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**High annualized bleeding rates in pediatric patients with inherited platelet function disorders**

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**Running Head**: Pediatric Platelet Disorders

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**Contributions:** S. Saini and A. Zia conceptualized, designed, and performed research. S. Saini, S. Zhang, and A. Zia analyzed the data. S. Yates and R. Sarode blindly and independently adjudicated abnormal whole blood aggregation results for all participants. S. Saini and A. Zia wrote, and all other authors critically edited the manuscript.

Platelet function disorders are common inherited bleeding disorders.[1, 2] While severe inherited platelet function disorders (IPFD) such as Glanzmann Thrombasthenia and Bernard Soulier syndrome are easier to diagnose, diagnosing milder phenotypes of IPFD remains complex. Up to 9% of healthy children can have epistaxis, and 12% of infants in the general pediatric population demonstrate bruising, complicating the ability to diagnose IPFD in otherwise healthy children.[3, 4] Structured bleeding assessment tools (BAT), such as those developed by the International Society of Thrombosis and Hemostasis (ISTH), offer utility as a screening instrument to guide bleeding disorder testing.[5,6] Our group has previously established an IPFD incidence of 4.5% in an unselected, prospective cohort of adolescents referred for heavy menstrual bleeding (HMB) using ISTH-BAT and systematic testing for IPFD.[7] We aimed to determine the prevalence and types of IPFD in children referred for bleeding, examine bleeding events and annualized bleeding rates (ABR), and investigate the predictive ability of the ISTH-BAT for IPFD diagnosis, treatment for bleeding events, and severe bleeding events. We hypothesized that bleeding scores (BS) are higher in pediatric patients with IPFD than those without, and the ISTH-BAT will predict bleeding events and receipt of treatment in IPFD.

Our retrospective IRB-approved study included patients aged 0 to 18 referred for bleeding symptoms between 2019-2021 to The University of Texas Southwestern Medical Center (UTSW) Pediatric Hemostasis and Thrombosis Program. A standardized hemostatic evaluation is undertaken for every patient with high suspicion for primary hemostatic defect. The minimum standardized evaluation includes a complete blood count with mean platelet volume, blood smear, prothrombin time, activated partial thromboplastin time, fibrinogen activity, von Willebrand panel, and platelet aggregation using whole blood impedance aggregometry (WBA). Additional testing is individualized and may include clotting factor assays, evaluation for disorders of hyperfibrinolysis, platelet flow cytometry and/or genetic testing. To be eligible, we included patients who completed more than one clinic visit and either had an ISTH-BAT documented in the medical chart or sufficient bleeding history captured to calculate the ISTH-BAT and underwent the minimum standardized hemostatic evaluation. Only patients with reproducible (≥2) abnormal WBA findings were included. We excluded patients without documented bleeding histories, those with anticoagulant-associated bleeding, or those with additional causes of increased bleeding risk.

Demographic and clinical information from each patient's electronic medical record was recorded. IPFD was diagnosed when there was impaired aggregation to ≥2 agonists (excluding collagen or ristocetin) and/or impaired ATP secretion on ≥2 occasions using WBA and luminescence as previously described.[7, 8,] Von Willebrand disease (VWD) was defined as quantitative VWF levels <0.50 IU/dL (VWF antigen, VWF:RCo or VWF:GP1bM) on ≥2 occasions. All patients met Type 1 VWD (VWD-1) criteria based on previously established guidelines.[9] Controls had a bleeding phenotype but no identifiable bleeding disorder on comprehensive laboratory evaluation.

193 participants (67% female) with a median age of 13 years (IQR 7-15) were included. 18% (n=34) were diagnosed with IPFD, 24% (n=46) with VWD-1, and in 58% (n=113) the bleeding disorder evaluation did not reveal an identified hemostatic defect (Table 1). Of the IPFD participants, twelve (35%) had aspirin-like defect, 1 (3%) had Bernard Soulier, and in the remaining 20 (59%) the identified defect was non-specific (reduced aggregation and/or secretion to ≥1 agonist).

