in liver transplantation has recently been highlighted, and particular attention has been given to their effects beyond hemostasis and thrombosis. Platelet therapies that increase platelet count, such as thrombopoietin, thrombopoietin receptor agonist, platelet transfusion, splenectomy, and intravenous immunoglobulin treatment, have a potential role for improving graft survival; however, clinical trials are still lacking, and further studies are warranted.

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INTRODUCTION

Platelets are anucleate cytoplasmic discs derived from megakaryocytes in the bone marrow[1-3]. The normal life span of platelets is 8-10 d, and they are removed from circulation by sequestration in the spleen[4]. Platelets contain three types of secretory granules: alpha granules, dense granules, and lysosomal granules. Each granule contains growth factors and cytokines, such as platelet-derived growth factor, hepatocyte growth factor (HGF), insulin-like growth factor-1 (IGF-1), vascular endothelial growth factor (VEGF), serotonin, epidermal growth factor, and transforming growth factor-β[5,6]. Platelets have major roles in hemostasis, thrombosis, inflammation, and vascular biology and have recently been discovered to have additional functions in antimicrobial defense, angiogenesis, tissue repair and regeneration[7-10].

Orthotopic liver transplantation (LT) is the treatment of choice for patients with end-stage liver disease and hepatocellular carcinoma within the Milan criteria[11,12]. The short and long term outcomes of this procedure have dramatically improved as a result of innovations in both immune suppression and surgical techniques[11]. The total number of adult LTs performed in the world was 27759 in 2015, of which living donor LT (LDLT) accounted for 21%[13]. The number of transplant candidates on a waiting list has also steadily increased despite organ shortage being a worldwide issue. According to the 2015 annual report from the Scientific Registry of Transplant Recipients, the incidence of graft failure in the United States continues to decrease; in 2014, there were 6-mo graft failure rates of 7.8% and 12.5% and 1-year rates of 10.3% and 15.1% in deceased donor LT (DDLT) and in LDLT, respectively[14].

Post-transplant thrombocytopenia occurs in the majority of patients immediately after LT, with reported incidences of up to 90%[15,16]. After LT, platelet count decreases and reaches a nadir on postoperative days (PODs) 3-5, with an average reduction in platelet counts of 60%; platelet count recovers to preoperative levels approximately two weeks after LT[17]. Thrombocytopenia in the postoperative period is not simply an academic observation but can lead to catastrophic events, such as postoperative bleeding, cerebral hemorrhage, and infection, which eventually lead to graft failure and mortality. The putative mechanisms involved include decreased platelet production, increased platelet consumption, sequestration in the liver graft or spleen, dilution, medication, or a combination of these processes[18-22]. However, the precise mechanism is still unknown. In this review, we aimed to describe the clinical and experimental evidence of the role of platelets in LT. This review differs from previous reviews in the following three points. First, we describe the role of platelets in LT specifically with a focus on "post-transplant thrombocytopenia". Second, the involvement of platelets in DDLT and LDLT are described separately, since they are different in many aspects including the graft quality, the length of ischemia, and the recovery of portal hypertension after LT. Third, we delve into the potential mechanisms of post-transplant thrombocytopenia. We report previous evidence with consideration for future perspectives.

PLATELETS AND DDLT

Post-transplant thrombocytopenia after DDLT has been reported since the advent of liver transplantation and has been described in many articles. It was first reported by Hutchison *et al*[23] in 1968 (Table 1). They reviewed 8 LT recipients who received DDLT at the University of Colorado, which included 2 auxiliary and 6 orthotopic LT. An acute drop in platelet count to less than $10 \times 10^3/\mu L$ was observed in most patients within the first three postoperative days. To better comprehend this phenomenon, they performed experimental LT in dogs and found platelets located in the space of Disse along with Kupffer cells, some of which were ingesting the platelets. They concluded that post-transplant thrombocytopenia was primarily caused by the mechanical entrapment of platelets in the grafts, which were then destroyed by the Kupffer cells. The next report of this phenomenon came after a twenty year interval and was described by Plevak *et al*[16]. They observed that platelet counts dropped from preoperative levels of $137 \times 10^3/\mu L$ to $72 \times 10^3/\mu L$ on POD 3. Using ^{111}In-labeled platelets, they demonstrated that transplant recipients showed a delayed recovery of platelet counts after LT.

