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**August 31, 2021**

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Koo Jeong Kang

Nikolaos Pyrsopoulos

Editors-in-Chief

*World Journal of Hepatology*

Dear Editors:

On behalf of all co-authors I would like to submit our revised manuscript titled, “**Angle of covered self-expandable metallic stents after placement is a risk factor for recurrent biliary obstruction**” (Manuscript number: 68821) for publication in the *World Journal of Hepatology*. We appreciate the opportunity provided to submit a revised version of our manuscript, and would like to thank the reviewers for their helpful suggestions, which have helped us improve our manuscript considerably.

We have addressed all the concerns raised by the reviewers, and have revised the manuscript as suggested. Our point-by-point responses to each of the comments have been provided below.

All authors concur with the decision to submit this manuscript. None of the data in this manuscript have been previously reported, and the manuscript is not under consideration for publication elsewhere.

We hope that the manuscript is now suitable for publication in this journal, and would be pleased to respond to any further queries regarding this submission.

Thank you for your consideration. I look forward to hearing from you.

Sincerely,

***Hirotsugu Maruyama***

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## **Point-by-Point Responses**

### **Responses to the comments from reviewer #1:**

We appreciate your constructive comments and pertinent suggestions, which have helped us in revising and improving this manuscript. We have considered these comments and suggestions during revision of our manuscript, as indicated in the following responses. Please note that all text changed in response to the comments has been highlighted in yellow in the revised manuscript.

### **Comment #1**

- This is a retrospective study.

### **Response to major comment #1**

We appreciate your pertinent observations. Based on your observations, we have added the following sentence in the first limitations of the **Discussion**.

“We acknowledge that patient assignment to different interventions was subject to selection bias. There were differences in the length, diameter, and type of CSEMS used in our study; these factors can influence RBO. However, on multivariate analyses, these factors did not significantly influence RBO. In our results, the angle after placement was a risk factor for RBO, regardless of the CSEMS characteristics selected.”

### **Comment #2**

- Several factors influence the outcome of the study. Please discuss these.

### **Response to major comment #2**

Thank you for your helpful suggestion. There is only one report, which demonstrated the risk of RBO with CSEMS; the associated factor was chemotherapy. Multivariate analysis in our study showed that the risk factor for RBO in cases with CSEMS was not chemotherapy, but the angle of the CSEMS after placement. This is a new finding, and to the best of our knowledge, no reports have demonstrated this fact.

### **Comment #3**

- Please review the literature and add more details in the discussion section.

### **Response to major comment #3**

Thank you for your valuable suggestion. We have performed a thorough literature review, and have revised the text in the **Discussion**, as follows: “A CSEMS’s angle of  $< 130^\circ$  is a risk factor for early RBO. This result suggests that CSEMS with low AF cause sludge formation, food impaction, and stent migration. Several previous studies support these reasons <sup>[7]</sup> <sup>[17-19]</sup>. First, the placement of CSEMS with large diameter across the papilla causes loss of sphincter dysfunction, resulting in duodenal-biliary reflux to bile duct because of pressure gradient by food or duodenal contents. These results suggest that disruption of the sphincter mechanism may represent the most important etiologic factor in the development of cholangitis after metallic stent placement for malignant biliary obstruction <sup>[18]</sup>. In addition, the previous reports were suggested that food debris is an etiologic factor for acute cholangitis and warned that occlusion might be caused by reflux of duodenal contents <sup>[19-21]</sup>. A CSEMS with low AF decrease flow velocity and increase the resistance of bile juice. Therefore, a CSEMS’s angle of  $< 130^\circ$  easily causes sludge and food impaction and induces early RBO.”

#### **Comment #4**

- What is the new knowledge of the study?

#### **Response to major comment #4**

We appreciate your pertinent question. The new knowledge added by this study is that the angle of CSEMS after placement is a risk factor for RBO in unresectable distal MBO. This has been mentioned in the beginning of the **Discussion**. The text reads:

“We found that the angle of CSEMS after placement was a risk factor for RBO in unresectable distal MBO. In addition, our study demonstrated that the cut-off value of the angle of CSEMS after placement for RBO was  $130^\circ$ , and that TRBO in the group with an angle of  $< 130^\circ$  was significantly shorter than that in the group with an angle of  $\geq 130^\circ$ .”

#### **Comment #5**

- Please recommend to the readers “How to apply this knowledge in clinical practice?”.

#### **Response to major comment #5**

Thank you for your helpful suggestion. We have provided a recommendation in the **Discussion**, as follows:

“In our study, among patients who experienced RBO of CSEMS in the  $< 130^\circ$  angle group, 86% patients had elevated liver enzymes in the latest laboratory data before the occurrence of RBO, compared with previous laboratory data; all patients were asymptomatic (**Table 5**). Thus, the risk of RBO may be considered to be potentially high if the CSEMS angle is  $< 130^\circ$  and liver enzymes are elevated. Hence, while managing such patients, we suggest the replacement of CSEMS even in asymptomatic patients if the liver enzymes are elevated and the CSEMS angle is  $< 130^\circ$ . We believe that this information has great significance in the management of patients undergoing CSEMS

placement in clinical practice. Additionally, by deploying a new CSEMS with high AF as needed, long-term maintenance may be expected without stent dysfunction.”

### **Responses to the comments from reviewer #2:**

We appreciate your constructive comments and valuable suggestions. They have helped us considerably in revising and improving this manuscript. As indicated in the responses below, we have considered these comments and suggestions during the revision of our manuscript.

#### **Comment #1**

- Does the angle of stent change all the time due to the tumor growth?

#### **Response to major comment #1**

We appreciate your pertinent question. In this study, it was unclear whether tumor growth causes the angle of the CSEMS to change all the time. We speculate that tumor growth, tumor type, and fibrosis of tumors may be associated with changes in stent angle. Your comment raises an interesting issue; however, this was a retrospective study and it was difficult to observe changes in the angle of stents and tumors over time.

#### **Comment #2**

- Does the conclusion apply to the uncovered self-expandable metallic stent?

#### **Response to major comment #2**

We appreciate your pertinent question. In this study, it was unclear whether the angle of the uncovered self-expandable metallic stent (USEMS) after placement is also associated with the risk of RBO. This is because we excluded cases where uncovered self-expandable metallic stents were

placed for unresectable distal malignant biliary obstruction. However, we speculate that in cases of USEMS placement, tumor ingrowth is more likely to be a risk factor for early RBO than the angle of the stent after placement.