Annualized bleeding rate (ABR) was calculated by dividing the number of clinically significant episodes 1 year before the first evaluation by history and/or emergency department, office, or hospital visits for bleeding. Median ABR was 12 (IQR 2-13) for IPFD, 12 (IQR 4.5-14) for VWD-1, and 12 (IQR 1-13) for controls (p=0.13; Figure 1A). The most frequent bleeding event in all groups was HMB (n=96, 48.2%). The subsequent most frequent bleeding event in the IPFD cohort was surgical bleeding, while in VWD-1 and controls it was epistaxis (Figure S1A).

Severe bleeding events, defined as any bleeding event requiring medical or surgical interventions including high dose oral hormonal therapy every 6 or 8 hours/day for several days, IV estrogen, blood transfusion, and surgical interventions to stop bleeding, occurred in 18 (53%) IPFD, 20 (43%) VWD-1, and 50 (44%) control participants. The median number of bleeds requiring treatment was 2 (IQR 1-12) for IPFD, 12 (IQR 1-13) for VWD-1, and 3 (IQR 0-12) for controls (p=0.16; Figure 1B). Receipt of treatment was defined as any bleeding requiring systemic therapy or surgical intervention for bleeding symptoms, but excluding topical agents (i.e., oxymetazoline for epistaxis). Hormonal therapy was the most utilized treatment in VWD-1 (n=26; 43%) and

controls (n=56; 48%), whereas surgical therapy, including packing, suturing, and cauterization, was highest in IPFD (n=14; 33%) (Figure S1B).

Median BS was 3 (IQR 2.75-4) in the IPFD group, 4 (IQR 3-5) in VWD-1, and 3 (IQR 3-4) in controls (Figure 1C). BS between the VWD-1 and control groups varied significantly (p=0.012), while no significant difference was found between IPFD and VWD-1 or controls. Clinically significant bleeding events were defined as bleeding involving all sites but excluding bleeding lasting <10 minutes, events not requiring intervention, and all cutaneous bleeding except for wound bleeds lasting >10 minutes. Median BS was significantly higher in those with clinically significant bleeding events than those without ($p<0.05$) in all study groups (Figure 2).

A BS >4 in IPFD (area under the curve [AUC]=0.85) and VWD-1 (AUC=0.85) groups predicted clinically significant bleeding events with very good accuracy (Figure S2A). For bleeding events requiring treatment, a BS >3 in the IPFD group (AUC = 0.95) predicted treatment with excellent accuracy, while a BS >2 in the VWD-1 group (AUC = 0.71) predicted treatment with good accuracy (Figure S2B). Severe bleeding events were predicted at BS >7 in the IPFD group (AUC = 0.89) with very good accuracy and BS >5 in the VWD-1 group (AUC = 0.62) with sufficient accuracy (Figure S2C). The likelihood of clinically significant bleeding events, bleeds requiring treatment, and severe bleeding events were significantly higher in the IPFD and VWD-1 groups when the BS was above the respective identified cut-off values, except for severe bleeding in VWD-1 (Figure S3).

We show that IPFD is common among pediatric patients referred to a tertiary care center, with 18% of our participants diagnosed with IPFD. Varying incidence seen in other studies, such as 5% by Bidlingmaier et al. and 21% by Adler et al., can be explained by differences in sample size, prospective nature, and different methods of platelet function testing.[10,11]

We demonstrate high ABRs in IPFD participants that were not significantly different than those with VWD-1. Gresele et al. found higher bleeding rates in IPFD than VWD patients, but once patients with Glanzmann Thrombasthenia and Bernard Soulier were removed, similar to our study population, no significant differences remained.[12] A higher proportion (20%) of IPFD participants suffered surgical bleeding events

compared to VWD-1 and required more invasive interventions, such as surgery. This is in stark contrast to Gresele et al.'s data, which reported <5% of pediatric IPFD bleeding events to be surgical, likely explained by the prospective nature of the study where IPFD diagnosis was already established and early intervention possible.[12]

ISTH-BAT scores were comparable for IPFD and VWD-1 participants. Gresele et al. found a significantly higher bleeding score in pediatric IPFD versus VWD-1 participants (8 vs. 4, respectively).[12] However, Bidlingmaier et al. found no difference in BS, with both pediatric IPFD and VWD-1 participants having a BS of 3.[10] This is likely driven by the inclusion of severe platelet disorders in the Gresele study, whereas the Bidlingmaier study included a similar cohort of IPFDs as ours, leading to comparable results.

