

CLINICAL FEATURES IN PATIENTS WITH NON-SEVERE HEMOPHILIA A: THE DISCOVERY SCORE PROPOSAL FOR PROPHYLAXIS PRESCRIPTION

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Background. In non-severe hemophilia A (HA), classification based exclusively on factor VIII (FVIII) activity does not fully reflect bleeding phenotype heterogeneity. Consequently, some patients with clinically relevant bleeding manifestations may remain undertreated and prophylaxis may be underused. We aimed to identify clinical characteristics associated with prophylaxis indication and to develop a phenotype-driven clinical score to support treatment decision-making.

Methods. This retrospective real-world study included consecutive patients with non-severe HA (FVIII 1% to <40%) managed at Italian hemophilia centers. Clinical, bleeding, joint-related, and treatment-related variables were collected and compared between patients receiving physician-indicated prophylaxis and those managed on demand. Candidate predictors associated with prophylaxis indication were identified through univariate analyses and least absolute shrinkage and selection operator (LASSO) penalized logistic regression. Predictors retained in the final parsimonious multivariable model were converted into an integer-based risk score.

Results. Seventy-three patients were included (50.7% moderate and 49.3% mild HA); 67.1% received indication to prophylaxis. Compared with patients treated on demand, those

receiving prophylaxis had significantly higher annual bleeding rate (ABR) and annual joint bleeding rate (AjBR), earlier age at first bleed, higher prevalence of severe bleeding history, more problem joints, and more frequent synovial hypertrophy. Following prophylaxis initiation, median ABR decreased from 2.76 to 0.57 and median AjBR from 2.12 to 0.16 (both $p < 0.001$). The DISCOVERY score included five predictors: AjBR ≥ 2 (+3), synovial hypertrophy (+2), history of severe bleeding (+2), antithrombotic therapy (+4), and ABR ≥ 2 (+1), for a total score range of 0-12. The model showed good discrimination, with an area under the curve of 0.84 (95% CI 0.70-0.96). A threshold ≥ 4 provided the best balance between sensitivity (75.5%) and specificity (75.0%), whereas higher thresholds increased specificity up to 100%.

Conclusions. A substantial proportion of patients with non-severe HA exhibit a clinically relevant bleeding phenotype that may warrant prophylaxis despite residual FVIII levels above the severe range. The DISCOVERY score integrates bleeding burden, joint disease activity, and treatment-related risk factors into a simple phenotype-driven tool that may support individualized prophylaxis decisions. External prospective validation is warranted.