Title: Hemophagocytic Lymphohistiocytosis Machine Learning Prediction in Subcutaneous Panniculitis-Like T-Cell Lymphoma

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INTRODUCTION: Subcutaneous panniculitis-like T-cell lymphoma (SPTCL) is a rare hematological malignancy. Although SPTCL usually has a good prognosis, with a 5-year overall survival (OS) rate of >80%; 20% of patients suffer from fatal hemophagocytic lymphohistiocytic syndrome (HLH). Recent studies revealed that germline mutations in *HAVCR2* were associated with HLH in SPTCL patients. We aimed to investigate the *HAVCR2* status in the Vietnamese population and constructed a machine-learning (ML) model to predict HLH-like symptoms.

METHODS: We collected 27 in-house cases, 21 of whom had available information about HLH-like illness, diagnosed as SPTCL within 5 years (2018 – 2023) from 10 Vietnamese institutions including 4 children's hospitals, 3 general hospitals, 1 hematology hospital, 1 dermatology hospital, and 1 national cancer center. All cases with available hematoxylin and eosin slides, immunohistochemistry slides (CD3, CD20, CD4, CD8, CD56, T-cell receptor βF1, and Ki-67) and PCR for TCR-γ results were reviewed and confirmed the diagnosis by an experienced hematopathologist. Sanger sequencing for *HAVCR2* was performed for all cases by using formalin-fixed, paraffin-embedded samples. Using published data (n=145), we constructed a variable-interacting logistic regression model to predict HLH-like systematic illness and validated it in our in-house data.

RESULTS: The median age of the patients at the time of diagnosis was 22 (range: 6-64) years old, with female gender predominance (66.7%). *HAVCR2*^{Y82C} mutation was detected in 22 cases (81.5%) while no *HAVCR2*^{Y82C} mutation was detected in 5 cases (18.5%). No HAVCR2 p.I97M or p.T101I mutations were detected in our cohort. The patients with *HAVCR2*^{Y82C} mutation had a tendency of higher risk for HLH/HLH-like systemic illnesses than wildtype *HAVCR2*^{Y82C} patients despite no statistical significance (62.5% in *HAVCR2*^{Y82C} vs. 20% in *HAVCR2*^{wildtype}; p=0.150). We compared the clinicopathological characteristics of *HAVCR2*^{Y82C} and

HAVCR2^{wildtype} SPTCL patients (**Table 1**). There were no statistical differences in age (p=0.975), gender (p=0.295), and HLH/HLH-like illness (p=0.149) between *HAVCR2*^{Y82C} and *HAVCR2*^{wildtype} SPTCL patients. The prediction model showed high performance with AUC=0.88, Accuracy=0.81 in the internal test set (n=21), and AUC=0.77, Accuracy=0.81 in our in-house data (n=21) (**Figure 1**). The sensitivity/specificity of the model was 100%/66.7% and 90.9%/70.0% in the internal test and in-house test, respectively. There were no false-negative cases in the internal test cohort while there was only 1 false-negative case in the in-house cohort, whose sample was *HAVCR2*^{wildtype}. The model can be used as an online web-based application (https://lkhangkv1995.shinyapps.io/SPHeLyP/).

CONCLUSION: In conclusion, the *HAVCR2*^{Y82C} mutation was common in the Vietnamese SPTCL population and was associated with unique clinicopathological features. However, our multi-institutional data illustrated that *HAVCR2* mutations did not always indicate the presence of HLH. Therefore, a prediction model combining clinicopathological parameters and *HAVCR2*^{Y82C} mutation status could aid in predicting the prognosis for patients with SPTCL. A negative prediction of a *HAVCR*^{Y82C} sample had a high precision.