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Peripheral platelet count correlates with liver atrophy and predicts long-term mortality on the liver transplant waiting list

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Summary

Several studies have shown a direct role of liver atrophy in the pathogenesis of thrombocytopenia of cirrhosis via reduced production of thrombopoeitin. About 181 patients listed for liver transplantation at a single transplant center were evaluated at the time of listing with laboratory tests and volumetric liver measurements using computed tomography. Expected normal liver volume was calculated using the Heinemann formula. Liver volume ratio (LVR) was calculated as actual liver volume over expected liver volume. Patients were predominantly male (70.7%), with viral hepatitis (60.2%), had a mean age of 51.8 years (SD 8.7), model for end stage liver disease (MELD) of 14 (SD 6.4), LVR of 0.95 (SD 0.3), and platelet count of 105 000/mcL (SD 66 000). Platelet count ($P < 0.0001$) correlated more strongly with LVR than MELD, MELD components ($P = 0.27$) or serum albumin ($P = 0.003$). Platelet count (HR 0.987, 95% CI 0.979–0.994, $P = 0.001$) was a strong independent predictor of mortality. Patients with platelet count < 100 000/mcL had a shorter survival (935 vs. 1396 days, $P = 0.002$) and higher death rate (42.2% vs. 23.6%, $P = 0.01$), but no different transplantation rate (36.7% vs. 33.3%, $P = 0.64$) compared to those with platelet count $\geq$ 100 000/mcL. Low platelet count corresponds to higher waiting list mortality and is a sign of advanced liver atrophy.

Introduction

A significant percentage of patients with chronic liver disease will progress to develop cirrhosis thereby carrying high morbidity and mortality rates [1,2]. Thus, various scoring systems have been developed to assist in predicting mortality in this patient population. The most commonly used scoring system in the United States and Europe is the model for end stage liver disease (MELD) and it has been accepted over Child-Pugh-Turcotte (CPT), as it is more objective and has a wider continuous disease severity scale [3–6].

Despite its well-established accuracy in predicting short-term mortality, MELD is not a perfect system and it has known shortcomings [7,8]. Although bilirubin and international normalized ratio (INR) are good markers of the synthetic function of the liver and serum creatinine reflects severity of renal impairment related to liver disease, MELD does not directly account for severity of portal hypertension. In addition, all three components of MELD can be significantly affected by nonliver related conditions, such as the use of anticoagulants, renal failure unrelated to liver disease, and benign hyperbilirubinemia or cholestatic liver disorders [9–11]. Furthermore, the reliability of standardization of INR in patients with liver disease has been questioned and the interlaboratory variability in all the three components of MELD has been shown to significantly

affect the calculated MELD score and thus patient transplant status [12–14].

The role of platelet count in predicting mortality on the liver transplantation list has not been completely studied. Thrombocytopenia is a known complication of cirrhosis and it has been for many years considered to be simply a result of portal hypertension and splenomegaly. Further studies have suggested a direct role of cirrhosis and loss of liver mass due to parenchymal extinction caused by microthrombosis and in lowering the production of megakaryocytes via decreased levels of circulating thropopoietin [15,16]. These findings could possibly indicate that the degree of thrombocytopenia may reflect the severity of liver atrophy as well as the associated complications of portal hypertension.

The aim of this study was to evaluate the relation between peripheral blood platelet count and liver atrophy and mortality on the liver transplantation waiting list.

Patients and methods

This retrospective study was conducted at Beth Israel deaconess Medical Center (BIDMC), Boston, MA and the University of Virginia, Charlottesville, VA and was approved by the institutional review boards (IRB) of both facilities. All adult patients referred to the Liver Transplant Institute at BIDMC between January 2001 and April 2006 were evaluated. Patients with a known history of hepatocellular carcinoma (HCC), patients who were evaluated for living donor liver transplantation (LDLT), and those receiving MELD exception points were excluded (Fig. 1).

Study personnel reviewed the electronic medical record system and collected demographics on the study population, including age, gender, serum bilirubin, serum creatinine, INR, serum albumin, and etiology of liver disease at time of evaluation for liver transplantation (entry point). MELD score was calculated using the published formula (0.957 * ln(Serum Cr) + 0.378 * ln(Serum Bilirubin) + 1.120 * ln(INR) + 0.643) * 10 [8]. Actual liver volume was measured by 3 dimensional reconstruction of computed tomography (CT) images of the liver.

