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## Retrospective Study

**Iron metabolism imbalance at the time of listing increases overall and infectious mortality after liver transplantation**

Elodie Fallet, Michel Rayar, Amandine Landrieux, Christophe Camus, Pauline Housnel-Debry, Caroline Jezequel, Ludivine Legros, Thomas Uguen, Martine Ropert-Bouchet, Karim Boudjema, Dominique Guyader, Edouard Bardou-Jacquet

**ORCID number:** Elodie Fallet (0000-0002-8784-071X); Michel Rayar (0000-0003-3113-2260); Amandine Landrieux (0000-0001-7645-4605); Christophe Camus (0000-0002-2055-3003); Pauline Housnel-Debry (0000-0001-9271-9810); Caroline Jezequel (0000-0002-7220-7751); Ludivine Legros (0000-0002-7097-1713); Thomas Uguen (0000-0002-2672-7676); Martine Ropert-Bouchet (0000-0002-3431-1670); Karim Boudjema (0000-0002-3894-8767); Dominique Guyader (0000-0001-9752-1280); Edouard Bardou-Jacquet (0000-0002-0784-0710).

**Author contributions:** Bardou-Jacquet E contributed to study design and supervision; Fallet E and Bardou-Jacquet E drafted the manuscript; Fallet E, Uguen T and Rayar M gathered the Data; Bardou-Jacquet E and Rayar M performed statistical analysis; Landrieux A, Camus C, Housnel-Debry P, Jezequel C and Legros L managed the patients; all authors critically revised the manuscript.

**Institutional review board**

**statement:** This study was approved by the Rennes University Ethics Committee on the 20<sup>th</sup> of October 2015.

**Informed consent statement:**

According to this law (Loi Jardé n° 2012-300 the 5<sup>th</sup> of March 2012) the retrospective use of clinical and biological data generated during

Elodie Fallet, Amandine Landrieux, Pauline Housnel-Debry, Caroline Jezequel, Ludivine Legros, Thomas Uguen, Dominique Guyader, Edouard Bardou-Jacquet, Service des Maladies du Foie, CHU Rennes, University Rennes, Rennes 35033, France

Michel Rayar, Pauline Housnel-Debry, Karim Boudjema, Service de Chirurgie Hepatobilaire, CHU Rennes, University Rennes, Rennes 35033, France

Christophe Camus, Service de Réanimation médicale, CHU Rennes, University Rennes, Rennes 35033, France

Martine Ropert-Bouchet, Laboratoire de biochimie, CHU Rennes, University Rennes, Rennes 35033, France

**Corresponding author:** Edouard Bardou-Jacquet, MD, PhD, Professor of Medicine, Service des Maladies du Foie, CHU Rennes, University Rennes, CIC1414, Rennes 35033, France. [edouard.bardou-jacquet@chu-rennes.fr](mailto:edouard.bardou-jacquet@chu-rennes.fr)

**Abstract****BACKGROUND**

Liver transplantation (LT) is the best treatment for patients with liver cancer or end stage cirrhosis, but it is still associated with a significant mortality. Therefore identifying factors associated with mortality could help improve patient management. The impact of iron metabolism, which could be a relevant therapeutic target, yield discrepant results in this setting. Previous studies suggest that increased serum ferritin is associated with higher mortality. Surprisingly iron deficiency which is a well described risk factor in critically ill patients has not been considered.

**AIM**

To assess the impact of pre-transplant iron metabolism parameters on post-transplant survival.

**METHODS**

From 2001 to 2011, 553 patients who underwent LT with iron metabolism parameters available at LT evaluation were included. Data were prospectively recorded at the time of evaluation and at the time of LT regarding donor and recipient. Serum ferritin (SF) and transferrin saturation (TS) were studied as continuous and categorical variable. Cox regression analysis was used to

the routine care of patient does not require signed informed consent for patients included in this kind of study.

**Conflict-of-interest statement:**

Authors have no conflict of interest to declare.

**Data sharing statement:** No additional data are available.

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determine mortality risks factors. Follow-up data were obtained from the local and national database regarding causes of death.