For our IPFD participants, BS >4 predicted subsequent bleeding events, BS >3 predicted bleeding events requiring treatment, and BS >7 predicted severe bleeding events. Our study predicted bleeding events at a lower BS than Gresele et al (BS >7), likely due to higher ABRs within our study population.[12] Gresele et al. found that 75% of adult IPFD patients with a BS >2 required treatment but did not comment on the ability of ISTH-BAT to predict treatment requirements.[13] Gresele et al. found that a BS >6 was predictive of severe bleeding events in adult IPFD participants.[12] Their inclusion of severe bleeding disorders, such as Glanzmann Thrombasthenia and Type 2 and 3 VWD, likely increased their ability to predict severe bleeding events at lower bleeding scores.

In summary, IPFD is common in children referred for bleeding and characterized by high ABRs. IPFD presentation overlaps with children without an identified bleeding disorder and VWD-1. The ISTH-BAT alone was not discriminatory for IPFD in our cohort, highlighting the need for platelet aggregation testing in children referred for bleeding. High ISTH-BAT scores at IPFD diagnosis are more likely to experience severe bleeding events and require treatment. While HMB was the most common cause of bleeding in all cohorts, IPFD participants received more surgical interventions compared to VWD-1 and controls whose most common treatment was hormonal therapy. As such, HMB was undertreated in IPFD. Our results underscore the

importance of high diagnostic suspicion for IPFD in children referred for a bleeding disorder evaluation. Further, we confirm the utility of the ISTH-BAT for IPFD and bleeding prognosis in pediatric patients.

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**Tables and Figures**:

**TABLE 1**. Patient demographics and clinical characteristics.

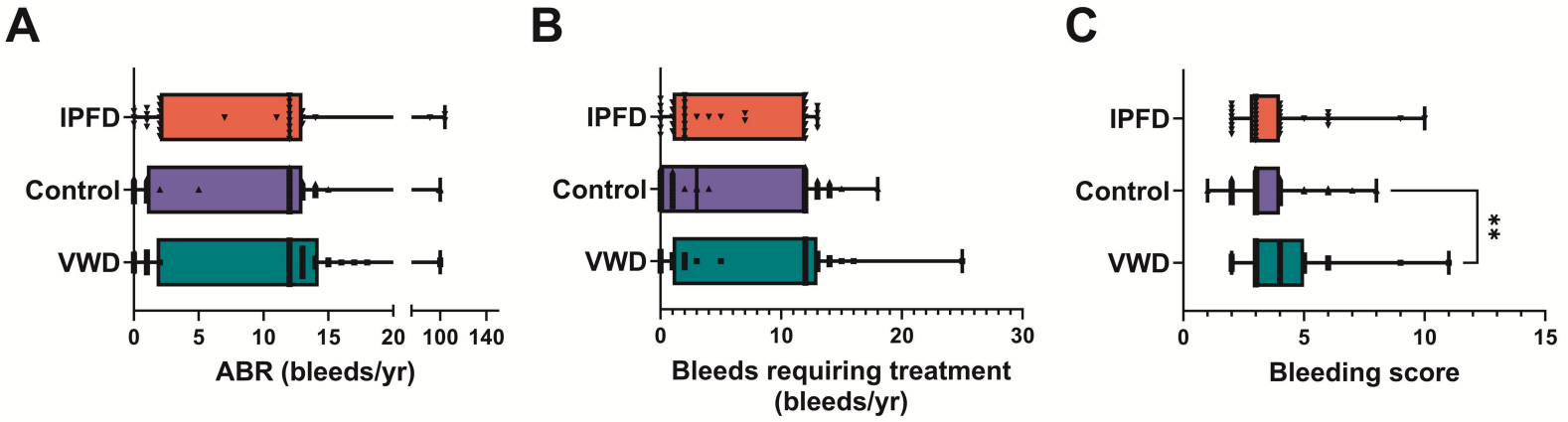
| Clinical Characteristics | *Control n=113* | *VWD n=46* | *IPFD n=34* |
|---|---|---|---|
| Age, y | 12 (IQR 7-14.5) | 13 (IQR 7.75-15.25) | 13.5 (IQR 5.75-15) |
| Gender, $n_{male}$ (%) | 35 (30.97%) | 10 (21.74%) | 19 (55.88%) |
| Location of bleed | - | - | - |
| *Cutaneous, n (%)* | 6 (5.31%) | 2 (4.35%) | 4 (11.76%) |
| *Mucosal, n (%)* | 94 (83.19%) | 38 (82.61%) | 21 (61.76%) |
| *Surgical, n (%)* | 13 (11.50%) | 6 (13.04%) | 9 (26.47%) |
| Treatment, yes % | 83 (73.45%) | 37 (80.43%) | 27 (79.41%) |
| ISTH-BAT, total | 3 (IQR 3-4) | 4 (IQR 3-5) | 3 (IQR 2.75-4) |
| ABR, total | 12 (IQR 1-13) | 12 (IQR 1.75-14.25) | 12 (IQR 2-13) |

