PEER-REVIEW REPORT

Scientific quality	[ ] Grade A: Excellent [ ] Grade B: Very good [ ] Grade C: Good [Y] Grade D: Fair [ ] Grade E: Do not publish
Language quality	[ ] Grade A: Priority publishing [ ] Grade B: Minor language polishing [ ] Grade C: A great deal of language polishing [Y] Grade D: Rejection
Conclusion	[ ] Accept (High priority) [ ] Accept (General priority) [ ] Minor revision [Y] Major revision [ ] Rejection
Re-review	[Y] Yes [ ] No

Peer-reviewer statements	Peer-Review: [Y] Anonymous [ ] Onymous
	Conflicts-of-Interest: [ ] Yes [Y] No

SPECIFIC COMMENTS TO AUTHORS

The study explored the role of cyst fluid biomarkers in differential benign and malignant PCLs. However, the study was not wrote in the regular form, which makes the study difficult to read. The result section was not well orgnised, I can't get what I want to know easily. Some comments: 1. These makers have been proved to have little value in predicting malignant PCLs. However, the predictive value was proved in this study. What are the advantages of the study make the conclusion reliable? 2. There were 31 pseudocyst in the study. The median amylase level was only 130 U/L, the data seems unlikelihood. 3. Too many table. Some tables can be mixed together. 4. The study design was more like a retrospective study rather than prospective study.

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Conclusion	[ ] Accept (High priority) [ ] Accept (General priority) [ ] Minor revision [ ] Major revision [Y] Rejection
Re-review	[ ] Yes [Y] No

| **Peer-reviewer statements** | Peer-Review: [Y] Anonymous   [   ] Onymous |
| | Conflicts-of-Interest: [   ] Yes   [Y] No |

SPECIFIC COMMENTS TO AUTHORS

The study is somewhat novel. The Author gathered as much biochemical information possibile to assess which parameters should a clinician rely on to establish the need of resecting a pancreatic cyst. However, I have major concerns as follows: - The Authors selected the patients to submit to cyst fluid (and EUS) assessment, namely those having cysts greater than 3 cm. The cut-off is arbitrary for each pancreatic cyst considered, and none of the Guidelines recommend surgery for a cyst "only" greater than 3 cm. What about the cysts smaller than 3 cm? - The primary outcome is not clear: did the Authors proposed surgery by default each patient, regardless of the findings obtained, due to have a final histology for confirmation? This resize also the concept of "comparison" proposed. - The 18 months period proposed is not suffragate by appropriate evidence, even produced by the Authors - I don't see any demographics - Tables are too much, some of them should be placed under supplementary material - Given the title itself proposed, I would expect a more detailed description of the EUS findings, that, nowadays, are the features on whom the decision to perform surgery relies on. - The Authors should focus on the features associated with pre-malignancy (high-grade dysplasia), that may become curative, rather than on malignancy ones (if a patient has been under surveillance, then probably surgery arrived late) - The Authors should provide also information on the features associated with "futile/unnecessary" surgery

PEER-REVIEW REPORT

Name of journal: *World Journal of Gastrointestinal Endoscopy*

Manuscript NO: 72633

Title: Role of EUS, EUS-FNA, and Cyst Fluid Tumor Markers in the Diagnosis of Cystic Pancreatic Lesions

Provenance and peer review: Invited manuscript; Externally peer reviewed

Peer-review model: Single blind

Reviewer's code: 06198447

Position: Peer Reviewer

Academic degree: MD

Professional title: Research Assistant

Reviewer's Country/Territory: Russia

Author's Country/Territory: Egypt

Manuscript submission date: 2021-10-22

Reviewer chosen by: AI Technique

Reviewer accepted review: 2021-10-23 19:44

Reviewer performed review: 2021-11-02 19:25

Review time: 9 Days and 23 Hours

Scientific quality	[ ] Grade A: Excellent [Y] Grade B: Very good [ ] Grade C: Good [ ] Grade D: Fair [ ] Grade E: Do not publish
Language quality	[Y] Grade A: Priority publishing [ ] Grade B: Minor language polishing [ ] Grade C: A great deal of language polishing [ ] Grade D: Rejection
Conclusion	[ ] Accept (High priority) [ ] Accept (General priority) [Y] Minor revision [ ] Major revision [ ] Rejection
Re-review	[Y] Yes [ ] No

Peer-reviewer statements	Peer-Review: [ ] Anonymous [Y] Onymous
	Conflicts-of-Interest: [ ] Yes [Y] No

