Research Article
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Study of factors contributing to persistent thrombocytopenia following liver transplantation

Abstract

Background and aim: Thrombocytopenia is one of the common features of advanced liver cirrhosis. Liver transplantation is the only treatment for end stage liver disease, but even after transplantation thrombocytopenia is frequent. The aim of this study was to monitor platelets count and to identify factors contributing to persistence of thrombocytopenia following liver transplantation.

Methods: 36 patients who underwent LDLT in Ain Shams Center of Organ Transplantation (ASCOT) in one year (2013). Preoperative platelet count was recorded. Following transplantation, platelets count was recorded daily for the first two weeks, then at one month, 3 months, 6 months and 12 months. Splenic size and portal venous blood flow were measured at the same intervals by doppler ultrasound. Thrombopoietin was measured before surgery then at 2 weeks and 6 months following transplantation. Persistent thrombocytopenia was defined as a platelet count less than 150 x 10^9/L at one year post-transplantation.

Results: 56% of patients had persistent thrombocytopenia at 1 year. Factors that showed significant correlation with persistent thrombocytopenia were lower preoperative platelet count, lower preoperative portal vein flow velocity, greater preoperative spleen size, higher GRWR and longer operative time. Highest sensitivity was found for preoperative portal flow velocity and highest specificity was to GRWR. HCV recurrence, rejection episodes, CMV infection, biliary and vascular complications postoperative were not independent factors for persistent thrombocytopenia.

Conclusion: preoperative platelet count, operative time, preoperative AST level, and preoperative PV flow velocity are independent predictors of postoperative persistent thrombocytopenia. They may also predict the outcome of liver transplant.

Keywords: persistent thrombocytopenia, liver transplantation, thrombopoietin

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Introduction

Patients with advanced liver cirrhosis have a complex hemostAatic disturbance. Thrombocytopenia is one of the common features of this derangement. The pathogenesis of thrombocytopenia is complex; splenic pooling, increased platelet consumption and/or impaired production have been variably suggested to contribute as etiologic factors.[1]

Liver transplantation is the only treatment for end stage liver disease, but even after transplantation thrombocytopenia is frequent, and during the first post-operative week a moderate reduction in platelet count (20,000-50,000/mcl) occurs in about half of the patients, and counts below 20,000/mcl are reported in about 8% of patients. Spontaneous resolution usually begins during the second week, and by the third week platelet count reaches or exceeds the levels measured before liver transplantation.[2]

Several mechanisms may potentially account for thrombocytopenia in the transplanted patient; decreased platelet production, increased platelet consumption, or sepsis.[2,3] In living donor liver transplant (LDLT), the small-for-size syndrome causes elevated portal venous pressure (PVP) which may also result in thrombocytopenia.[4]

Pre-existing hypersplenism makes an important contribution. Following either cadaveric LT or LDLT the spleen gradually shrinks over a period of months.[5] However, about 20% of these patients remain with moderate to intense hypersplenism 1 year after LT.[6] Thrombopoietin level may also play a role. A low thrombopoietin (TPO) level in the blood, which is regulated by portal venous hemodynamics, causes thrombocytopenia in cirrhotic patients.[7] In addition, several transplant medications, including Mycophenolate Mofetil (MMF) and its predecessor azathioprine, can induce bone marrow suppression by direct nucleic acid synthesis inhibition.[8] Sirolimus can induce leukopenia and thrombocytopenia but the risk appears to be directly related to trough concentration of sirolimus greater than 15ng/mL.[9]

Aim of the study

i. To monitor changes in platelets count following liver transplantation.

ii. Identify possible factors contributing to persistence of thrombocytopenia.

Patients and methods

The study was conducted on patients with end stage liver disease who were listed for LDLT in Ain Shams Centre of Organ Transplantation (ASCOT). Adult patients who underwent LDLT surgery in the period from January 2013 to December 2013 were included and followed up for one year. The study was approved by the scientific and ethical committee of Ain Shams University Hospital.

A written consent was taken from each patient before enrolment for data collection and analysis during the one year follow up post liver transplantation.

Study Design

All patients had preoperative platelet count recorded one day before surgery. Following transplant, platelets count was recorded daily for the first two weeks, then at one month, 3 months, 6 months and 12 months. Splenic size and portal venous blood flow were measured at the same intervals by doppler ultrasound. Thrombopoietin (TPO) was measured by ELISA for all patients included in the study before surgery then at 2 weeks (early) and 6 months (late) following transplantation. Thrombocytopenia was defined as a platelet count less than 150 x 10^9/L, persistent thrombocytopenia was defined as thrombocytopenia at 1 year post-transplantation.

