December 21, 2019

Subrata Ghosh and Andrzej S Tarnawski
Editors-in-Chief
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Dear Editors:

I, along with my coauthors, would like to resubmit the attached manuscript titled

"Pre-hepatectomy type IV collagen 7S predicts post-hepatectomy liver failure and recovery" as an original article. The manuscript ID is 52223.

The manuscript has been carefully rechecked and appropriate changes have been made in accordance with the reviewers' suggestions. The responses to their comments have been prepared and attached herewith. Changes in the manuscript are shown in yellow highlights, and a clean copy of the manuscript has also been attached.

We thank you and the reviewers for your thoughtful suggestions and insights, which have enriched the manuscript and produced a more balanced and better account of the research. We hope that the revised manuscript is now suitable for publication in your journal.

I look forward to your reply.

Sincerely,
Osamu Itano, M.D., Ph.D.
Hepato-Biliary-Pancreatic and Gastrointestinal Surgery, International University of Health and Welfare School of Medicine, 3-4-1Mita Minato-ku Tokyo, Japan.
Tel: +81-03-3451-8121
Fax: +81-03-3451-8336
E-mail: laplivertiger@gmail.com

Responses to the reviewer comments

Reviewer: 03074879

General Comment: The authors analyzed the clinical information215 patients and find the liver function of patients with type IV collagen 7S≤6 ng/dL will recovor sooner than those type IV collagen 7S >6 ng/dL. The experiment design is reasonable and the analysis have no obvious mistakes. I have some questions for the article. 1. How do you decide the grouping criteria? How do you find 6 ng/dL is the demarcation line of patients. Do you have a ROC curve or other anlysis? Do the level of type IV collagen 7S is correlated with the recovery time? If the patients have a higher type IV collagen 7S level, the recovery time will be sooner?　2. If the resection volume of live infuence the outcome of the analysis?

Answer: We appreciate your critique of this manuscript and have revised it based on your comments. Please see our detailed responses to your comments below, with clarifications and a list of the changes. To facilitate easy identification of the changes that were made we have highlighted these in red in the manuscript.

Comment 1.　How do you decide the grouping criteria? How do you find 6 ng/dL is the demarcation line of patients. Do you have a ROC curve or other anlysis?

A1: Thank you for pointing out this important issue. We apologize it is not clear to decide the grouping criteria. The patients were divided into two groups - serum type IV collagen 7S ≤6 ng/mL and that with serum type IV collagen 7S >6 ng/mL-,

because type IV collagen 7S ≤6 ng/mL is defined as within normal limit in many companies which measure type IV collagen 7S. We also apologize the unit of type IV collagen 7S, Hyaluronic acid and Blood platelet was wrong. We have added the text accordingly:

Page8 line22-24

blood products between the samples. The patients were divided into two groups - serum type IV collagen 7S ≤6 ng/mL and that with serum type IV collagen 7S >6 ng/mL-, because type IV collagen 7S ≤6 ng/mL is defined as within normal limit in many laboratory companies which measure type IV collagen 7S. The minimum time to recovery was 1 day.

Page10 line5-7

Long-term postoperative recovery of liver function was compared between the group of patients with serum type IV collagen 7S ≤6 ng/mL and that with serum type IV collagen 7S >6 ng/mL (in Japan, type IV collagen 7S >6 ng/dL is defined as abnormal) using the Kaplan–Meier method.

type IV collagen 7S ≤6 ng/dL→type IV collagen 7S ≤6 ng/mL

Hyaluronic acid (ng/dL)→Hyaluronic acid (ng/mL)