The CT evaluation of the liver was performed as part of a protocol for liver transplantation. Laboratory data, height, and weight were collected within 1 month of the time of CT. The liver CT scan was performed as contrast-enhanced multiphase helical imaging using a 64-row multidetector CT scanner. The intravenous injection of 180 ml of contrast material was performed at 5 ml/s. Arterial phase images were acquired at 18 s (collimation, 1.25 mm; table speed, 7.5) and portal phase images at 60 s (collimation, 2.5 mm; table speed, 15). The actual liver volume (ALV) was assessed on the delayed-phase axial reformatted images using 3D reconstruction techniques. These techniques have been previously described by Kamal *et al.* [17,18]

The expected liver volume (ELV) was determined using the Heinemann formula (Liver volume (ml) = 1072.8 * body surface area (m^2)−345.7) [19]. Body surface area (BSA) was calculated using the Dubois and Dubois formula [20]. BSA = 0.20247 × height $(m)^{0.725}$ × weight $(kg)^{0.425}$. Subsequently, the liver volume ratio (LVR) was expressed as a ratio of ALV to ELV. As an illustration of this, a patient with body height of 170 cm and weight of 79.4 Kg would have a BSA of 1.937 m^2. Subsequently, the Heinemann formula gives him an expected liver volume of 1732 ml. If his actual liver volume using CT volumetry were 1247 ml, the LVR would be 1247/1732 = 0.72. This indicates that the liver has lost 28% of its predicted volume due to cirrhosis.

Subsequently, we prospectively followed the patients from April 2006 until January 2011. The primary endpoint of this study was determined as death on the liver transplant waiting list. A total of 28 patients were lost to follow up. The social security death index (SSDI) (www.rootsweb.ancestry.com) was used to determine any deaths among this group.

All statistical analyses and data manipulation were performed using SAS© Version 9.2 (SAS Institute Inc., Cary, NC, USA) or SPSS (version 19.0, IBM SPSS, NY, USA). Categorical variables were compared using chi-square analysis or Fisher exact test where appropriate. Continuous variables were analyzed using the Wilcoxon sign-rank test or independent sample *t*-test as appropriate. Unadjusted survival was calculated using Kaplan–Meier estimates. Multivariate survival models were constructed using logistic regression and proportional hazards modeling with an endpoint of death on the waiting list and censoring at the time of liver transplantation using the method of maximum likelihood estimates. Type one error differences at the 0.05 level or less were considered statistically significant. All statistical tests were two-sided.

Results

A total of 253 patients were evaluated at the Liver Transplant Center at BIDMC over the study time period. Of these patients, a total of 181 patients were included in the study after excluding those who met an exclusion criterion or did not have liver volume determined using CT volumetry. Among the 181 patients included in the study, there were 63 deaths (34.2%), 64 liver transplants (35.4%), and 54 (30.4%) survivals at the last follow up (Fig. 1). The patients in this cohort were predominantly male (70.7%), suffered from chronic viral hepatitis (60.2%), had a mean age of 51.8 years (SD 8.7), a mean MELD score of 14 (SD 6.4), and a mean platelet count of 103 000/mcL (SD 66 000) at the time of the liver volumetric assessment. The

