Reviewer #1:

Specific Comments to Authors: The review by Zhang M-H et al. provides an overview of the latest advancements in the utilization of miRNAs for the diagnosis and therapy of HBV-HCC. It elucidates the molecular mechanisms through which HBV regulates miRNAs and examines the precise role of miRNAs in HCC development. The significance of miRNA-based applications in diagnosis, prognosis, and therapy is discussed, considering their potential future integration into the clinical standard of care. Suggestions: It is suggested to include a brief section discussing the main techniques employed for miRNA detection. Although the authors mention the limitations of these techniques, it is important to present their opinions in order to provide a balanced perspective regarding the associations cited throughout the text. Reference 7, which is a review on this topic, should be included to incorporate the authors' viewpoint.

---Thank you for your careful reading of our article and providing detailed suggestion. In the first paragraph of the final section titled "Future prospects —— challenges and potential clinical use of miRNAs in diagnosis and treatment of HBV-HCC," we describe the extant common methods for detecting miRNAs and discuss the existing issues. We agree with the view proposed in reference 7 that "using standardized measures with unified standards to collect trusted miRNA data, as well as minimizing the influence of confounding factors, is essential". Additionally, we believe that developing new simple, inexpensive, and accurate miRNA detection techniques is equally important. Therefore, we present the miRacles instrument to support this position.

Could the description of a long list of markers be avoided by integrating a panel with a specific purpose, which could also be detailed in a table? This would enhance readability and shorten the text.

---Thank you for your careful reading of our article and posing this detailed question. In the section on" Dysregulated miRNAs in the diagnosis of HBV-HCC", we have condensed the marker description and included only representative markers. In order to make the content more representative, we have also modified the table to include only miRNAs with sensitivity and specificity data for diagnosis.

There are numerous specific terms that are abbreviated and need clarification when they are initially mentioned. This includes HBV-related terms such as "HBp" (referring to HBV-associated serologic markers) and specific markers or stages such as BCLC, AFP, among others.

---Thank you for your careful reading our article and for raising this detailed question. In response to your feedback, we have made the following revisions. Firstly, in the third section titled "Mechanisms of HBV-induced dysregulation of miRNA", we have added the full names and abbreviations of all HBV-related proteins. Additionally, in the first section, we have included the full names of BCLC, AFP, PIVKA-II and other markers. This change will ensure that readers are fully informed about the markers and their significance in the context of the article.

Please review the English grammar and spelling throughout the text.

---Thank you for your suggestions. The manuscript has been edited and reviewed by a professional company.

Reviewer #2:

Specific Comments to Authors: no specific comment

---Thank you for your approbation of our article.

Reviewer #3:

Specific Comments to Authors: Dear author Thank you for the submission of your article to our journal. I respect you for writing your paper with a huge number of reference papers on miRNAs. However, from the reader's point of view, it is very difficult for many readers to read a paper that consists of such a huge amount of sentences and references. Scientific papers should aim to efficiently impart knowledge to researchers by reading papers of appropriate length. You should shorten the text length, limit the references as representative ones, and make your paper as the excellent time performance one before discussing the content of your paper.

---Thank you for your careful review of our article and for raising this detailed question. After revising the article, we reduced the word count from 10,667 to 7,992, and the number of citations decreased from 321 to 235. The most significant change in the article is the reduction of the fourth section, where we removed the claim that HBV affects various cellular processes such as cell cycle, cell proliferation, apoptosis, migration and invasion, and epithelial mesenchymal transition, leading to the promotion of HCC via dysregulating miRNAs. We made this decision because these contents have already been extensively covered in other reviews[1-5]. However, we have included in the supplementary file the list of miRNAs dysregulated by HBV that participate in these processes. During the writing of the original manuscript, we conducted an extensive search and summary of existing studies on how HBV promotes HCC by influencing miRNAs. We believe it is valuable to preserve these summaries. Additionally, we have made revisions to all tables in the first section titled 'Dysregulated miRNAs in the diagnosis of HBV-HCC' (Table 1-5). We have only included miRNAs that provide sensitivity and specificity data for the diagnosis of HBV-HCC in order to ensure the content is more comprehensive and reliable. Lastly, we have removed some content based on the actual circumstance, making the expression more concise, and we have also adjusted the citations to make them more representative.

1 Zhang B, Han S, Feng B, Chu X, Chen L, Wang R. Hepatitis B virus X protein-mediated non-coding RNA aberrations in the development of human hepatocellular carcinoma. *Exp Mol Med* 2017; **49**(2): e293 [PMID: 28186085 PMCID: PMC5336563 DOI: 10.1038/emm.2016.177]

2 Sartorius K, Makarova J, Sartorius B, An P, Winkler C, Chuturgoon A, Kramvis A. The Regulatory Role of MicroRNA in Hepatitis-B Virus-Associated Hepatocellular Carcinoma (HBV-HCC) Pathogenesis. *Cells* 2019; **8**(12) [PMID: 31771261 PMCID: PMC6953055 DOI: 10.3390/cells8121504]

3 Sartorius K, Swadling L, An P, Makarova J, Winkler C, Chuturgoon A, Kramvis A. The Multiple Roles of Hepatitis B Virus X Protein (HBx) Dysregulated MicroRNA in Hepatitis B Virus-Associated Hepatocellular Carcinoma (HBV-HCC) and Immune Pathways. *Viruses* 2020; **12**(7) [PMID: 32664401 PMCID: PMC7412373 DOI: 10.3390/v12070746]

4 Sartorius K, An P, Winkler C, Chuturgoon A, Li X, Makarova J, Kramvis A. The Epigenetic Modulation of Cancer and Immune Pathways in Hepatitis B Virus-Associated Hepatocellular Carcinoma: The Influence of HBx and miRNA Dysregulation. *Front Immunol* 2021; **12**: 661204 [PMID: 33995383 PMCID: PMC8117219 DOI: 10.3389/fimmu.2021.661204]

5 Xie KL, Zhang YG, Liu J, Zeng Y, Wu H. MicroRNAs associated with HBV infection and HBV-related HCC. *Theranostics* 2014; **4**(12): 1176-1192 [PMID: 25285167 PMCID: PMC4183996 DOI: 10.7150/thno.8715]