## RESULTS

At the end of a 95-mo median follow-up, 196 patients were dead, 38 of them because of infections. In multivariate analysis, overall mortality was significantly associated with TS > 75% [HR: 1.73 (1.14; 2.63)], SF < 100 µg/L [HR: 1.62 (1.12; 2.35)], hepatocellular carcinoma [HR: 1.58 (1.15; 2.26)], estimated glomerular filtration rate (CKD EPI Cystatin C) [HR: 0.99 (0.98; 0.99)], and packed red blood cell transfusion [HR: 1.05 (1.03; 1.08)]. Kaplan Meier curves show that patients with low SF (< 100 µg/L) or high SF (> 400 µg/L) have lower survival rates at 36 mo than patients with normal SF ( $P = 0.008$  and  $P = 0.016$  respectively). Patients with TS higher than 75% had higher mortality at 12 mo ( $91.4\% \pm 1.4\%$  vs  $84.6\% \pm 3.1\%$ ,  $P = 0.039$ ). TS > 75% was significantly associated with infection related death [HR: 3.06 (1.13; 8.23)].

## CONCLUSION

Our results show that iron metabolism imbalance (either deficiency or overload) is associated with post-transplant overall and infectious mortality. Impact of iron supplementation or depletion should be assessed in prospective study.

**Key words:** Iron deficiency; Overload; Cirrhosis; Infection; Death; Ferritin; Transferrin saturation

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**Core tip:** Iron is an essential element for many biological functions. Its deficiency or overload is associated with poor outcomes in many settings. Few data are available in patients undergoing liver transplantation, and more specifically on infection related deaths. Our study is the first to describe in a large number of patients, the impact of iron metabolism imbalance on mortality after liver transplantation. Our results show that both iron deficiency and overload are significantly associated with increased mortality. Further we show that transferrin saturation higher than 75% is associated with mortality.

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## INTRODUCTION

Liver transplantation (LT) is the most effective treatment for patients with end-stage liver disease. However, it is still associated with significant mortality thus promoting the search for associated factors whose optimization could improve survival. Since 2002 in France, liver graft allocation is based on the Model of End-Stage Liver Disease (MELD), which is an objective score improving 3-mo mortality prediction compared to the Child-Turcotte-Pugh score<sup>[1-3]</sup>. Other factors of mortality in addition to MELD have been studied to better manage patients waiting for LT like serum sodium<sup>[4-7]</sup>, renal function<sup>[8]</sup>, sarcopenia<sup>[9]</sup> and ferritin<sup>[10,11]</sup>.

Serum ferritin (SF) concentration is a reproducible and routinely available biochemical marker. It is the major intracellular iron storage protein and although it correlates with body iron stores, serum level is also influenced by inflammation and cell lysis. Therefore SF increases in patients with elevated body iron stores or in many liver diseases as chronic hepatitis C, alcohol-related liver disease and non-alcoholic steatohepatitis<sup>[12]</sup> or in extra-hepatic causes like systemic inflammatory states, systemic immune-mediated diseases (rheumatoid arthritis, adult Still's disease)<sup>[13,14]</sup>, metabolic syndrome<sup>[15]</sup>, in case of chronic kidney failure<sup>[16,17]</sup>, or hematological disease<sup>[18,19]</sup>.

The relevance of the iron burden in LT was first raised by studies suggesting that patients who undergo LT for cirrhosis related to hereditary hemochromatosis have

higher morbidity and mortality<sup>[20,21]</sup>, mainly due to an increased risk of infections and recurrence of hepatocellular carcinoma<sup>[22]</sup>.

Results of studies investigating SF as a risk factor in LT are discordant. Increased SF was associated with an increased risk of death in patients on waiting list and following LT<sup>[10,11]</sup>.

In contrast, Al-Freah *et al*<sup>[23]</sup> using different cut-off values and without considering serum transferrin saturation (TS), showed the lack of influence of SF on wait-list or post-transplant survival, but a significant negative impact of hepatic iron overload on 12 mo' survival. Conversely in a retrospective study addressing iron metabolism and liver iron content, Stuart *et al*<sup>[24]</sup> showed that increased hepatic iron concentration was a marker of the severity of the liver disease but was not associated with lower survival after LT.