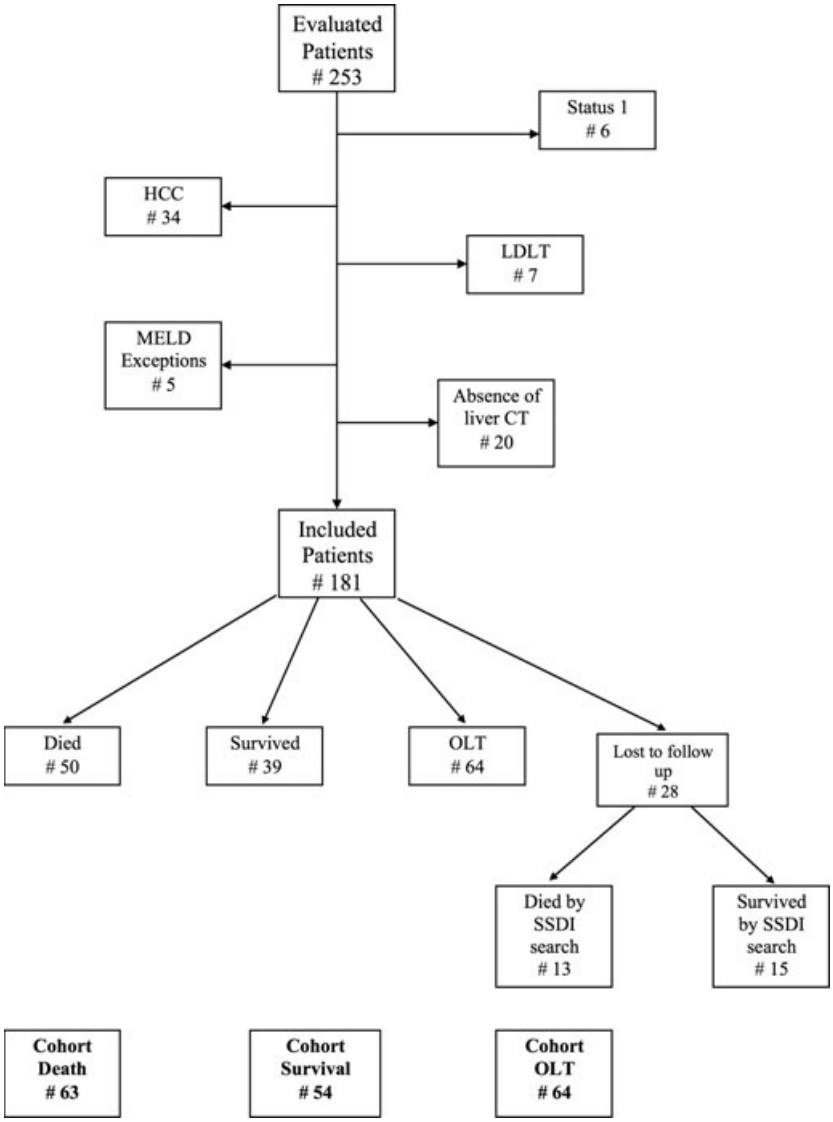

Figure 1 Flow Chart. HCC, Hepatocellular carcinoma; LDLT, Living donor liver transplant.

mean LVR was 0.96 (SD 0.31). (Table 1) The rate of death and transplantation rapidly increased over the first 2.5 years on the waiting list and at a 10-year time interval only 30.3% of the patients were alive without transplantation (Fig. 2). The cause of death was liver related in 85.9% of the cases (liver failure, variceal bleeding, and hepatocellular carcinoma). In 3.5% of the cases, the death was not liver related (lung cancer and lymphoma), 8.8% (unknown) and 1.7% was due to motor vehicle accident.

Patients who died on the waiting list had a significantly lower platelet count (104 000 vs. 116 000 per mcl, $P < 0.0001$) and smaller actual liver volume (LVR 0.88 vs. 0.98, $P = 0.044$) compared to those who survived to the end of the study. Neither MELD score (13.7 vs. 13.9, $P = 0.78$) nor any of MELD's components were statistically different between the two groups. In addition, there was no statistically significant difference between the two groups with regards to etiology of liver disease, height, weight, BSA, expected liver volume, or serum albumin. (Table 1)

In a univariate survival analysis, several factors were predictive of waiting list mortality, including INR (HR 2.145, 95% CI 1.370–3.358, $P = 0.001$), bilirubin (HR 1.037, 95% CI 1.005–1.070, $P = 0.023$), albumin (HR 0.443, 95% CI 0.286–0.689, $P < 0.0001$), MELD (HR 1.064, 95% CI 1.026 –1.102, $P = 0.001$), and platelet count (HR 0.986, 95% CI 0.978–0.993, $P < 0.0001$). Creatinine was not predictive of waiting list mortality (HR 0.802, 95% CI 0.401–1.604, $P = 0.5$). In multivariate Cox–regression analysis, platelet

Table 1. Comparison between patients who died and those who survived on the waiting list.