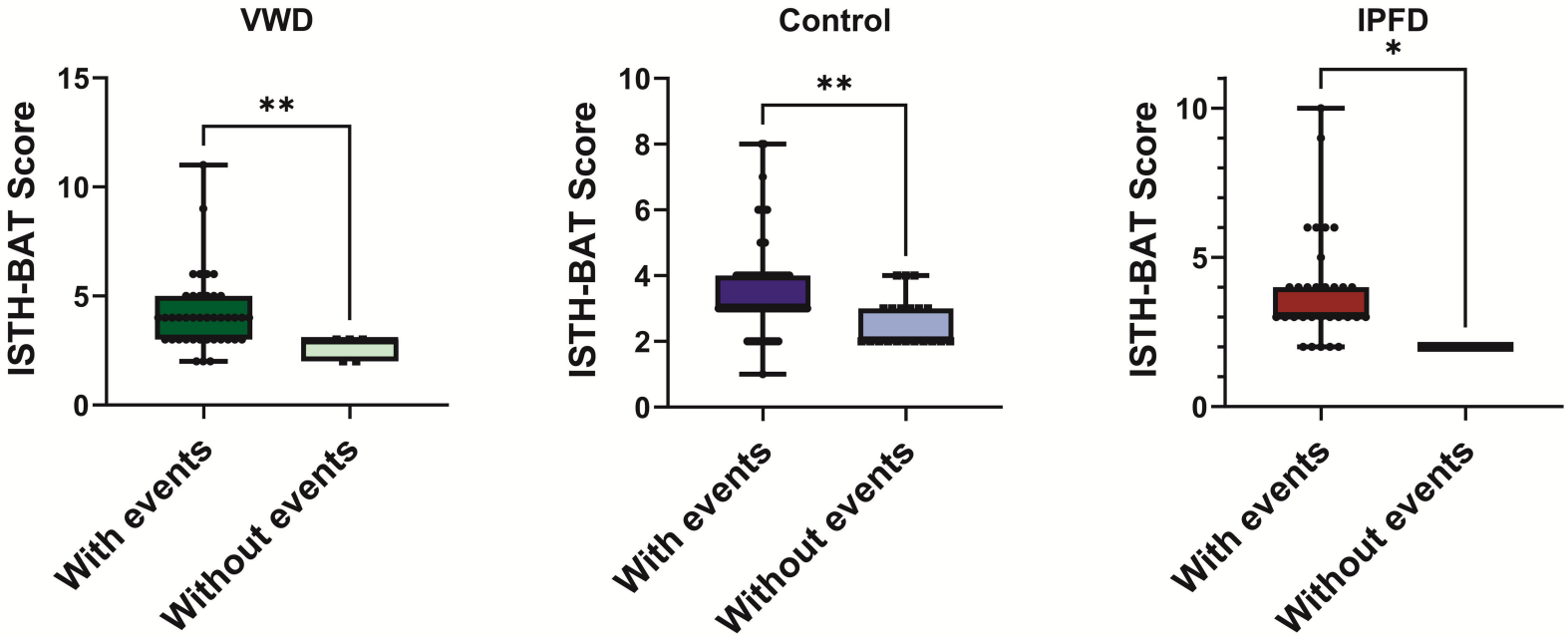
*VWD: von Willebrand Disease; IPFD: inherited platelet function disorder; IQR: interquartile range*

