

February 10, 2015

Dear Editor,

Please find enclosed the edited manuscript in Word format (file name: 14796-review.doc).

Title: Underestimation of chronic renal dysfunction after liver transplantation: ICEBERG Study

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The manuscript has been improved according to the suggestions of reviewers:

(1) Reviewer 00503199

The paper suffers from limitations in methodology, especially definition of CRD using a rather high and not justified level of serum creatinine, and a formula for eGFR that has not been validated in this population. More specifically:

1. Spell out ICEBERG

ICEBERG Study name does not come from spelling out words. It is used to refer to a situation in which you see only a small part of what is really a bigger problem to highlight the importance of early detection of renal dysfunction.

2. Methodology: "Chronic renal dysfunction was defined according to sCr based criteria in routine clinical practice (≥ 2 mg/dl)". The cut-off point of 2 mg/dL is not documented. In clinical practice every creatinine measurement above normal for the specific laboratory raises the suspicion of renal dysfunction (or defines it, except in the rare cases of increased muscle mass or increased consumption of proteins and meat or use of drugs that inhibit creatinine excretion). If this persists for more than 3 months we define it as chronic.

a. Thus redo the analysis using the reference value of the laboratory.

The cut-off point of 2 mg/dl was previously used by Grinyó et al. (2011) in renal transplant patients. The reference has been added. In addition, it has been mentioned as study limitation.

b. In addition method of creatinine measurement was the same for all centers?

No, local creatinine determinations were collected and so, heterogeneity in diagnosis cannot be ruled out. It has been added as study limitation.

c. Was it enzymatic or not? Was it traceable to IDMS?

One of the most common methods used is ADVIA 2400 Chemistry System from Siemens Healthcare Diagnostics, traceable to IDMS.

3. MDRD Formula:

a. Is it the right formula to estimate GFR in liver transplant patients? Has it been validated in this population? If yes provide the relative reference.

The four-variable modification of diet in renal disease (MDRD-4) has been validated in liver

transplant patients and, indeed, it was the method used in the H2304 pivotal study (De Simone et al. 2012), in which the approval of everolimus for the prophylaxis of organ rejection in adult patients receiving a liver transplant was based. The reference has been added.

- b. Why have you used the abbreviated form and not the full one that incorporates albumin and other parameters?

The H2304 pivotal study (De Simone et al. 2012) confirmed the equivalence between MDRD-4 and MDRD-6 (data not shown), CKD-EPI, Cockcroft-Gault, and Nankivell formulas. We chose MDRD-4 to improve data collection in a retrospective study. The reference has been added.

4. Where patients on medications that inhibit creatinine excretion (like TMP and others) excluded from the study?

The use of creatinine secretion inhibitors was not an exclusion criterion. It has been added as study limitation.

5. “Time since transplantation was also significantly associated with the risk of developing CRD (hazard ratio = 1.95 for transplantations performed prior to 1999 vs. those carried out after that date)”.... It is not time since transplantation (in this case you should report months or years since transplantation), but when the transplantation was performed in relation to the specific year 1999, that is associated with risk of CRD. Why have you chosen the year 1999? Is this a specific year that you made any changes in the transplantation policy or something else special?

In our study population, the mean time since liver transplantation was seven years. In addition, the inclusion of patients took place between September and November 2009 and patients eligible for inclusion must have at least two years of post-transplant data. Then, we chose 1999 due to its clinical significance to differentiate between patients with more or less than seven years since transplantation.

In summary, to answer the comments 2a, 2b, 3, and 4 of Reviewer 00503199, the following writing has been modified / added in the study limitations section of the manuscript (page 13):

(...)However, the laboratory criteria used to define CRD were arbitrarily established using a cut-off point of 2 mg/dl that has been used in other studies in solid organ transplantation^[36]. Furthermore, local creatinine assessment techniques were not analyzed.. Thus, heterogeneity in diagnosis cannot be ruled out. In addition, the use of creatinine secretion inhibitors was not an exclusion criterion. Also, the use of a simplified MDRD equation for GFR estimation also carries some limitations^[37, 38] although it has been validated in liver transplant patients^[39].(...)

(2) Reviewer 00503255

1. Abstract AIM: “among maintenance liver transplant patients” should be added after “To compare.....glomerular filtration rate (eGFR)”

It has been added.

2. Materials and methods. page 6, line2: What is “ICEBERG”? Please spell out full words before you use an abbreviation at first.

ICEBERG Study name does not come from spelling out words. It is used to refer to a situation in which you see only a small part of what is really a bigger problem to highlight the importance of early detection of renal dysfunction.

3. What variables did you analyze for the predictors of CRD after LT in this study? Please describe in the text.

They have been added in the text as footnote in the Table 4.

Finally, references were updated according to two added: Grinyó et al. (2011) and De Simone et al. (2012).

Thank you again for publishing our manuscript in the *World Journal of Transplantation*.

Sincerely yours,

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