Peer Review File

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Reviewer A

This study is an impressive report that uses HIBS scoring to classify types with good and poor prognosis, but there are some problems.

Comment 1: PPLELC is a very rare tumor, accounting for less than 1% of all lung cancers. Is this scoring, HIBS, specific to PPLELC? Can it be applied to other histological types of lung cancer?

Reply 1: Thanks for your professional review work on our article and we really appreciate all your comments and suggestions on improving the quality of our manuscript. In this present study, we introduce a novel prognostic approach known as the Haematological Indices-Based Signature (HIBS) constructed by linearly combining the 14 routine hematological features and their respective LASSO regression coefficients in patients with PPLELC. HIBS largely represents a non-specific but sensitive scoring of an immune state. Whether HIBS can be used for prognostic prediction and immunotherapy response assessment with other histological types of lung cancer is a very interesting research question and we expect to investigate this issue in our next study.

Comment 2: (Figure4) What is the proportion of each treatment line in high-risk and low-risk groups? Is it possible that the prognosis is better because the low-risk group includes many cases of first-line treatment?

Reply 2: Thank you for your nice comment and this is an especially important issue. We used the chi-square test to analyze the proportions of patients with each treatment line in low-risk and high-risk group. In the training cohort, the low-risk group exhibited proportions of 81.8% for first-line treatment and 18.2% for second or greater-line treatment, while the high-risk group showed corresponding proportions of 74.1% and 25.9%. The line of immunotherapy (first-line

vs second-line or greater) did not influence the risk grouping of the model ($P = 0.42$). Similarly, there was no significant difference (P=0.90) observed in terms of treatment proportions between the low-risk (63.6% first-line, 36.4% second-line or greater) and high-risk group (61.5% first-line, 38.5% second-line or greater) in the validation cohort.

Comment 3: (Table2) Was Cox regression analysis performed on 117 cases including the training cohort and validation cohort? If so, please state this point in the text.

Reply 3: Thank you for the detailed review and valuable suggestion. For our study, We applied the training cohort to build the Cox regression model and used the validation cohort to evaluate predictive performance. Table 2 summarizes the prognostic factors that have been studied in the univariate and multivariate Cox regression analyses in the training cohort. We have modified our text (see Page 9, line 221-227) and Table 2 title as advised.

Reviewer B

This paper is interesting because the authors analyzed the prognostic value of rare histologic types of lung cancer using a machine learning approach. However, there are several questions.

Comment 1: The validity of this HIBS score and the validity of the high and low cutoff values for this score is unclear and the authors should clarify this point in the paper.

Reply 1: Thanks for your comments and professional advice. These opinions help to improve academic rigor of our article. Based on your suggestion and request, we have made corrected modifications on the revised manuscript as follow: Haematological Indices-Based Signature (HIBS) for each patient constructed by linearly combining the 14 routine hematological features and their respective LASSO regression coefficients. An optimal cutoff value of 0.64, determined by the median value of HIBS score, was used to classify patients into high and low HIBS groups in the training cohort. This same cutoff value was subsequently applied to the validation cohort for similar patient stratification. We have modified our text as advised (see Page 8, line 209-214)

Comment 2: It is difficult to understand why 14 hematological values were selected and constructed from 41 hematological values for the HIBS score; the validity with which the 14 hematological values were selected should be clarified.

Reply 2: Thank you for your nice comments. The least absolute shrinkage and selection operator (LASSO) is a machine learning method for simultaneous feature selection and regularization，which can effectively analyze the high-dimensional sequencing data. In our study, we mined the haematological Indices-Based Signature from 41 hematological features which extracted from routine laboratory tests using the LASSO Cox regression algorithm. LASSO shrinks coefficients for weaker predictors toward zero and the final HIBS which comprises 14 hematological features with non-zero coefficients. We have added the detail to the manuscript (see Page 7, line 168-172).

Comment 3: Why did you divided into a training cohort and a validation cohort in a 7:3?

Reply 3: We appreciate the reviewer raising this important point. When constructing predictive models, the development dataset is used to train the model which needs to be sufficiently large sample sizes so that it consists of a sufficient number of observations to reach the optimal performance. The commonly adopted approach for randomizing patients into a training or validation set to a 7:3 distribution when dealing with small sample sizes in the existing literature.

Comment 4: Some of the ICI therapies you treated are not approved outside of China. What is the global approval status of these agents?

Reply 4: Thank you again for your valuable suggestions to improve the quality of our manuscript. PPLELC is a rare and histologically distinctive subtype of non-small cell lung cancer (NSCLC), accounting for approximately 0.7% of total cases. The rarity of PLELC had prevented the researchers to conduct a randomized controlled trial and to develop a standard therapeutic strategy specifically for PPLELC. ICI therapies agents has not received worldwide approval for the treatment of advanced PPLELC. The present study provide a strong rationale for considering first-line combination chemotherapy and immunotherapy as a treatment approach for PPLELC. In the future we hope to use this information to stratify patients more accurately and for more efficient treatment.