Peer Review File

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Reviewer A

I read this manuscript with interest. The authors examined a large cohort of patients with extranodal NK/T cell lymphoma, nasal type, and described new prognostic models for this rare disease using 2 methods. The study provides confirmatory evidence for previously-described prognostic variables and little novel data is presented.

1) One major problem lies in the language used, and I strongly suggest the authors send the manuscript either to a native English speaker or to a language editing service for review. It was difficult to read through the paper smoothly, much less understand it clearly.

We have sent the manuscript to AME Editing Service for review as advised and we hope the revised version is easier to read and better understandable (changes are in red color).

2) Risk tables should be included for all Kaplan-Meier plots

We have added risk tables for all Kaplan-Meier plots (seen in Figure 3).

3) One of the main variables used in both models is disease stage, and clearly this will be affected by the modalities used. The authors should state clearly which patients received PET/CT staging (which is probably more sensitive), and if their prognostic model also works well in this group of patients.

In our study, out of all 250 patients analyzed, 195 (78%) patients received whole-body PET-CT imaging before initial treatment, and in 55 patients who did not received PET-CT, 38 were in early stage (Ann Arbor stage I or II) and 17 were in advanced stage (Ann Arbor stage III or IV). So in general, our prognostic model were developed based on the patients who received PET/CT, so models work well in these patients.

We added “Out of all 250 patients analyzed, 195 (78%) patients received whole-body PET-CT imaging before initial treatment. In 55 patients who did not receive PET-CT, 38 were in early stage (Ann Arbor stage I or II) and 17 were in advanced stage (Ann Arbor stage III or IV)” to Page 12, Line 5-8, and “Involved regions and lymph nodes are determined by CT/enhanced CT/PET-CT, MR/enhanced MR and ultrasound, 195/250 (78%) received whole-body PET-CT. In 55 patients who

did not received PET-CT, 38 were in early stage (Ann Arbor stage I or II), and 17 were in advanced stage (Ann Arbor stage III or IV)" to Table 2 legend.

4) How were the cut-offs for hematological variables (Hb, LDH etc) selected?

We used X-tile[1] software to determine the cut-offs, and we found the lower Hb or higher LDH, the better discrimination power, the results were not satisfactory, so we referred to other models and chose the usual cutoff values for the normal range, as described in previous studies[2-4] in which the prognostic value of these parameters were reported, and we found these values also had good discrimination powers and they were user friendly in clinical practice. And as for monocyte, platelet and PNI, they were not currently widely accepted as prognostic factors and have been reported only in several studies[5,6], so we used cut-offs that had been validated in their studies in our study.

We add "We separated continuous variables into low and high groups either using the well-known cutoff (age) or on the basis of the usual cutoff value for the normal range (such as LDH and hemoglobin) or the cutoffs of which prognostic value had been validated in previous studies (platelet, monocyte, PNI) (22,23)." to Page 9, Line 16-20.

1. Camp RL, Dolled-Filhart M, Rimm DL. X-tile: a new bio-informatics tool for biomarker assessment and outcome-based cut-point optimization. Clin Cancer Res. 2004;10(21):7252-7259.
2. Kim S J, Yoon DH, Jaccard A, et al. A prognostic index for natural killer cell lymphoma after non-anthracycline-based treatment: a multicentre, retrospective analysis. Lancet Oncol 2016;17(3):389-400.
3. Wang L, Xia ZJ, Lu Y, et al. A modified international prognostic index including pretreatment hemoglobin level for early stage extranodal natural killer/T cell lymphoma[J].Leuk Lymphoma,2015,56(11):3038-3044.
4. Luo H, Quan X, Song XY, et al. Red blood cell distribution width as a predictor of survival in nasal-type, extranodal natural killer/T-cell lymphoma. Oncotarget. 2017;8(54):92522-92535.
5. Huang JJ, Li YJ, Xia Y, et al. Prognostic significance of peripheral monocyte count in patients with extranodal natural killer/T-cell lymphoma. BMC Cancer. 2013;13:222.
6. Yao N, Hou Q, Zhang S, et al. Prognostic Nutritional Index, Another Prognostic Factor for Extranodal Natural Killer/T Cell Lymphoma, Nasal Type. Front Oncol. 2020;10:877.

5) Units of all variables need to be included (e.g. Hb, LDH etc) in the tables and text

We have supplemented units of all variables in the tables and text (in red color, Table 1, Table 3) as advised.

6) The reference group for survival analyses in Table 3 should be clearly stated.

We have modified Table 3 as advised (explanatory legend for reference group "15 variables in 250 patients first received univariate analysis and 13 statistically

significant ones received multivariable analysis. In multivariable analysis, 5 variables were statistically significant" was supplemented.)

7) The illustrated patient in Figure 5 - can this be done as well for Figure 4 using the nomogram? Was the predicted survival very different?

In Figure 5, the illustrated patient's 3-year OS likelihood was 0.348, and in nomogram the predicted 3-year OS likelihood was approximately 0.29. To some extent, they can both be interpreted as relatively high risk. Due to different algorithms and variables, it is hard to get the same results using these two models, but in general the results are close. For machine learning model analyses more variables, we assume its predicted results are closer to the reality.

8) In the concluding paragraph, the statement that the current models outperform PINK is an overstatement. PINK is a widely validated model, whereas the current models are not.

It is true that what our models still needs further validation, it is an overstatement that the current models outperform PINK, so we modified our conclusion ("The models were preliminarily validated to have good discriminatory power; however, this still needs to be verified by prospective study").

Reviewer B

This study was to develop new risk models for ENKTL using nomogram and machine learning. However, the results do not have novel information compared to that of previous studies.

Variables in our models are stage, age, ECOG score, B symptoms and LDH level, it is true that there are little novel variables. However, they are common and relevant to clinical practice, so they are user friendly. Besides, prospective study for CA stage has just finished in 2020, it is the first time that CA stage served as prognostic factors for ENKTL in prognostic models. What is more, our models are totally based on patients treated with non-anthracycline-based treatment, while most previous models are not, so our models are applicable in the era of new mode of treatment. Last, this is also the first attempt to develop prognostic model for ENKTL using machine learning method.