	Total population	Alive	Died	*P*
Number	181	118	63	N/A
Age	51.82 (8.7)	51.9 (8.0)	51.7 (10.0)	0.90
Sex (male)	71%	72%	70%	0.76
Etiology				
Cholestatic	5%	6%	3%	0.42
Alcohol	27%	31%	19%	0.076
Viral	60%	57%	67%	0.20
Others	8%	6%	11%	0.21
Height (cm)	172 (9.4)	172 (9.3)	172 (9.5)	0.99
Weight (kg)	82 (18.7)	83 (18.4)	80 (19.2)	0.34
BSA	1.97 (0.26)	1.98 (0.25)	1.95 (0.27)	0.40
Bilirubin	4.2 (6.2)	4.2 (5.7)	4.1 (7.0)	0.95
INR	1.5 (0.4)	1.5 (0.4)	1.6 (0.4)	0.63
Creatinine	0.99 (0.5)	1.03 (0.5)	0.92 (0.4)	0.15
Albumin	3.2 (0.6)	3.3 (0.6)	3.1 (0.6)	0.21
MELD	14 (6.4)	13.9 (6.7)	13.7 (5.8)	0.78
Platelet count	103.6 (65.8)	116.3 (75)	80 (33)	<0.0001
ALV	1665.5 (572)	1728.4 (597.2)	1547.5 (505.2)	0.042
ELV	1769.5 (275.5)	1782.3 (270.2)	1745.4 (285.9)	0.39
LVR	0.95 (0.3)	0.98 (0.3)	0.88 (0.2)	0.044
Survival (days)	1118.2 (1009.6)	1313.5 (1077)	752.4 (749)	<0.0001
Survival (%)	30.4%	100%	0%	N/A
Death (%)	34.2%	0%	100%	N/A
Transplant (%)	35.4%	54.24%	0%	N/A

BSA, Body surface area; INR, international normalized ratio; MELD, model for end stage liver disease; ALV, actual liver volume; ELV, expected liver volume; LVR, Liver volume ratio.

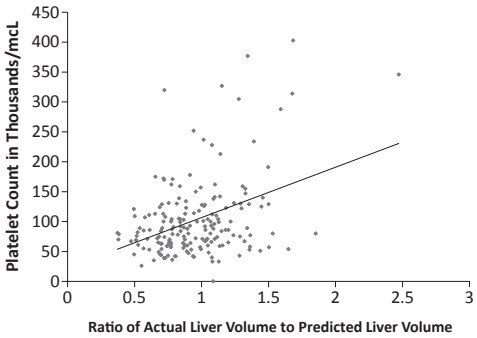

Figure 2 Platelet Count versus Ratio of Actual Liver Volume to Expected Liver Volume. This scatter plot demonstrates a strong correlation between peripheral platelet count and liver volume ratio (LVR) calculated as the ratio of actual liver volume determined using CT volumetry and expected liver volume. LVR reflect the degree of liver atrophy thereby platelet count strongly correlates with liver atrophy.

count (HR 0.987, 95% CI 0.979–0.994, $P = 0.001$) and MELD score (HR 1.046, 95% CI 1.006–1.087, $P = 0.024$) were strong predictors of mortality. This significance persisted after adjusting for etiology of liver disease in the multivariate analysis regarding platelet (HR 0.987, 95% CI 0.980–0.995, $P = 0.0013$) and MELD score (HR 1.076, 95% CI 1.029–1.124, $P = 0.0012$). There was a linear correlation between platelet count and length of survival on the liver transplant waiting list ($P = 0.01$). In these analyses, death was considered as the negative outcome, whereas patients who underwent liver transplantation were censored at the time of transplantation. Furthermore, we repeated the analyses using a competing risks technique in which death and orthotopic liver transplantation (OLT) were considered competing events. This did not significantly alter the results (platelet: HR 0.987, $P = 0.003$; MELD: HR 1.055, $P = 0.02$).

