Reply to the reviewers

REVIEWER #1:

Specific Comments to Authors:

Thank you very much for your valuable and constructive comments.

The 'Introduction' and the 'Conclusion' section have been modified and supplemented by information and notes as recommended by a reviewer.

(1). Could you please highlight what are the original findings and novelty of this manuscript?

This minireview briefly summarises general morphological aspects of small-duct cholangiopathies relevant to the routine diagnostic process and highlights some new conditions recently described in association with implementation of new drugs and therapeutic procedures:

…Although the majority of cholangiopathies are long established, recent entities such as SSC-CIP and CPI-induced cholangiopathy have complicated the application of new therapeutic agents and approaches. Cholangiopathy has also developed in some critically ill patients infected by β-coronavirus SARS-CoV2, isolated for the first time in Wuhan in December 2019….

(2) Could you please explain the significance of cholangiopathies (including a brief review clinical aspect, epidemiological aspect, therapy, etc) which made you wrote his article and their correlation with morphological aspects of non-neoplastic small-duct cholangiopathies in background as the quality and importance of this manuscript?

The manuscript has been modified and expanded to highlight the clinical importance of biliary diseases, and main issues associated with liver biopsy interpretation.

…. Given their progressive nature and limited curative options, biliary diseases account for significant morbidity and mortality in both the adult and paediatric populations. Cholangiopathies often result in end-stage liver disease requiring liver transplantation. ..

…. Early identification of the pathological mechanisms that compromise cholangiocytes and the small bile ducts is crucial in determining appropriate treatment. While large bile duct pathology is usually visualised by imaging methods, liver biopsy is still considered an effective tool in the diagnosis of small bile duct injury. However, discrepancies between histomorphological, clinical, and biochemical presentations of small bile duct disorders can hinder the diagnostic process. Clinically clear cholestatic

conditions manifesting in pruritus and elevated serum ALP, GGT, cholesterol and bile salts can progress without significant bilirubinostasis on biopsy. In addition, pathognomonic morphological signs of small duct cholangiopathies are often focal and may be easily overlooked during percutaneous liver biopsy. On the other hand, early-stage cholangiopathy with a fully developed histomorphological pattern may be accompanied by only minimal and non-specific biochemical abnormalities.
Uneven fibrosis progression within the liver parenchyma is another factor that complicates the diagnostic process, notably when staging fibrosis in a chronic biliary disease. The application of standard semiquantitative scoring systems can serve to underestimate or overestimate the fibrosis stage, particularly in a limited tissue specimen. The clinician should consider not only the data obtained from the liver biopsy but also the results of imaging and other methods (FibroScan, elastography) relevant to the assessment of liver fibrosis.
…….

Understanding the underlying pathogenetic mechanisms, familiarity with basic morphological patterns, and the ability to correlate microscopical findings with clinical and laboratory results are important elements when forming an overall clinical picture and selecting the optimal therapeutic approach in patients with biliary diseases. To that end, the close cooperation of all medical specialists participating in the diagnostic process is recommended.

(3) Could you please explain what are the future directions of the topic described in this manuscript? and what are the questions/issues that remain to be solved?
The 'Conclusion' section has been modified as follows:

…. The implementation of new, predominantly non-invasive diagnostic tools and methods that bridge the shortcomings of liver biopsy is needed. Moreover, further studies are required to elucidate the environmental, genetic, and epigenetic background of the processes affecting the biliary tree and to improve the clinical management of both hereditary and acquired small duct cholangiopathies. ....

REVIEWER #2:
Thank you very much for your valuable comments.

Specific Comments to Authors:

1. please add some new information regarding IgG4-related sclerosing cholangiophaty and also neoplasic cholangiophaty

Two new sections 'IgG4-related sclerosing cholangiopathy' and 'Neoplastic cholangiopathy' with figures No. 6 and 10 have been supplemented. References have been modified accordingly.

2. the discussion about the drug induction cholangiophaty should be further developed

The section **'**Drug- and toxin-induced cholangiopathy' has been reviewed and supplemented. General mechanisms of drug injury and checkpoint inhibitor-induced biliary injury are discussed in more detail.

3. there are some typing english errors

The original and revised text has been reviewed and modified by a certified language editor/native speaker.

REVIEWER #3:

Specific Comments to Authors:

Thank you very much for your kind evaluation of our manuscript and your valuable comment.

1. **What is the importance kindly mention in conclusion of the study.**

The CONCLUSION section of our manuscript has been significantly modified and supplemented by information regarding the significance of the topic reviewed, very brief epidemiological notes, common problems associated with liver biopsy interpretation, as well as future perspectives. In addition, CORE TIP has been modified accordingly.