The following data were reported for patients included in the study:

Pre-operative: Age and gender, aetiology of liver disease, Child-Pugh and MELD (Model for End-Stage Liver Disease) scores, donor age, GRWR (Graft weight/ Recipient's Body Weight Ratio), pre-existing diabetes, hypertension or other co-morbidities.

Intraoperative data: Operative time, cold ischemia time, portal blood pressure, blood products transfused and intraoperative complications if any.

Post-operative: Serial measurements of liver functions, serum creatinine, immuno-suppression regimen, postoperative complications; rejection episodes, major infections (fungal or severe bacterial infection), and recurrence of original disease.

Exclusion criteria

i. Patients transplanted for fulminant hepatic failure.

ii. Cases with previous splenectomy before LDLT.

iii. Previous renal or liver transplant recipients.

iv. Patients with incomplete records or lost follow up.

v. Early postoperative mortality (within 3 months).

At the end of the study patients were categorized in two groups; group I: cases with persistent thrombocytopenia at 12 months and group II included cases with normal platelet count at 12 months. Data were analyzed to identify the day that platelets reached a nadir (lowest count), and possible factors contributing to persistent thrombocytopenia at one year.

Postoperative follow-up of recipients: In the early postoperative period all recipients were followed up daily by clinical examination, liver function tests, renal profile, CBC, coagulation profile, serum immunosuppressive level and abdominal U\S with dupler US on portal circulation. Following discharge of the patient, regular (clinical, laboratory and radiological) follow up visits are done at weekly intervals at the transplantation outpatient clinic for the first 3 months then at one month interval till the end of first year. Frequent follow up visits were mandatory if any complications developed.

Postoperative immunosuppressant regimen: Calcineurine inhibitors (CNIs) based immunosuppression regimen is given to all patients with complete withdrawal of corticosteroids within the first 3 months. Patients without HCC also receive an antiproliferative agent (Mycophenolate Mofetil (MMF) or Mycophenolate Sodium (MPA)) in addition to CNIs. Level of CNIs is monitored and adjusted to each patient in his follow up visits. Changes in immunosuppressant agents and regimens are tailored for each patient according to response and complications. Sirolimus is given to patients who develop CNI complications mainly renal impairment.

Statistical methods

Data were analyzed using PASW statistics software ver. 18. Quantitative data were expressed as Mean ± SD. Qualitative data were expressed as number of cases and their percent of expression. Comparative analysis was done using Student t test and Mann whitney test for parametric and nonparametric data respectively. Difference among proportions derived from categorical data was compared using the Fisher's exact test and Chi Square test. P value < 0.05 was considered significant.

ROC curve analysis was done to estimate the predictive performance of significant factors obtained by univariate analysis. Multivariate linear regression analysis was done to determine the independent risk factors for persistent thrombocytopenia.

Results

During the study duration, a total of 38 LDLT surgeries were done. They were all males. Two cases were excluded from the study; both of them died at 1 month after LT, one due to severe sepsis and the other had haemophagocytosis which led to severe pancytopenia, severe infection and septic shock. So, enrolled patients were only 36. At the end of the study (after one year follow up), patients were divided into two groups; Group I: patients with persistent thrombocytopenia at 1 year. They were 20 patients (56%). Group II: patients with no thrombocytopenia at 1 year. They were 16 patients (44%).

Preoperative data

All patients had HCV related liver cirrhosis. Group I included two patients with dual infection with HBV and HCV. In each group 6 patients had HCC (Table 1). All included patients had preoperative thrombocytopenia except two cases had normal preoperative platelets count.

Table 1 Aetiology of liver disease in included patients

	Group I n=20	Group II n=16	P value
HCV	12 (60%)	10 (62.5%)	1.32**F**
HCV + HBV	2 (10%)	0	0.492 **F**
HCV+ HCC	6 (30%)	6 (37.5%)	1 **F**

F-Fisher Exact test

Preoperative clinical data of patients are summarized in Table 2. Estimated GRWR was significantly higher in group I patients with persistent thrombocytopenia. Preoperative mean AST level had a statistically significant less value in group I patients compared to group II. Preoperative WBCs count was significantly less in group I patients who had also a significant mean spleen size bigger than patients in group II who hadn't have persistent thrombocytopenia at one year. In group I patients mean portal vein flow velocity was significantly less compared to group II. The significant differences between the two groups are mainly related to parameters that reflect worse portal hypertension in patients with persistent thrombocytopenia.

