

PEER-REVIEW REPORT

Name of journal: World Journal of Hepatology

Manuscript NO: 56899

Title: Biomarkers for hepatocellular cancer

Reviewer's code: 02832130

Position: Peer Reviewer

Academic degree: MD

Professional title: Doctor

Reviewer's Country/Territory: China

Author's Country/Territory: Canada

Manuscript submission date: 2020-05-27

Reviewer chosen by: AI Technique

Reviewer accepted review: 2020-05-27 13:35

Reviewer performed review: 2020-06-01 14:29

Review time: 5 Days

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 Grade E: Do not publish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 type="checkbox"/> Minor revision <input checked="" type="checkbox"/> Major revision <input type="checkbox"/> Rejection
Re-review	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No
Peer-reviewer statements	Peer-Review: <input checked="" type="checkbox"/> Anonymous <input type="checkbox"/> Onymous Conflicts-of-Interest: <input type="checkbox"/> Yes <input checked="" type="checkbox"/> No

SPECIFIC COMMENTS TO AUTHORS

Hepatocellular carcinoma (HCC) is the third leading cause of cancer-related deaths worldwide. Early diagnosis and treatment can improve the prognosis of patients with HCC. Biomarkers may play a crucial role in the diagnosis and management of HCC. The author provided an overview of the different biomarkers of HCC. This paper is of value, with effects on clinical practice and related study; but there are defects need to be modified. 1. As it is presented the paper is not easy-to-read for clinicians: It lacks of summary tables. Should the author use tables to show the types of biomarkers and the specific biomarkers. 2. According to the classification, whether the “mathematical scoring models” is suitable as a kind of biomarker? The position/section of this it should be reconsidered according to the new structure of the article. 3. The structure of this paper is not clear. The following structures or sections are confusing me. Introduction, A.) Serum Biomarkers, B.) Scoring Models, C.) Micro-RNAs, D.) Genetic Markers, E.) Liquid Biopsy, Discussion. Should the author redesign the structure of this paper. 4. A biomarker, as defined by the World Health Organisation is: “any substance, structure, or process that can be measured in the body or its products and influence or predict the incidence of outcome or disease[12].” Biomarkers can originate from a variety of different biomolecules such as proteins, carbohydrates, lipids, DNA, and RNA. Overall, biomarkers aim to objectively measure or confirm the presence, quantitatively or qualitatively, a disease of interest in a reproducible manner. Biomarkers can be broadly categorized into four types: diagnostic, prognostic, predisposing/risk and predictive. In this section, the author defined the biomarker (WHO), and indicated that biomarkers originated from a variety of different biomolecules such as proteins, carbohydrates, lipids, DNA, and RNA, and biomarkers can be broadly categorized into four types: diagnostic, prognostic, predisposing/risk and predictive. However, the author did not describe biomarkers according to the above classification or types in the paper, but



**Baishideng
Publishing
Group**

7041 Koll Center Parkway, Suite
160, Pleasanton, CA 94566, USA
Telephone: +1-925-399-1568
E-mail: bpgoffice@wjgnet.com
https://www.wjgnet.com

described it according to others, such as serum biomarkers section, etc. If it is necessary to arrange it in this way, these subtitles should be described in the previous paragraph. This arrangement or description is confusing. The author should reconsider the biomarker classification and article structure. 5. A.) Serum Biomarkers section: The aldo-keto reductase family 1 member 10 (AKR1B10) has been linked as a potential biomarker indicating diagnostic and prognostic value. AKR1B10, is a part of a family of NAD(P)H linked oxidoreductases; found on chromosome 7 (7p33) AKR1B10 is involve..... Is there a missing punctuation between (7p33) and AKR1B10 words? 6. A.) Serum Biomarkers section: A study with 68 patients diagnosed with HCC were evaluated for GP73 levels 2 days prior to a transcatheter arterial chemoembolization (TACE) and 7 and 30 days following the procedure. Using ELISA, the protein expression was observed to be markedly higher on average in patients with HCC compared to the controls, 152.5 versus 49.3 $\mu\text{g/l}$, respectively. In regards to the Barcelona clinic liver cancer stages, increasing GP73 concentrations were observed for advanced stages of the disease[32]. The changes of GP73 levels 2 days before and 7 and 30 days after TACE should be described in this section. 7. Are there any new biomarkers not discussed? If yes, they should be listed or mentioned briefly in their sections. 8. Figures: Good.

