

PEER-REVIEW REPORT

Name of journal: *World Journal of Gastroenterology*

Manuscript NO: 72825

Title: Novel approaches in search for biomarkers of cholangiocarcinoma

Provenance and peer review: Invited Manuscript; Externally peer reviewed

Peer-review model: Single blind

Reviewer's code: 02543955

Position: Peer Reviewer

Academic degree: FEBS, MD

Professional title: Associate Professor, Senior Researcher, Surgical Oncologist

Reviewer's Country/Territory: Germany

Author's Country/Territory: Romania

Manuscript submission date: 2021-10-31

Reviewer chosen by: AI Technique

Reviewer accepted review: 2021-11-03 16:50

Reviewer performed review: 2021-11-04 17:47

Review time: 1 Day

Scientific quality	<input type="checkbox"/> Grade A: Excellent <input type="checkbox"/> Grade B: Very good <input checked="" type="checkbox"/> Grade C: Good <input type="checkbox"/> Grade D: Fair <input type="checkbox"/> Grade E: Do not publish
Language quality	<input type="checkbox"/> Grade A: Priority publishing <input checked="" type="checkbox"/> Grade B: Minor language polishing <input type="checkbox"/> Grade C: A great deal of language polishing <input type="checkbox"/> Grade D: Rejection
Conclusion	<input type="checkbox"/> Accept (High priority) <input type="checkbox"/> Accept (General priority) <input checked="" type="checkbox"/> Minor revision <input type="checkbox"/> Major revision <input type="checkbox"/> Rejection
Re-review	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No
Peer-reviewer	Peer-Review: <input checked="" type="checkbox"/> Anonymous <input type="checkbox"/> Onymous

statementsConflicts-of-Interest: [☐] Yes [☒] No**SPECIFIC COMMENTS TO AUTHORS**

This is an review on an important topic. It summarizes a large number of potential biomarker in cholangiocarcinoma (CCA). However this leave the review somehow unfocused. For most of the biomarkers there is no real solid evidence and positive and negative predictive values are not reported. It would be important to clearly state at the beginning the definition of biomarker, that here seems to be very extensive. It should also be clearly stated whether a certain biomarker is supposed to be of diagnostic or prognostic value. In addition, the authors should go carefully through the manuscript to detect mistakes (e.g. CAE instead of CEA). What is meant by the abbreviation OSN on page 12? What is a cCCA on page 16?

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Peer-review model: Single blind

Reviewer's code: 05469117

Position: Editorial Board

Academic degree: PhD

Professional title: Adjunct Professor, Chief Physician, Deputy Director

Reviewer's Country/Territory: China

Author's Country/Territory: Romania

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Scientific quality	<input type="checkbox"/> Grade A: Excellent <input checked="" type="checkbox"/> Grade B: Very good <input type="checkbox"/> Grade C: Good <input type="checkbox"/> Grade D: Fair <input type="checkbox"/> Grade E: Do not publish
Language quality	<input type="checkbox"/> Grade A: Priority publishing <input checked="" type="checkbox"/> Grade B: Minor language polishing <input type="checkbox"/> Grade C: A great deal of language polishing <input type="checkbox"/> Grade D: Rejection
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Re-review	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No
Peer-reviewer	Peer-Review: <input checked="" type="checkbox"/> Anonymous <input type="checkbox"/> Onymous

statements

Conflicts-of-Interest: [] Yes [Y] No

SPECIFIC COMMENTS TO AUTHORS

Thank you for giving me a chance to review this research regarding the developments in non-invasive cholangiocarcinoma diagnosis and prognosis, and the manuscript describes the circulating nucleic acids, proteomic and metabolomic-derived biomarkers, extracellular vesicles, and circulating tumor cells in an attempt to outline promising results for future research and clinical use. My major comments are as follows: 1. In the "INTRODUCTION" Page 4, Paragraph 2, :“ The risk factors for iCCA are the same as HCC, including hepatitis...”and" To this point, CCA lacks definite diagnostic criteria "should be corrected. ICCA and HCC are different diseases, and their etiologies are obviously different.. The diagnosis of CCA is difficult, but the diagnostic criteria is clear. 2. It is suggested to number the chapters of the article for easy reading. 3. It seems that some attributives need to be added to the title in order to accurately cover the content.

