Factor VIII Coagulant Activity (FVIII:C) as an Independent Predictor of Bleeding across Different Subtypes of Von Willebrand Disease (VWD)

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INTRODUCTION

- VWD is the most common, inherited bleeding disorder caused by deficiency or dysfunction of the platelet adhesive protein, von Willebrand factor (VWF), resulting in prolonged bleeding of variable severity and frequency.*(Ruggeri ZM, 2007)*
- VWD patients present with a wide spectrum of bleeding manifestations that oftentimes do not correlate with FVIII activity, VWF antigen (VWF:Ag), VWF ristocetin cofactor activity (VWF:RCo), or mutation type; the bleeding phenotype can be quite different within the same family. The basis for this wide heterogeneity is poorly understood.
- Associations between thrombin generation (TG),VWF panel biomarkers, and bleeding are not well characterized to date.

AIM

- **To comprehensively characterize and evaluate the predictors of bleeding, including TG, across different subtypes of VWD.**

METHODS

- **Study type:** This is an ongoing, retrospective and prospective, diagnostic and observational study from a single center in Mumbai, India
- **Sample size:** 46 VWD patients (Type 1=6, Type 2=16, Type 3=24) with a new or historical diagnosis of VWD were enrolled in the study. The subtyping was done as per the most recent ASH/ISTH/NHF/WFH-guidelines for the diagnosis of VWD..*(James PD, 2021)*
- **Inclusion/Exclusion criteria:** Patients who have a FVIII activity ≤50 IU/dL were included in the study. Patients with acquired and platelet type VWD were excluded.
- **IRB:** Approval from the KJS Hospital's Institutional ethics committee was obtained, and informed consent was received from patients prior to enrollment.
- **Assessments:** Pertinent medical history was recorded; ISTH Bleeding Assessment Tool (BAT) was used to assess bleeding phenotype.
- **Lab tests:** Blood samples were collected for quantifying levels or activity of VWF:Ag, VWF:RCo, FVIII activity, and VWF gene sequencing. TG was assessed using platelet-poor plasma obtained after a 2-step centrifugation process.
- **Statistics:** Statistical analysis was performed using GraphPad Prism software (Boston, MA, USA). ANOVA or Pearson's nonparametric correlation test was employed where indicated.

RESULTS

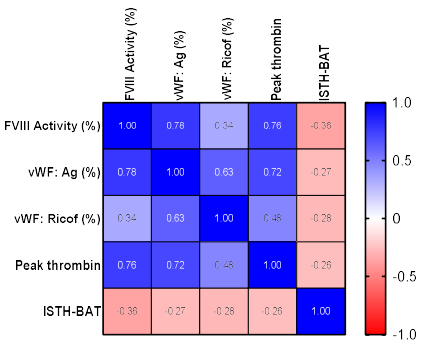

Figure 1:. Correlation matrix depicting associations between VWF panel biomarkers and bleeding (i.e., ISTH-BAT score).

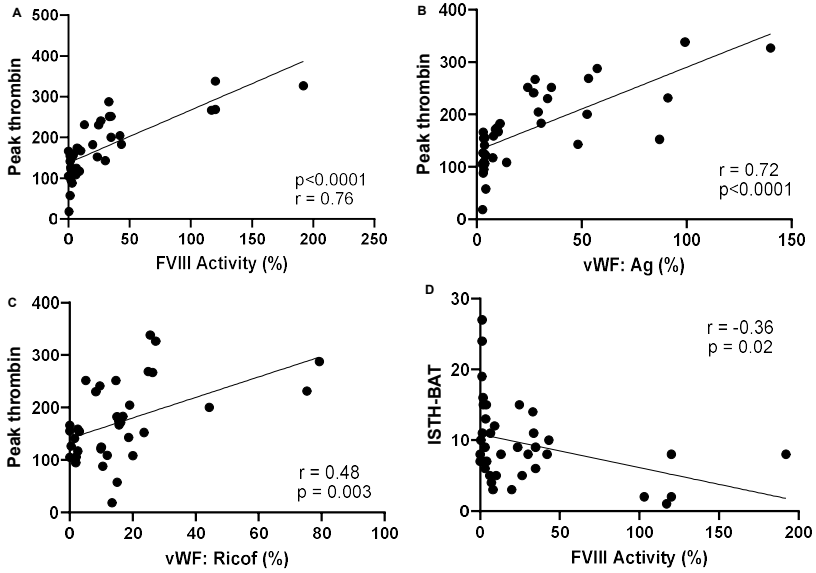

Figure 2. Correlations between peak thrombin and VWF panel biomarkers & bleeding.

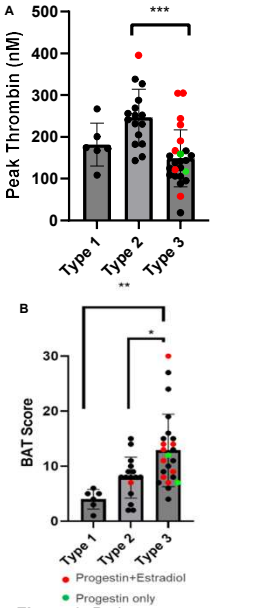

Figure 3. Patients on estrogen-containing hormonal therapy had higher peak thrombin(A) but still had high bleeding scores(B).

CONCLUSIONS

- Peak thrombin demonstrated strong correlations with FVIII activity, VWF:Ag, and VWF:RCo.
- Among the VWF panel biomarkers, FVIII:activity was found to have the strongest correlations with both peak thrombin and bleeding.
- Bleeding scores were associated with VWD Type.
- Estrogen-containing hormonal therapy, which is known to modulate Protein S levels, was associated with increased peak TG, even in Type 3 VWD patients.
- It is hypothesized that more effective Protein S-targeting therapies may improve bleeding in VWD.

REFERENCES

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