PREDICTION OF SEVERE ADAMTS13 DEFICIENCY IN PATIENTS WITH THROMBOTIC MICROANGIOPATHIES

Félix De La Fuente Gonzalo* , Jorge M. Nieto, Fernando A. González, Ana Villegas, Paloma Ropero
Hematology, Hospital Clínico San Carlos, Madrid, Spain

Background:
Thrombotic microangiopathies (TMA) are a rare and heterogeneous group of diseases that include atypical Hemolytic Uremic Syndrome (aHUS), Shiga toxin *E. coli* HUS (STEC-HUS), Thrombotic Thrombocytopenic Purpura (TTP) and other TMAs secondary to several conditions (ie, SLE, cancer or hematopoietic stem cell transplant).
TTP is characterized by extreme deficiency of ADAMTS13 activity. Plasma exchange therapy and immunosuppression are the current treatment for TTP but are ineffective for most other forms of TMA.

Aim of the study:
Assays exploring ADAMTS13 activity are limited to only some specialized reference laboratories. To identify clinical features which may allow to predict rapidly an acquired ADAMTS13 deficiency, we performed an analysis of our TMA registry. The primary goal was to identify cut-offs for variables that would prove useful in excluding the possibility of TTP. The early exclusion of a severe ADAMTS13 deficiency may allow to start alternative therapies based on the etiology of TMA.

Patients and Methods:
The Registry included 158 patients with TMA, of which 55 had an associated condition (hematopoietic stem cell transplant, cancer and chemotherapy, HELLP syndrome, SLE or systemic sclerosis, Disseminated intravascular coagulation, HIV, drugs associated TMAs or sepsis) and were excluded from the analysis.
All the statistical analysis were performed on a final cohort of 103 adults with idiopathic TMAs.
Patients with severe (<5% of normal activity) ADAMTS13 deficiency (n= 50) were compared for clinical, biological, and biochemical features to patients with detectable (≥5%) ADAMTS13 activity (n=53).
A subset of variables from the available data was considered from a clinical standpoint as potential predictors of low ADAMTS13 activity. Then, for the statistically significant variables, we generated receiver operator characteristics (ROC) curves and compared area under the curve (AUC) values to find cut-offs and to discern the predictive quality of the variables.
Finally, we conduct multivariate logistic analysis to test if combined variables improve the prediction capability of the variables taken alone.

Results:
Significant correlations for severe ADAMTS13 deficiency were seen for three of the observed variables: age, platelet count and creatinine.
Receiver operator characteristics curves for individual variables had area under the curve (AUC) values of 0.613 (age), 0.83 (platelet count) and 0.85 (creatinine); continuous variables were dichotomized at thresholds of 60 years old for age, 32×10^9/L for platelet count and 2.02 mg/dL for creatinine.
The combined model (Table 1) had an AUC of 0.93, thus improving the prediction capability of the individual variables.

Table 1. Multivariate logistic regression model (predicting a severe ADAMTS13 deficiency).

Variable	p	Odds Ratio	I.C. (95%)	Specificity	Sensibility	Positive Predictive Value	Negative Predictive Value
Creatinine <2.02 mg/dL	<0.001	36.14	6.33-206.46	84%	92%	85.2%	91.3%
Platelet <32×10^9/L	0.004	7.11	1.84-27.46				
Age <60 years	0.017	5.23	1.34-20.4				

Conclusions:
TMA are rare diseases and only registries allowing the analysis of hundreds of patients may be the basis of reliable data about pathophysiologic, diagnostic and therapeutic issues.
TTP share features of atypical HUS. Our results may enable the rapid exclusion and accurate diagnosis of TTP using readily available laboratory data, and this could allow to chose the suitable therapy for different pathophysiological groups, including aHUS in which an early anticomplement treatment is crucial to stop the TMA process.

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H) Clinical Nephrology, primary and secondary glomerulonephritis.
Félix De La Fuente-Gonzalo
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