Further, high SF and TS were found to be risk factors of mortality in other contexts than LT. High SF and TS are associated with increased mortality in acute-on-chronic liver failure<sup>[25]</sup> and allogeneic hematopoietic stem cell transplantation<sup>[26]</sup>. Similarly in the setting of intensive care, serum iron parameters at admission were correlated with short and long term mortality<sup>[27]</sup>. From a biochemical point of view, elevated TS is associated with the appearance of non-transferrin bound iron (NTBI) and labile plasma iron (LPI), which are toxic forms of iron which induce reactive oxygen radicals promoting oxidative stress, leading to cellular damage<sup>[28-30]</sup>. Depending on the underlying disease and the assay, NTBI can be detected starting from TS level of 50% to 75%, on the other hand, LPI is always present if TS is higher than 75%<sup>[28,31]</sup>. NTBI Imbalance of iron metabolism also fosters siderophilic bacterial infection<sup>[32,33]</sup>, including pneumonia<sup>[34]</sup>, with involvement of NTBI<sup>[35]</sup>.

These discrepant results and the multiple factors influencing or influenced by iron metabolism suggest that more data are required to assess the relevance of iron metabolism imbalance in the management of patients with cirrhosis listed for LT. The aim of our study was to evaluate in a large retrospective cohort of liver transplanted patients the impact of pre-transplant iron metabolism imbalance on post-transplant survival.

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## MATERIALS AND METHODS

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### **Patients**

All patients who underwent LT between January 2001 and December 2011 in our centre and with iron metabolism parameters available at the time of LT listing evaluation were included. Patients with previous history of LT, emergency LT or multiple-organ transplantation were excluded.

Following data were prospectively recorded at the time of evaluation: age, sex, body mass index (BMI) of donor and recipient, cause of cirrhosis, presence of hepatocellular carcinoma, Child-Pugh score, serum sodium, serum iron, TS, serum ferritin, cystatin C, warm and cold ischemia times, perioperative transfusion (red blood cell units, platelets, fresh frozen plasma units), duration of surgery, intensive care unit (ICU) and regular unit length of stay. MELD score was available for all patients after March 2007 and retrospectively calculated for others when INR was available.

### **Iron metabolism parameters**

Iron metabolism parameters (serum iron, SF, transferrin, TS) were routinely measured during pre-transplant evaluation. Serum ferritin was determined using chemiluminescence immunoassay from 2001 to 2009 (ACS 180 Bayer), then turbidimetric assay (Olympus AU 800) from 2009 to the end of the study, internal control and calibration proved consistent measurement and comparability of value between assay.

### **Transplantation procedure and postoperative care**

All patients had orthotopic liver transplantation with inferior vena cava preservation. The graft was harvested from a brain death donor in all cases. No organs from executed prisoners were used. After the procedure, patients were transferred to the ICU until graft function was satisfactory. Routine immunosuppression consisting on low-dose tacrolimus (TAC), mycophenolatemofetil and a short course of corticosteroids was initiated. TAC dosage was initiated at 0.1 mg/kg daily or at 0.06 mg/kg daily in case of concomitant administration of fluconazole and then adapted according to TAC blood through concentration with a target value between 6 and 10 ng/mL. No significant modification regarding the surgical procedure or the postoperative medical care was observed during the study period.

### Patient's follow-up

Follow-up data were obtained from the local database and the National Biomedicine Agency database in March 2017. The following complications are prospectively recorded during the follow-up: Anastomotic complications (arterial, venous, biliary), cardiovascular event, renal failure (dialysis), graft rejection.

Patients lost to follow up were considered to be dead. Causes of death were prospectively recorded and categorized as: Cancer (including recurrence of hepatocellular carcinoma), infection related [any causes of bacterial, viral (excluding chronic hepatitis) or fungal infection identified as the main cause leading to death], recurrence of the initial liver disease, graft failure, cardiovascular event, other causes, and undetermined.

This study protocol conformed to the declaration of Helsinki and was approved by the Rennes University Ethics Committee. According to French law, the corresponding database was declared to the "National Committee of Informatics and Freedom" (CNIL, n°96-025).

### Statistical analysis

Quantitative variables are described as median [quartiles] and qualitative variables are presented as number and percentage (%).

As SF distribution was skewed and exhibited nonlinearity (according to martingale residuals) in the Cox regression model, it was studied as a categorical variable using tertiles (lower than 100 µg/L - between 100 and 400 µg/L - higher than 400 µg/L). TS was studied as a categorical variable with a cut-off value of 75% as at this level NTBI and LPI are always present<sup>[28]</sup>.

