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Effect of Preoperative Iron Deficiency in Liver Transplant Recipients on Length of Intensive Care Unit Stay

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ABSTRACT

Liver transplant (LT) recipients often display iron deficiency preoperatively, which significantly increases the quantity of blood that needs to be transfused intraoperatively, A risk factor for a prolonged intensive care unit (ICU) stay. The aim of this retrospective study was to determine whether there was a clinically significant association between iron deficiency and the length of ICU stay, among 153 patients scheduled for OLT from September 2011 to June 2012. Patients were divided into 2 groups according to their baseline iron status: iron- deficient (ID) and non-ID (normal iron profile) cohorts. Iron deficiency was assessed on the basis of several parameters; transferrin saturation as well as serum iron, ferritin, soluble transferrin receptor, and C-reactive protein levels. We retrospectively analyzed the data regarding demographic and clinical features, preoperative laboratory values, intraoperative transfusions, and length of ICU stay. Patient demographic features and preoperative values were similar between the groups. Preoperative iron deficiency, which was diagnosed in 72 patients (58.6%), was associated with a greater intraoperative use of fresh frozen plasma and red blood cell transfusions ($P = .0001$). The median length of ICU stay after LT was longer among the ID versus the non-ID group (5 and 3 days per patient, respectively; $P = .0001$). Therefore, we have suggested that preoperative iron deficiency may be a prognostic factor for the length of ICU stay after LT.

The intensive care unit (ICU) plays a vital role in the practice of liver transplantation (LT). A prolonged ICU stay consumes physical and financial resources. Among LT patients, it may be associated with an increased risk of complications and greater mortality.[1–3] Improvements in preoperative evaluation, surgical techniques, and intraoperative anesthesia of LT recipients during the past decade have resulted in shorter ICU stay.[4]

Preoperative anemia is a common condition in surgical patients, particularly those with end-stage liver failure.[5] The preoperative diagnosis and treatment of anemia is vital to minimize adverse postoperative outcomes.[6] The prevalence of iron deficiency among LT recipients ranges from 45% to 60%.[7] Preoperative iron deficiency is a prognostic factor for greater intraoperative transfusion requirements. Furthermore, the quantity of blood products administered intraoperatively is a well known independent risk factor for a prolonged ICU stay after LT.

Several studies have sought to identify patients at high risk and determine preoperative prognostic factors for a prolonged ICU stay.[8] However, iron deficiency is not known to influence the length of ICU stay after LT. The aim of the present retrospective study was to examine whether there was a clinically significant association.

METHODS

From September 2011 to June 2012, we performed 153 liver transplantations in adult patients. This retrospective study included data collected from medical records. Iron deficiency was determined according to values on the day of transplantation. The inclusion and exclusion criteria for the study are shown in Fig 1. Exclusion criteria were iron overload (n = 16), retransplantation (n = 7), LT for acute liver failure (n = 2), and residence in the ICU

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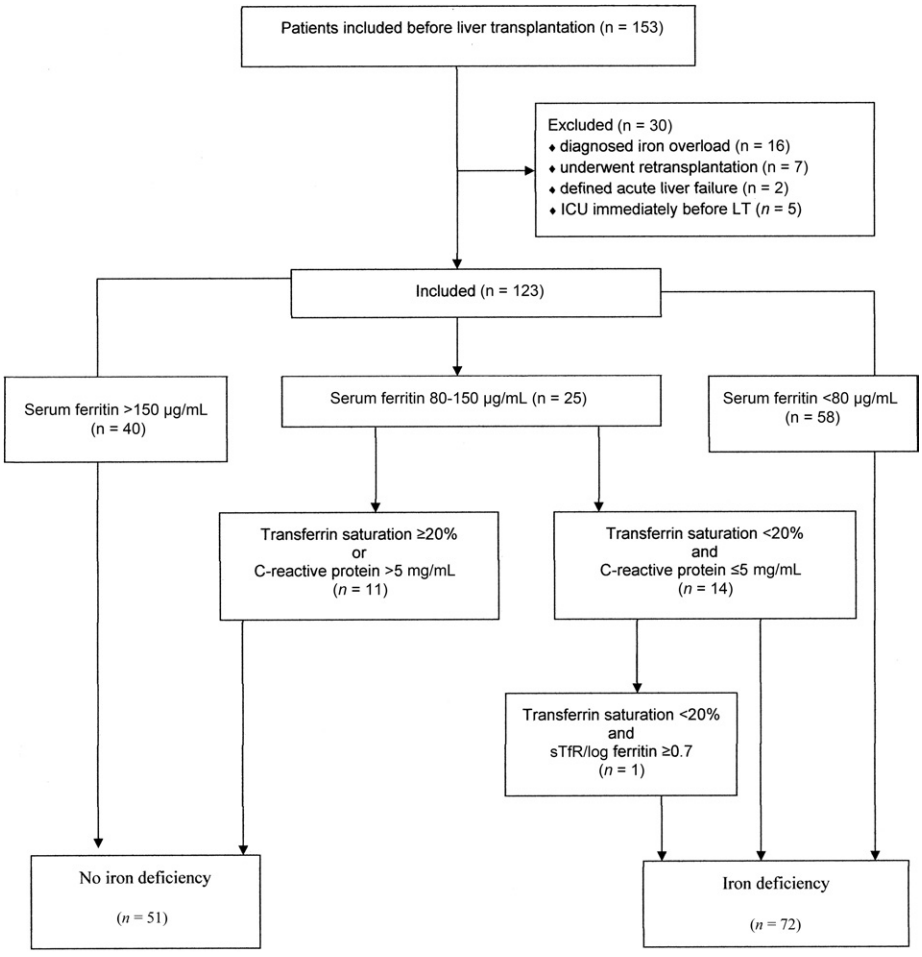