Table 2 Preoperative clinical and laboratory data

Parameter	Group I (mean±SD) n=20	Group II (mean±SD) n=16	t-Test	P value
Age (yrs)	48.00±6.38	50.25±6.27	-1.059	0.297
Child Pugh Score	9.10±1.68	9.75±0.93	-1.383	0.176
MELD Score	14.25±2.20	15.31±4.74	-0.892	0.379
Donor Age (yrs)	27.45±6	26.88±6.47	0.275	0.785
GRWR	1.15±0.21	0.95±0.17	3.062	0.004
WBC(4-11x10^3/mcL)	3.71±1.98	5.04±1.82	-2.082	0.045
HGB (13-17g/dl)	11.27±1.48	11.48±2.13	-0.359	0.721
Plt (150-500x10^3/mm^3)	55.50±41	95.25±24	-3.43	0.002
ALT(0-30 U/L)	32.3±19.1	35.1±17.6	0.446	0.658
AST(0-40 U/L)	73.2±40.9	50.2±23.6	2.117	0.0042
ALP(50-160 U/L)	78.3±30.4	97.8±47.4	1.493	0.145
GGT(0-51 U/L)	28.7±16.6	26.6±11.1	0.429	0.67
TBil (<1.0 mg/dL)	2.1±1.3	3.1±2.8	1.436	0.16
DBil (<0.2mg/dl)	0.9±0.7	1.4±1.3	1.241	0.223
Alb (3.5-5.5g/dL)	2.1±0.4	2.0±0.4	0.262	0.795
INR (0.8-1.2)	1.4±0.2	1.5±0.3	0.521	0.605
Creatinine (0.6 to 1.5mg/dl)	0.9±0.3	0.8±0.2	1.339	0.189
Spleen size (7-12cm)	16.8±1.8	14.5±1.4	4.112	0
PV flow velocity (15.2 +/- 2.6 cm/sec)	14.4±5.9	32.3±10.3	5.569	0
Thrombopoietin(pg/mL)	139.5±109.8	131.8±35.8	0.193	0.848

Operative data

Table 3 shows the recorded operative time, transfusion units required and measured portal blood pressure in both groups. The mean duration of operation was significantly longer (11.80±2.65) hrs in patients with persistent thrombocytopenia compared to (8.75±1.08) hrs in patients with normal platelets count. The mean intraoperative portal blood pressure was 85±3 mmHg, 78.5±2.5mmHg for group I and II respectively and it was which showed significant difference as well.

Intra operative complications (Table 4) were significantly more frequent in patients with persistent thrombocytopenia at one year postoperative.

Table 3 Operative data

Parameters	Group I (n=20)	Group II (n=16)	Test	P value
Operative time* (hr)	11.80±2.65	8.75±1.08	t= 4.319	0.0001
Cold ischemia time* (min)	45.05±31.34	40.50±16.84	t=0.522	0.6051
Packed RBCs#(units)	3 (1-24)	3 (0-8)	t=1.57	0.125[1]
FFP# (units)	1 (0-24)	2 (0-8)	Z= 0.217	0.8382
Cryoprecipitate# (units)	0 (0-24)	0 (0-1)	Z= 1.15	0.2492
Fibrinogen* (units)	0.20±0.62	0.50±1.37	t=0.879	0.3861
Intraoperative portal blood pressure (5-10 mmHg)	85±3	78.5±2.5	t=0.879	0.08[1]

t- Test; *-mean±SD; Mann Whitney test- #median (range)

Table 4 Intraoperative Complications

	Group I (n=20)	Group iI (n=20)	P value
Intraoperative complications	10 (50%)	2 (12.5%)	**0.032**
Local bleeding	3	0	
Intra and postoperative vascular anastomosis complication with stent insertion	2	0	
Weak hepatic artery flow	3	0	
Ligation of splenic artery	0	2	
Hepatic artery thrombosis	2	0	

Citation: Hussein M, Elmeteini M, Bahaa M, et al. Study of factors contributing to persistent thrombocytopenia following liver transplantation. *Gastroenterol Hepatol Open Access.* 2016;5(4):268–276. DOI: 10.15406/ghoa.2016.05.00146

Postoperative data

Serial changes in platelets count, portal haemodynamics and thrombopoietin levels: The mean platelet count of all patients showed tendency to decrease during the first postoperative week to reach a nadir around day 3 then gradually rise through follow up (Figure 1). As we separated both groups (Figure 2), we observed that platelets in group I increased gradually and reached maximum value at 1st postoperative month, then decreased and remained below normal levels till 12 m postoperatively. In group II, platelets showed mild decrease in the first week following LDLT and then increased gradually and recovered to normal value 2 weeks postoperatively then showed gradual rise till the end of the 12th postoperative month.