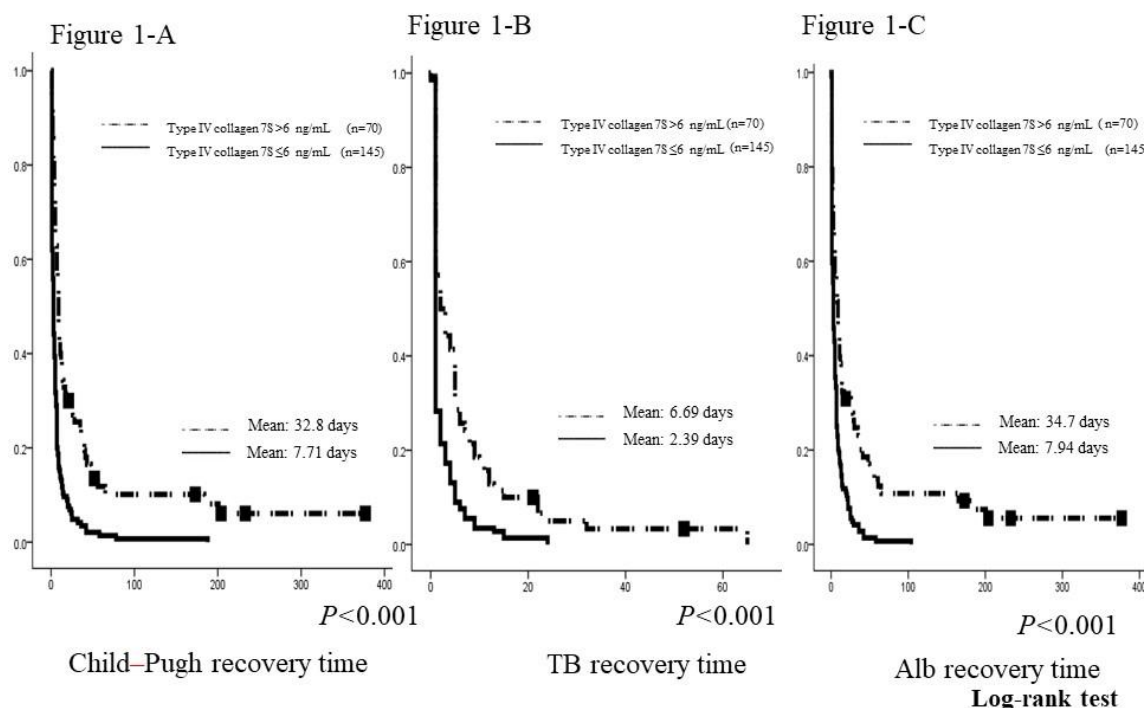Blood platelet ((/μL)→　Blood platelet ($\times 10^4$/μL)

Comment 2.　Do the level of type IV collagen 7S is correlated with the recovery time? If the patients have a higher type IV collagen 7S level, the recovery time will be sooner?

A2: Although we analyzed the level of type IV collagen 7S is correlated with the recovery time, I apologize it is unclear for you. We appreciate your comment and have now added the analyze method. Preoperative type IV collagen 7S level was a significant independent factor associated with the number of days until recovery to serum total bilirubin (TB) and albumin (Alb) levels to return to levels of <2 mg/dL and >2.8 g/dL, respectively, and the time taken for Child–Pugh score to return to Child–Pugh class A in Cox regression analyses of time to recovery. If the patients have a higher type IV collagen 7S level, the recovery time will be longer (Figure 1).

We have added the text accordingly:

Page11 line10-12

Preoperative type IV collagen 7S level was a significant independent factor associated with the number of days until recovery to these levels in Cox regression analyses.

Figure 1-A — Child–Pugh recovery time — P<0.001
Figure 1-B — TB recovery time — P<0.001
Figure 1-C — Alb recovery time — P<0.001
Log-rank test

Comment 3. If the resection volume of liver influence the outcome of the analysis?

A3: Thank you for your comment. Although we analyzed the resection volume of liver, I apologize it is unclear for you. We analyzed resection volume of liver as Extent of hepatic resection in General Rules for the Clinical and Pathological Study of Primary Liver Cancer in Japan. But, in our study, Extent of hepatic resection was not a significant independent factor associated with early postoperative liver failure and long-term recovery of hepatic reserve.

We added the reference: Page21 line4-5

26   Makuuchi M, Arii S, Kanematsu T, Kudo M, Takayasu K, Nakanuma Y, Sakamoto M. General Rules for the Clinical and Pathological Study of Primary

Reviewer: 02860849

General Comment: This paper is a Retrospective Cohort Study. It is pretty interesting and the results will be useful for clinical practice and forecasting of chronic liver diseases. The manuscript and figures are prepared very well.

Answer: We appreciate your comment. Thank you for reviewing.