

Reviewer 1:

Patients and Methods: It was mentioned in the methods section that the study included patients who underwent liver transplantation between January 2001 and December 2011. For how long after last liver transplantation (December 2011) follow up has been performed?

The reviewer is right to mention that we did not mention the follow-up end date. Follow up data were gathered up to March 2017. The manuscript was modified accordingly.

Results: What are the types of infections that caused deaths after liver transplantation? There is no data in this regard.

Of the 38 patients who died of infection, 13 died of septicemia, 12 of pulmonary bacterial infection, 5 of peritonitis, 3 of angiocholitis, 3 of severe viral infection and 2 of fungal infection. Manuscript was modified to specify causes of death.

Reviewer 2

Fallet et al., find that imbalance of iron metabolism in patients with liver disease is involved in mortality after liver transplantation. This finding is interesting in a lot of readers in this field. However, following points should be revised before publication in this journal.

1. Author should describe in detail why the mechanism for serum iron levels are involved in mortality after LT. In discussion, although it is described "TS >75% and low SF were risk factors of overall mortality", why both lower and higher levels of iron bring low survival rate. If you consider that oxidative stress and immunosuppression are key events in understanding relationship between iron imbalance and mortality, you should measure biomarkers for evaluation of oxidative stress and immune function.

The reviewer is right to mention the lack of details about the molecular mechanism involved in increased mortality. Further results using biomarkers of oxidative stress and immune function would significantly improve the manuscript. However as this is an epidemiological retrospective study we do not have access to biological samples for all patients that would allow us to perform such tests.

As we mentioned in the discussion section (Second and fourth paragraph) both iron overload and iron deficiency have deleterious impact on survival. The negative effect of iron deficiency on survival has been widely described in critically ill patients (reference 36-38 in the manuscript), in the setting of cardiac surgery (Rossler Brit J Anaest 2020), and at the population level (Lopez Lancet 2015). The negative effect of iron overload has also been widely described as discussed in the introduction section (fifth paragraph).

2. The groups in the figure of Kaplan Meier survival curves cannot be distinguished in my PC. Please revise the figure 1 and 2.

Figure 1 and 2 were revised

Reviewer 3

This is an important study that shows that iron metabolism has an important impact on the survival after liver transplantation. The dataset includes a large group of patients and the statistical analysis have been well studied performed in detail. I want to congratulate the researchers for their effort.

Albeit, the study seems to have two major methodological limitations that might affect the results.

The first one is: Patients lost to follow up were considered to be dead. This might causes a bias since the patients might not be dead but moved to another referral center etc. This must be clarified.

The reviewer is right to emphasize this issue. However this concerns only a very small number of patients (N=6). When performing the statistical analysis after exclusions of these patients, or using the information available at the last of their follow-up did not change the results. To avoid underestimating the number of death and because patients with liver transplantation are usually keen to ask for their medical records to be transferred when they change their referral center, we chose to consider them as dead as it is usually done in the liver transplantation literature.

The second one is: There both male and female patients in the study group. It is well known that average serum ferritin levels differ a lot between man and woman. The authors might argue that most of the woman included in the study group are post-menopausal: Average age of the study group is 55 [49-60.5] years. yet the difference in ferritin levels still persist after the menopause. So, it would be wiser to analyze iron status in man and woman separately.

We thank the reviewer for raising this issue. Actually the number of woman is low in this population and they in did are post-menopausal. Moreover menstruation frequently stops in woman with cirrhosis making the difference in iron metabolism less significant with man. This may explain why sex is not significant in the statistical analysis and not selected for the multivariate model. Performing the same multivariate analysis with sex entered a variable, it was not significantly associated with death (HR: 0.76[0.53-1.12], $p=0.16$) and did not change the results of other variable. Therefore we choose not to distinguish man and woman and used the same cut-off for both.