Fig 1. Flow diagram. Classification of iron deficiency on day 0. sTfR-F index, (soluble transferrin receptor)/log ferritin. Patients were classified as having iron deficiency or not according to the algorithm described in the Methods section.

immediately before LT (n = 5). To define iron deficiency, we used the modified criteria proposed by Theusinger et al[9] (Fig 1).

The following data were collected for all transplant recipients: age, height, weight, hemoglobin level, serum iron profile, platelet count, prothrombin time (PT), activated partial thromboplastin time (aPTT), fibrinogen, international normalized ratio (INR), serum bilirubin, serum blood urea nitrogen (BUN), serum creatinine, alanine aminotransferase (ALT), aspartate aminotransferase (AST), Model for End-Stage Liver Disease (MELD) score, operative time, estimated intraoperative blood loss, transfusions of red blood cells (RBC) and/or fresh frozen plasma (FFP), warm ischemia time, cold ischemia time, diuresis, ventilation days, and length of ICU stay.

Statistical Analyses

Power analysis indicated that a minimum of 45 patients were required in each group based on the following: type I error (α) 0.05; type II error (β) 0.20; difference 2, 4; SD of group I 5, 5; and SD of group II 1, 8. The normality of distribution of our data was confirmed with the use of the Kolmogorov-Smirnov test. All between-group comparisons were made with the Mann-Whitney *U* test. The distribution of sex regarding to the groups was analyzed with the use of the Yates chi-square test. A value of $P < .05$ was considered to be statistically significant. All results are presented as median (range).

RESULTS

Table 1 presents the preoperative iron profiles of the 2 groups. The remaining 123 patients were divided into 2 groups according to their baseline iron status: iron-deficient (ID; n = 72; 58.6%) and non-ID (normal iron profile; n = 51; 41.4%). Clinical features and demographic data of the 123 patients are presented in Table 2. The median ICU length of stay after LT was longer among the ID than the non-ID group (5 and 3 days/patient, respectively; $P = .0001$; Table 2). The ID group experienced a longer mean ventilation period after LT than the non-ID group ($P = .0001$; Table 2).

DISCUSSION

The main finding of this study was that preoperative iron deficiency was associated with an increased length of postoperative ICU stay among LT patients. This finding was not unexpected, because the quantity of blood products administered intraoperatively is known to be an independent risk factor for a prolonged ICU stay. Oberkofler et al[10] showed that >10 units of FFP and >7 units of RBC transfused intraoperatively were independent risk factors for a pro-

Table 1. Preoperative Iron Profile

Variable	Normal Values	ID (n = 72)	Non-ID (n = 51)	*P* Value
Serum iron (μmol/L)	12–35	31 (10–124)	175 (125–285)*	.0056
Transferrin saturation (%)	20–50	32 (24–34)	35 (28–39)	.356
Serum ferritin (mg/L)	30–300	66 (15–210)	305 (200–457)*	<.0001
Soluble serum transferrin receptor (mg/L)	0.83–1.76	0.94 (0.72–1.12)	1.03 (0.96–1.25)	.542
TfR-f index	<0.7	0.5 (0.4–0.6)	0.6 (0.4–0.7)	.587
C-reactive protein (mg/L)	<10	1.69 (1.27–7.14)	1.70 (1.21–5.21)	.253