Since then, several consecutive reports have been

Table 1 Reports of postoperative thrombocytopenia after liver transplant

Author	Year	Type	Number of patients	Results
Hutchison *et al*[23]	1968	DDLT	8	Platelet count change from 200-400 × 10^3/μL to 67 × 10^3/μL on POD 3
Plevak *et al*[16]	1988	DDLT	76	Platelet count change from 137 × 10^3/μL to 72 × 10^3/μL on POD 3
Munoz *et al*[15]	1989	DDLT	3	Three patients with severe postoperative thrombocytopenia were successfully treated with high-dose gamma-globulin
McCaughan *et al*[17]	1992	DDLT	53	Patients who died during their hospital stay had lower postoperative platelet counts at the nadir, and the day of the nadir tended to be delayed
Chatzipetrou *et al*[24]	1999	DDLT	541	A platelet nadir of < 20 × 10^3/μL was associated with allograft dysfunction, graft rejection and poorer patient and graft survival
Chang *et al*[25]	2000	DDLT	50	Fungal infection was frequent in patients with a platelet nadir of < 30 × 10^3/μL
Ben Hamida *et al*[26]	2003	DDLT	161	Patients with a platelet count < 50 × 10^3/μL for three consecutive days showed a high mortality rate.
Nascimbene *et al*[19]	2007	DDLT	8	Infusion of high-dose gamma-globulins induced a prompt, complete and persistent resolution of postoperative severe thrombocytopenia in more than 70% of patients
Kim *et al*[47]	2010	LDLT	87	A total unit of platelet transfusion was significantly associated with graft regeneration
Lesurtel *et al*[28]	2014	DDLT	247	A platelet count of < 60 × 10^3/μL on POD 5 was related to poor graft survival within 90 d after LT
Sonny *et al*[27]	2015	DDLT	223	A preoperative platelet count of < 45 × 10^3/μL was related with short-term outcomes in patients ≥ 60 years old
Li *et al*[49]	2015	LDLT	234	Patients with an immediate postoperative platelet count of < 68 × 10^3/μL had a higher chance of developing EAD and severe complications
Takahashi *et al*[29]	2016	DDLT	975	A platelet count of < 72.5 × 10^3/μL on POD 5 was related to poor graft survival
Han *et al*[48]	2016	LDLT	441	An intraoperative platelet transfusion was also independently associated with enhanced graft regeneration at 14 ± 2 d after surgery
Pamecha *et al*[50]	2016	LDLT	120	A platelet count of < 30 × 10^3/μL on POD 3 was a strong predictor of complications and EAD
Gwiasda *et al*[31]	2017	DDLT	134	A higher preoperative platelet count was related to graft loss
Takahashi *et al*[30]	2017	DDLT	771	Persistent thrombocytopenia within 5 d after LT was related to progression of biliary anastomotic stricture
Akamatsu *et al*[51]	2017	LDLT	445	A Low platelet count on POD 3 was an independent predictor of grade Ⅲb/Ⅳ complications

LT: Liver transplant; DDLT: Deceased donor liver transplant; LDLT: Living donor liver transplant; POD: Postoperative day; EAD: Early allograft dysfunction.

published on this topic, and the majority of these studies indicate that postoperative thrombocytopenia may influence post-LT outcomes and have a negative impact on grafts and patient survival in the short and long term after LT[17,19,24-27]. McCaughan *et al*[17] reported a drop in postoperative platelet counts by 63%, which was the only independent predictor of short-term patient survival post-LT. In their analysis of a large cohort of 541 patients of DDLT in a single institute, Chatzipetrou *et al*[24] described that a post-transplant platelet count nadir of < 20 x 10^3/μL was associated with allograft dysfunction, graft rejection and poorer patient and graft survival. Chang *et al*[25] reported that the incidence of fungal infection was more frequent in patients with a platelet nadir of < 30 × 10^3/μL, leading to higher mortality rates. Sonny *et al*[27] focused on the elderly population and found that the length of intensive care unit (ICU) and hospital stays were longer in patients with preoperative platelet counts of < 45 × 10^3/μL. Factors such as low preoperative platelet counts, massive intraoperative platelet transfusions, retransplantation, and poor general preoperative conditions such as the need for dialysis, were found to be associated with post-transplant thrombocytopenia[24,26]. For the treatment of post-transplant thrombocytopenia, Munoz *et al*[15] and Nascimbene *et al*[19] separately reported that an infusion of high-dose gamma-globulins could induce resolution of severe postoperative thrombocytopenia However, they could not explain its mechanism of action.