In both groups there was a progressive decrease in spleen size and portal vein flow velocity during the one year follow up period. Although preoperative spleen size and portal vein flow velocity were significantly correlated with changes in platelet count, on follow up this relation was lost (Figures 3 & 4).

The measured serum levels of TPO preoperative, early (12 weeks) and late postoperative (6 months) periods are presented in Figure 5. Serum TPO levels were not significantly different between the two groups preoperatively and late postoperatively, however, early postoperative period showed significant increase in serum TPO level in patients with persistent thrombocytopenia (group I) (p=0.031).

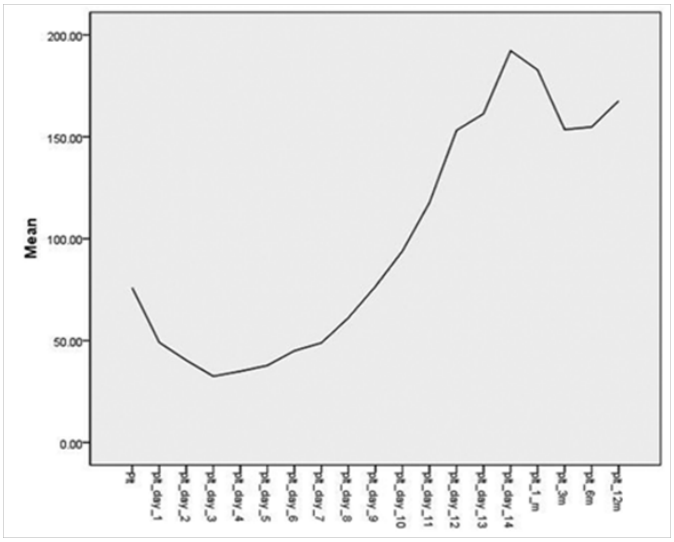

Figure 1 Serial follow up of platelet count in the whole study population.

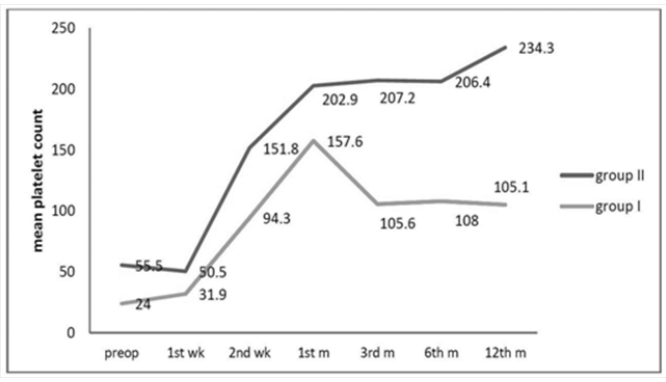

Figure 2 Serial mean platelet count of both groups during follow up.

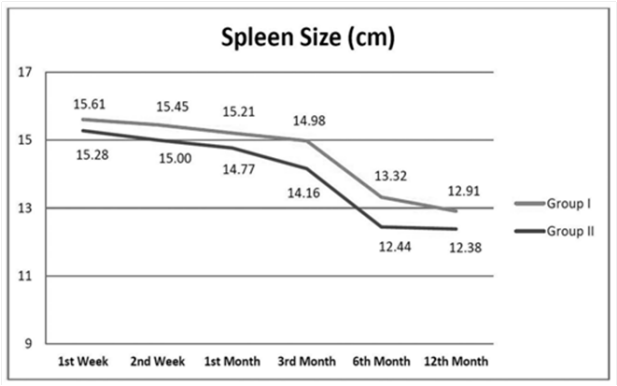

Figure 3 Mean spleen size of both groups during follow up.

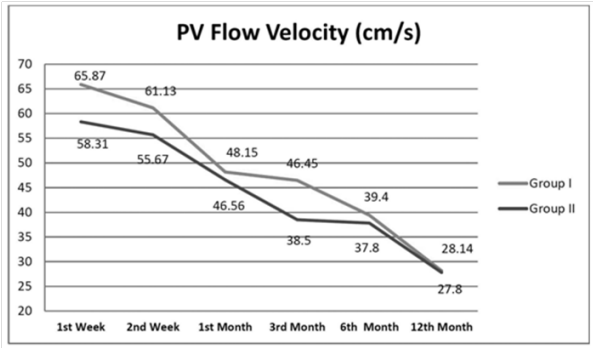

Figure 4 Mean portal vein flow velocity during follow up.

