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Bleeding risk of surgery and its prevention in patients with inherited platelet disorders. The Surgery in Platelet disorders And Therapeutic Approach (SPATA) study.

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Bleeding risk of surgery and its prevention in patients with inherited platelet disorders. *The Surgery in Platelet disorders And Therapeutic Approach (SPATA) study.*

Running title: Surgery in inherited platelet disorders

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On behalf of European Hematology Association - Scientific Working Group (EHA-SWG) on thrombocytopenias and platelet function disorders

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Article summary

- Surgery-associated bleeding risk is high in inherited platelet disorders, especially in inherited platelet function disorders, and varies according to diagnosis and procedure
- Antihemorrhagic pre-operatory prophylaxis prevents excessive bleeding in most cases in IPFD but not in IPND.

ABSTRACT

Excessive bleeding at surgery is a feared complication in patients with inherited platelet disorders, however very few studies have evaluated the frequency of surgical bleeding in these hemorrhagic disorders. We performed a multicentric, retrospective worldwide study to assess the bleeding complications of surgery, the preventive and therapeutic approaches adopted and their efficacy in patients with inherited platelet disorders by rating the outcome of 829 surgical procedures carried out in 423 patients with well defined forms of inherited platelet disorders (238 inherited platelet function disorders and 185 inherited platelet number disorders). Frequency of surgical bleeding was high in patients with inherited platelet disorders (19.7%), with a significantly higher bleeding incidence in inherited platelet function disorders (24.8%) than in inherited platelet number disorders (13.4%). The frequency of bleeding varied according to the type of inherited platelet disorders, with biallelic Bernard Soulier syndrome having the highest occurrence (44.4%), and was predicted by a preoperative World Health Organization's bleeding score ≥2. Some types of surgery were associated with a higher bleeding incidence, like cardiovascular and urologic surgery. The use of preoperative prohemostatic treatments was associated with a lower bleeding frequency in patients with inherited platelet function disorders but not in inherited platelet number disorders. Desmopressin, alone or with antifibrinolytic agents, was the preventive treatment associated with lowest bleedings. Platelet transfusions were used more frequently in patients at higher bleeding risk. Surgical bleeding risk in inherited platelet disorders is substantial, especially in inherited platelet function disorders, and bleeding history, type of disorder, type of surgery and female gender are associated with higher bleeding frequency. Prophylactic preoperative prohemostatic treatments appear to be required and associated with a lower bleeding incidence.

INTRODUCTION

Inherited platelet disorders (IPDs) are a heterogeneous group of bleeding diseases of variable clinical severity associated with a reduction of platelet number (inherited platelet number disorders, IPNDs) and/or function (inherited platelet function disorders, IPFDs). Spontaneous hemorrhages are mainly mucocutaneous and rarely serious, while the hemorrhagic risk of trauma or surgery is not well defined[1-3].

Excessive bleeding at surgery is a feared complication of IPDs and is empirically prevented or treated with platelet transfusions, antifibrinolytic agents, desmopressin, or recombinant activated factor VII (rFVIIa), although evidence of the effectiveness of these measures is mostly anecdotal[4-7].

Two recent international collaborative studies have assessed the delivery-associated bleeding risk and pregnancy outcome in a large series of patients with well-defined forms of IPNDs or IPFDs and have shown that delivery-related maternal bleeding was more frequent in IPDs than in healthy pregnant women and that the degree of thrombocytopenia and history of severe bleeding were predictive of delivery-related hemorrhagic risk[8,9].

Although guidelines for the management of bleeding and of invasive procedures in patients with platelet disorders and/or thrombocytopenia have been generated[10,11] they were not based on objective data on the incidence of surgery-related bleeding, and thus were necessarily rather generic. Indeed, very few studies on surgery in IPDs have been carried out. One retrospective study including 44 children with mild bleeding disorders undergoing adeno-tonsillar procedures, among which 27 with an unspecific platelet function disorder, concluded that prophylactic treatment with desmopressin and tranexamic acid is effective in preventing perioperative bleeding[12]. Another retrospective study in 113 patients with congenital hemostatic disorders undergoing general surgery or endoscopic procedures, including five with platelet disorders, showed low morbidity and mortality rates with desmopressin pretreatment[13].