Recently, some groups have focused on platelet counts particularly on POD 5, when platelet counts start to rise after the nadir. In 2014, Lesurtel *et al*[28] proposed the 60-5 criteria, in which a platelet count of < 60 × 10^3/μL on POD 5 was an independent risk factor associated for severe postoperative complications, early graft failure, and patient mortality in the short term after DDLT. Takahashi *et al*[29] focused on the long term impact after DDLT and noted that a platelet count of < 72.5 × 10^3/μL on POD 5 was a predictor for poor graft and patient survival. More recently, Takahashi *et al*[30] described that low perioperative platelet counts within 5 d after DDLT were associated with biliary anastomotic stricture (BAS) with duct-to-duct biliary reconstruction. They found that persistent postoperative thrombocytopenia, which

was defined as platelet counts of < 41 × 10^3/μL and < 53 × 10^3/μL on POD 3 and POD 5, respectively, was an independent risk factor for BAS.

In contrast, Gwiasda *et al*[31] stated that higher preoperative platelet count was associated with graft loss because platelets contribute to reperfusion injury after graft ischemia. Further, Eldeen *et al*[32] described that recipients who experienced early hepatic arterial thrombosis (HAT) had higher preoperative platelet counts, but this was not associated with the development of late HAT.

Clinical studies suggest that increasing postoperative platelet counts might improve graft and patient survival after DDLT[28-30]. This "protective effect of platelets" may be compatible with a study by Hisakura *et al*[33] who showed that thrombopoietin-mediated thrombocytosis protected the liver from damage after an extended hepatectomy in a pig model. However, transplant surgeons prefer relatively low postoperative platelet counts due to fear of HAT, and this preference has made it difficult to perform prospective trials.

PLATELETS AND LDLT

After LDLT, the liver undergoes two different processes, namely, liver regeneration and ischemia-reperfusion[34-36]. The liver regeneration process after LDLT has been divided into three phases[34]. The early phase is rapid regeneration, which occurs during the first two weeks and is associated with vascular engorgement and tissue edema. The second phase is volume decline, which may be attributed to the normalization of transient vascular engorgement or tissue edema at one to two months after hepatectomy. The third phase is a slow increase in volume, which occurs until the volume reaches a constant level[34]. Partial liver grafts need rapid regeneration to meet the functional demands of recipients; otherwise, liver failure would occur, and the short- and long-term outcomes would be affected. Liver regeneration is orchestrated by the interplay of various cells and mediators, and platelets are understood to have a role as well[37,38]. The role of platelets in accelerating liver regeneration after partial hepatectomy was first reported by Murata in 2004[39], and Lesurtel *et al*[40] reported platelet-derived serotonin-mediated liver regeneration using transgenic mice. Since then, many studies have been reported in this field, and it was implicated by a Japanese group that liver regeneration after partial hepatectomy is promoted by platelets through three different mechanisms: (1) a direct effect on hepatocytes; (2) a cooperative effect with liver sinusoidal endothelial cells; and (3) a collaborative effect with Kupffer cells[41-45]. On the other hand, in ischemia-reperfusion, platelets are generally considered to act in concert with activated Kupffer cells and leukocytes, and a triangular interaction between Kupffer cells, leukocytes, and platelets has been demonstrated to be the core mechanism of liver injury[46]. Thus, platelets have two ambivalent roles in LDLT.

