Reviewer A

The paper titled “Increase in GPIHBP1 expression in advanced stage colorectal cancer indicates poor immune surveillance” is interesting. The increased expression of GPIHBP1 is involved in the progression of CRC. High GPIHBP1 level of advanced CRC indicates efficient immune evasion in tumour microenvironment. However, there are several minor issues that if addressed would significantly improve the manuscript.

1) Please analyze the potential molecular mechanism and pathobiology of GPIHBP1 in colorectal cancer based on the existing results and literature.
-----Thank you for your comment. We are working on a follow-up study.

2) The number of model animals in this study was not mentioned. Is it sufficient to complete all experiments? Please explain the use of animals in the experiment.
-----Thank you for your comment. We have modified our text as advised (see figure legend 5).

3) What are the cell types and expression characteristics in the immune microenvironment of colorectal cancer? How are the dynamic changes and connections between cells in different tissues? What is the role of GPIHBP1 in the process? It is recommended to add relevant content.
-----Thank you for your comment. We are working on a follow-up study.

4) How valuable are GPIHBP1 in predicting survival and drug sensitivity in colorectal cancer patients? It is recommended to add relevant content.
-----Thank you for your comment. We have previously studied its impact on survival and found that it is not relevant. We have discovered a drug that targets GPIHBP1 to repress the progression of colorectal cancer and we are verifying its therapeutic efficacy.

5) There are many genes that regulate colorectal cancer. Why did the author choose GPIHBP1 for research? Please describe the reason.
-----Thank you for your comment. Colorectal cancer is something we have been studying for a long time. Cancer metastasis usually involves the enhancement of fatty acid metabolism. GPIHBP1 plays a vital role in the lipolytic process and has been identified as responsible for transporting lipoprotein lipase into capillaries, which is crucial for triglyceride metabolism. We speculate that GPIHBP1 may affect CRC progression.

6) The introduction part of this paper is not comprehensive enough, and the similar papers have not been cited, such as “Spatiotemporal Immune Landscape of Colorectal Cancer Liver Metastasis at Single-Cell Level, Cancer Discov, PMID: 34417225”. It is recommended to quote this article.
-----Thank you for your comments. In this study, we explore variations of GPIHBP1 expression levels across different stages of CRC and analyses the potential impact of GPIHBP1 levels on the immune microenvironment. Colorectal cancer liver metastasis is not involved in our study.
7) It is recommended to increase the functional experimental study of the GPIHBP1 gene.

----- Thank you for your comments. We are working on a follow-up study.

8) It is suggested to increase the in-depth study on the function of GPIHBP1 in the occurrence and metastasis of different cancers, which may make this study more complete.

----- Thank you for your comments. We are working on a follow-up study.

**Reviewer B**

1. A **highlight box** is needed to highly summarize the key findings/recommendations, innovation, and potential implications of the study. Please provide.
   - No reference should be cited in the highlight box. The box should be concise with **no more than 250 words**.
   - Here is the template:

<table>
<thead>
<tr>
<th>Key findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Report here about key findings of the study.</td>
</tr>
<tr>
<td><strong>What is known and what is new?</strong></td>
</tr>
<tr>
<td>• Report here about what is known.</td>
</tr>
<tr>
<td>• Report here about what does this manuscript adds.</td>
</tr>
<tr>
<td><strong>What is the implication, and what should change now?</strong></td>
</tr>
<tr>
<td>• Report here about implications and actions needed.</td>
</tr>
</tbody>
</table>

   --- The Highlight box file is uploaded. Thank you!

2. For an Original Article, the Methods section should contain a subsection of ‘**Statistical Analysis**’ in the main text. Please provide.

   --- The statistical Analysis are updated now. Thank you!

3. Please revise the word.

   | even under a chow diet[3]. The mutation of GPIHBP1 results in severe hypertriglyceridemia and pancreatitis. Similarly, the **GPIHBP1** autoantibody syndrome |

   --- The GPIHBP1 is revised. Thank you!

4. Figures
   - **All abbreviations** in figures and legends should be explained. “GPIHBP1” “mRNA” “CRC” “TCGA” “TNM” “HR” in Figure 1 for example. Please check all abbreviations and provide the full names in the corresponding figure legend.
--- All abbreviations in figures and legends are explained. Thank you!

- Please indicate how data are presented and revise “p” to “P” in Figure 1C.

<table>
<thead>
<tr>
<th>Overall Survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>HR=1.661(1.122-2.458)</td>
</tr>
<tr>
<td>p=0.01</td>
</tr>
</tbody>
</table>

- Please check whether it should be “(C, D)” in Figure 2 legend.

“(C) Correlational study of GPIHBP1 presence in cancer foci or stroma with CRC progression.”

- Please double check the citation of Figure 2 in the text. The citation of Figure 2D is missing.

“In the stroma of CRC, GPIHBP1 expression was gradually up-regulated with disease progression (Figures 2B and 2C).”

- Figure 3C-D: the trend line is missing in iNOS. Please check.

- Please unify to use “Arg1” and “ARG1”, “iNOS” and “INOS” in Figure 3 and Figure 5I.

- Please check whether it should be “GZMB” in Figure 4A.
- Please check whether it should be “Granzyme B” in Figure 4B.

- Please indicate the meaning of “ns” in Figure 5 legend.
- Please check whether it should be “F4/80” in Figure 5I.

- It is suggested to unify “Glut1” and “GLUT1” in Figure 5C and the text.

--- All figures are updated now. Thank you!

5. Supplementary
- Please provide the Supplementary Table 1 in editable table format.
- Please add unit for Age, CEA and CA199 in Supplementary Table 1.
- In Supplementary Table 1, please uppercase the first letter of each column.
- Please indicate how data are presented in Supplementary Table 1.

<table>
<thead>
<tr>
<th></th>
<th>CEA</th>
<th>CA199</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>3.93(1.99, 8.63)</td>
<td>12.26(8.82, 19.95)</td>
</tr>
</tbody>
</table>

- Please indicate the meaning of “ns” in Supplementary Figure 1.
- Please double check the citation of Supplementary Figure 1 in the text. The citation of Supplementary Figure 1I, 1J is missing.
- **All abbreviations** in the Supplementary figures/table and legends should be
explained. “SSC” “FSC” “GPIHBP1” “MDSCs” in Supplementary Figure 1 for example. Please check all abbreviations and provide the full names in the corresponding figure legend.

--- All supplementary files are updated now. Thank you!

6. Reporting Checklist

1) It should be noted that once your paper is accepted, the reporting checklist you provided will be published as additional information for readers. Therefore:

- please indicate at the end of the **Introduction** section of the Main Text: “We present this article in accordance with the ARRIVE reporting checklist."

- please indicate the following information in the **Footnote** section: “Reporting Checklist: The authors have completed the ARRIVE reporting checklist.”

2) Please describe this information in both the Main Text and Item 19 in the checklist.

- Suggested wording: “A protocol was prepared before the study without registration”

- Or “A protocol was prepared before the study with registration in XXXX (where)”

> **Protocol registration**
> **19** Provide a statement indicating whether a protocol (including the research question, key design features, and analysis plan) was prepared before the study, and if and where this protocol was registered.

--- Reporting Checklist item is updated now. Thank you!