Dear Editor and Reviewers

Thank you for your excellent and important comments. We followed all your instructions and answered all your questions. The changes and additems are highlighted in red.

Reviewer #1:

1. -Platelet count is sometimes falsely decreased by automatic methods because of circulating platelet aggregates. Manual counting is time consuming and it is not systematically performed. The authors should stress the need of individual manual counting to confirm clinically significant platelet count reduction, at least anytime before considering platelet transfusion.

⇨ ***We discussed this important point at the "Future prospective" section and stressed the need for manual counting before initiating and monitoring platelet therapy***

2. In some cases, platelet count acts as a marker of complications/graft dysfunction rather than a cause for such clinical situations. The authors should try to delineate clearly in which clinical complications raising platelet count (by using transfusion, immunoglobulin infusion…) would be helpful, and how to monitor such strategies.

⇨ ***We consider that platelet therapy is especially useful in living donor liver transplant (LDLT) to prevent small-for-size syndrome by promoting liver regeneration, on the basis of previous animal and clinical studies. We added***

description as the following at the "Future perspective" section. "In particular in LDLT, these strategies may be able to prevent small-for-size syndrome by promoting liver regeneration[47,48,112,118]".

Regrading monitoring, we stressed the need of manual counting in order to confirm the precise platelet counts at the "Future prospective" section as well.

3. - Regarding preservation solutions it can be read: "Williams et al. and Himmelreich, et al. reported correlations between lower post-transplant thrombocytopenia and use of UW solution". The authors quoted refs 56 and 57 to support this statement. Are these randomized trials? If they are observation retrospective studies, this statement may be taken with caution. –

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

4. I missed information about the emerging role thromboelastography as a tool to guide intraoperative management.

   ⇨ ***We added the following description about the role of thromoboelastrography (TEG) for LT. "With the hope of limiting the use of blood products, some transplant centers use 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. prospectively validated the use of TEG for reducing total blood product use[109]. Lawson et al. described that the maximum amplitude measured preoperatively by TEG had high predictability for intraoperative massive transfusion[107]. Krzanicki et al. 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[110]. On the other hand, Wikkelsoe et al 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 liver transplantation, and found that the former had no impact on mortality, the amount of blood transfused, or the incidence of surgical reinterventions[111].”

5. Aligning with the previous comment, the authors have focused on platelet count but nothing is said about platelet function. It may well be that some patients with normal platelet count have a derangement in platelet function, being the paradigm the use of anti-platelet therapy. –

⇨ ***We added “Platelet function and antiplatelet therapy after LT” section. “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. reported decreased platelet aggregation immediately after reperfusion in 10 patients after DDLT[55]. 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]. Juttner et al. 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[57]. Eyraud et al. 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 days after DDLT [58]. From these reports, platelet function is temporally impaired immediately after LT but recovers in 3 -7 days.

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; thus, they

have low evidence levels. A randomized clinical trial should be undertaken to analyze the risks and benefits of the use of post-transplant antiplatelet therapy."

6. Aspirin use (or other anti-platelet drugs) is becoming increasingly popular to prevent vascular complications (in absence of solid supporting evidence). In opinion of the authors, and taking into account the clinical relevance of platelets for graft regeneration, what would be the potential consequences of using aspirin in most liver transplant recipients?

⇨ ***I agree that this is very important point. We discussed separately in this paper that both platelet therapies and antiplatelet therapies have beneficial effects on the liver graft after LT. But most studies for both consisted of small number of patients and basically retrospective in nature. To clarify whether platelet therapy or anti-platelet therapy has beneficial effect after transplant, we need to conduct multi-institutional prospective trials. We discussed this weakness at the "Limitation" and "Platelet function and antiplatelet therapy after LT" sections. Also, we added description at the "Conclusion" section that "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."***

7. There is no defined threshold to establish the need of platelet reposition after liver transplantation. This should be highlighted in the manuscript.

   ⇨ ***We added the flowing at the "Limitation" section. "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."***

8. As a general recommendation, the quality of the evidence supporting the potential role of platelet count on worse outcome after liver transplantation is generally low. Most results are based on small retrospective series coming from a single center. Therefore the strength of the conclusions made in the review is also diminished. A comment on this is warranted.

   ⇨ ***We added the following at the "Limitation" section. "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."***

Reviewer #2

1. Please, read carefully the Format for references and make corrections (the first author should be typed in the bold-faced letter, etc.).

   ⇨ ***We made corrections for all.***

2. There are few syntax and spelling errors; please, make corrections.

   ⇨ ***We corrected for all and got English corrected by a recommended company by WJG.***

3. The platelets in relation to LT is a topic reported in several other review articles. It would be helpful if you mention why your review is distinct from other published reviews.

   ⇨ ***We described what is different from the previous review at the "Introduction section" as followings. "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."***

4. Several paragraphs are rather confusing (e.g., page 4 "Pelveak et al. ..performing a clinical experiment in transplant recipients and healthy volunteers"). Please, make corrections.

⇨ ***We changed this simple. "The next report of this phenomenon came after a twenty year interval and was described by Pelveak et al.[16]"***

5. Please, discuss the limitations of your review.

⇨ ***We discussed limitation of this study at "Limitation" section. "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. "***

6. You should indicate the reference at page 5, last paragraph, line 5. 7.

⇨ ***We added reference here.***

7. You should write the Conclusion of the review.

   ⇨ ***We added "Conclusion" section. "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."***

8. Fig. 1 and Fig. 2 should be deleted as both the mechanisms of platelets promoting liver regeneration after partial hepatectomy (Fig. 1) and mechanisms of thrombocytopenia after LT (Fig.2) are presented in details at pages 6/7 and 7/8, respectively.

   ⇨ ***We deleted the Fig. 1 and 2.***