Kim *et al*[47] were the first to report the positive role of platelets in LDLT in 2010 (Table 1). They investigated the relationships between clinical variables and liver graft regeneration rates in their study population of 87 recipients with adult-to-adult living donor recipients, all receiving right lobe grafts. They found that total units of platelet transfusion were significantly associated with graft regeneration. Han *et al*[48] studied the relationship between platelets and liver regeneration after LDLT. They described that intraoperative platelet transfusion was independently associated with enhanced graft regeneration at 14 ± 2 d after surgery without increasing morbidity and mortality rates. Furthermore, platelet count during the reperfusion phase was identified as a prognostic factor for graft regeneration. Li *et al*[49] focused on platelet count immediately after transplant and reported that patients with an immediate postoperative platelet count of < 68 × 10^3/μL had a higher chance of developing early allograft dysfunction and severe complications. Pamecha *et al*[50] demonstrated that a platelet count of < 30 × 10^3/μL on POD 3 was a strong predictor of major postoperative complications and was associated with early graft dysfunction, prolonged ascites, and sepsis. Akamatsu *et al*[51] also focused on POD 3 and described that a low platelet count on POD 3 was an independent predictor of grade ⅢIb/Ⅳ complications.

Only recently has post-transplant thrombocytopenia been reported to be associated with LDLT. Lower platelet counts lead to poor graft regeneration but lower incidences of ischemia-reperfusion injury in partial grafts. Overall higher platelets counts are beneficial because their impact on liver regeneration outweighs the associated risk of ischemia-reperfusion injury, most notably during the early post-LDLT period[52]. Animal experiments to explain this phenomenon are still lacking, and basic studies and prospective clinical trials are warranted.

PLATELET FUNCTION AND ANTIPLATELET THERAPY AFTER LT

In patients with end-stage liver disease (ESLD), platelet function is often reported to be compromised[53]. However, recent studies have demonstrated that platelet function in patients with ESLD was not as compromised as it was previously believed[54]. A few observational studies that evaluated platelet function after LT have been reported in the past, but these studies involved a small number of patients. Himmelreich *et al*[55] reported decreased platelet aggregation immediately after reperfusion in 10 patients after DDLT. The authors considered that a dysfunction in platelet aggregation may have been a major cause of intraoperative bleeding[55]. They also mentioned that administration of a small amount of University of Wisconsin (UW) solution into systemic circulation during reperfusion might further

decrease platelet function[56]. Jüttner *et al*[57] found marked depressed GPⅡb/Ⅲa and P-selectin expression in circulating platelets, and maximum aggregation of platelets was restored on the third day after reperfusion among patients with all types of underlying disease. Eyraud *et al*[58]. conducted platelet function testing with aggregometry using platelet-rich plasma obtained from 15 patients after DDLT. Compared with pre-transplant conditions, no significant difference was found in platelet function at 7 and 28 d after DDLT From these reports, platelet function is temporally impaired immediately after LT but recovers in 3-7 d.

Regarding the use of antiplatelet therapy, some studies have indicated favorable effects on LT, including a reduced incidence of post-transplant hepatic arterial thrombosis[59,60] and the prevention of progression of liver fibrosis after postoperative recurrence of hepatitis C[61]. Antiplatelet therapy has also been described to prevent the recurrence of hepatocellular carcinoma after curative hepatectomy[62] and to suppress hepatocellular carcinogenesis in patients with chronic hepatitis[63,64]. However, most of these studies were performed at a single institution or were retrospective in nature. A randomized clinical trial should be undertaken to analyze the risks and benefits of the use of post-transplant antiplatelet therapy.

MECHANISM OF POST-TRANSPLANT THROMBOCYTOPENIA

Thrombocytopenia, which is defined by a platelet count of < 150 × 10^3/μL, has been reported to occur in more than 70% of patients with cirrhosis[65-67]. This disorder is considered to be a result of reduced synthesis of thrombopoietin (TPO) and increased sequestration by hypersplenism[67]. In LT, post-transplantation thrombocytopenia can occur due to the following: hemodilution; decreased production of TPO; increased platelet sequestration in the liver graft or spleen; immunological reactions; platelet activation and consumption due to thrombosis, such as in disseminated intravascular coagulation (DIC), thrombotic microangiopathy, or venous thromboembolism; medication; infections; or a combination of these processes[18-22].