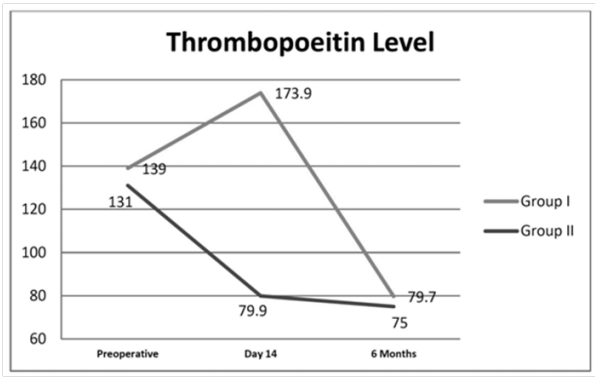

Figure 5 Serial follow up of TPO level in the 2 subgroups.

Immunosuppression and Postoperative complications: Table 5 shows the used immunosuppression medications in both groups which had no relation to differences in platelets count. Figure 6 shows frequency of postoperative complications occurred during follow up. None of them was significantly higher in either of the two groups.

In Table 6 all statistically significant data obtained by univariate analysis were compared to obtain their sensitivity and specificity as predictors of post-transplant thrombocytopenia. The highest sensitivity was for preoperative portal flow velocity and highest specificity was for GRWR. The table also shows that preoperative platelet count, operative duration and GRWR have highest positive predictive values. Accordingly, the following cut off values can be used to predict postoperative thrombocytopenia; prolonged operative time more than 10 hours, preoperative platelet count less than 72x 109/L, preoperative portal vein flow velocity less than 30 cm/sec and preoperative AST greater than 55 U/L can all be used to predict thrombocytopenia postoperatively.

Citation: Hussein M, Elmeteini M, Bahaa M, et al. Study of factors contributing to persistent thrombocytopenia following liver transplantation. *Gastroenterol Hepatol Open Access.* 2016;5(4):268–276. DOI: 10.15406/ghoa.2016.05.00146

Table 5 Postoperative immunosuppressive medications

Drugs	Group I (n=20)	Group II (n=16)	P Value
CNI	20 (100%)	16 (100%)	>0.05**F**
MMF	12 (60%)	14 (87.5%)	>0.05**F**
mTOR inhibitors	9 (45%)	7(43.8%)	>0.05**F**

F Fisher Exact test

Table 6 Predictors of post liver transplant persistent thrombocytopenia

Predictor	Cut off	Predictive accuracy	Sensitivity	Specificity	PPV	NPV
Preoperative Portal Vein flow velocity	≤30	90.60%	100%	43.80%	69%	100%
Operative duration	≥10	90.20%	85%	87.50%	89.50%	82.40%
Preoperative Plt	≤72	89.50%	90%	87.50%	90%	87.50%
GRWR	≥1.11	80.30%	70%	100%	100%	72.70%
Preoperative Spleen size	≥16	78%	70%	87.50%	87.50%	70%
Preoperative AST	≥55	73%	80%	68.80%	76.20%	73.30%
Preoperative WBC	≤3.6	70.50%	60%	87.50%	85.70%	63.60%

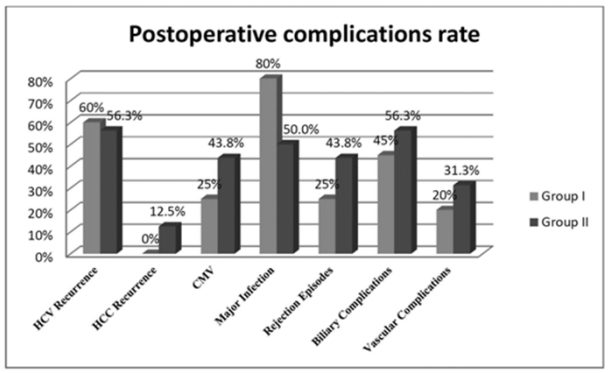

Figure 6 Postoperative complications in both groups.