PEER-REVIEW REPORT

Name of journal: World Journal of Hepatology

Manuscript NO: 56899

Title: Biomarkers for hepatocellular cancer

Reviewer's code: 02523682

Position: Peer Reviewer

Academic degree: PhD

Professional title: Associate Professor

Reviewer's Country/Territory: China

Author's Country/Territory: Canada

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Scientific quality	<input type="checkbox"/> Grade A: Excellent <input type="checkbox"/> Grade B: Very good <input type="checkbox"/> Grade C: Good <input checked="" 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 type="checkbox"/> Minor revision <input checked="" type="checkbox"/> Major revision <input type="checkbox"/> Rejection
Re-review	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No
Peer-reviewer statements	Peer-Review: <input checked="" type="checkbox"/> Anonymous <input type="checkbox"/> Onymous Conflicts-of-Interest: <input type="checkbox"/> Yes <input checked="" type="checkbox"/> No

SPECIFIC COMMENTS TO AUTHORS

The manuscript described the different biomarkers of HCC including serum biomarkers, scoring models, micro-RNAs, genetic markers, as well as the advancing field of liquid biopsies used for the diagnosis and prognosis of HCC. Due to the threats and hazards of HCC to human health, the manuscript will be benefit to the researchers and clinical doctors to improve the prognosis, diagnosis and clinical treatment of HCC. However, there are some limits for this manuscript. Firstly, in the introduction section, the description seems to wordy. For example, the definition of biomarker was described in the manuscript, and it may be popular science to professional journal. The description of sensitivity and specificity is also redundant. Thus, the authors should cut the some contents. In addition, besides the diagnosis and prognosis value of HCC biomarkers, the clinical application targeting biomarkers also have reported in previous studies. Recently, CicroRNA becomes the research hot, and it should include HCC. List of different biomarkers for HCC is needed. The manuscript reviewed biomarkers ofr HCC. However, the sections of scoring Models and Liquid Biopsy don't seem related with HCC biomarkers. Moreover, the language and writing of the manuscript should also be improved.

PEER-REVIEW REPORT

Name of journal: World Journal of Hepatology

Manuscript NO: 56899

Title: Biomarkers for hepatocellular cancer

Reviewer's code: 03896270

Position: Peer Reviewer

Academic degree: MD, MSc, PhD

Professional title: Assistant Professor

Reviewer's Country/Territory: China

Author's Country/Territory: Canada

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Review time: 13 Days and 16 Hours

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 checked="" type="checkbox"/> Grade A: Priority publishing <input 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 statements	Peer-Review: <input checked="" type="checkbox"/> Anonymous <input type="checkbox"/> Onymous Conflicts-of-Interest: <input type="checkbox"/> Yes <input checked="" type="checkbox"/> No

SPECIFIC COMMENTS TO AUTHORS

Manuscript ID: 56899 This is a fairly good article written on a very important medical topic. A variety of Hepatocellular carcinoma biomarkers in clinical biochemistry were reviewed. Various molecular types such as serum biomarkers, scoring models, micro-RNAs', genetic markers et al were included to discuss the accuracy of these HCC biomarkers. Then, the author systematically expounds and prospects the research situation in this field. This review is very interesting. However, there have been a lot of progress in the research of non coding RNA(circRNA、LncRNA) related to miRNA in liver cancer recently, and the author would like to show and discuss these latest progress in this review.

RE-REVIEW REPORT OF REVISED MANUSCRIPT

Name of journal: World Journal of Hepatology

Manuscript NO: 56899

Title: Biomarkers for hepatocellular cancer

Reviewer's code: 03896270

Position: Peer Reviewer

Academic degree: MD, MSc, PhD

Professional title: Assistant Professor

Reviewer's Country/Territory: China

Author's Country/Territory: Canada

Manuscript submission date: 2020-05-27

Reviewer chosen by: Ya-Juan Ma

Reviewer accepted review: 2020-07-30 05:49

Reviewer performed review: 2020-07-30 05:52

Review time: 1 Hour

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 checked="" type="checkbox"/> Grade A: Priority publishing <input 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 checked="" type="checkbox"/> Accept (General priority) <input type="checkbox"/> Minor revision <input type="checkbox"/> Major revision <input type="checkbox"/> Rejection
Peer-reviewer statements	Peer-Review: <input checked="" type="checkbox"/> Anonymous <input type="checkbox"/> Onymous Conflicts-of-Interest: <input type="checkbox"/> Yes <input checked="" type="checkbox"/> No

SPECIFIC COMMENTS TO AUTHORS

After substantial improvement the paper can be accepted for publication in the



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Group**

7041 Koll Center Parkway, Suite
160, Pleasanton, CA 94566, USA
Telephone: +1-925-399-1568
E-mail: bpgoffice@wjgnet.com
https://www.wjgnet.com

presented revised form.