With regard to well defined IPFDs, surgery outcome was described mostly in case reports of patients with Glanzmann thrombasthenia (GT), Bernard Soulier syndrome (BSS), or Hermansky-Pudlak syndrome (HPS). Platelet transfusion for major surgery and antifibrinolytics for minor invasive procedures were reported as effective prophylactic measures for GT[14-16]. Surgery-related bleeding, when occurred, was successfully treated with rFVIIa[17-19] or platelet transfusions[15]. Platelet transfusions, alone or in combination with antifibrinolytics[20-22] or desmopressin [22], prevented bleeding in BSS patients, while platelet transfusions, alone[23] or in combination with rFVIIa[24], were used for HPS patients. However, no data on the rate of bleeding complications and its prevention can be drawn from these studies.

Concerning the prevention and treatment of surgical bleeding, the largest experience reported so far

is the recent evaluation of rFVIIa effectiveness and safety in 96 GT patients from an international observational registry, showing that rFVIIa, administered alone or together with platelet transfusions and/or antifibrinolytics, was effective for both minor and major surgery[25].

With regard to IPNDs, platelet transfusions and more recently eltrombopag have been reported to successfully prevent bleeding without side-effects in a few MYH9-related disease (MYH9-RD) patients[26-28].

Aim of the SPATA (Surgery in Platelet disorders And Therapeutic Approach) study was to evaluate the bleeding complications associated with surgical procedures, the therapeutic approaches adopted for the prevention and treatment of hemorrhage, and their efficacy in a large series of IPD patients diagnosed according to well-defined, standardized criteria and undergoing a wide range of invasive procedures. Here we report the results of the analysis of the outcome of 829 surgical interventions carried out in 423 patients with IPD.

METHODS

Study population

This study was promoted by the Scientific Working Group (SWG) on Thrombocytopenias and Platelet Function Disorders of the European Hematology Association (EHA). The Institutional Review Board of the coordinating center (CEAS Umbria, Italy) approved the study, each center complied with local ethical rules and all patients or their legal representatives signed a written informed consent.

Participating investigators were asked to review their records and extract data on surgery and invasive procedures carried out in patients with IPDs over the last years (median eight; IQR four-18 years) and to obtain additional data directly from the surgeon who carried out the intervention or, in case this was not possible, from the patient or his/her relatives. Only patients with a definite diagnosis of IPD confirmed according to well-defined laboratory and/or molecular genetic criteria[6,8-9] (**supplementary table 1 and 2**) were eligible for the study. IPDs were subdivided in IPNDs, when low platelet count was the main phenotypic characteristic (e.g. MYH9-RD), and IPFDs, when platelet dysfunction was the dominant phenotypic feature independently of platelet count (e.g. autosomal dominant GT-variant) (**Table 1**). Patients with acquired platelet disorders of any aetiology were excluded. All types of surgical procedures, including invasive diagnostic procedures (e.g. angiography, endoscopic and tissue biopsies) and dental extractions, were included. Caesarian sections were excluded because analysed in a previous study[8,9].

Surgical procedures were categorized post hoc as major surgery, minor invasive procedures and dental procedures according to the following criteria: major, any procedure in which a body cavity

was entered, a mesenchymal barrier was crossed, a facial plane was opened, an organ was removed or normal anatomy was altered; minor invasive, any operative procedure in which only skin, mucous membranes or superficial connective tissue were manipulated, gastroscopy, colonoscopy and similar; dental, i.e. extraction, abscess removal, apicectomy and similar[25].