Hemodilution

Hemodilution due to intensive use of blood products, colloids and crystalloids during the transplant procedure may lead to a drop in the platelet count immediately after surgery, but the platelet nadir usually occurs on days 3-4, which does not validate hemodilution as a potential cause of postoperative thrombocytopenia.

Preservation solution

A correlation between lower post-transplant thrombocytopenia and the use of UW solution was implicated by Williams *et al*[68] However, their study was an observational study that consisted of a small number of recipients, and the level of evidence was low[69].

Sequestration in the spleen

Richards *et al*[20] described that patients in a hyposplenic state exhibit the same pattern of post-transplant thrombocytopenia as those with intact splenic function. Nascimbene *et al*[19] also noted that thrombocytopenia occurred regardless of the presence of hypersplenism. Thus, the spleen is not considered to be a major site of platelet consumption[20].

Consumption in the liver graft by Kupffer cells

Sindram *et al*[46] demonstrated that reperfusion of rat livers preserved for 24 h at a cold temperature resulted in rapid sequestration of platelets in the liver graft and platelet adherence to the sinusoidal lining, which induced apoptosis of the sinusoidal endothelial cells in concert with leukocytes and activated Kupffer cells. Cywes *et al*[18] detected significantly increased adherence of platelets to the hepatic endothelium after reperfusion of the liver graft. Porte *et al*[70] reported that thrombocytopenia started immediately after reperfusion, and sequestration of platelets was observed as platelets accumulated in the sinusoids and were phagocytized by Kupffer cells, which was similar to an earlier study. On the other hand, Takahashi *et al*[41] suggested that platelets that accumulate in the liver graft have with contact with Kupffer cells and release growth factors, such as HGF, IGF-1, and VEGF, that protect the liver graft and lead to improved graft survival in patients with higher platelet counts after DDLT[29].

Consumption at the liver graft with local thrombin generation

Richards *et al*[20] found that the levels of fibrin and fibrinogen degradation products are elevated postoperatively, which they speculated was due to endothelial damage in the liver graft during the preservation period, which lead to hepatic sequestration due to local thrombin generation. Nobuoka *et al*[71] focused on activity of a disintegrin-like and metalloproteinase with thrombospondin type-1 motifs member 13 (ADAMTS13), which is produced by stellate cells. ADAMTS13 is an enzyme that specifically cleaves multimetric von Willebrand factor (vWF), which mediates the adhesion of platelets to the site of vascular damage. They described that decreased activity of ADAMTS13 accompanied by elevated vWF levels was associated with thrombocytopenia 2 wk after LDLT. They considered that prolonged thrombocytopenia after LDLT was due to decreased production of ADAMTS13 in the graft with local thrombin generation and platelet aggregation. Nakanuma *et al*[72] found that platelet aggregation was mainly present at zone 3 in the liver graft as extravasated platelet aggregation (EPA), and peripheral platelet counts were lower after LDLT in the EPA-positive patients than the EPA-negative patients. They considered that EPA in the zone 3 caused the platelet consumption, activation, and degranulation, following the release of negative cytokines by platelets, and

might be involved in liver damage and poor outcomes after LDLT[72].

TPO production

Serum TPO concentration is inversely related to platelet concentration in patients with hematopoietic disorders characterized by deceased megakaryocytes in the bone marrow[5]. The level of expression of mRNA for TPO is high in the liver, indicating that the liver is the main source of TPO synthesis[73].

Richards *et al*[74] reported that thrombocytopenia following LT was accompanied by an increased rate of thrombopoiesis in the early period after transplantation, shown by increased reticulated platelets following the platelet nadir. Peck-Radosavljevic *et al*[75] observed that serum thrombopoietin levels increased significantly on the first day after LT, which preceded the increase in reticulated platelets by 3 d and in peripheral platelets by 5 d. This delayed rise in platelet count was compatible with the time lag between the appearance of reticulated platelets and peripheral platelets after *in vivo* administration of a recombinant human thrombopoietin analogue, and rules out the impaired production of TPO as a possible cause of post-transplant thrombocytopenia. Usui *et al*[76] reported the TPO levels in the prolonged thrombocytopenic group were significantly decreased. They considered that prolonged post-transplant thrombocytopenia was secondary to a decrease in TPO production suggesting graft dysfunction.