Discussion

Thrombocytopenia occurs in the majority of cirrhotic patients. Platelets count typically normalizes after liver transplantation (LT). In most instances early thrombocytopenia recovers with restoration of hepatic function and resolution of portal hypertension, but generally nadir during the first postoperative week.[10]

In the current study, 36 recipients of LDLT were followed for one year after surgery to monitor changes in their platelets count. We observed that at the early postoperative period, there was a drop in platelets count in most of the included patients reaching a nadir (minimal value) at POD 3. Then a gradual rise occurred to reach and even exceed the preoperative count in the second week. Patients with persistent thrombocytopenia at one year showed initial early improvement without complete recovery in platelets count during the first month before it drops slightly and then remained below normal values through follow up but it was generally higher than the preoperative value.

While, platelets count showed complete recovery within two weeks in recipients without persistent thrombocytopenia and kept within normal values during their follow up. Many studies had described the early drop in platelets count after LT; Goulis et al.[11] reported decrease in *platelet count from baseline in all the transplanted patients in the first days after OLT to reach a nadir concentration on POD 5.*[11] Other study by Richards et al.[2] *reported significant fall in median platelet count from preoperative levels by the 1st POD. The median day of the nadir platelet count in all patients was day 4. The platelet count then increased and the median preoperative platelets count was exceeded on day 11.*[2]

Fayed et al.[13] also *described continued decline of platelet count after LT with nadir at POD 5.*[12] *Others showed that* platelets count remained at low levels until POD7 and significantly increased on POD14 regardless of splenectomy.[13]The mechanism of early drop in platelets count following LT mechanism has been thought to be sequestration of platelets in the graft liver. The local thrombin generation released due to graft injury by hypoxia contributes to platelets aggregation inside the graft.[12,13]

Frequency of persistent thrombocytopenia observed in our study at one year was (56%) which is similar to that reported by Sutedja et al.[14] (54% at one year). In their study, this percentage decreased to 25% after 3 years of follow up.[14] Analysis of our results suggested that preoperative portal hypertension is the major factor influencing the results. Recovery of severe preoperative portal hypertension may need more than one year thus resulting in late platelets recovery.

However, Cezar et al.[15] reported that only 16.9% of their patients remained with thrombocytopenia one year after LT. This lower percentage can be explained by the cut off value used to define thrombocytopenia; Cezar and his colleagues defined thrombocytopenia as platelets < 100 x 109/L.[15] In contrast, Sutedja et al.[14] and our study considered platelets count <150 x 10^9/L as thrombocytopenia.

Preoperative, operative and post operative factors significantly related to thrombocytopenia at one year

Patients included in our study were comparable as regard severity of liver disease before liver transplant surgery as their mean value of both Child and MELD scores were not significantly different. However analysis of their preoperative laboratory data showed strong evidence that patients with thrombocytopenia at one year had more severe portal hypertension; First, preoperative CBC in patients with persistence of thrombocytopenia (group I) showed significantly lower platelets and WBCs count. They also had lower mean Hb value compared to the

other group. Second, splenomegaly was more marked in patients with thrombocytopenia (being 16.8±1.8cm) compared to those without thrombocytopenia (their mean size was 14.5±1.4 cm). A third point is that the estimated PV flow by doppler US was significantly lower (14.4±5.9 cm/sec) in group of persistent thrombocytopenia compared to recipients with recovered platelets count (mean PV flow 32.3±10.3 cm/sec). It is to be mentioned that in severe parenchymal liver disease, portal venous flow is reduced.[16]

The effect of the severity of preoperative portal hypertension on postoperative platelets count can be explained by the fact that worsening of portal hypertension leads to increased platelets sequestration and destruction in the enlarged spleen and thus there is an inverse relation between platelets count and progression of liver fibrosis.[17] Our findings are supported by some previous reports; Chang et al.[18] suggested that severe thrombocytopenia before transplant is closely associated with delayed recovery of platelet count after transplant.[18] They explained their findings that splenomegaly is sustained for several years after operation even though the graft liver restores normal portal hemodynamics relatively soon after the operation.

Stanca et al.[19] showed that increased spleen size and low platelet count at the time of LT are associated with persistent thrombocytopenia after LT.[19] They are also independent predictive factors of platelet levels at 3 and 12 months after LT. Ohira et al.[20] found that if both splenomegaly and thrombocytopenia coexist (PLT count ≤ 50x103 / mm3); persistent thrombocytopenia is predictable after LT.[20]

Honda et al. also reported that preoperative platelets count was the only factor significantly associated with thrombocytopenia at 12 months after LDLT in pediatric patients.[21] Our conclusions about the role of preoperative portal hypertension in prediction of persistent thrombocytopenia following liver transplantation are supported by Sutedja et al.[14] findings. They identified pretransplant variceal bleeding, splenomegaly, and thrombocytopenia at 3 and 6 months post-transplant as factors associated with persistent thrombocytopenia.[14] After multivariate analysis only the latter represented independent factors for persistent thrombocytopenia at 1 and 3 years post-transplant.