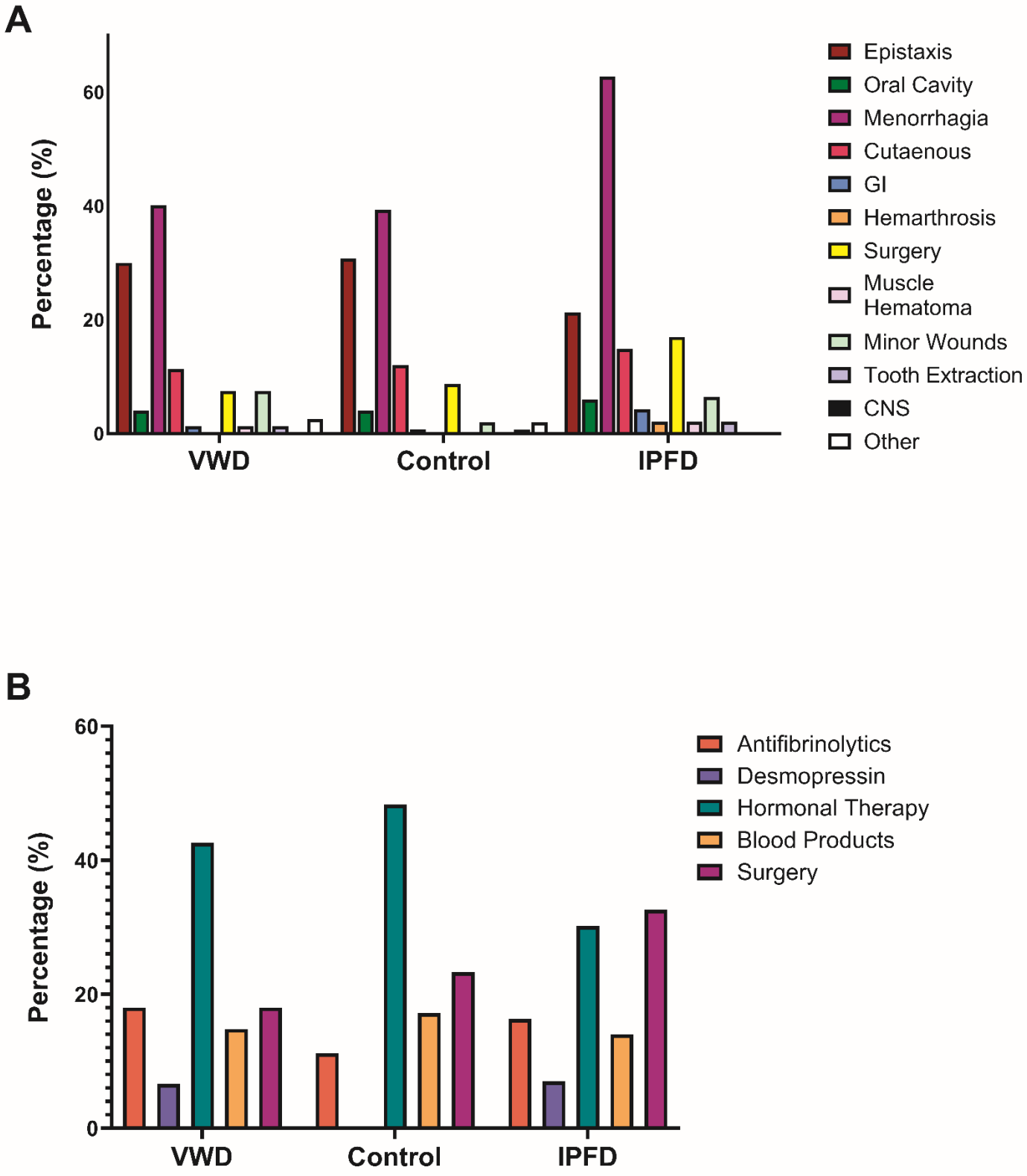
*Controls had a bleeding phenotype but no identifiable bleeding disorder on comprehensive laboratory evaluation.*

**Figure 1. ISTH Bleeding Assessment Tool (ISTH-BAT) bleeding score (BS), annual bleeding rate (ABR) and bleeds requiring treatment among study population.** (A) ABR, (B) bleeding events requiring treatment, and (C) ISTH-BAT BS between study group participants. Data are medians and interquartile ranges. **p < 0.01. VWD: von Willebrand Disease; IPFD: inherited platelet function disorder. *Controls had a bleeding phenotype but no identifiable bleeding disorder on comprehensive laboratory evaluation.*