Medication

Immunosuppressive medications (*e.g.*, azathioprine, mycophenolate mofetil, cyclosporine and tacrolimus), heparin, anti-thymocyte globulin (ATG), antiviral drugs (ganciclovir and valganciclovir), trimethoprim sulfamethoxazole, *etc*., can cause thrombocytopenia after LT. Antimetabolites, such as azathioprine and mycophenolate mofetil, have myelosuppressive effects on the bone marrow in a dose-dependent manner[77,78]. Nascimbene *et al*[19] performed bone marrow aspirates during the early post-LT period and noticed marked megakaryocytic hyperplasia in all cases, ruling out drug-induced myelosuppression as a cause of post-transplant thrombocytopenia. Calcineurin inhibitors, such as cyclosporine and tacrolimus, may cause thrombocytopenia. The presentation is similar to thrombotic thrombocytopenic purpura (TTP), in which renal dysfunction is accompanied by thrombocytopenia[79-81]. Lee *et al*[79] described that the incidence of cyclosporine-induced TTP was low (incidence of 1%) and was seen only in the pediatric population, occurring at 2 to 30 wk after LT.

Heparin-induced thrombocytopenia (HIT) after LT has been reported in several articles[22,82-85]. Kaneko *et al*[22] demonstrated that the percentage of heparin-induced thrombocytopenia (HIT) antibody-positive patients was low (incidence of 5.6%), and none of the patients developed HIT. Bakchoul *et al*[82] also described that HIT was clinically suspected in 16% of recipients at a median of POD 6. However, only one of these patients was positive for anti-platelet factor 4/heparin IgG antibodies. ATG induces dose-dependent T-cell depletion by complement-dependent cytotoxicity, antibody-dependent cellular cytotoxicity, and apoptosis[86,87]. ATG-induced platelet aggregation is a specific reaction responsible for thrombocytopenia. Platelet surface antigen-CD32 has been suggested to play a crucial role in ATG-induced thrombocytopenia[88]. Ganciclovir and valganciclovir are suspected to have direct bone marrow toxicity. Gabardi *et al*[89] reported that the incidence of thrombocytopenia with low-dose valganciclovir, used as prophylaxis for cytomegalovirus (CMV) infections in post-transplant patients, was 24%. Trimethoprim sulfamethoxazole, when used as prophylaxis against *Pneumocystis jiroveci* pneumonia, causes drug-induced immune thrombocytopenia (ITP) by antibody formation[90].

ITP and infection

Viral infections, including CMV, Epstein-Barr virus (EBV), parvovirus B19, herpes zoster, human herpes virus 8, and some donor-derived viral infections, can induce ITP[91-97]. The early onset of ITP after LT occurs due to reactivation of CMV, EBV or varicella infection when patients are receiving high-dose immunosuppression. On the other hand, Taylor *et al*[21] reported 8 cases of ITP after LT (incidence of 0.7%), in which they could not find any evidence of infection. The majority of their patients developed ITP more than one year post-LT. Maar *et al*[98] described that recipients with CMV infection showed delayed thrombocytopenia, occurring later than 24 d after LT. They considered that CMV infection induced systemic endothelial activation with the expression of tissue factor on the endothelial cell surface and the release of vWF. These processes activate the clotting cascade and may augment platelet aggregation.

Considering that post-transplant thrombocytopenia mostly occurs during the early period after LT, sequestration in the new liver graft has the strongest potential to explain the temporal drop in platelet counts. However, the precise mechanism of sequestration is still unknown. Prolonged thrombocytopenia, which occurs more than one month after LT, may be attributed to other causes such as impaired TPO production due to graft dysfunction, viral infections, and medications.

PLATELETS AND TRANSFUSION

The median blood loss associated with LT has fallen dramatically with the development of surgical and anesthetic techniques. However, there are still a number of patients who require significant amounts of blood products perioperatively.

