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PEER-REVIEW REPORT

Name of journal: *World Journal of Gastroenterology*

Manuscript NO: 72107

Title: An Update On The Applications And Limitations Of Alpha-Fetoprotein (AFP) For Hepatocellular Carcinoma

Provenance and peer review: Invited Manuscript; Externally peer reviewed

Peer-review model: Single blind

Reviewer's code: 03003481
Position: Editorial Board
Academic degree: MD, PhD
Professional title: Associate Professor, Doctor
Reviewer's Country/Territory: China
Author's Country/Territory: United States

Manuscript submission date: 2021-10-04

Reviewer chosen by: AI Technique

Reviewer accepted review: 2021-10-05 10:44

Reviewer performed review: 2021-10-05 14:43

Review time: 3 Hours

Scientific quality	[ ] Grade A: Excellent [ ] Grade B: Very good [ ] Grade C: Good [Y] Grade D: Fair [ ] Grade E: Do not publish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

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

SPECIFIC COMMENTS TO AUTHORS

Hanif H et al. provided a comprehensive review on the applications and limitations of AFP for HCC. It reviewed the detection performance of AFP in HCC, liver diseases and cirrhosis, and conditions in the absence of liver disease. It also reviewed the combined detection by AFP, AFP-L3 and DCP (GALAD score), which was shown to enhance the HCC detection performance. I think the review was well-written and covered most key aspects around AFP in HCC and hepatic disease diagnosis. However, most contents in this review have been reviewed in previous papers. I found quite a few published review papers in the following aspects, which compromised the novelty and significance of the present paper. 1,detection of AFP in HCC Sonbol MB, Riaz IB, Naqvi SAA, et al. Systemic Therapy and Sequencing Options in Advanced Hepatocellular Carcinoma: A Systematic Review and Network Meta-analysis. JAMA Oncol. 2020;6(12):e204930. doi:10.1001/jamaoncol.2020.4930 Luo P, Wu S, Yu Y, et al. Current Status and Perspective Biomarkers in AFP Negative HCC: Towards Screening for and Diagnosing Hepatocellular Carcinoma at an Earlier Stage. Pathol Oncol Res. 2020;26(2):599-603. doi:10.1007/s12253-019-00585-5 Wang X, Wang Q. Alpha-Fetoprotein and Hepatocellular Carcinoma Immunity. Can J Gastroenterol Hepatol. 2018;2018:9049252. Published 2018 Apr 1. doi:10.1155/2018/9049252 Sauzay C, Petit A, Bourgeois AM, et al. Alpha-foetoprotein (AFP): A multi-purpose marker in hepatocellular carcinoma. Clin Chim Acta. 2016;463:39-44. doi:10.1016/j.cca.2016.10.006 2,detection of AFP in cirrhosis

Tzartzeva K, Obi J, Rich NE, et al. Surveillance Imaging and Alpha Fetoprotein for Early Detection of Hepatocellular Carcinoma in Patients With Cirrhosis: A Meta-analysis. Gastroenterology. 2018;154(6):1706-1718.e1. doi:10.1053/j.gastro.2018.01.064 Parikh ND,

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Singal AG, Hutton DW, Tapper EB. Cost-Effectiveness of Hepatocellular Carcinoma Surveillance: An Assessment of Benefits and Harms. Am J Gastroenterol. 2020;115(10):1642-1649. doi:10.14309/ajg.0000000000000715 Thompson Coon J, Rogers G, Hewson P, et al. Surveillance of cirrhosis for hepatocellular carcinoma: systematic review and economic analysis. Health Technol Assess. 2007;11(34):1-206. doi:10.3310/hta11340 Kim DY, Han KH. Epidemiology and surveillance of hepatocellular carcinoma. Liver Cancer. 2012;1(1):2-14. doi:10.1159/000339016 3,detection of AFP in hepatitis Peng C, Li Z, Xie Z, et al. The role of circulating microRNAs for the diagnosis of hepatitis B virus-associated hepatocellular carcinoma with low alpha-fetoprotein level: a systematic review and meta-analysis. BMC Gastroenterol. 2020;20(1):249. Published 2020 Jul 31. doi:10.1186/s12876-020-01345-5 Inoue T, Tanaka Y. Novel biomarkers for the management of chronic hepatitis B. Clin Mol Hepatol. 2020;26(3):261-279. doi:10.3350/cmh.2020.0032 Kobeisy MA, Morsy KH, Galal M, Sayed SK, Ashmawy MM, Mohammad FM. Clinical significance of elevated alpha-foetoprotein (AFP) in patients with chronic hepatitis C without hepatocellular carcinoma in upper EGYPT. Arab J Gastroenterol. 2012;13(2):49-53. doi:10.1016/j.ajg.2012.06.004 Gupta S, Bent S, Kohlwes J. Test characteristics of alpha-fetoprotein for detecting hepatocellular carcinoma in patients with hepatitis C. A systematic review and critical analysis. Ann Intern Med. 2003;139(1):46-50. doi:10.7326/0003-4819-139-1-200307010-00012 4,detection of AFP in NAFLD Singal AG, Lampertico P, Nahon P. Epidemiology and surveillance for hepatocellular carcinoma: New trends. J Hepatol. 2020;72(2):250-261. doi:10.1016/j.jhep.2019.08.025 Pennisi G, Celsa C, Giammanco A, Spatola F, Petta S. The Burden of Hepatocellular Carcinoma in Non-Alcoholic Fatty Liver Disease: Screening Issue and Future Perspectives. Int J Mol Sci. 2019;20(22):5613. Published 2019 Nov 9. doi:10.3390/ijms20225613 Sumida Y, Yoneda M, Seko Y, et al. Surveillance of

