Peer Review File

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Reviewer A

Comment 1: Clarity of Presentation: The article would benefit from improved clarity in presentation, especially in the description of methods. Some sections, such as the identification of LMR-lncRNAs, could be better organized to enhance readability.

Reply 1: Thank you so much for your kindly and professional advice. We have revised the description according to your suggestion.

Changes in the text: See page 3-4, line 118-125 and line 142-154.

Comment 2: Validation: While the study uses internal validation with training and test sets, external validation from independent datasets could strengthen the generalizability of the proposed prognostic signature.

Reply 2: Thank you for your detailed comments and suggestions. We attempted to verify this model by collecting relevant data from other public databases, but so far we have been unable to locate all the expression data of the six lncRNAs in KIRC. Due to current limitations, we will strive to improve in future studies.

Comment 3: Experimental Validation: The article lacks experimental validation of the proposed LMR-lncRNA signature using in vivo or in vitro experiments. Incorporating experimental data would provide more robust evidence supporting the clinical relevance of the identified signature.

Reply 3: We sincerely appreciate your valuable insights and fully concur with the significance of incorporating experimental validation to enhance the robustness of our findings. Regrettably, due to time and resource constraints, we were only able to conduct limited experiments for validating the expression levels of partial lncRNAs, without delving deeper into functional research. We will conduct functional experiments on these key lncRNAs in the future to provide a more comprehensive demonstration of the mechanism. We have also acknowledged this constraint in our discussion section (See page 11, line 453).

Comment 4: Discussion Section: The discussion could be expanded to provide a more in-depth exploration of the potential mechanisms by which LMR-lncRNAs may influence the prognosis and immune response in KIRC. This would enhance the theoretical foundation of the study. In further discussing the implications of lactate metabolism-related long noncoding RNAs (LMR-lncRNAs) in kidney renal clear cell carcinoma (KIRC), it is pertinent to consider the broader context of cancer stem cells (CSCs). As highlighted in a recent review (PMID: 37685983), CSCs are characterized by clonogenic ability, stem cell marker expression, differentiation into diverse lineages, growth in nonadhesive spheroids, and in vivo tumorigenicity. The emergence of CSCs is attributed to genetic/epigenetic mutations or the fusion of tissue-specific stem cells with circulating bone marrow stem cells. In expanding the discourse on kidney renal clear cell carcinoma (KIRC), the article with PMID: 37373581 offers valuable insights into the global landscape of this prevalent cancer type. Acknowledging the significance of surgery in KIRC treatment, it is pivotal to address the challenges posed by metastatic cases and post-nephrectomy recurrence, affecting a substantial portion of patients. These therapeutic modalities target not only cancer cells but also consider the intricate dynamics of the tumor microenvironment (TME). The TME, encompassing non-malignant cell types and an altered extracellular matrix (ECM), plays a pivotal role in cancer development. The interactions between cancer cells and TME components are recognized as promising therapeutic targets. I suggest to include the suggested citations.

Reply 4: Thank you so much for your kindly and professional advice. We have added the suggested citations in our discussion section.

Changes in the text: See page 10, line 359-432.

Reviewer B

Comment 1: Renal cell carcinoma (RCC) is essentially a metabolic disease characterized by a reprogramming of energetic metabolism (PMID: 36960789; PMID: 30983433, PMID: 36430837,PMID: 36310399). In particular the metabolic flux through glycolysis is partitioned (PMID: 29371925, PMID: 28933387), and mitochondrial bioenergetics and OxPhox are impaired, as well as lipid metabolism (PMID: 30538212; PMID: 32861643, PMID: 29371925, PMID: 36430448). In this scenario it has been shown an inverse LDH-A/LDH-B ratio between normal

and neoplastic tissue in accordance with the higher efficiency lactate production observed in ccRCC (PMID: 25945836). These findings should be referenced and discussed.

Reply 1: Thank you so much for your kindly and professional advice. We have referenced and discussed those relevant findings in our discussion section.

Changes in the text: See page 10, line 359-432.

Comment 2: In addition, renal cell carcinoma is one of the most immune-infiltrated tumors (PMID: 31527133, PMID: 30738745; PMID: 27063186). Emerging evidence suggests that the activation of specific metabolic pathway have a role in regulating angiogenesis and inflammatory signatures (PMID: 32345771, PMID: 28359744). Features of the tumor microenvironment heavily affect disease biology and may affect responses to systemic therapy (PMID: 37189689; PMID: 33265926; PMID: 36902242; PMID: 37373581). Lactate metabolism can modulate immune cell infiltration and regulate immunoflogosis. These processes should be explored and discussed.

Reply 2: Thank you so much for your kindly and professional advice. We have referenced and discussed those relevant processes in our discussion section.

Changes in the text: See page 10, line 359-432.