

July 2, 2021

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Anastasios Koulaouzidis, MD, PhD
Sang Chu Lee, MD, PhD
Editors-in-Chief
World Journal of Gastrointestinal Endoscopy

Dear Prof. Hu, Prof. Koulaouzidis and Prof. Lee,

The science editor of the *World Journal of Gastroenterology* recommended transferring my manuscript to the *World Journal of Gastrointestinal Endoscopy*. Therefore, I wish to submit an opinion review for publication in the *World Journal of Gastrointestinal Endoscopy*, titled "Proposal of the term 'gallstone cholangiopancreatitis' to specify gallstone pancreatitis that needs urgent endoscopic retrograde cholangiopancreatography."

The comments of the five reviewers who previously reviewed my manuscript have been helpful in revising my manuscript. I have attempted to address the questions raised by the four referees (Reviewer #1, 2, 3, and 4), and my responses are as following:

Reviewer #1:

1. I agree with this reviewer and the term "hepatopancreatitis" has been replaced by the term "cholangiopancreatitis."
2. In 1985, the author proposed the term "gallstone hepatitis" as a new clinical entity, which is defined as a marked elevation in serum transaminase levels due to acute inflammatory liver cell degeneration and necrosis during the early stage of gallstone impaction in the bile duct: the marked elevation in transaminase levels alone may lead to a diagnosis of so-called hepatitis, and hepatocellular degeneration and necrosis have been histologically shown to be acute inflammatory reactions to liver injury caused by acute bile duct obstruction, which is transient and reversible after its early resolution (Reference 21). The preceding statement has been included in the revised manuscript. Gallstone hepatitis refers to the presence of acute bile duct obstruction due to gallstones before the development of acute cholangitis due to persistent bile duct obstruction. On the other hand, gallstone cholangiopancreatitis is defined as a severe disease with minimal or mild pancreatitis complicated with life-threatening acute cholangitis due to persistent biliopancreatic obstruction caused by impacted ampullary stones.
3. The term "gallstone cholangiopancreatitis" may be valuable in clinical practice for specifying gallstone AP that needs urgent ERCP with ES.
4. Following the reviewer's comment, I have made an algorithm to define patients in need of ERCP (shown in Figure 2 in the revised manuscript).

Reviewer #2:

1. There is a possibility that the levels of liver enzymes are elevated due to acute cholecystitis itself in the absence of a hepatocellular injury. However, as this reviewer pointed out, we rarely see acute cholecystitis and acute pancreatitis. Therefore, acute inflammation of the gallbladder may not be the initial process responsible for transaminase elevation but secondary to bile duct obstruction. The preceding statement has been included in the revised manuscript.
2. Stones might block both BG and ampulla simultaneously. However, in clinical settings, we rarely ever see this happening.
3. The comments of this reviewer have been helpful in making a patient flow chart, with the starting point including index patients with gallstone pancreatitis and then having several

branching points, suggesting management as per the branching algorithm. I have included the algorithm (Figure 2) in the revised manuscript.

Reviewer #3:

1. Considering that the pathophysiology is exhaustively long, I have attempted to explain as concisely as possible.

Reviewer #4:

1. GSH, the abbreviation of gallstone hepatitis, has been avoided. Gallstone acute pancreatitis has been abbreviated as gallstone AP.
2. The pathogenesis of gallstone hepatitis differs from ordinary hepatitis in that hepatocyte necrosis occurs as a consequence of cholestasis: hepatocellular degeneration and necrosis have been histologically shown to be the acute inflammatory reactions to liver injury caused by acute bile duct obstruction, which is transient and reversible after its early resolution(Reference 21). The statement has been included in the revised manuscript.
3. In reply to this reviewer, the development of acute cholangitis in patients with biliopancreatic obstruction has been reflected using the term "gallstone cholangiopancreatitis" instead of "gallstone hepatopancreatitis".
4. I almost agree with this reviewer in dividing the liver disorders caused by bile duct obstruction into two conditions: one with a marked elevation of serum transaminase levels (gallstone hepatitis), the hepatic histopathological changes of which are cholestasis, acute cholangitis, and hepatocyte necrosis due to acute biliary tract obstruction, and the other with an elevation of the serum bilirubin level caused by persisting bile duct obstruction. Elevation of serum transaminase is consistent with the concept of transient ampullary obstruction in gallstone AP, and is useful in establishing gallstone etiology. The statement has been included in the revised manuscript.

I appreciate the detailed review of this manuscript and have attempted to answer each of the questions raised. In reply to the Science editor, the title has been shortened and a running title has been included in the revised version. Furthermore, subheadings have been included, and after the paragraph 「Conventionally, clinicians paid less attention to hepatobiliary diseases characterized by markedly elevated liver enzyme levels caused by impacted bile duct stones; this seems to be the Achilles heel in the management of patients with gallstone AP. This may be unavoidable because the term "gallstone AP" refers to "pancreatitis" alone.」, the following is included in the revised manuscript for readers to understand what I want to emphasize; 「The term "gallstone hepatopancreatitis" reflects elevated liver and pancreatic enzyme levels that may better direct the clinician's attention to hepatobiliary pancreatic lesions occurring in both the liver and the pancreas caused by transiently impacted stones at the ampulla of Vater early in the course of gallstone AP.」

This manuscript has not been published or presented elsewhere in part or in entirety and is not under consideration by another journal. I have read and understood your journal's policies, and I believe that neither the manuscript nor the study violates any of these. There are no conflicts of interest to declare.

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

Sincerely,

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