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Peer-review model: Single blind

Reviewer's code: 03725766

Position: Peer Reviewer

Academic degree: MD

Professional title: Doctor

Reviewer's Country/Territory: China

Author's Country/Territory: Romania

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Scientific quality	<input type="checkbox"/> Grade A: Excellent <input type="checkbox"/> Grade B: Very good <input checked="" type="checkbox"/> Grade C: Good <input type="checkbox"/> Grade D: Fair <input type="checkbox"/> Grade E: Do not publish
Language quality	<input type="checkbox"/> Grade A: Priority publishing <input checked="" type="checkbox"/> Grade B: Minor language polishing <input type="checkbox"/> Grade C: A great deal of language polishing <input type="checkbox"/> Grade D: Rejection
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Re-review	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No
Peer-reviewer	Peer-Review: <input checked="" type="checkbox"/> Anonymous <input type="checkbox"/> Onymous



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statements

Conflicts-of-Interest: [] Yes [Y] No

SPECIFIC COMMENTS TO AUTHORS

Firstly, thank you for opportunity to review the article. 1. As the author mentioned intrahepatic (iCCA) and extrahepatic (including both: peri-hilar (pCCA) and distal (dCCA)), had different aspects in etiology, molecular alterations, pathogenesis, behavior, and management. The different of biomarkers were not mentioned. 2.AFP was not included. Approximately 10-15% ICC the level of AFP may elevated.

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Reviewer's code: 04093286

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Professional title: Surgeon

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Author's Country/Territory: Romania

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Scientific quality	<input type="checkbox"/> Grade A: Excellent <input type="checkbox"/> Grade B: Very good <input checked="" type="checkbox"/> Grade C: Good <input type="checkbox"/> Grade D: Fair <input type="checkbox"/> Grade E: Do not publish
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Conflicts-of-Interest: [] Yes [Y] No

SPECIFIC COMMENTS TO AUTHORS

The manuscript represents a literature review of available and potential diagnostic and prognostic biomarkers in cholangiocarcinoma. The topic is interesting and relevant, and in view of this it is also useful. The review is generally well-written. As a general

remark there is quite extensive use of literary, abstract and pompous language which is not always suitable to support the scientific background. This should be addressed.

Furthermore, a number of specific revisions are recommended as follows:

Importantly, it would be useful to clarify within the text the applicability of various statements in relation to the different types of cholangiocarcinoma by location, where appropriate. Several statements are provided in a generalized manner, while they may not be uniformly applicable as such. The authors should make reference to the main

predictors of clinical outcomes in patients with cholangiocarcinoma (i.e., resectability, T stage, N stage, margin status, metastasis, etc.). In particular, as the authors make repeated reference to the diagnostic performance of several biomarkers in predicting recurrence, it should be highlighted in the first place that the only treatment with curative intent is radical surgery with clear surgical margins. Few typographic

errors throughout the text should be corrected. Abstract As a general remark, it appears that the abstract contains a degree of exaggerated language, probably deriving from the fact that the authors do not seem to take into account the fact that cholangiocarcinoma can be intrahepatic, perihilar and distal. As such a number of statements are either unjustifiably generalized or exaggerated. More specifically:

“Cholangiocarcinoma (CCA) is a biliary-derived neoplasia marked by an exceptionally dim prognosis” - this is a generalized statement which is literally not valid (exceptionally dim prognosis). “ an overwhelming proportion of cases are

discovered beyond the moment of curative intent." Again, this is a generalized statement and as such it is an overstatement. " Moreover, the diagnostic process is

typically laborious, and histology, the hallmark of any cancer diagnosis, is painstakingly challenging to obtain." This is not applicable of all types of cholangiocarcinoma.