In the study by Eyraud et al.[22] PBF was lower before OLT, than after OLT. Yet, the evolution of PBF did not correlate with platelet counts either before or after OLT.[22] They concluded that platelet count and PBF increase rapidly after LT, whereas spleen size slowly decreases. Thrombocytopenia and splenomegaly are results of portal hypertension, but the rapid normalization of PBF does not completely or rapidly reverse these two phenomena.[22] Jiang et al. .[23] found that PBF velocity of the recipients increased significantly after LDLT then decreased.[23]

In our work, patients with persistent thrombocytopenia had higher intraoperative portal venous pressure (PVP) which was 85±3mmHg in group I and 78.5±2.5 mmHg in group II. This correlation was not strongly significant (P=0.08). Marubashi et al.[24] showed that PVP was the most significant determinant of platelet counts after LDLT. This is reasonable because PVP, which is influenced by the graft portal venous vascular resistance and the recipient's splanchnic flow to the portal vein, is closely related to splenomegaly and hypersplenism.[24]

Patients with advanced liver disease are characterized by high portal resistance, which results in low PBF, splenomegaly, and thrombocytopenia. After OLT, portal resistance rapidly decreases, except in patients with small-for-size liver grafts, whereas the spleen volume slowly decreases but remains high months after transplantation, especially in patients with major splenomegaly.

GRWR: Analysis of our data also showed that GRWR was significantly higher in recipients with persistence thrombocytopenia compared to recipients with recovered platelets count. The early changes that occur after graft reperfusion include immediate pooling of platelets in the liver graft.[25] So, reduction in platelets count expected in early postoperative period maybe directly proportional to the size of the graft. However, this finding does not necessarily explain why thrombocytopenia persisted till 1 yr post-transplant. In our results, multivariate analysis showed that GRWR was not an independent risk factor for persistent thrombocytopenia.

Preoperative AST level: In our study patients with high preoperative AST levels were significantly associated with persistent thrombocytopenia after LT. This mostly reflects the severity of hepatic fibrosis before transplantation. It was previously proposed that progression of liver fibrosis may reduce AST clearance, leading to increased serum levels; in addition, liver disease may be associated with mitochondrial injury, resulting in further AST release from the hepatocytes especially in cases of HCV due to oxidative injury that occurs as a direct result of HCV core protein expression.[26] Several authors agreed that AST level is an indicator of liver fibrosis.[27–29]

Serial follow up of spleen size and portal blood flow postoperative: In the current study, we found that platelet count was significantly different between the two groups not only in the preoperative period but also through the whole year of follow up. Recipients who remained thrombocytopenic by the end of the first year showed significant difference in their platelets count at 1st wk, 2nd wk, 1st month, 6th month and one year compared to recipients with recovered platelets count at same intervals.

In our study, portal blood flow increased in both groups (all patients) early postoperative period to reach a higher than average normal levels due to resolution of portal hypertension. Then it showed gradual decrease and stabilization in both groups. Reported values were not significantly different between both groups all through the follow up period which can be explained by the recovery of portal hypertension following liver transplantation. Spleen size showed gradual decline in both groups all through the follow up period but its mean size remained bigger in patients with persistent thrombocytopenia which was significant between both groups at 6 months of follow up.

Cezar et al.[15] demonstrated that LT reverses hypersplenism in the majority of patients and that thrombocytopenia post LT correlates with spleen size. They suggested that in cases of splenomegaly, the structural changes in the spleen, including fibrosis and hyperplasia, do not allow the complete return to normal size following normalization of portal hypertension after LT.[15] Thus, some degree of splenomegaly and thrombocytopenia persists in a significant number of patients who were subjected to LT. They also concluded that persistence of hypersplenism after LT in the absence of other clinical findings does not necessarily mean presence of portal hypertension secondary to recurrent liver disease or the presence of vascular complication.

In other study done by Chikamori et al.[30] pre- and post liver transplantation spleen volumes were significantly bigger in patients with persistent thrombocytopenia compared to patients with recovered platelets count. They concluded that patients with severe hypersplenism might have a potential risk of thrombocytopenia recurrence in the follow-up period after LT.[30] Many investigators agreed with that.[10,14,20,22]

Blood products transfusion: Requirements of transfusion of various blood products in our study did not significantly differ between the two groups, although several studies proposed that blood products transfused may affect postoperative platelet count.

