Answering Reviewers

Name of journal: World Journal of Transplantation

Manuscript NO: 38412

Title: Cumulative positive fluid balance is a risk factor for acute kidney injury and requirement for renal replacement therapy after liver transplantation

Dear Editor and reviewer(s),

Thank you very much for revising our manuscript. We believe it has increased its quality significantly.

Please find below our reply to your comments together with the summary of the main modifications. Please note that for your ease, we have marked the changes within the manuscript text.

Reviewer's code: 02844701

• Weather biomarkers for AKI were used in early diagnosis and treatment of AKI? Weather all patients were managed by a Nephrologist ? What is impact of pre-transplant co-morbid condition like Diabetes on post-transplant AKI? What are study limitations and confounding factors?

Although there is an increasing interest in the use of biomarkers to help identify AKI at an earlier stage, they were not used in the study.

Patients were evaluated by a nephrologist when dialysis was indicated.

Patients with cirrhosis frequently have predisposing factors for the development of kidney diseases, such as advanced age, diabetes, and hypertension. In addition, specific liver diseases may be associated with kidney disease, such as HBV/ HCV-associated glomerulonephritis or alcohol-related IgA nephropathy. In this study, the definition of AKI was based on The Kidney Disease Improving Global Outcomes (KDIGO) criteria. This definition has been validated and it considers increases in serum creatinine from baseline known or presumed to have occurred within the prior 7 days. Early recognition of AKI in cirrhosis or on post-transplant is important in order to avoid factors that may contribute to further deterioration of renal function and to initiate appropriate management.

One of the major limitations of the present study is its retrospective design. It is difficult to determine cause or consequence, but these results show that a cumulative positive fluid balance is a marker of severity of illness. We tried to control confounding factors through multivariate analysis.

Reviewer's code: 02454185

Thank you for your suggestions. We have made the proposed changes and we are sure that these modifications have improved the quality of the article.

- We have added statistics dates at the abstract :

Cumulative FB in 4 days was independently associated with occurrence of both AKI and requirement for RRT **(OR 2.3; 95% CI 1.37-3.86, p= 0.02 and OR 2.89; 95% CI 1.52-5.49, p= 0.001 respectively)**. Other variables on multivariate analysis associated with AKI and RRT were, respectively, male sex and APACHE II levels and sepsis or septic shock. Mortality was shown to be independently related to AST and APACHE II levels **(OR 2.35; 95% CI1.1-5.05, p=0.02 and 2.63; 95% CI 1.0-6.87, p=0.04 respectively)**, probably reflecting the degree of graft dysfunction and severity of early postoperative course of LT. No effect of FB on mortality after LT was disclosed.

- About the length of stay (LOS) in the ICU, we explained that **the patients were evaluated in a single admission, when they entered the hospital to be transplanted.**

- We inserted references about statistical analysis as suggested:

38. Zhang Z. Univariate description and bivariate statistical inference: the first step delving into data. Ann Transl Med. 2016; 4:91 [doi: 10.21037/atm.2016.02.11].

39.Zhang Z. Variable selection with stepwise and best subset approaches. Ann Transl Med. 2016 ; 4:136 [doi: 10.21037/atm.2016.03.35].

- We corrected **table 4** in relation to the use of vasopressors.

Table 4: Comparison of baseline, intra-operative and postoperative features of patients submitted to liver transplantation according to requirement of RRT

	No RRT (n=95)	RRT (n= 26)	p
Age (years)	49± 12	53±12	0.96
Male sex	80 (84%)	26 (100%)	0.0001
Child-Pugh score at admission	9±2	10±2	0.8
MELD score at admission	18±6	19±7	0.42
APACHE II 24 hours after admission	14±4	18±6	0.03
Cold ischemia time (minutes)	506±166	587±175	0.47
Duration of surgery (minutes)	322±103	372±102	0.50
Use of blood products	59%	81%	0.03
Number of packed red blood cell units	1.6±2.7	2.7±4.2	0.08
Use of vasoactive drugs	25 (26%)	13 (50%)	0.02
Peak of arterial lactate in the first 24 hours (mmol/L)	2.1±1.3	3.3±3.5	0.0001
Peak AST levels (U/L)	2144±2157	6599±9060	0.0001

Postoperative complications

Early allograft dysfunction	14 (15%)	13 (50%)	0.0001
Biliary strictures and/or leaks	3 (3%)	2 (8%)	0.292
Arterial thrombosis or stenosis	5 (5%)	0 (0)	0.29
Acute rejection	27 (28%)	5 (19%)	0.249
Sepsis or septic shock	23 (24%)	15 (58%)	0.0001
Cumulative FB in the first 12 hours	5014±2181	7146±2538	0.005
Cumulative FB in the first 4 days	9868±3677	14924±7345	0.0001
Length of stay in ICU (days)	9±9	20±14	0.002
Length of stay in the hospital (days)	17±10	24±14	0.007
Mortality	2 (2%)	9 (35%)	0.0001

Thank you very much once more for your useful comments.

Best regards,

Dr. Liana Codes, MD, PhD (on behalf of all the authors)