Clinically relevant variables and variables associated with mortality in univariate analysis (Cox regression) with a *P* value < 0.2 were included in the multivariate analysis. Multivariate Cox regression analysis was performed with backward stepwise selection of variable according to likelihood ratio.

Survival curves were established using the Kaplan-Meier method and compared using the Log-rank test.

Data were analyzed using version 22.0 of SPSS (SPSS Inc., Chicago, IL, United States). *P* < 0.05 was considered significant with a two-tailed test.

## RESULTS

### Patient characteristics

A total of 553 patients underwent LT during the study period with iron metabolism parameters available at the time of evaluation. Their clinical and biochemical characteristics are described in [Table 1](#).

The median age at evaluation for LT was 55 (49-60.5) years. They were preferentially men (74.9%) with alcohol-related liver disease (61.5%). The median SF was 241 (75.5-593.5) µg/L, 168 patients had SF < 100 µg/L and 200 had SF > 400 µg/L. The median TS was 43.6% (25.1%-74.5%) with 24.6% of patients having a TS higher than 75%. MELD was available in 407 (73.6%) patients and median MELD was 15.1 (10.6-20.7). Median time between listing and LT was 4 (2-9) mo. Median follow-up time after LT was 95 (55-126) mo. At the end of the follow-up period, 5 patients were lost to follow up, and 196 patients died, 38 (6.9%) of died from infection. Of them 13 died of septicaemia, 12 of pulmonary bacterial infection, 5 of peritonitis, 3 of angiocholitis, 3 of severe viral infection and 2 of fungal infection. Patient outcomes and causes of death are summarized in [Table 2](#).

### Overall mortality

In univariate analysis, variable associated (*P* < 0.2) with overall mortality were: fresh frozen plasma transfusion units (*P* < 0.001), packed red blood cell transfusion (*P* < 0.001), estimated glomerular filtration rate through the CKD Epi Cystatin C equation (*P* = 0.01), duration of surgery (*P* = 0.07), cirrhosis etiology (*P* = 0.07), SF (*P* = 0.08), TS > 75% (*P* = 0.08), ascites (*P* = 0.04), albumin (*P* = 0.10) and Cystatin C (*P* = 0.11).

Results from the multivariate analysis are reported in [Table 3](#). In multivariate analysis, TS higher than 75% was significantly associated with mortality [HR: 1.73 (1.14; 2.63)]. Low SF was significantly associated with mortality [HR: 1.62 (1.12; 2.35)] whereas high SF was not significant.

Because one could consider that abnormal SF or TS may only be markers of advanced liver disease, we performed an analysis entering the MELD score in the final model. MELD was not significantly associated with mortality [HR: 1.00 (0.96; 1.03), *P* = 0.87], this did not change significance of SF or TS, nor significantly changed their Hazard Ratio.

**Table 1** Baseline patient characteristics

Variable	n = 553
Age, yr	55 (49-60.5)
Sex male/female	414 (74.9)/139 (25.1)
BMI, kg/m <sup>2</sup>	26.2 (23.3-29.7)
Iron metabolism	
Serum iron, µmol/L	21.9 (1.6; 57.9)
Transferrin, g/L	2.10 (1.5-2.5)
Transferrin saturation, %	43.6 (25.1-74.5)
Transferrin saturation > 75%	136 (24.6)
Serum ferritin, µg/L	241 (75.5-593.5)
< 100	168 (30.4)
100-400	185 (33.5)
> 400	200 (36.2)
Cirrhosis etiology	
Alcohol	340 (61.5)
Viral hepatitis C	89 (16.1)
Viral hepatitis B	18 (3.3)
Primary sclerosing cholangitis	20 (3.6)
Primary biliary cholangitis	12 (2.2)
Auto-immune	10 (1.8)
Hemochromatosis	17 (3.0)
Others	47 (8.4)
Hepatocellular carcinoma	214 (38.7)
Child pugh score	
A	206 (39.1)
B	158 (30.0)
C	163 (31.0)
MELD	15.1 (10.6-20.7)
Donor age, yr	49 (37-62)
Donor BMI, kg/m <sup>2</sup>	24.3 (21.9-27.6)
Cold ischemia, minutes	592 (446-723)
Perioperative transfusion	
Packed red cell, n	5 (2-8)
Fresh frozen plasma, n	6 (2-9)
ICU length of stay, d	4 (3-7)

For categorical variables, data are given as n (%). For continuous variables, data are given as median (range). BMI: Body mass index; ICU: Intensive care unit; MELD: Model of End-Stage Liver Disease.

