ISSN 1948-5204 (online)

World Journal of *Gastrointestinal Oncology*

World J Gastrointest Oncol 2021 November 15; 13(11): 1544-1849

Published by Baishideng Publishing Group Inc

World Journal of Gastrointestinal Oncology

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NAME OF JOURNAL

World Journal of Gastrointestinal Oncology

ISSN

ISSN 1948-5204 (online)

LAUNCH DATE

February 15, 2009

FREQUENCY

Monthly

EDITORS-IN-CHIEF

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https://www.wjgnet.com/1948-5204/editorialboard.htm

PUBLICATION DATE

November 15, 2021

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https://www.f6publishing.com

World Journal of Gastrointestinal Oncology

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World J Gastrointest Oncol 2021 November 15; 13(11): 1847-1849

DOI: 10.4251/wjgo.v13.i11.1847

ISSN 1948-5204 (online)

LETTER TO THE EDITOR

Hepatocellular carcinoma biomarkers, an imminent need

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Author contributions: Zamora-León SP wrote the letter.

Conflict-of-interest statement: The author declares having no conflict of interest related to this letter.

Provenance and peer review: Invited article; Externally peer reviewed.

Specialty type: Oncology

Country/Territory of origin: Chile

Peer-review report's scientific quality classification

Grade A (Excellent): 0
Grade B (Very good): 0
Grade C (Good): C
Grade D (Fair): 0

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Abstract

Hepatocellular carcinoma (HCC) is the most common malignant neoplasm of the liver and one of the deadliest cancers worldwide. The identification of novel, highly specific and more sensitive biomarkers for HCC is crucial because existing ones are deficient and non-confirmatory without histological biopsy or imaging techniques.

Key Words: Hepatocellular carcinoma; Biomarker; Blood; Urine; Feces; Gut microbiota

Core Tip: The identification of specific, sensitive and validated biomarkers for hepatocellular carcinoma (HCC) is complex because of the variability in genetic profiles, but their requirement is urgent to achieve earlier detection of HCC. Body fluids and feces for biomarker detection constitute feasible and low cost screening tools for early diagnosis, prognosis and treatment of HCC.

Citation: Zamora-León SP. Hepatocellular carcinoma biomarkers, an imminent need. *World J Gastrointest Oncol* 2021; 13(11): 1847-1849
URL: https://www.wjgnet.com/1948-5204/full/v13/i11/1847.htm
DOI: https://dx.doi.org/10.4251/wjgo.v13.i11.1847

TO THE EDITOR

I read the review by Guan *et al*[1], "Biomarkers for hepatocellular carcinoma based on body fluids and feces", published in the April 2021 issue of the *World Journal of Gastrointestinal Oncology*, with profound interest.

Grade E (Poor): 0

Received: May 25, 2021
Peer-review started: May 25, 2021
First decision: July 4, 2021
Revised: July 5, 2021
Accepted: September 19, 2021
Article in press: September 19, 2021
Published online: November 15, 2021

P-Reviewer: Tajiri K
S-Editor: Gao CC
L-Editor: A
P-Editor: Li X

Hepatocellular carcinoma (HCC) is the leading malignant neoplasm of the liver and one of the most common lethal cancers worldwide. For this reason, an early detection is crucial to decrease mortality, since symptomatology appears at later stages of the disease. The identification of novel, highly specific and sensitive biomarkers, or a combination of them, is of special concern because the existing ones are deficient and non-confirmatory without histological biopsy or imaging techniques. The utilization of body fluids and feces for biomarker detection constitutes a feasible minimally- or non-invasive and low-cost screening method that facilitates studies for early diagnosis, prognosis and treatment of HCC.

Since HCC can arise from a variety of etiological factors, such as metabolic disorders, virus infections or toxin exposure, the genetic profiles are considerably variable, resulting in diverse hepatic immune microenvironments. This implies that the metabolomic, proteomic and glycomic profiles should be better clarified for the various HCCs in order to improve overall understanding of the disease and allow for identification of appropriate and validated biomarkers[2].

Alpha-fetoprotein (AFP) is the most common biomarker utilized for HCC diagnosis, but its sensitivity is only 39%-65% and its performance at early stages of the disease is suboptimal. Therefore, to improve detection of the malignancy, AFP has to be combined with imaging findings as well as other parameters, such as age and sex, which increase the sensitivity. In addition, AFP-L3, the highest glycoform of AFP, has exhibited much higher sensitivity, and the AFP-L3/AFP ratio can be considered as a risk factor for the development of HCC[3].

Several metabolites have displayed higher accuracy than AFP, showing aberrant levels that can be detected at earlier stages of HCC[4]. Circulating tumor (ct)DNA also has great potential to became a biomarker, since it contains several tumor-specific mutations or epimutations, constituting a good approach for HCC detection and prognosis, and to serve as a tool for monitoring therapeutic response. Additionally, several different micro (mi)RNAs and other non-coding (nc)RNAs have been shown to be deregulated in HCC, implying that their aberrant expression should be evaluated and validated as potential prognostic biomarkers. Unfortunately, miRNA variabilities have been detected depending on whether they are measured in serum or plasma, thereby complicating interpretation[5-8].

Moreover, circulating tumor cells (CTCs) have shown partial sensitivity but high specificity and are considered to have great potential in prediction of recurrence and prognostic evaluation of HCC. On the other hand, extracellular vesicles (EVs), such as exosomes and microvesicles, the contents of which are very heterogeneous, do not present better diagnostic performances than CTCs or circulating cell-free DNA, but they do have good potential as future therapeutic agents[5,8,9].

The above-mentioned biomarkers, ctDNA, miRNAs, CTCs and EVs, are tumor-specific, which is of great advantage, because they exhibit the heterogeneity of the tumor and its evolution. These features cannot be detected with other plasma biomarkers.

Additionally, several urine molecules have the potential to be classified as biomarkers for prevention, detection, progression monitoring, and recurrence prediction of HCC[10]. It is possible that they can be used as auxiliary diagnostic tools in combination with AFP. Moreover, feces-based biomarkers, which reflect the gut microbiota — which is itself known to vary with different pathological stages, are under evaluation for their potential utility in early diagnosis, prognosis and progression monitoring of HCC. In addition, the use of antibiotics to modulate gut microbiota appears to be a favorable strategy to influence the progression of HCC. Promising results have also been obtained with probiotics in mouse HCC models, which have shown a reduction in the development of this malignant neoplasm, opening avenues of possible application as a therapy in humans in the future[11-13].

The identification of more specific and sensitive biomarkers for HCC, and their variability over time, is an urgent requirement due to their critical role for early detection and prognosis, for choosing appropriate therapy, or for use as a tool to follow-up the patient's treatment response. Ideally, biomarkers should detect HCC months before the tumor is visible, to improve surveillance and facilitate initiation of an earlier therapy. Clearly, the identification of new biomarkers for prompt HCC detection is complex, nonetheless because of the diverse type of tumors (genetic heterogeneity). However, efforts must be made to combat this devastating tumor malignancy. Moreover, the performance of new biomarkers will have to be clinically validated to optimize the current therapeutical strategies.

ACKNOWLEDGEMENTS

I would like to thank the Faculty of Medicine and Universidad Católica del Maule for giving me the time to write this letter.

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