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Endoscopic ultrasound diagnostic gain over computed tomography and magnetic resonance cholangiopancreatography in defining etiology of idiopathic acute pancreatitis

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Reviewer comments

Reviewer #1
This manuscript describes the role of endoscopic ultrasound in idiopathic acute pancreatitis in which the etiology could not be determined by various examinations. While there is no dispute that EUS is useful in the etiologic diagnosis of acute pancreatitis, a study of the Diagnostic gain of EUS after US, CECT or MRI would be very informative. I think this is a well-structured study. However, there is not much novelty and the sample size is small. Furthermore, it has already been summarized in a meta-analysis and has the same conclusion.

Thank you for the comment. We are aware that our conclusions are consistent with previously published data, including meta-analyses. However, we focused on the diagnostic gain of EUS in case of failure of multiple previous examinations, since data about the EUS diagnostic gain are still limited. We are also aware about the small sample size, that strongly depends on the single-center nature of the study. Larger and prospective studies addressing the EUS diagnostic gain in this setting are needed.

Reviewer #2
The study by Mazza et al. concluded that EUS is superior to CT/US/MRCP in determining the etiology of idiopathic acute pancreatitis. The topic is important, and the manuscript is well written. However, many studies had been published on this topic for years. Even meta-analysis on this topic has been published with 22 studies included (PMID: 32557477). Hence, the novelty is low for this study. Moreover, the sample size for this study is small and it was a single center retrospective study. In general, I recommend this study to be published in World journal of Gastrointestinal endoscopy.

Thank you for the comment. As mentioned above, data about the usefulness of EUS in IAP are robust and corroborated by meta-analyses. Therefore, we focused on the EUS diagnostic gain after US, CECT and MRCP failure. Despite the small sample size and the retrospective nature of the study, our data are homogeneous and the follow-up adequate to detect AP recurrences and to assess patients' course.

Reviewer #3

This is a retrospective study that aimed at assessing the role of EUS in idiopathic acute pancreatitis (AP). The study concludes that EUS that was able to identify the etiology of AP in 79%. More importantly, EUS was able to identify the etiology of AP in 63% of patients where both CT and MRI failed to find the cause. In addition, the authors were able to identify some clinical parameters that increases the probability of certain etiologies, for example elevated liver enzymes and the risk of biliary etiology of AP. TITLE: Appropriate for the purpose of the study ABSTRACT: Appropriate and summaries the main findings in clear and concise way.

Thank you for the comment.

INTRODUCTION: I think this part can be summarized more. It includes some unnecessary basic information for the purpose of the study such as the definition and mechanisms of acute pancreatitis. I think the authors should include more data from the literature on idiopathic pancreatitis and the role of EUS in this scenario. There has been multiple studies assessing the role of EUS in idiopathic pancreatitis so the authors should mention this part and discuss why this study is important and how it is different from published literature.

Thank you for the important review. We proceeded to summarize the introduction according to your advice. We have also added more data about the role of EUS in IAP and better specified that the main novelty of the study is to evaluate the diagnostic gain of EUS in case of failure of multiple previous imaging techniques.

METHODS: Well-described, using validated and clear definitions for the exposures and the outcomes. The inclusion and the exclusion criteria were very clear. The follow up period long enough to detect most recurrent episodes (median 31.5 months). Under statistical analysis (page 14): "The continuous variables with normal distribution are described as median ± standard deviation (SD) ". I think the authors meant "MEAN ± standard deviation". Please correct if appropriate.

Thank you. We proceeded to correct "median" with "mean".

RESULTS: Clear and well-written. The authors found that biliary etiology and chronic pancreatitis are the most underlying causes of AP on EUS. This is in keeping with previous literature that has shown the superiority of EUS in detecting microlithiasis and early changes of chronic pancreatitis over other imaging techniques. The surprising findings (at least to me) include the superiority of EUS over MRCP in detecting pancreas divisum and ductal anomalies. Previous meta-analysis (Wan et al. GIE 2017) have shown that MRCP is superior to EUS in detecting pancreas divisum in patient presenting with idiopathic AP. Would be interesting to hear the authors perspective on this point (could be added to the discussion section).

Thanks for pointing this out. In the meta-analysis by Wan et al., EUS and MRCP showed similar efficacy in the diagnosis of pancreas divisum in IAP, while MRCP after secretin stimulation was superior to both techniques. However, secretin-enhanced MRCP is not routinely performed in our center and in general is not widely available in the territory. We have better emphasized this in the discussion.

Another important finding which was highlighted by the authors is the usefulness of EUS is more among patients who did not have previous cholecystectomy (since missed biliary etiology is more likely in this sub-group). Another point that the authors discussed in the results (but I think it should be highlighted more in the discussion part) is the fact that EUS findings changed the management of patients significantly including referral to cholecystectomy, ERCP for ductal stenting/sphincterotomy and surgical referral for tumor removal. This is important to highlight since it provides even stronger argument as to why EUS should be utilized more often in patient with idiopathic AP.

This is a very important point. EUS can modify the patients' management through the identification of small pancreatic lesions or lithiasis missed at previous exams. This is obviously of paramount importance for small pancreatic cancers, that could be suitable for curative therapy. We have better emphasized this in the discussion.

DISCUSSION: Gives a good summary of the findings. I think the authors should discuss previous literature in this field and if their findings are in keeping with previous studies (most previous studies and meta-analyses in this field agree with the study findings). Overall, nicely done and well-written study but the main limitations are the small size (81 pts), retrospective nature of the study. More importantly even though this study looks at a very important and common clinical scenario (idiopathic pancreatitis), multiple larger previous studies have been published which

were summarized in a number of meta-analyses (Wan et al. GIE 2017, Umans et al. Endoscopy 2020) which came to the same conclusion as the current study. So overall, this study does not add much to the current literature.

Thank you for the comment. The role of EUS in IAP has been established by multiple previous studies. However, we wanted to focus on the diagnostic gain of EUS in case of failure of multiple previous examinations; indeed, data about the diagnostic gain of EUS are still limited. As we state in the discussion, the small sample size is a limit of the study, that depends on its single-center nature. Larger and prospective studies addressing the diagnostic and prognostic value of EUS in IAP are needed.