"Not least, there is an acute lack of prognostic predictors following the diagnosis, which further complicates disease management." - "prognostic predictors" should be

changed to either predictors or prognostic factors / biomarkers or similar. -How does the lack of prognostic biomarkers complicate disease management? Core tip

What do the authors mean by "critically most recent"? INTRODUCTION "To this point, CCA lacks definite diagnostic criteria." - In the form this statement is provided, it is not valid. There are for instance well-defined histopathological criteria.

"curative intended surgical resection" - "surgical resection with curative intend" is a preferable phrasing. "However, only a dismal 15% of cases are fit for surgery at the initial diagnosis due to advanced stages[6]." - This statement is inaccurate and controversial. If the authors wish to refer to the limited number of surgical candidates relating to a high percentage of advanced stage at diagnosis (inoperable), this is irrelevant to the patients' fitness. If they wish to refer to the percentage of unfit patients, this is irrelevant to the stage. The provided percentage is lower than the actual for those with potentially resectable disease; moreover, it is not the same for all types of cholangiocarcinoma according to localization. "Mortality rates are high, and thus

the prognosis is abysmal[7]," - It needs to be clarified whether the authors refer to the general population of patients with cholangiocarcinoma, those with inoperable disease, and whether they refer to all types of cholangiocarcinoma. For instance, resectable cases in general have a much better prognosis. In any case the word "abysmal" is unsuitable.

"charbohydrate antigen 19-9" should be "Carbohydrate antigen 19-9". (e.g., Fibroblast growth factor receptor 2 (FGFR2) gene - Use punctuation appropriately.

“As an alternative to tissue” should be “As an alternative to tissue biopsy” in this sentence. The authors state: “The current review aims to explore the nascent waters

of the non-invasive biomarkers for CCA and provide an evidence-based input to aid clinical decisions and provide grounds for future researchtumor cells (Figure 1).” I appears that the part “and provide an evidence-based input to aid clinical decisions” is stronger than implied by the conclusions. **PROTEINS** “The field of proteomics

has gained notoriety” - “notoriety” is unsuitable. “and carcinoembryonic antigen (CAE)” - it should be (CEA). “There are three protein-based biomarkers, their

levels being measured from serum samples usually by ELISA.” - The sentence needs to be rephrased. What is the diagnostic sensitivity and specificity of the protein-based

biomarkers that the authors discuss? Their value is provided in a very general descriptive manner. Specific numbers should be provided/discussed. “Being a

well-known biomarker, CA125 is currently used primarily on ovarian cancer clinical management” should be rephrased. “However, various other protein-based

biomarkersin recent CCA studies (Table 2 and Table 3).” should be rephrased.

Table 3 is not meaningful without outcomes-related columns. Potential protein-based

diagnostic biomarkers The description is very vague and does not highlight the potential clinical applicability of these biomarkers. The authors need to be specific rather than using general terms such as “better results”, “good value”, “high diagnostic powers”.

“Out of a protein multimarker panel consisting of serum S100A9, MUC5AC, TGF- β 1, Ang-2, and CA19-9, serum levels of TGF- β 1 and Ang-2 provided effective prognosis in CCA patients with metastasis and severe cancer[64].” The phrasing needs to change in any case. Furthermore, what was the “effective prognosis”?

What is “severe cancer”? “In tumors of combined HCC and CCA (cHCC-CC),....after resection[72].” should be rephrased. “However, future validation

studies on large patient cohorts are needed to distinguish false paths from real



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solutions." - "false paths" is unsuitable.

METABOLITES "A panel of four metabolites attained a diagnostic accuracy (HCC vs iCCA) or 99.7%[91]." - Which ones?

"A combination of serum levels of nine metabolites could discriminate between dCCA and PDAC with a sensitivity of 55.9% and specificity of 89.5%[91]." - Which ones?

CONCLUSIONS AND FUTURE DIRECTIONS "However, most available reports are deeply heterogeneous, study protocols are not harmonized, and the number of included patients is still relatively small." The authors have made very little reference to the number of patients/samples in the studies they have reviewed.