Patients with lower platelet counts had significantly higher risk of death on the waiting list. Using platelet count of 100 000/mcL as a cut-off value, patients with platelet count of less than 100 000/mcL had a mean survival of 935 days in comparison to 1396 days for the group with higher platelet counts ($P = 0.002$). At the same time, 21% of the patients with lower platelet count survived without transplantation in contrast to 43% of the group with higher platelet count ($P = 0.0026$). Lower platelet count was associated with slightly younger age (50.5 vs. 53.8, $P = 0.011$), less cholestatic and alcoholic liver disease (0.9% vs. 11%, $P = 0.003$ and 20.2% vs. 37.1%, $P = 0.016$, respectively), more viral hepatitis (71.6% vs. 43.1%, $P = 0.0002$), smaller liver volume (LVR 0.89 vs. 1.02, $P = 0.005$), marginally lower albumin (3.14 vs. 3.32, $P = 0.058$) and higher

Table 2. Comparison between patients using platelet count of 100 000 as cut-off.

	Platelet < 100 000/μl	Platelet ≥ 100 000/μl	$P = 0.001$
Number	109	72	N/A
Age	50.5 (8.5)	53.8 (8.7)	0.011
Sex (male)	73.4%	68%	0.44
Etiology			0.0001
Cholestatic	1%	8%	
Alcohol	22%	49%	
Viral	78%	31%	
Others	8%	6%	
Height (cm)	172.4 (9.3)	171.9 (9.6)	0.72
Weight (kg)	83.2 (18.8)	80.4 (18.5)	0.34
BSA	1.99 (0.26)	1.95 (0.25)	0.34
Bilirubin	4.7 (6.9)	3.4 (4.8)	0.17
INR	1.61 (0.43)	1.44 (0.36)	0.006
Creatinine	0.97 (0.430)	1.02 (0.51)	0.51
Albumin	3.14 (0.58)	3.32 (0.67)	0.058
MELD	14.61 (6.8)	12.68 (5.5)	0.047
Platelet count	66.5 (17.2)	159.3 (72.3)	N/A
ALV	1586.6 (520.5)	1784.8 (627.4)	0.022
ELV	1785.3 (277.1)	1745.4 (273.3)	0.34
LVR	0.89 (0.28)	1.02 (0.33)	0.005
Survival (days)	934.7 (916.3)	1396 (1084.9)	0.002
Survival (%)	21.1%	43.1%	0.0026
Death (%)	42.2%	23.6%	0.01
Transplant (%)	36.7%	33.3%	0.64

BSA, Body surface area; INR, international normalized ratio; MELD, model for end stage liver disease; ALV, actual liver volume; ELV, expected liver volume; LVR, Liver volume ratio.

MELD (14.61 vs. 12.68, $P = 0.047$). Among MELD components, only INR was significantly different between the two groups (1.61 vs. 1.44, $P = 0.006$). The group with lower platelet count had a 42.2% death rate on the waiting list in comparison to 23.6% in the group with higher platelet count ($P = 0.01$), whereas the percentage of patients receiving liver transplantation was not different between the two groups (36.7% vs. 33.3%, $P = 0.64$). (Table 2) Patients with platelet count higher than 100 000/mcL had a significantly higher rate of event-free survival than patients with lower platelet count ($P = 0.002$) (Figs 3 and 4).

In a multivariate regression model, low platelet counts ($P < 0.0001$) correlated more strongly with lower than expected liver volumes than MELD score or any individual component of MELD ($P = 0.27$) or serum albumin ($P = 0.003$). Each 1000/mcL decrement in platelet count below 105 000/mcL correlated with 36 ml of lower liver volume ($P < 0.0001$) than expected based on body surface area.

Discussion

Thrombocytopenia is a common complication of cirrhosis affecting up to 76% of this patient population. The etiology of thrombocytopenia associated with cirrhosis is multifactorial [21]. Although thrombocytopenia is known to be associated with portal hypertension and hypersplenism, it has also not uncommon in cirrhosis patients with normal spleen size [15,22]. In addition, reduction in portal hypertension by means of surgical shunting or placement of transjugular intrahepatic portosystemic shunt (TIPS) does not frequently correct thrombocytopenia [23–26]. Furthermore, in a study by Shah, *et al.*, measurement of spleen volume using ultrasonography and radionuclide testing failed to show a linear correlation between spleen size and peripheral blood platelet counts [22]. Another study that compared spleen volume in patients with cirrhotic versus noncirrhotic portal hypertension found the spleen to be significantly larger in patients with noncirrhotic portal hypertension; however, despite this, the platelet counts of both groups were similar [27].