**Figure 2. ISTH Bleeding Assessment Tool (ISTH-BAT) bleeding score between participants with and without clinically significant bleeding events in each study group**. Data are medians and interquartile ranges. *p < 0.05; **p < 0.01. VWD: von Willebrand Disease; IPFD: inherited platelet function disorder. *Controls had a bleeding phenotype but no identifiable bleeding disorder on comprehensive laboratory evaluation.*

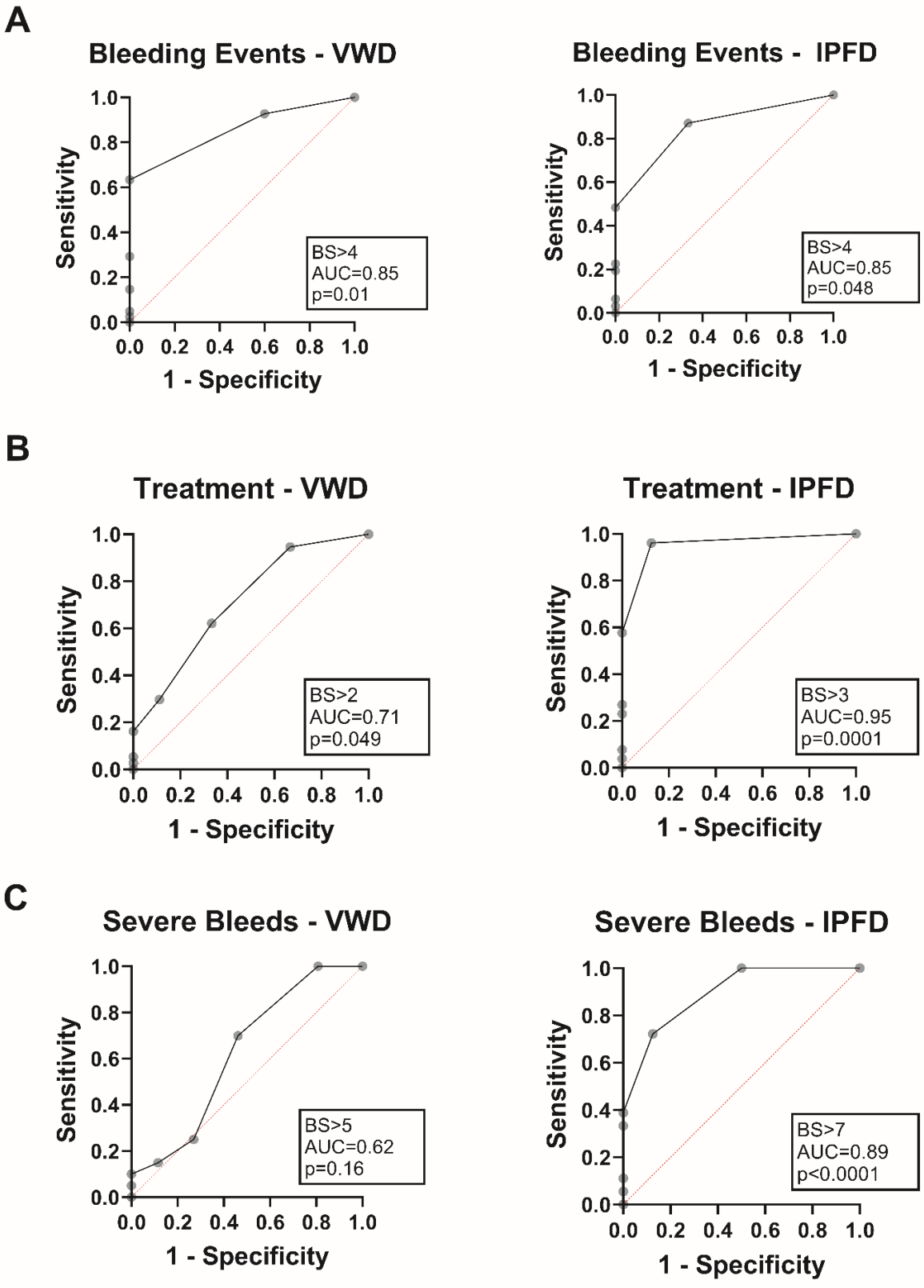

A
IPFD
Control
VWD
0
5
10
15
20
100
140
ABR (bleeds/yr)
B
IPFD
Control
VWD
0
10
20
30
Bleeds requiring treatment
(bleeds/yr)
C
IPFD
Control
VWD
**
0
5
10
15
Bleeding score