### Overall survival and serum ferritin

Kaplan Meier survival analysis was performed to explore the relationship between serum ferritin and overall survival. Kaplan Meier survival curves suggest that patients with low SF and high SF have a lower survival than patients with SF within the normal range (Figure 1). This difference was not statistically significant between the three groups over the whole study period ( $P = 0.07$ ). But short-term survival analysis restricted to 6, 12 and 36 mo of follow-up showed a significant difference between the three groups ( $P = 0.016$  at 6 mo,  $P = 0.026$  at 12 mo and  $P = 0.032$  at 36 mo). At 36 mo, patients with ferritin < 100 µg/L and patients with ferritin > 400 µg/L had lower survival than patients with ferritin 100-400 µg/L ( $P = 0.008$  and  $P = 0.016$  respectively).

### Overall survival and TS

Kaplan Meier survival curves show that overall survival was similar between the two groups of TS (lower or higher than 75%) ( $P = 0.08$ ) (Figure 2). However short term survival analysis restricted to 6 and 12 mo of follow-up showed a significant difference with an increased mortality in patients with TS higher than 75% ( $92.6\% \pm$

Table 2 Patient outcomes

	n (%)
Dead	196
Lost to follow up	5
Causes of death	
Cancer	41 (20.92)
Infection	38 (19.39)
Recurrence of initial liver disease	30 (15.31)
Graft failure	12 (6.12)
Cardio vascular event	28 (14.29)
Others	31 (15.82)
Undetermined	16 (8.16)

1.3 vs 86.0%  $\pm$  3.0,  $P = 0.012$  at 6 mo and 91.4%  $\pm$  1.4% vs 84.6%  $\pm$  3.1%,  $P = 0.039$  at 12 mo) suggesting an impact of TS on the early phase after LT.

### Factors associated with infection related deaths

Because iron overload and NTBI are thought to promote sepsis, we then addressed the impact of iron metabolism on infection related deaths and infections after LT.

In univariate analysis, factors associated ( $P < 0.2$ ) with infection related deaths were: ICU length of stay ( $P < 0.001$ ), estimated glomerular filtration rate through the CKD Epi Cystatin C equation ( $P = 0.03$ ), recipient BMI ( $P = 0.07$ ), packed red blood cell transfusion ( $P = 0.07$ ), TS  $> 75\%$  ( $P = 0.15$ ), SF ( $P = 0.16$ ), bilirubin ( $P = 0.17$ ), and fresh frozen plasma transfusion ( $P = 0.17$ ).

In multivariate analysis using Cox regression (Table 4), increased TS was significantly associated with the risk of infection related deaths [HR: 3.06 (1.13; 8.23)]. SF was associated with infection related deaths with high SF associated with lower infection related death [HR: 0.35 (0.12; 0.98)] whereas low SF was not significant.

## DISCUSSION

In our study, we examined the impact of iron metabolism at the time of evaluation for LT on post-transplant mortality. Our results show that TS  $> 75\%$  and low SF were risk factors of overall mortality. This suggests that iron metabolism is a double-edged sword as both overload and deficiency are associated with mortality. Kaplan Meier survival curves show that increased mortality in patients with TS  $> 75\%$  is seen at 6 and 12 mo after LT. Further our results show that TS  $> 75\%$  was significantly associated with infection related deaths after LT.

The first interesting results of our study was the surprising fact that low SF was associated with mortality while high SF was not, contrary to other studies<sup>[10,11]</sup>. Because iron metabolism can be either in excess or deficiency situation, we think that both must be considered. Our results show that iron deficiency and overload were both risk factors of overall mortality. This U shape association is consistent with previous finding. Iron deficiency has already been demonstrated as a risk factor of mortality in ICU<sup>[36-38]</sup> and as a risk factor of infections because of immune depression induced by iron deficiency<sup>[39-44]</sup>. On the other hand, iron supplementation particularly by perfusion is associated with an increased risk of infections<sup>[45-47]</sup> and low SF is a protective host mechanism<sup>[48]</sup>. This two-way effect could explain the discrepant results regarding the impact of SF on mortality after LT<sup>[11,23]</sup>.