Classification of bleeding

Bleeding history was assessed by the World Health Organization (WHO) bleeding assessment scale[29] and, when available, by the ISTH bleeding score scale[30]. Severity of surgical bleeding was defined according to three different criteria: the bleeding academic research consortium (BARC) classification, considering as excessive any bleeding with a BARC ≥ 2[31]; a subjective evaluation from the surgeon or, when not available, from the patient[8,9]; and duration (from less than six hours to more than three days), considered as excessive when >6 hours. Procedures associated with excessive bleeding according to any of the above three criteria were classified as any excessive bleeding (AEB).

When available, maximal drop of haemoglobin after surgery (g/dl) was registered.

Outcome of treatment of surgical bleeding was classified as successfully controlled, not responsive or re-bleeding. Not responsive was an excessive bleeding episode that the treatment(s) applied were not able to stop. Re-bleeding indicates a new episode of bleeding occurring at a later time point after the procedure.

Statistical analysis

Data are reported as medians and 25^{th}-75^{th} percentiles (IQR) when continuous and as counts and percentages when categorical. Logistic regression was used to assess the association between patient or surgery characteristics with bleeding outcome. Chi-square test and Cochran-Armitage's Trend Test were used to compare categorical data. The R software (R Foundation for Statistical Computing, Vienna, Austria. www.R-project.org) was used for all analyses. A two-sided $p<0.05$ was considered as statistically significant.

RESULTS

Patients' characteristics

Four hundred and twenty three patients (age 2 to 91 years; median 40; IQR 23.7-54; 56% females), with 25 different forms of IPDs (16 IPFDs and 9 IPNDs) enrolled by 49 centers across 17 countries underwent a total of 829 surgical procedures. Two hundred and thirty eight (56.3%; median age 36 years; 58% females), for a total of 455 procedures, had an IPFD and 185 (43.7%; median age 43

years; 53.5% females), for a total of 374 procedures, an IPND. Diagnosis and baseline characteristics are reported in **table 1**. In order of frequency IPFDs were GT, primary secretion defect, biallelic BSS (bBSS), δ granule deficiency, HPS, Gray platelet syndrome (GPS) and autosomal dominant GT-variant; while IPNDs in order were MYH9-related disorder, ANKRD26-related thrombocytopenia, monoallelic BSS (mBSS), ACTN1-related thrombocytopenia. Bleeding history was on average mild (WHO grade median 2, IQR 1-3), but 25% of patients had a WHO grade 3 (79.8% of which were IPFD) and 3.3% a WHO grade 4 (64.3% of which were IPFD) **(supplementary figure 1)**. Thrombocytopenia in IPNDs was on average mild (median $68x10^9$/L; IQR 30-81 $x10^9$/L) but 50% of patients had a platelet count $<50x10^9$/L and 25% $<30x10^9$/L. The ISTH BAT bleeding score was available for 143 patients (33.5%), with a median score of 3 in the overall IPD population (IQR 1-7), 6 (IQR 2-11.25) for IPFD (n=89) and 1 (IQR 0-1) for IPND (n=54).

Type of surgery and prophylactic treatments

Procedures were for 59.7% major surgeries, 28.1% dental and 12.2% minor invasive. Among major surgeries the most frequent procedures were abdominal (15.2%), otorhinolaryngologic (12.8%), gynecologic (6.8%) and orthopedic (6.8%). Median age at surgery was 31 years for both IPFDs (IQR 15-52) and IPNDs (IQR 14-47.5). In IPND, median platelet count at surgery was $56x10^9$/L (IQR 40-93). **Table 2** summarizes the characteristics of surgical procedures according to IPD diagnosis.

An anti-hemorrhagic prophylactic preoperative treatment was administered in 57.2% of the procedures, in particular in 80.6% of procedures in patients with IPFDs and in 20.6% of procedures in IPNDs. Frequency of use of preoperative prophylaxis was independent of type of the surgery, in fact for IPFDs 77.4% of major surgeries, 87.7% of minor invasive procedures and 82.8% of dental procedures were treated; for IPNDs 28.7%, 35.7% 26.3% respectively. On the contrary administration of a prophylactic treatment was positively correlated with preoperative WHO bleeding score (Cochran-Armitage trend test $p<0.0001$) (**Figure 1A**). Moreover, among IPNDs the use of prophylactic pro-haemostatic treatment was negatively associated with platelet count quartiles (Cochran-Armitage trend test $p<0.0001$) (**Figure 1B**).