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Hepatocellular Carcinoma in Nonalcoholic Fatty Liver Disease. Diagnostics (Basel). 2020;10(8):579. Published 2020 Aug 10. doi:10.3390/diagnostics10080579 5,combined use of AFP, AFP-L3 and DCP in HCC detection Wong RJ, Ahmed A, Gish RG. Elevated alpha-fetoprotein: differential diagnosis - hepatocellular carcinoma and other disorders. Clin Liver Dis. 2015;19(2):309-323. doi:10.1016/j.cld.2015.01.005 Wang X, Zhang Y, Yang N, et al. Evaluation of the Combined Application of AFP, AFP-L3%, and DCP for Hepatocellular Carcinoma Diagnosis: A Meta-analysis. Biomed Res Int. 2020;2020:5087643. Published 2020 Sep 17. doi:10.1155/2020/5087643 Bertino G, Ardiri A, Malaguarnera M, Malaguarnera G, Bertino N, Calvagno GS. Hepatocellualar carcinoma serum markers. Semin Oncol. 2012;39(4):410-433. doi:10.1053/j.seminoncol.2012.05.001 Zhou L, Liu J, Luo F. Serum tumor markers for detection of hepatocellular carcinoma. World J Gastroenterol. 2006;12(8):1175-1181. doi:10.3748/wjg.v12.i8.1175 Toyoda H, Kumada T, Tada T, Sone Y, Kaneoka Y, Maeda A. Tumor Markers for Hepatocellular Carcinoma: Simple and Significant Predictors of Outcome in Patients with HCC. Liver Cancer. 2015;4(2):126-136. doi:10.1159/000367735

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Name of journal: *World Journal of Gastroenterology*

Manuscript NO: 72107

Title: An Update On The Applications And Limitations Of Alpha-Fetoprotein (AFP) For Hepatocellular Carcinoma

Provenance and peer review: Invited Manuscript; Externally peer reviewed

Peer-review model: Single blind

Reviewer's code: 06076339
Position: Peer Reviewer
Academic degree: PhD
Professional title: Associate Professor
Reviewer's Country/Territory: Egypt
Author's Country/Territory: United States

Manuscript submission date: 2021-10-04

Reviewer chosen by: AI Technique

Reviewer accepted review: 2021-10-09 12:05

Reviewer performed review: 2021-10-10 18:01

Review time: 1 Day and 5 Hours

Scientific quality	[ ] Grade A: Excellent [Y] Grade B: Very good [ ] Grade C: Good [ ] Grade D: Fair [ ] Grade E: Do not publish
Language quality	[ ] Grade A: Priority publishing [Y] 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	[ ] Yes [Y] No

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

SPECIFIC COMMENTS TO AUTHORS

1- The title should be written with prepositions in small letters. 2- In the "Core tip" third line from bottom: "Combination with other novel markers have shown…" should be corrected to "Combination with other novel markers has shown…" 3- The authors may have also reported the other most recent prospective which includes studies suggesting the combination between lncRNA and AFP measurements. 4- In Page No.4, the authors mentioned the techniques used to measure AFP starting with immunoelectophoresis and ending with quantitative automated chemiluminescent enzyme immunoassay. They used the word "lately" which gives the reader an impression that chemiluminescent enzyme immunoassay is developed in the 2000s, as they started with the older techniques which appeared between 1970s and 1980s. The two references that they referred to were dated back between 1980s and 1990s! 5- In Fig. 1 B, the authors did not show how exactly interfering antibodies bind to both capture and detect antibodies to give false positive results and high value. 6- In Page No.7, the authors referred to some studies in which AFPL-3 was used as a biomarker for HCC. However, they ignored other studies that showed higher sensitivity and specificity (Ibrahim, A. A. A., et al. Benha Medical Journal, 35(2018) (3), 312 ; Cerban, R., et al. Surg. Gastroenterol, 24(2019) (1), 37-44 ; El-Halawany, F., et al. MAGHREB-MACHREK, 2(2020) (2), 01-12 ; Ibrahim, H. M., et al. SJBS, 28 (2021) 5760–5764). 7- In Page No.8, second line from bottom: "…..3000 to 7190 ng/ml have been reported" should be replaced by " "…..3000 to 7190 ng/ml has been reported" 8- At the end of Page No.9, the authors wrote" Use this reference here instead: PMID: 32620274"!!!! In fact, it is reference No.55! 9- In the references, the authors put the doi link for reference No.23 which was not the case for

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the rest of the references!