DDLT

In 1989, Miyata *et al*[99] described that there was positive correlation between the number of platelet

units transfused and endotoxin concentrations at the end of the anhepatic phase, which they considered to be the reason for increased pulmonary complications. de Boer *et al*[100] demonstrated that intraoperative platelet transfusion was an independent risk factor for one- and five-year survival after DDLT. A subsequent report from Pereboom *et al*[101] noted that platelet transfusion led to an increased one-year mortality from acute lung injury. More recently, Chin *et al*[102] reported that graft survival was reduced significantly in patients receiving intraoperative platelet transfusions at one year, but not at 90 d, and considered that intraoperative transfusion and not thrombocytopenia was associated with a poor outcome after LT. They found a relationship between intraoperative platelet transfusion and postoperative septicemia as a cause of death. Nacoti *et al*[103] focused on a pediatric population and found that platelet transfusion was an independent risk factor for developing major complications in the first year after DDLT. In contrast, Nixon *et al*[104] found that there was no substantiated effect of platelet transfusion on survival after LT, due to their use of plateletpheresis. They insisted on using single-donor platelet transfusions rather than random donor platelet preparations, along with leucocyte reduction strategies.

LDLT

Authors from two different institutes in South Korea described that platelet transfusion after LDLT was a protective factor for graft regeneration and survival[47,48]. Li *et al*[105] described that although massive red blood transfusion led to poor long-term survival, higher postoperative infection rates and prolonged ICU stays, platelet transfusion was not a risk factor for long-term graft survival.

Thromboelastography

With the hope of limiting the use of blood products, some transplant centers use thromboelastography (TEG) to monitor and detect coagulopathies[106]. TEG is a viscoelastic test that is performed on whole blood to analyze complete hemostasis, from platelet plug formation through coagulation and fibrinolysis. There is growing evidence to support the use of TEG as a technique to guide transfusion strategies for LT[107-109]. Kang *et al*[109] prospectively validated the use of TEG for reducing total blood product use. Lawson *et al*[107] described that the maximum amplitude measured preoperatively by TEG had high predictability for intraoperative massive transfusion. Krzanicki *et al*[110] performed a retrospective review of 124 DDLT recipients and found a higher incidence of a hypercoagulable state in patients with a background of cholestatic diseases and an intraoperative hypercoagulable state that was correlated with early HAT after LT. On the other hand, Wikkelsoe *et al*[111] performed a systemic review and meta-analysis including a sequential analysis of randomized clinical trials of a TEG/thromboelastometry-based algorithm compared with standard treatment in patients with cardiac surgery and LT, and found that the former had no impact on mortality, the amount of blood transfused, or the incidence of surgical reinterventions.

There was a significant difference in the impact of platelet transfusion between DDLT and LDLT, the former being negative, and the latter being positive. The reason for this difference could be due to graft type; partial grafts require postoperative liver regeneration. This result is compatible with a report from Matsuo *et al*[44] that transfusion of platelet-rich plasma accelerated liver regeneration, including liver/body weight ratio and hepatocyte Ki-67 labeling index during the early phase after hepatectomy in a rat model. However, it is still unknown how platelets interact with other cells when under ischemia-reperfusion conditions. The precise mechanisms need to be clarified by animal experiments. TEG may be a good option to stratify the risk of perioperative transfusions. However, it is still debated whether the use of TEG is realistically efficient for predicting the need for transfusions.

PLATELET, LT AND SPLENECTOMY

Splenectomy is currently one of the therapeutic procedures for avoiding small-for-size syndrome, and it is a choice for preventing postoperative thrombocytopenia in LDLT[112,113]. It has been indicated for the completion of post-transplant interferon therapy for hepatitis C virus (HCV) infection and ABO incompatible LT[113,114]. However, due to recent advances in interferon (INF)-free direct-acting antivirals for HCV infection and rituximab induction for ABO incompatible transplantation, the necessity for splenectomy is currently decreasing[114]. Partial splenic embolization is a minimally invasive treatment that can be performed as an additional treatment after LT; however, its efficacy may be insufficient, and serious complications, such as splenic abscess, splenic rupture, and venous thrombosis, have been reported[115]. On the other hand, simultaneous splenectomy in DDLT is not usually performed based on historical reports of septic complications after LT[116].