Weismüller *et al*<sup>[11]</sup> showed that SF  $\geq 365$   $\mu\text{g/L}$  in combination with TS  $< 55\%$  before LT was an independent risk factor for mortality following LT, suggesting an impact of both iron overload and other factors (acute phase, immune response). However the cut-off level of  $< 55\%$  for TS was chosen by receiver operating curve analysis in a subgroup of patients with SF  $> 365$   $\mu\text{g/L}$  with the goal to distinguish which patients survived. Although this may represent iron deficiency or inflammation, there is little information on the potential mechanisms by which low TS could be associated with increased mortality. Further, multivariate analysis was only performed using a binary variable distinguishing patients with TS  $< 55\%$  and SF  $\geq 365$   $\mu\text{g/L}$  to all others, without describing multivariate results regarding SF or TS separately.

We choose to assess TS from a physiological point of view, in agreement with the appearance and toxicity of NTBI and LPI we choose high TS  $> 75\%$  as a cut-off<sup>[28]</sup>. This

**Table 3** Cox multiple regression analysis for overall mortality

Parameters	HR (95%CI)	P value
Hepatocellular carcinoma (yes/no)	1.58 (1.15; 2.16)	0.004
eGFR CKD EPI Cystatin C (mL/min)	0.99 (0.98; 0.99)	0.01
Cirrhosis aetiology (HCV as reference)		0.028
Alcohol	0.57 (0.39; 0.83)	0.003
Hepatitis B virus	0.50 (0.19; 1.28)	0.14
Other	0.66 (0.41; 1.08)	0.10
Transferrin saturation > 75%	1.73 (1.14; 2.63)	0.01
Ferritin (100-400 µg/L as reference)		0.009
< 100 µg/L	1.62 (1.12; 2.35)	0.01
> 400 µg/L	0.90 (0.59; 1.37)	0.63
Packed red blood cell (per unit)	1.05 (1.03; 1.08)	< 0.001

CI: Confidence interval; HCV: Hepatitis C virus; HR: Hazard ratio; ICU: Intensive care unit.

might be considered a better surrogate of functional iron overload, as it represents a high level of biologically available iron in the bloodstream. Our multivariate analysis taking into account TS > 75% shows that high serum ferritin is not associated with overall mortality. Further high serum ferritin is associated with a lower infection related mortality, while TS > 75% is associated with higher infection related mortality. This emphasizes the paradoxical situation between functional iron overload (TS > 75%) and high serum ferritin that may only reflect inflammation as ferritin is also an acute phase protein.

For Al-Freah *et al*<sup>[23]</sup> SF as a categorical variable (> or < 300 µg/L) is not associated with post LT survival, but patients with explant siderosis grade  $\geq 2$  had inferior 12-mo post-LT survival ( $P = 0.03$ ). As the fast and efficient uptake of NTBI by liver parenchymal cell is well described<sup>[49]</sup>, and is a major mechanism for liver siderosis, this could be in accordance with our result showing that high TS is a risk factor. However TS was not assessed in this study.

