ANSWERING REVIEWERS

January 8, 2014

Dear Editor,

Please find enclosed the edited manuscript in Word format (file name: 2429-review.doc).

Title: Aetiology and risk factors of post-transplant ischaemic cholangiopathy

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

2 Revision has been made according to the suggestions of the reviewer
(1),(3), (5), (3), and (6)

Reviewer 1

Specifically, Section Title:"Donor, graft characteristics, procurement and preservation process and IC" Pg 11, paragraph 5 The discussion about higher viscosity preservation solutions causing higher incidents of IC by less capillary perfusion is not accurate. At best, the data overall show that the viscosity of the preservation solution is irrelevant to IC. In fact, some of the references cited as supporting the high viscosity hypothesis show no change between UW (high) and HTK (low). This section should be deleted or modified to reflect the correct conclusions about viscosity of flush solutions, as reflected by the prevailing data

Thank you for advice

We agreed and this part has been changed according to that…. Please refer to section: donor, graft characteristics, procurement and preservation process and ischaemic cholangiopathy, paragraph: 2

Reviewer 3

In the "Definition, incidence, and types of IC" the authors report the difference among anastomotic and non-anastomotic strictures, describe the NAS, but not the anastomotic ones and give a brief paragraph on

the pathogenesis.

Thank you…

This is done and please refers to section: definition, incidence, pathogenesis, and types of ischaemic cholangiopathy, paragraph: 2

The incidence of IC, ranging 2-20%, is referred to old studies (1993 and 1995); I would suggest updating the references, if available. I also suggest including the pathogenensis of anastomotic strictures.

Thank you

References are updated

Finally, the paragraph is entitled definition and types of IC, but in the text different types of ICs are not mentioned. - "clinical presentation" is quite descriptive, reporting only "increase" incidence of complications (gallstone formation, cholestasis, cholangitis, etc). Are there any data on the incidence and prevalence of these complications among patients with un-complicated OLT and ICs? Are there any histologic diagnostic criteria to perform diagnosis?

Thank you

Different types of IC are mentioned… pleas refers to section: definition, incidence, pathogenesis, and types of ischaemic cholangiopathy, paragraph 4

Unfortunately, there are no data on the incidence and prevalence of these complications among patients with un-complicated OLT and ICs

The only histologic diagnostic criteria to perform diagnosis are mentioned in section: clinical presentation of ischaemic cholangiopathy, paragraph 2

The risk of IC is increased in graft with prolonged cold ischemia; could the authors reported this relative risk, reported in the studies cited [12,13,41-3]; - does the underlying liver disease could play a role or represents a risk factor for ICs?

Thank you….

The relative risk was incorporated, please refer to section**: ischaemia reperfusion (IR) injury, paragraph 2**

Sclerosing cholangitis and autoimmune hepatitis are associated with high incidence of IC, please refer to section: other risk factors, paragraph 1

The management section cuuld be improved; I suggest to describe first the possible terapeutic options available to prevent or reduce the risk of IC development; after that, I would stress the endoscopic (ERCP) and percutaneous trans-hepatic management of bile duct stenosis and gallstones.

Thank you….

We agreed your suggestions and all has been incorporated according to the reviewer's opinion. Refer to the section: management

Minor: In the introduction, in my opinion, biliary and vascular complications are not the only issues in post-OLT setting; I would cite also graft reinfection and immune disease (rejection).

Thank you…

This phrase has been modified

Reviewer 4

The paper is a clinically exhaustive review and represent an innovative contribution. in the text (section of types of IC) different types of ICs are not described. References updating is recommended.

Thank you….

References are updated

As previously mentioned, types of the IC were incorporated in the final manuscript

Reviewer 5

In the abstract, authors had accidentally typed DCD as 'after donation circulatory death' instead of 'donation after circulatory death'.

Thank you…

It has been corrected

In the DCD and ischaemic cholangiopath section, the authors mentioned Taner et al showed that DWIT was not a significant factor. However, Taner et al showed the different case when considering individual time points like the asystole-to-crossclamp duration, which includes the mandatory waiting time in DWIT. Maybe the authors want to explain this clearer.

Thank you…

It has been corrected

Reviewer 6

The authors should give the full name and not the abbreviated name in the introduction. Some abbreviated words i.e CIT and WIT have been described in the abbreviations list but they should be reported in the text as well.

Thank you….

All abbreviations have been checked and corrected

In the "Introduction" section paragraph three the authors write "…hepatic artery thrombosis or stenosis 16" is the 16 a typo or has a meaning?

Thank you…

It is corrected in the final manuscript

3) The authors need to conclude whether it should be "ischaemia" or "ischemia"

Thank you…

We agreed to use ischaemia in this manuscript and all have been changed to that

Similar to comment 2, in the section "Blood supply of the biliary tree" paragraph 2 " 28 hepatic artery damage…" what is the meaning of 28?

Thank you…

It is corrected

In the section "other risk factors" paragraph 2: the authors should consider expanding the mechanisms by which the bile ducts are lost. "(1) a direct immunological destruction of the biliary epithelium" which immune cells have been reported to be responsible for this destruction? "(2) an indirect , ischemic damage" what is the actual mechanism of this?

Thank you….

We agreed and the two mechanisms are completely discussed in the final manuscript

3 References and typesetting were corrected

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

Sincerely yours,

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