Marubashi *et al*[112] revealed that 7 patients who underwent a simultaneous splenectomy showed remarkable increases in platelet counts 2 wk after LDLT and found that graft size was positively associated with post-transplant thrombocytopenia. Morimoto *et al*[117] demonstrated that with simultaneous splenectomy, the platelet count increased to > 100 $\times$ $10^3/\mu L$ one month post-transplantation in recipients with HCV infection and achieved better sustained virological response after INF therapy. Additionally, a similar report by Chu *et al*[114] noted that patients with simultaneous splenectomy had significantly higher platelet counts at 1 and 6 mo after transplantation, with a higher HCV anti-therapy completion rate. On the other hand, Ito *et al*[116] observed that simultaneous splenectomy increased

platelet count more than 2 wk after LDLT but not during the early postoperative period. In addition, the incidence of reoperation for postoperative hemorrhage increased within the first week. The authors further demonstrated that simultaneous splenectomy was an independent predictor for postoperative lethal infectious complications. On the other hand, Takahashi *et al*[118] described the usefulness of pre-transplant splenectomy in pediatric recipients suffering from biliary atresia. After splenectomy, the platelet count was significantly elevated, with an improvement in the PT-INR and Model for End-Stage Liver Disease score. However, the complication rate for this procedure was relatively high.

The effect of splenectomy on restoring postoperative platelet counts during the early post-LT period may be delayed from the time when a higher platelet count is necessary. This issue may be resolved by pre-transplant splenectomy, which can elevate preoperative platelet counts. However, the decision to perform pre-transplant splenectomy should be given much care and consideration due to the poor general condition of the patients and their bleeding tendencies.

FUTURE PERSPECTIVES

TPO[33,43,45,119,120], TPO receptor agonists[121], artificial platelets[122,123], and freeze-dried platelets[124] are developing and beginning to be utilized in various clinical settings, and the importance of platelets is becoming more obvious. Additionally, the infusion of high-dose immunoglobulins may provide a safe, prompt, complete, and persistent resolution of severe post-transplant thrombocytopenia[15,19]. These platelet therapies, splenectomy and intravenous immunoglobulin treatment may have potential as therapeutic strategies to resolve post-transplant thrombocytopenia, leading to improved graft and patient survival after LT. In particular in LDLT, these strategies may be able to prevent small-for-size syndrome by promoting liver regeneration[47,48,112,118]. However, decreases in platelet count are sometimes falsely overestimated by automatic analyzers due to platelet aggregation. Therefore, manual counting to confirm a platelet reduction before initiating platelet therapies and monitoring precise platelet counts after therapy are necessary.

LIMITATIONS

We acknowledge there are limitations to this review. First, most studies are based on small retrospective series from single institutions. The reason for this is there is still no consensus regarding the role of platelets in LT (*i.e.*, "Are platelets a friend or foe in LT?"). This fact has led to difficulty in conducting multi-institutional prospective trials to clarify the role of platelets in LT. Second, it is still difficult to prove whether thrombocytopenia is a "result" or a "cause" of postoperative complications. Many studies describe post-transplant thrombocytopenia as a phenomenon, but there has been no direct evidence that show whether thrombocytopenia is a cause or a result of poor graft function or complications. It is necessary to clarify this important point with basic animal experiments. Third, since thrombocytopenia is common after LT, it is still unclear how to determine which patients need platelet therapies to prevent postoperative complications and yield better outcomes. By conducting multi-institutional prospective trials, it is important to generate a standardized cut-off value to specify the target patients for platelet therapies.

CONCLUSION

We described convincing evidence of post-transplant thrombocytopenia and the role of platelets in LT and discussed future perspectives. The mechanisms of thrombocytopenia and its effect on postoperative outcomes are still not completely understood. Since platelets have both beneficial and detrimental effects on liver grafts, therapeutic strategies to increase perioperative platelet counts, such as the use of thrombopoietin, thrombopoietin receptor agonist, platelet transfusion, splenectomy, and intravenous immunoglobulin treatment, could be targeted to enhance the beneficial effects while minimizing potential detrimental effects.

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