Peer Review File

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Reviewer A

Comment 1: This study has analyzed the prognostic impact of baseline index (LIPI) based on LDH levels and neutrophil to lymphocyte ratio (NLR) in patients with metastatic prostate cancer. The results showed that LIPI has a significant prognostic role in patients with hormone-sensitive (mHSPC) and castration-resistant prostate cancer (mCRPC) and patients could be classified in three groups, with significant differences in progression and overall survival. These results could be useful to stratify these patients according to their prognosis and can be easily implemented in clinical practice. However, the study has several important limitations, mainly that the results should be validated in mHSPC patients treated with new hormonal therapies, which are now the standard in mHSPC.

Moreover, the manuscript requires major revision in order to be acceptable for publication:

Reply: Thanks for your professional advice. As you mentioned, NHT/DOC combined with ADT has now been recommended as the standard therapy for mHSPC patients. However, this study was performed in the west China which was a relatively less developed area. Therefore, the traditional maximal androgen blockage (MAB) treatment was still widely used there.

Following your suggestion, we have validated the predictive power of the LIPI in mHSPC patients treated with ABI/DOC. Due to the small number of patients with LIPI-Poor (N=5), we combined the LIPI-Intermediate and -Poor groups. The results showed that cases of LIPI-Intermediate and -Poor (N=26) had significantly shorter CRPC-free survival (CFS) than those of LIPI-Good (N=28) (mCFS: 14.8-mo vs. 24.7-mo, P=0.012). However, in terms of OS, neither group of patients reached the median survival time.

Changes in the text: We have added the updated analysis about the predictive power of LIPI in mHSPC patents treated with ABI/DOC (see Page 9, line 167 to line 176). Supplementary figure 1 has also been updated.

Comment 2: Patients with mHSPC include a small subgroup of patients (11%) treated with abiraterone +/- docetaxel. The analysis should be focused on patients treated with MAB alone to avoid confusing results.

Reply: Thanks for your rigorous advice. As you suggested, to avoid confusing results we have performed a subgroup analysis in mHSPC patients treated with either MAB or ADT plus ABI/DOC. The results showed that the LIPI had prognostic value not only in patients treated with MAB but also in those treated with NHT/DOC (Shown in Reply to comment 1).

Changes in the text: We have added the updated analysis about the predictive power of LIPI in mHSPC patents treated with ABI/DOC (see Page 9, line 167 to line 176). Supplementary figure 1 has also been updated.

Comment 3: The Discussion is too long and some paragraphs (eg, the second paragraph) repeats information explained in the Introduction.

Reply: Thanks for your advice. We have shortened the discussion as you suggested.

Changes in the text: We have shortened the discussion part of the revised manuscript as advised (see Page 12, line 228 to 263).

Comment 4: The role of LDH levels and NLR has been widely explored in mCRPC. This should be mentioned in the Discussion and references regarding their prognostic impact should be included.

Reply: Thanks for your constructive comment. We have added in the discussion part of the revised manuscript regarding the prognostic impact of LDH and dNLR in PCa.

Changes in the text: The discussion part of the revised manuscript has been updated (see Page 13, line 252 and line 259).

Comment 5: The language should be reviewed by a native English speaker.

Reply: Thanks for your kind advice. The language of the manuscript will be further polished by the editor office.

Reviewer B

Comment 1: This study is the first study to investigate the prognostic value of LIPI in metastatic prostate cancer, including mHSPC and mCRPC. The methodology is robust, and no major remarks in this manuscript. I would recommend some minor suggestions:

Reply: Thanks for your suggestion. Please find our responses to your comments below.

Comment 2: Abstract

・In the Methods (Lines 39-40), I would suggest that the authors should add more detailed information on mHSPC treatment. For example, "502 mHSPC patients treated with combination systemic therapy, (such as NSAA, abiraterone, or docetaxel plus ADT.)" or "primarily treated with MAB (89% of patients receiving MAB)"

・In the Results (Lines:58-59), this sentence does not make sense. Better to change like "LIPI was an independent prognosticator of OS in mCRPC patients treated with abiraterone. "

・Line 62: "treatment-decision making in clinical practice" can be just rephrased as "clinical decision-making"

Reply: Thanks for your detailed comments. We have modified our text as your suggestion.

Changes in the text: We have modified our text as advised (see Page 3, line 39 to 41; see page 4 line 60 and line 64).

Comment 3: Results

・I sometimes confuse the information, including both settings of mHSPC and mCRPC in one section. I would suggest that the authors completely divide the section into two (mHSPC and

mCRPC) for better readability. Like below.
3.1. mHSPC
3.1.1. Patient characteristics
3.1.2. Prognostic value of LIPI for patients with mHSPC

3.2. mCRPC
3.2.1. Patient characteristics
3.2.2. Prognostic value of LIPI for patients with mCRPC

Reply: Thanks for your advice. We have adjusted the article structure in the part of Results according to your comments.

Changes in the text: We have adjusted the article structure in the part of Results (see Page 8, line 149).

Comment 4: Discussion

・LDH has been considered as one of the prognostic factors even for metastatic prostate cancer.

Please discuss more detail regarding LDH as a prognostic factor in prostate cancer, referring previous publications (for example, PMID: 31558410)

Reply: Thanks for your professional advice. According to your suggestion, the role of LDH in PCa was introduced in the discussion part of the revised manuscript.

Changes in the text: We have added some content about the role of LDH in PCa in the discussion part (see Page 13, line 259).