Several recent studies have suggested a direct role of liver atrophy in the pathogenesis of thrombocytopenia via the reduction in liver derived platelet growth factor thrombopoietin (TPO) [28]. This cytokine is a potent regulator of platelet production and maturation by means of specific receptors on the surface of bone marrow stem cells, megakaryocytes, and platelets [29]. Low level of circulating TPO in cirrhosis is related to decreased hepatic production and increased degradation in the spleen [30]. A study by El-Sayed *et al.* confirmed the reduced level of TPO in cirrhosis patients, whereas its levels were normal in patients with noncirrhotic portal hypertension caused by portal vein thrombosis. In addition, the severity of thrombocytopenia

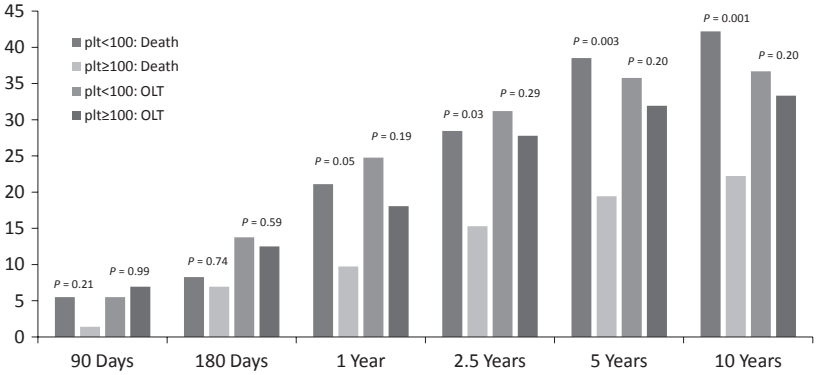

Figure 3 Death and orthotopic liver transplantation (OLT) rates at various time intervals. This chart compares the death and transplantation rate between patients with platelet count < 100 000/mcl and those with platelet count ≥ 100 000/mcl at various time intervals.

was worse in cirrhosis patients than in those with noncirrhotic portal hypertension. This study also showed that lower platelet counts and TPO levels correlated with increased severity of liver disease graded by the CPT scoring system [31]. Furthermore, Koruk *et al.* showed that TPO levels are normal in patients with noncirrhotic chronic liver disease and are below normal with the development of cirrhosis [16].

Liver transplantation has been shown to cause rapid elevation of serum TPO levels followed by normalization of platelet counts after a lag of few days [32]. This has been shown in patients receiving orthotopic [33] or heterotopic liver transplants [34]. Peck-Radosavlievic *et al.* have shown that the serum level of TPO increases within 1 day after liver transplantation and the platelet count rises in 4–5 days, normalizes within 2 weeks, and does not further change over the following year [35]. The facts that reduction in portal hypertension using surgical or radiological procedures does not correct thrombocytopenia, whereas liver transplantation rapidly normalizes platelet counts and that liver graft dysfunction has been shown to be associated with rapid reduction in platelet counts [36,37] indicate a direct role of liver dysfunction and cellular failure in the pathogenesis of thrombocytopenia of cirrhosis.

The size of the liver and its various lobes changes during different stages of cirrhosis and small atrophic livers have been known to be associated with poor liver function and poor prognosis. In their study, Zhou *et al.* evaluated liver volume using CT and demonstrated worsening liver atrophy as CPT class advances [38]. In addition, the liver volume varies based on etiology of liver disease. In a study by Schiano *et al.*, the liver volumes were largest in patients with cholestatic liver disease, followed by those with alcoholic or viral hepatitis, and the smallest liver volumes were noted in patients with cryptogenic cirrhosis [39]. The accuracy of CT in determining the liver volume has been demonstrated in several autopsy and explant studies [39,40]. The correlation between liver atrophy and the severity of thrombocytopenia has not been studied.