Abbreviations: ID, iron-deficient; non-ID, normal iron profile; TfR, soluble transferrin receptor; TfR-f Index, ratio of TfR/log ferritin.
Variables are expressed as median (range).
*$P < .05$ vs ID.

longed ICU stay. Moreover, these patients are more likely to require RBC transfusions, and allogeneic FFP and RBC transfusions are associated with well known adverse effects, including an increased incidence of viral and bacterial infections, activation of inflammatory and coagulation pathways, and immunologic reactions.[11–13] In addition, the intraoperative transfusion of packed RBC is associated with more complications and infections after LT.[14–16] These findings may explain the increased length of ICU stay among our ID group, because preoperative iron deficiency is associated with a high volume of intraoperative transfusions.

Another important finding of the present study was the association of iron deficiency with a longer ventilation period after LT. The duration of ventilation is known to be affected by persistent metabolic failure of the transplanted organ.[17] Rapid resolution of interstitial edema occurs in cases where the transplant shows good function, as supported by a favorable trend of the enzymes, biliary production, and improved blood coagulation indices.[8] In LT recipients, shortening the ventilation period may reduce the length of ICU stay.

There are a number of limitations to our study. The patients were treated at a single center and may not be representative of ICUs in other medical centers. A second important limitation is that because this was a retrospective analysis, the observed relationships cannot be assumed to be causal; effects of unmeasured potential

Table 2. Demographic Data and Surgical Characteristics of the 123 Patients

Variables	ID (n = 72)	Non-ID (n = 51)	*P* Value
Age (y)	38 (18–56)	43 (20–64)	.253
Weight (kg)	65 (55–100)	68 (54–105)	.249
Height (cm)	160 (145–175)	162 (156–170)	.365
Starting Hb (g/dL)	9.4 (8.6–11.2)	10.5 (10.2–12.3)	.256
Starting PT (s)	16.3 (12.5–45.7)	18.1 (12.4–47.5)	.484
Starting aPTT (s)	33.8 (24.8–70.2)	33.5 (21.4–54.6)	.357
Starting fibrinogen concentration (mg/dL)	204 (54–295)	206 (56–303)	.452
Starting INR value	1.48 (1.01–5.20)	1.45 (1.01–5.75)	.542
Starting platelet count (10^9 p1/L)	78 (34–325)	82 (45–328)	.065
Serum total bilirubin	8.5 (6.4–9.6)	7.2 (5.4–8.3)	.354
Serum BUN	13 (6–42)	14 (6–60)	.215
Serum creatinine	0.64 (0.37–1.26)	0.68 (0.38–1.25)	.519
Serum ALT	86 (75–254)	92 (85–325)	.254
Serum AST	73 (65–124)	85 (72–135)	.217
MELD score	16.45 (3.27–39.78)	15.25 (4.25–36.24)	.275
Blood loss (mL)	1,350 (1,010–1,650)	1,257 (1,012–1,450)	.547
Diuresis (mL)	468 (285–824)	484 (324–965)	.425
RBC transfusion (n)	5 (1–18)	1 (0–4)*	.0001
FFP transfusion (n)	2 (0–14)	0 (0–2)	.0001
Ventilation days	2 (1–4)	1 (0–2)*	.0001
Length of ICU stay (d)	5 (2–16)	3 (1–5)*	.0001
Clamping time (min)	34 (25–58)	32 (28–52)	.463
Warm ischemia time (min)	38 (24–125)	40 (28–138)	.647
Cold ischemia (min)	147 (77–213)	158 (88–215)	.325
Duration of surgery (min)	544 (435–647)	548 (432–685)	.426

Abbreviations: ID, iron-deficient; non-ID, normal iron profile; Hb, hemoglobin; PT, prothrombin time; aPTT, activated partial thromboplastin time; INR, international normalized ratio; BUN, blood urea nitrogen; ALT, alanine aminotransferase; AST, aspartate aminotransferase; RBC, red blood cells; FFP, fresh frozen plasma; ICU, intensive care unit; MELD, Model of End-Stage Liver Disease.
Variables are expressed as median (range).
*$P < .05$ vs ID.

confounders cannot be dismissed. Finally, this study included a relatively small sample size. Future studies with larger number of patients must be performed to verify our results.

In conclusion, our retrospective analysis indicated that preoperative iron deficiency may be able to identify patients who are likely to need a prolonged ICU stay after LT. Because we think that it is important to avoid a prolonged ICU stay, our findings may have significant implications for the management of patients in the ICU.

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