Editorial Commentary

Hepatocellular carcinoma extracellular vesicle ECG score as a diagnostic tool close to the ideal

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Comment on: Sun N, Zhang C, Lee YT, *et al*. HCC EV ECG score: An extracellular vesicle-based protein assay for detection of early-stage hepatocellular carcinoma. Hepatology 2023;77:774-88.

Keywords: Extracellular vesicles (EVs); hepatocellular carcinoma (HCC); early-stage; biomarker

Submitted Sep 29, 2023. Accepted for publication Oct 17, 2023. Published online Oct 27, 2023.
doi: 10.21037/hbsn-23-509
View this article at: https://dx.doi.org/10.21037/hbsn-23-509

Introduction

In recent decades, numerous indicators for early detection and monitoring of hepatocellular carcinoma (HCC) have been suggested and published in reputable journals. These markers have gained recognition and endorsement from prominent international associations such as the European Association for the Study of the Liver (EASL), the Asian Pacific Association for the Study of the Liver (APASL), as well as national professional organizations like the American Association for the Study of Liver Diseases (AASLD), among others.

Currently, none of the leading organizations is endorsing an earlier highly promoted and recommended clinical marker for the detection of HCC, including early-stage HCC as in case of alpha-fetoprotein (AFP) (1). In the past, AFP seemed promising and offered hope for enhancing HCC cancer management in various ways. However, meta-analyses conducted under real-life clinical conditions demonstrated that AFP did not perform satisfactorily as advertised. As a result, in 2005, AFP was no longer recommended and downgraded to and should not be used for screening unless ultrasound is not available (2).

The latest research is centered around identifying new minimally invasive biomarkers that are (I) easily accessible and (II) cause minimal discomfort to patients. Recently, several types of biomarkers have been proposed, and their effectiveness has been demonstrated in controlled clinical settings. These include circulating tumor cells (CTCs), cell-free DNA, messenger RNA (mRNA), microRNA (miRNA), long non-coding RNA (lncRNA) (3), and others as summarized by us (4). Additionally, extracellular vesicles (EVs) have gained attention as a potential promising biomarker while EVs may harbor mRNA, miRNA, and lncRNA besides proteins (5,6). The exact role and purpose of EVs may be in a novel pathway for cell-to-cell communication while EVs are carrying bioactive molecules, or to be a novel vector for personalized medicine (7). Another interesting aspect is their potential function as a mechanism for cargo-disposal of obsolete

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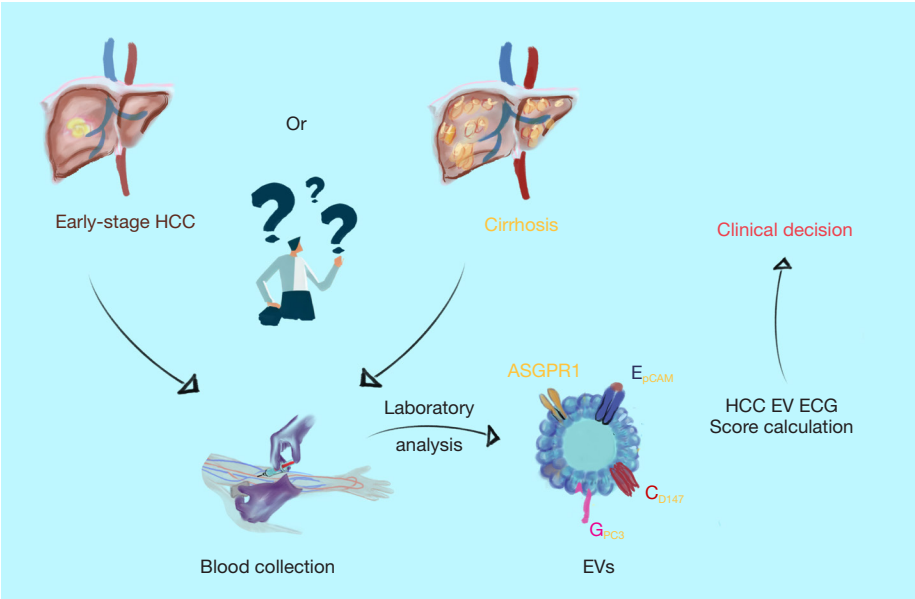

Figure 1 Depicted simplified concept of the major steps in the use of the ECG score in decision making if early-stage HCC is present as proposed by Sun *et al.* (12). HCC, hepatocellular carcinoma; EV, extracellular vesicle; ECG, $CD63^+EpCAM^+$ EVs, $CD63^+CD147^+$ EVs, and $CD63^+GPC3^+$ HCC EVs.

proteins (8).

Overall, EVs and their cargo were shown to be an interesting biomarker which is associated with the presence of cancers (9) including HCC (10,11). Actually, in 2017 we reported that differentiation among HCC *vs.* non-malignant cirrhosis might be technically feasible by large EVs by detecting simultaneously specific antigens as EpCAM, CD133, and ASGPR1 on those large EVs using flowcytometry (10). Now, Sun *et al.* refined by much these initial findings and showed successfully that same antigens as EpCAM, ASGPR1, CD147 (EMMPRIN) plus Glypican 3 (GPC3), if detected on small EVs with a more advanced methodology than flowcytometry in early HCC may actually be superior (12). Sun *et al.* did improve our previously published finding with their phase 2 biomarker (case-control) study and enhanced the previously reported sensitivity and specificity to 91% and 90%, respectively (12). Their proposed HCC EV ECG score had been calculated from the readouts of three HCC EV subpopulations consisting of $CD63^+EpCAM^+$ EVs, $CD63^+CD147^+$ EVs, and $CD63^+GPC3^+$ HCC EVs as depicted in *Figure 1*. They successfully conducted a phase 2 biomarker study to evaluate the performance of ECG score 1st in a training cohort (n=106) and 2nd in an independent validation cohort (n=72) (12). An impressive achievement.

When discussing the AFP's dilemma described earlier (1), an important question arises: will their findings be robust enough for real-life clinical applications? To ensure this, we need to address a few remaining questions. First, we must focus on standardizing the underlying methodology and ensuring reproducibility across multiple clinical centers. Additionally, it is vital to investigate whether synergistic effects can be observed when incorporating other well-known serological markers. And last but not least, is this ECG score that powerful to differentiate between intrahepatic CCA and HCC?

It is crucial to ask these legitimate questions in order to successfully navigate the first audit. However, it is also important to recognize that every step taken towards developing a reliable biomarker for early detection of HCC is significant and should be viewed as a promising start that must be exploited in depth further.

Acknowledgments

We are remarkably grateful to Wioleta Chomko "Art-tech" for assistance with figures.

Funding: This publication was funded by the Deutsche Forschungsgemeinschaft (DFG, German Research Foundation), grant number 410853455 to Miroslaw T.

Kornek and grant number 411345524 to Veronika Lukacs-Kornek.

Footnote

Provenance and Peer Review: This article was commissioned by the editorial office, *Hepatobiliary Surgery and Nutrition*. The article did not undergo external peer review.

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://hbsn.amegroups.com/article/view/10.21037/hbsn-23-509/coif). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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Cite this article as: Słomka A, Mocan T, Willms AG, Lukacs-Kornek V, Kornek MT. Hepatocellular carcinoma extracellular vesicle ECG score as a diagnostic tool close to the ideal. HepatoBiliary Surg Nutr 2023;12(6):930-932. doi: 10.21037/hbsn-23-509