Our study demonstrates the high mortality and morbidity associated with cirrhosis with only 30% of patients in this cohort surviving without a negative outcome defined

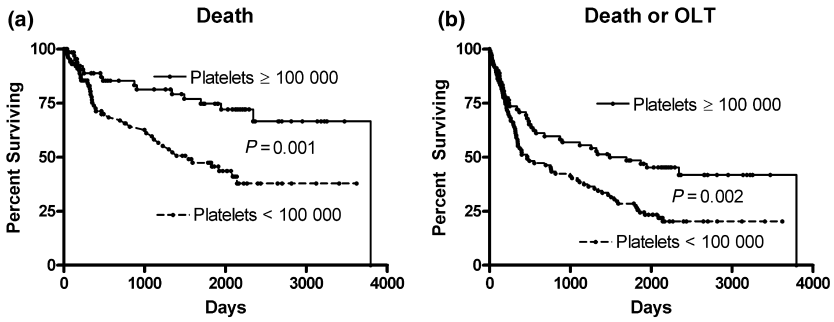

Figure 4 Survival Curves Panel (a) shows a comparison between actuarial survival curves (where death is the negative outcome) for patients with platelet count of less than 100 000/mcl and those with higher platelet counts on the transplant waiting list where patients who received liver transplantation are censored for analysis (Death HR 2.58, 95% CI 1.46–4.57, P = 0.001). Panel (b) shows a comparison between actuarial event-free survival curves (where death or orthotopic liver transplantation (OLT) are the negative outcomes) for patients with platelet count of less than 100 000/mcl and those with higher platelet counts. Death or OLT are counted as negative outcomes (HR for negative outcome: 1.82, 95% CI 1.25–2.65, P = 0.002).

as death or liver transplantation. In addition, despite of advances in the liver transplant prioritization only 35% of the patients in our cohort received a liver transplant and 34% died on the waiting list. The actual death rate was 17% at 1 year, 23% at 2.5 years, and 31% at 5 years. The event-free survival (survival without OLT) at these time intervals was 61%, 47%, and 35%, respectively.

The mean follow-up duration in this study was 1118 days (SD 1009) and only 6% of the patients received a liver transplantation within 90 days of listing. Of the 64 liver transplants seen in this cohort around half happened after more than 1 year of transplant list waiting time. MELD was predictive of mortality, however, despite of the dynamic pattern of listing and frequent upgrading of MELD score on the waiting list, a significant percentage of patients continue to die while waiting for liver transplantation. Platelet count was predictive of short-, mid-, and long-term mortality. Patients with platelet counts of less than 100 000/mcL had a 2.5-year predicted survival of 65% and a 5-year predicted survival of 45%, whereas patients with higher platelet counts had a predicted survival of 85% and 75%, respectively.

In addition, the higher mortality among patients with lower platelet counts was not matched with increased rates of liver transplantation in this group in comparison to patients with higher platelet counts and lower mortality. This happened despite of the dynamic nature of the liver transplant prioritization, which involves frequent updating of MELD scores. This indicates that certain factors associated with increased mortality are not accounted for by MELD and could be reflected by the difference in platelet counts. This fact is supported by the strong correlation between platelet count and the severity of liver atrophy reflected by LVR, which was much stronger than the correlation between MELD or individual MELD components with LVR.

This study has a number of limitations, including the relatively small number of patients, its retrospective nature, and being a single-center study with a homogenous population. Furthermore, the dataset reflects a relatively low MELD score and a low spread of platelet count. These factors limit our ability to generalize conclusions.

In summary, despite the accuracy of MELD in predicting short-term mortality in patients with decompensated cirrhosis, a significant percentage of patients continue to die on the waiting list due to multiple factors including the imperfection of the prioritization system and shortage of available organs. Any increase in the accuracy of the listing system would result in decrease in waiting list mortality and greater success in the process of transplantation. Adding platelet count as a continuous variable or using a particular cut-off may add to the accuracy of MELD and positively affect the waiting process. As our study is of a relatively small sample size, further large-scale studies are warranted to delineate the value of platelet count in predicting mortality in cirrhosis patients.

Authorship

Designed research: Michael Curry, Wissam Bleibel, Patrick Northup, and Stephen Caldwell. Performed research: Wissam Bleibel and Michael Curry. Manuscript writing: Wissam Bleibel, Stephen Caldwell. Data Analysis: Patrick Northup and Wissam Bleibel.

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