VWD
ISTH-BAT Score
15
10
5
0
**
With events
Without events
Control
ISTH-BAT Score
10
8
6
4
2
0
**
With events
Without events
IPFD
ISTH-BAT Score
10
5
0
*
With events
Without events



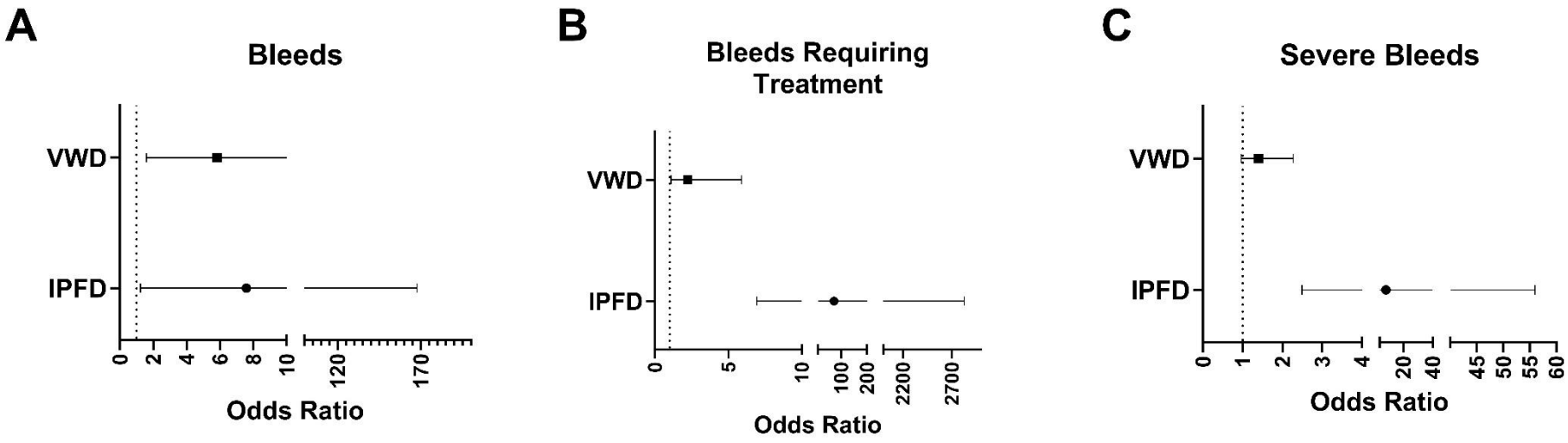

**Supplemental Figure 1. Frequency of different types of (A) hemorrhagic events and (B) treatments within each study group.** *Controls had a bleeding phenotype but no identifiable bleeding disorder on comprehensive laboratory evaluation.*

**Abbreviations**: VWD, von Willebrand Disease; IPFD, inherited platelet function disorder; GI, gastroenterological; CNS, central nervous system




**Supplemental Figure 2. ROC curves for prediction of bleeding outcomes.** ROC curves for the prediction of (A) bleeding events, (B) bleeds requiring treatment, and (C) severe bleeding events in IPFD and VWD subjects with a bleeding score (BS) above the indicated threshold.

**Abbreviations**: VWD, von Willebrand Disease; IPFD, inherited platelet function disorder; AUC, area under the curve




**Supplemental Figure 3**. **Odds ratio for likelihood of suffering bleeding outcomes**. Likelihood to suffer (A) clinically significant bleeding events, (B) bleeds requiring treatment, and (C) severe bleeds (odds ratio and 95% confidence interval) for subjects with a bleeding score above the identified cutoff.

**Abbreviations**: VWD, von Willebrand Disease; IPFD, inherited platelet function disorder