PREDICTING EXTRAVASCULAR HEMOLYSIS IN PAROXYSMAL NOCTURNAL HEMOGLOBINURIA

Munevver N. Duran[1], Zehra Tombul[1], Mutlu Mete[2], Ahmet Toprak[1], Olisaemeka D. Ogbue[3], Hussein Awada[3], Carmelo Gurnari[3,4], Jaroslaw P. Maciejewski[3], Ibrahim Ibrahim[1], Merve Ozturk[1], Yusuf Ozcan[5], Brielle Johnson[1], Christine Ejiofor[1], Alper Olcal[1], Taha Bat[1]

1 Division of Hematology-Oncology, UT Southwestern Medical Center, Dallas, TX, USA
2 Department of Information Science, University of North Texas, Denton, TX, USA
3 Translational Hematology and Oncology Research, Cleveland Clinic, Cleveland, OH 44195, USA
4 Department of Biomedicine and Prevention, University of Rome Tor Vergata, 00133 Rome, Italy
5 University of Texas Dallas, Dallas, TX, USA

INTRODUCTION

Paroxysmal Nocturnal Hemoglobinuria (PNH) is characterized by intravascular hemolysis due to increased vulnerability of blood cells to complement dysregulation. The introduction of C5 complement inhibitors has significantly improved PNH management by reducing the occurrence of intravascular hemolytic crises and thrombosis. However, a significant subset of patients experiences extravascular hemolysis (EVH) as a consequence of these treatments. The development of EVH complicates patients' treatment trajectories by making them transfusion-dependent, decreasing quality of life, and inducing sequelae due to long-term chronic hemolysis.

AIM

This study aims to develop a robust machine learning model trained on diagnostic workup data of PNH patients to predict the development of EVH. We aim to predict EVH before it happens based on initial original data obtained at the time of diagnosis. This predictive capability is significant because it can inform and optimize treatment strategies, particularly in the selection of complement inhibitor therapies, thereby minimizing the risk of EVH.

METHODS

We analyzed medical records of 172 PNH patients (with PNH granulocytes >0.02) from the University of Texas Southwestern and Cleveland Clinic Foundation (2000-2022). Data included clinical, laboratory, and next-generation sequencing (NGS) information, clinical diagnosis and in treatment regimens. EVH was defined as DAT positivity at the time of the testing per physician's discretion. Following the characterization of EVH, the index cases were further assessed to develop an algorithm to predict the occurrence of EVH. Feature selection and feature impact scores were achieved through a Random Forest algorithm.[12] A 5-layer (32, 16, 8, 4, 2 neurons, input through output) multilayer perception algorithm is trained and cross validated with Leave-one-out (LOO) statistical method[13,14]. This approach maximizes data usage and offers an unbiased estimate of the model's performance on small datasets.

RESULTS

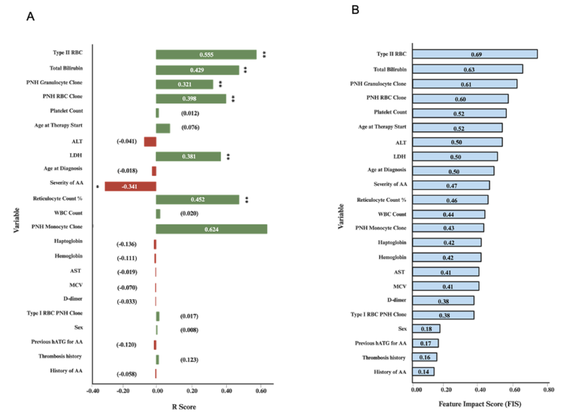
Overall, a cohort of 172 individuals diagnosed with PNH was examined, with almost equal female-to-male ratio and a median age of 38 years. The median follow-up was 67 months (IQR 29-132). Among these cases, 78 were identified as primary PNH (pPNH), and 94 had a history of antecedent aplastic anemia, classified as secondary PNH.

Results showed significant differences in clinical markers such as hemoglobin levels, LDH levels, and reticulocyte counts between EVH-positive and EVH-negative patients. The machine learning model provides clinicians with a predictive tool to assess the risk of EVH at the time of diagnosis, aiding in the selection of appropriate complement inhibitor therapy.