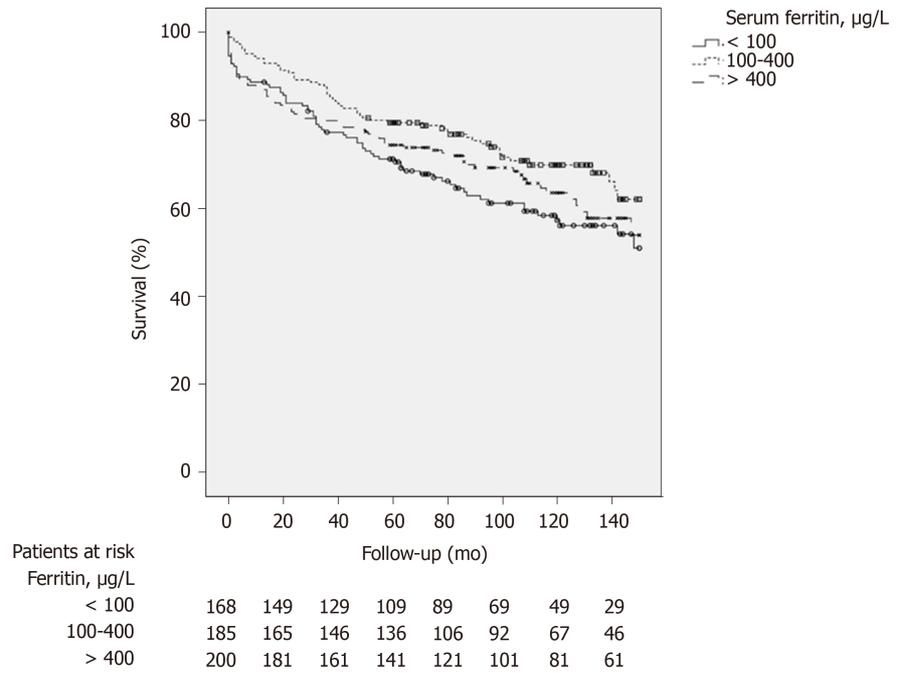
We think that a major limitation of these study is the lack of consideration for iron deficiency. Iron deficiency can affect a significant part of the population, even more in the setting of end-stage liver disease as chronic bleeding and frailty are common. Actually one third of our patient had a serum ferritin lower than 100 µg/L that can be considered as low in this setting. This may be a major cause of discrepancy between studies and this may also explain the non-linearity between SF and mortality that prevent its simple use as a continuous variable in Cox regression analysis.

The use of different SF cut-offs across studies is in part explained by the heterogeneity of biochemical methods used by centres and laboratories and the lack of international standards and reference materials. Moreover, SF may be affected by several factors besides iron metabolism, especially in the context of liver disease and inflammation. Therefore we think one should more consider an indication toward iron deficiency or overload rather than a definite cut-off that is hard to define in this setting.

Iron overload with high SF and TS have been shown to be risk factors of mortality in other situations than LT<sup>[25,27,30,51]</sup>. High SF has been demonstrated to be a risk factor of infections after kidney transplantation<sup>[52]</sup>. Chow *et al*<sup>[53]</sup> recently shown that increased levels of serum iron were independently associated with an increased risk for several types of infection and deaths. Recently, a second study of Chow *et al*<sup>[54]</sup> also showed a link between high SF, high Hcpidin and low serum iron, with infection after LT.

Our finding that TS higher than 75% is associated with increased overall and infection related mortality support our initial hypothesis of NTBI and LPI production, a toxic free iron present in case of TS > 75%<sup>[28,30]</sup>. Increasing iron availability with high TS and production of NTBI/LPI promotes development of bacterial infection via increased bacterial growth. Further our results suggest that these patients may be more prone to infection in the post-operative period.

Overall our results are in accordance with the fact that iron is an essential nutrient for all organisms but can paradoxically become toxic, inducing oxidative stress in case of iron overload<sup>[29,30]</sup>. Iron deficiency leads to immunosuppression, which in turn increases the risk of infections. Conversely, iron overload provokes production of free radicals and oxidative damage and influence pathogen growth.



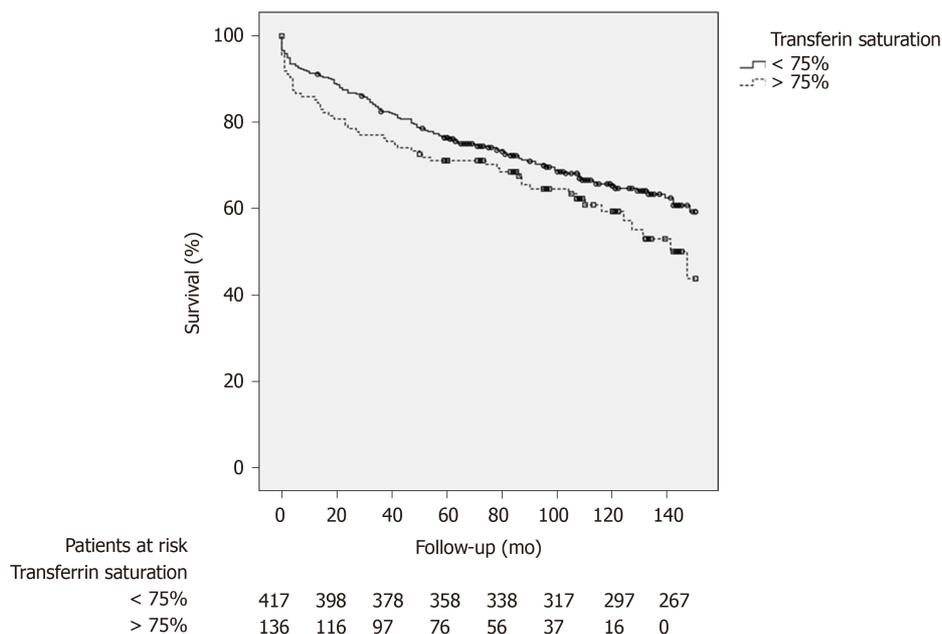
**Figure 1** Kaplan Meier survival curves according so serum ferritin.