A study done in Menoufeya University reported that platelet transfusion lead to delayed recovery of platelets, increased duration of mechanical ventilation and ICU stay.[12] deBoer et al.[31] found that all types of blood product transfusion (RBC, FFP, and platelets) were negatively associated with graft survival and patient survival. They suggested that the risk of allogeneic blood transfusion included allergic reactions, alloimmunization, bacterial sepsis, transfusion related acute lung injury, graft-versus-host-disease and renal failure.[31]

Operative time: In our work, univariate analysis revealed that operative time had significant correlation with persistence of thrombocytopenia after LT. The reason may be related to prolonged warm and cold ischemia times as our results showed that cold ischemia time was longer in group I compared to group II. Longer duration of surgery was also associated with intraoperative complications which were more frequent in group I.

Chang et al.[32] also reported that longer operation time was among the significant predictors of the severity of thrombocytopenia after the liver transplants.[32]

Thrombopoietin levels: Thrombopoietin (TPO) is produced primarily in the liver and degraded by circulating platelets. Data in the literature about TPO levels and its relation with thrombocytopenia in cirrhotic patients are conflicting .[33]. While some of the studies described low plasma levels of TPO in patients with liver cirrhosis,[34–38] others found normal or high plasma levels of TPO in cirrhotic patients.[39–41]

In our study preoperative TPO levels were not different significantly between both groups, they were within normal ranges. Early after LT, group I patients had an increase in TPO levels unlike group II. This rise in TPO can be explained by synthesis of excess TPO by the new liver to compensate for the marked preoperative thrombocytopenia. Such increase in TPO was not seen in group II patients because they already showed recovery of thrombocytopenia so there was no need for excess TPO. In other words, there was an inverse relation between platelets count and TPO level at the second week. Group II patients showed decline of TPO two weeks after transplantation and platelet counts were increasing. This could be attributed to the possibility that this group of patients had TPO peak earlier than two weeks which was not measured in our study. At six months, TPO level in both groups had normal values. The reason why group I had normal TPO levels at six months despite persistence of thrombocytopenia is unclear.

The pattern of TPO in group I was similar to the study by Faeh et al;[42] before transplantation, TPO levels did not differ significantly between patients. It was in lower normal range then a prominent rise was seen in all patients between day 2 and day 17 after transplantation. It was noticed that the TPO level peaks were followed within 3 days by a platelet concentration rise, which then continued to rise even that TPO levels fell to normal range. In their study, all patients had platelet concentrations in the normal range at the end of the1st month.[42] However, this study had a shorter follow up period up to 1st postoperative month.

Goulis et al.[43] had similar results. Thrombopoietin concentrations increased from day 1 after OLT and reached a peak on day 5. The rise in TPO concentrations was significant in patients with low baseline platelet count, but not in transplanted patients with normal baseline platelet count.[43] Others also observed the rise in TPO level in early postoperative period and its return to normal values by POD15.[44,45]

In our work, it was also noticed that thrombopoietin levels in patients of both groups fell to the lower normal range after 6 months of transplantation while platelet counts were decreased in group I and increased in group II at that time. More frequent measures of TPO levels may be needed for better understanding of its role in platelets recovery following LT.

Complications and postoperative data: Unlike intraoperative complications, complications occurred in postoperative period were not predictive to persistent thrombocytopenia. However, incidence of postoperative infections was interestingly higher in group I in our study. Some reports showed that thrombocytopenia following LT is linked to severe sepsis and higher morbidity.[46] Others showed that nadir platelets count was lower in patients who died.[18,47] The association between thrombocytopenia and infections was explained by an evident role of platelets' proteins as microbicidal agents.[46]

Fungal and viral infections are also related to lower platelets count in transplanted patients.[32,44] All fungal infections in a study by Chang et al. occurred in patients with nadir platelet counts of $43x10^9$/L. The authors suggest that platelets may have an important role in defense against fungal infection as well.[32] However, it is also possible that a common factor such as poor graft function may predispose to both thrombocytopenia and opportunistic infection.

Conclusion

In conclusion, our study showed that preoperative platelet count, operative time, preoperative AST level, and preoperative PV flow velocity were independent predictors of postoperative persistent thrombocytopenia. They may also predict the outcome of liver transplant.

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Conflicts of interest

The authors declare no conflicts of interest.

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