The incorporation of our machine learning algorithm represents a significant leap forward in identifying the risk of EVH in PNH patients at the time of diagnosis based on the easily accessible clinical variables that can be obtained at the time of the delineation for treatment options. By utilizing this algorithm, clinicians may receive predictive guidance in selecting the most likely effective upfront complement inhibitor.

Variables correlated with EVH risk in PNH patients, ranked by predictive score:

Variable	Predictive Score	Mean±Std All (N=27)	Mean±Std Neg (N=12)	Mean±Std Pos (N=15)
Type II RBC	0.72	30.37±26.35	16.15±11.06	41.75±29.34
Total bilirubin (mg/dL)	0.65	1.87±1.01	1.34±0.86	2.30±0.91
PNH granulocyte clone %	0.62	80.13±20.21	66.73±22.78	90.86±7.82
PNH RBC clone %	0.57	42.83±29.61	24.86±18.28	57.21±29.07
Platelet count, x10^9/L	0.54	112.79±69.56	111.17±77.76	114.08±62.19
Age at therapy start	0.52	44.82±16.02	42.55±14.90	46.64±16.64
ALT (IU/L)	0.52	34.36±35.31	37.01±46.48	32.24±22.49
LDH (U/L)	0.50	1391.28±920.49	1078.20±633.90	1641.73±1030.79
Age at diagnosis	0.50	39.52±16.38	36.25±16.56	42.13±15.76
Severe AA history	0.47	0.44±0.34	0.53±0.39	0.36±0.27
Reticulocyte count%	0.46	6.88±5.62	5.60±2.41	7.92±7.06
WBC (μL)	0.44	4.40±2.00	4.16±1.93	4.59±2.03
PNH monocytes clone %	0.43	76.93±10.59	74.12±11.09	79.18±9.60
Haptoglobin (mg/dL)	0.42	28.75±21.05	34.49±29.33	24.16±7.87
Hemoglobin (g/dL)	0.42	8.97±2.24	9.37±1.51	8.66±2.64
AST (units/L)	0.41	74.19±55.35	59.17±39.95	86.21±62.55
MCV (μm^3)	0.41	100.08±19.38	102.54±7.02	98.11±25.06
D-Dimer (ng/mL)	0.38	1094.73±1014.97	1114.29±1238.79	1079.08±791.25
Type I PNH RBC clone %	0.38	11.26±14.33	9.93±7.96	12.33±17.78
Sex	0.18	0.30±0.46	0.17±0.37	0.40±0.49
Previous hATG for AA	0.17	0.26±0.44	0.42±0.49	0.13±0.34
Thrombosis history	0.16	0.44±0.48	0.45±0.48	0.43±0.48
History of AA	0.14	0.48±0.50	0.58±0.49	0.40±0.49



A machine learning approach to predict extravascular hemolysis in paroxysmal nocturnal hemoglobinuria. Pearson Correlation Coefficients, Feature Impact Scores (FIS) for Variables in the Extravascular Hemolysis Prediction Machine Learning Model are presented in panel A and B. (C) Confusion matrix to evaluate the performance of the classification model. (D) ROC-AUC Curve for the machine learning model predicting the development of EVH with an AUC score of 0.80.

CONCLUSIONS

Our machine learning algorithm serves as a proof of concept, demonstrating the potential to predict the development of extravascular hemolysis (EVH) in paroxysmal nocturnal hemoglobinuria (PNH) patients. While not yet ready for clinical practice, this preliminary model paves the way for future enhancements through additional data and application to larger cohorts. By predicting EVH early on, clinicians can potentially begin with a more appropriate complement inhibitor therapy, optimizing patient outcomes.

In conclusion, the dynamic nature of PNH and the ongoing evaluation of various complement cascade modifier treatments underscore the critical need to provide clinicians with personalized decision-making tools, such as our advanced machine learning algorithms, to effectively evaluate the risk of EVH, potentially informing treatment strategies.

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CONTACT INFORMATION

Presenter: Munevver N. Duran, MS3
Division of Hematology-Oncology, UT Southwestern Medical Center, Dallas, TX
5323 Harry Hines Blvd. Dallas, TX 75390-9255
617-378-5429
Munevver.duran@utsouthwestern.edu

Correspondence: Taha Bat, MD
Division of Hematology-Oncology, UT Southwestern Medical Center, Dallas, TX
5323 Harry Hines Blvd. Dallas, TX 75390-9255
Office: 214-648-4943 | Fax: 214-648-4105
taha.bat@utsouthwestern.edu