

## Response to reviewers

We are thankful to the reviewers for their time, thorough review of our manuscript and valuable comments. We are also thankful to the editorial team for the considerate guidance. We have revised the manuscript accordingly, highlighting changes on yellow fond, and provide point-by-point responses below:

### Reviewer #1:

#### **Specific Comments to Authors:**

Thank you for the opportunity to review this review article about hepatolithiasis. The topic is very interesting and the article is very well organized and well written. I have just few comments. The title should be conservative like this. However, if changing a bit to be more attractive or flashy will be good.

We are thankful for the suggestion. We chose this title because it is very descriptive. However, following this suggestion we have changed it to "Hepatolithiasis: Epidemiology, Presentation, Classification and Management of a complex disease" as we feel this is more attractive.

Please add figure 1 into the manuscript. Figure 1 should be cited on the introduction part.

Thank you for pointing this out. We have made the correction.

Please use the consistent term for the ref authors. (for example Glenn et al, Wang and colleagues... I think using Wang et al might be suitable) and in table 1, the ref authors should be first author et al., not only the name of first author only.

Thank you for pointing this out. We have made the correction and consistently used "et al" where appropriate. That being said, "Dong's classification", "Tsunoda classification" and "LHO Classification System" and well known under these names, while Nakayama's classification was proposed by this single author. We have however added the relevant references on Table 1.

The authors mentioned about genetic risk factors of hepatolithiasis (ABCB4 and ABCB11). How about the genetic mutation in cystic fibrosis? Does it play vital role in hepatolithiasis as well?

Thank you for this question. We have indeed discussed the relationship between cystic fibrosis and hepatolithiasis in the revised manuscript.

### Reviewer #2:

### Specific Comments to Authors:

Major issue 1) The authors are kindly requested to provide some representative educative material (e.g. figures, videos) regarding the diagnostic approach and the management of hepatolithiasis.

This comment needs to be seen in conjunction with **Minor issues 3) Figure 2 is inaccessible; the authors are kindly requested to properly revise it.**

We are sorry that Reviewer 2 found Figure 2 inaccessible and we are unaware of the reason for this. Figure 2 was submitted along with the main text of the manuscript. We are in agreement that a review on the topic of hepatolithiasis should ideally contain "*original and educative content*".

However, Figure 2 represents effectively what Reviewer 2 requests as representative educative material regarding the management of hepatolithiasis. This Figure was created by our team following our extensive study of the literature, and provides a schematic summary of the management of hepatolithiasis in a synthetic fashion. To our knowledge, such a figure has not been created before. We consider it an essential part of our work as it is very practical, educative and we believe it is important. We are hopeful this will be easily accessible on the revised submission.

Minor issues 1) The authors are welcome to additionally focus on the pediatric population by adding a relevant paragraph.

Thank you for this recommendation. We have additionally focused on the paediatric population discussing the available literature, in the revised manuscript.

2) The authors are encouraged to discuss the potential risk factors of cholangiocarcinoma based on additional relevant references (e.g. Liu ZY, Zhou YM, Shi LH, Yin ZF. Risk factors of intrahepatic cholangiocarcinoma in patients with hepatolithiasis: a case-control study. *Hepatobiliary Pancreat Dis Int.* 2011 Dec;10(6):626-31. doi: 10.1016/s1499-3872(11)60106-9. PMID: 22146627).

Thank you for this recommendation. We have mentioned further risk factors for cholangiocarcinoma and added the reference in the revised document.