SPECIFIC COMMENTS TO AUTHORS

Role of EUS, EUS-FNA, and Cyst Fluid Tumor Markers in the Diagnosis of Cystic Pancreatic Lesions   1 Title.   The title reflects well the main subject of the manuscript. 2 Abstract.   The abstract summarizes and reflects the work described in the manuscript. 3 Key words.   The key words reflect the focus of the manuscript. In addition, you may also add such terms as pancreatic cystic neoplasm, MCN, IPMN. 4 Background.   The authors describe well the background, present status and significance of the study. 5 Methods.   The authors mention that the final diagnosis was based on histopathology after surgery (15 patients out of 76 according to table 11) and positive cytopathology. Could you please specify what do you mean under the term "positive cytopathology"? According to recent studies the accuracy of EUS-FNA in pancreatic cystic neoplasms is quite low. On the other hand, the morphologic EUS criteria themselves are not sufficient for final diagnosis of Pancreatic cystic neoplasms (Wu J, Wang Y, Li Z, Miao H. Accuracy of Fukuoka and American Gastroenterological Association Guidelines for Predicting Advanced Neoplasia in Pancreatic Cyst Neoplasm: A Meta-Analysis. Ann Surg Oncol. 2019 Dec;26(13):4522-4536. doi: 10.1245/s10434-019-07921-8. Epub 2019 Oct 15. PMID: 31617119). You also report that aspirated material was spread over dry slides for cytopathologic examination. Could you describe what kind of staining did you use (excluding mucin staining).   Could you please specify sensitivity and specificity of your cytopathological examinations? As it is one of the difficult problems in diagnostics of pancreatic cystic lesions. Was the aspirated fluid sufficient for cytopathologic verification of the cysts? How did you define low-grade and high-grade dysplasia in a case of IPMN (excluding postoperative pathological diagnosis)? You also mention such

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cyst characteristic as "wall thickness". Did you measure it? If "yes", please specify what values did you use for determining "thick" and 'thin" cystic wall? What diameter of main pancreatic duct did you rate as "dilated"? You mention in text that MPD was dilated in 66 patients, while in table 2 you give the opposite information. Check this point please. 6 Results.   It is very important and useful that the authors investigate this poorly highlighted issue of pancreatic cyst fluid examination, particularly wide range of tumor markers. It's better to use terms serous cystic neoplasms and mucinous cystic neoplasms instead of cystadenomas according to WHO classifications to avoid misunderstanding. This also will allow to use your manuscript in meta-analyses in the future. You unify malignant and potentially malignant lesions in one group. In my working group opinion, it would be better to divide these two groups in order to make proper conclusions, as treatment tactics differ in these groups.   7 Discussion.   In literature that you cite in discussion part, neoplastic and non-neoplastic groups of cysts are given. Think about using the same terms instead of malignant/ potentially malignant and benign.   8 Illustrations and tables.   Check please the values for pancreatic duct dilation in table 2 as you propose the opposite in results part of the text. For table 3 it's better to use terms serous cystic neoplasms and mucinous cystic neoplasms according to WHO classifications. In table 7 check please the values of glucose and CEA as you mention the opposite in the text. In table 11 check please the values for MCN.   9 Biostatistics.   The manuscript meets the requirements of biostatistics.   10 Units.   The manuscript meets the requirements of use of SI units.   11 References.   The citations are correct.   12   The manuscript organization and presentation are recommended to be slightly revised according to highlighted above questions and issues. The style, language and grammar are accurate and appropriate. 13 Research methods and reporting.   The authors prepared the manuscript according to the appropriate research methods.   14   The manuscript met the requirements of ethics.

Comments on writing. Cystic pancreatic neoplasms is very relevant subject in clinical practice. The authors performed very interesting, good arranged and useful investigation. Pancreatic cystic fluid has been poorly explored yet. In this study wide range of tumor markers is being estimated. The authors figured out tumor markers that can help in diagnosis of neoplastic pancreatic cysts. Long follow up period makes this investigation reliable. The combination of CEA, glucose and SPINK1 plus mucin stain are useful in predicting neoplastic nature of pancreatic cysts. Since the diagnostic accuracy of EUS-FNA for pancreatic cystic neoplasms remains low we need additional tools of diagnosis, except cytopathologic examination. Cystic fluid analysis can help in differential diagnosis of pancreatic cystic neoplasms. The limitations of the study and its findings. It's better to use terms serous cystic neoplasms and mucinous cystic neoplasms instead of cystadenomas according to WHO classifications in order to unify terms. This also will allow to use your manuscript in meta-analyses in the future. You unify malignant and potentially malignant lesions in one group. It would be better to divide these two groups, and to use "neoplastic and non-neoplastic" terms instead of "malignant/ potentially malignant and benign" in order to make more specified conclusions. Let me thank the authors for interest in this field and for the great job that has been done.