In conclusion, our results show that imbalance in iron metabolism is significantly associated with sepsis-related and overall mortality in the post-transplant period. The role of iron should be prospectively studied in these patients to identify patients at risk and guide optimization of iron metabolism management to improve post-transplant survival.

**Table 4** Multivariate analysis for risk factors of infection associated death

Parameters	HR (95%CI)	P value
Transferrin saturation > 75%	3.06 (1.13; 8.23)	0.02
Ferritin (100-400 µg/L as reference)		0.02
< 100 µg/L	1.74 (0.77; 3.93)	0.17
> 400 µg/L	0.35 (0.12; 0.98)	0.48
eGFR CKD EPI Cystatin C (mL/min)	0.98 (0.97; 0.99)	0.03
ICU length of stay (d)	1.02 (1.01; 1.03)	< 0.01

CI: Confidence interval; HR: Hazard ratio; ICU: Intensive care unit.



**Figure 2** Kaplan Meier survival curves according to serum transferrin saturation.

## ARTICLE HIGHLIGHTS

### Research background

Liver transplantation (LT) is the best treatment for patients with liver cancer or end stage cirrhosis, but it is still associated with a significant mortality. Therefore identifying factors associated with mortality could help improve patient management. The impact of iron metabolism, which could be a relevant therapeutic target, yield discrepant results in this setting. Previous studies suggest that increased serum ferritin is associated with higher mortality. Surprisingly iron deficiency which is a well described risk factor in critically ill patients has not been considered.

### Research motivation

Iron metabolism could be easily corrected before liver transplantation, thus assessing its impact on mortality is critical before designing clinical trials in that purpose.

### Research objectives

The main objectives, the objectives that were realized, and the significance of realizing these objectives for future research in this field should be described in detail.

### Research methods

Retrospective cohort analysis with Cox multivariate Regression. Survival was also estimated through Kaplan Meier analysis.

### Research results

A large number of patients was studied (553) and followed for 95 mo. At the end of follow-up 196 patients were dead, 38 of them because of infections. In multivariate analysis, overall

mortality was significantly associated with transferrin saturation (TS) higher than 75% [HR: 1.73 (1.14; 2.63)], serum ferritin lower than 100 µg/L [HR: 1.62 (1.12; 2.35)], hepatocellular carcinoma [HR: 1.58 (1.15; 2.26)], estimated glomerular filtration rate (CKD EPI Cystatin C) [HR: 0.99 (0.98; 0.99)], and packed red blood cell transfusion [HR: 1.05 (1.03; 1.08)]. Kaplan Meier curves show that patients with low serum ferritin (< 100 µg/L) or high serum ferritin (> 400 µg/L) have lower survival rates at 36 mo than patients with normal SF ( $P = 0,008$  and  $P = 0,016$  respectively). Patients with TS higher than 75% had higher mortality at 12 mo ( $91.4\% \pm 1.4\%$  vs  $84.6\% \pm 3.1\%$ ,  $P = 0.039$ ). Moreover TS higher than 75% was significantly associated with infection related death [HR: 3.06 (1.13; 8.23)].

### Research conclusions

Our study is the first to describe the respective impact of iron deficiency in patient undergoing liver transplantation. This suggests that active management of iron deficiency with iron supplementation before liver transplantation could significantly improves outcome after liver transplantation. Further this is the first study showing that high TS is associated with higher short term mortality. This suggests that exposure to toxic forms of iron increase cellular damages in the perioperative period and that treating iron overload before liver transplantation could improves outcome.

### Research perspectives

A prospective randomized clinical trial is required to assess the beneficial effect of correction iron metabolism imbalance before liver transplantation.

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