Most frequently used prophylactic treatments were platelet transfusions (26.8% for IPFDs and 20.6% for IPNDs), followed by antifibrinolytic agents (11.2% for IPFDs and 4% for IPNDs), a combination of both (12.3% for IPFDs and 1.3% for IPNDs), desmopressin (8.1% for IPFDs and 1.1% IPNDs), desmopressin with antifibrinolytic agents (7.9% for IPFDs and 0% in IPND) and

FVIIa (5.9% for IPFDs and 0% for IPNDs) **(Table 3).** The use of prophylactic treatments according to diagnosis is reported in **Table 4.**

Platelet transfusions consisted of fresh platelets from random donors in 97.1% of cases, 34.2% of which HLA-matched, and of cryopreserved platelets in 2.9% of the procedures. In IPNDs platelet transfusions were used more frequently in patients with platelet counts $\leq 50 \times 10^9$/L (OR 2.73, 95% CIs 1.63-4.61, p=0.0001) and in those undergoing major surgery (OR 1.94, 95% CIs 1.10-3.42, p=0.02), while in IPFDs they were used more frequently in patients with a WHO≥2 (OR 2.22, 95% CIs 1.37-3.59 p=0.001) and in those undergoing major surgery (OR 1.45, 95% CIs 1-2.12, p=0.051).

Bleeding outcome

Excessive bleeding after surgery occurred in 163 of the surgical procedures in the overall IPD population (19.7%), when assessed by any of the predefined criteria (i.e. AEB), i.e. 1 episode of bleeding every 5 procedures. Excessive bleeding occurred in 15.3% of the procedures when scored as ≥2 by the BARC classification, in 15.3% when assessed by subjective evaluation and in 10.5% when defined by a duration ≥ 6 hours (**supplementary Figure 2**).

When the two populations were analyzed separately, AEB was reported almost twice as frequently in IPFDs, who suffered AEB in 24.8% of the procedures, than in IPNDs, for whom AEB was reported in 13.4% of the procedures. Haemoglobin drop was 1.29 g/dL (95% CIs 0.89-1.68) for IPFD (n=83), and 0.53 g/dL (95% CIs 0.17-0.89) for IPND (n=30) (p=0.005).

Among IPFDs, AEB was reported more frequently in bBSS (44.4%), FPD/AML (30.7%), GT (29.1%), HPS (27.3%), GPS (23.5%) and autosomal-dominant GT-variant (22.7%) than in the overall IPFD population. bBSS and GT patients received pre-operative prophylactic treatment in 97.2% and 90.6% of procedures, respectively, emphasizing the perceived high surgical bleeding risk associated with these disorders.

Among IPNDs, AEB was reported more frequently in MYH9-RD patients (15.5%) than in the overall IPND population. The distribution of bleeding outcomes in the individual IPDs is shown in **supplementary Table 3**.

Frequency of excessive bleeding in the overall IPD population was 21.8% after major surgery, 23.8% after minor invasive procedures and 13.3% after dental procedures, (for IPFDs 28.6%, 28.8% and 15.7%, respectively, and for IPNDs 15%, 10.7% and 10.1%).

In the overall IPD population, AEB was reported more frequently after cardiovascular surgery (47.1%), followed by urological (34.2%), gynaecologic (26.8%), otorhinolaryngologic (24.5%), plastic (21.4%), eye (20%), and abdominal (19.8%) surgery. Incidence of bleeding in the different IPD populations according to the type of surgery is shown in **Table 5**.

AEB, occurring during the first procedure was a risk factor for the recurrence of bleeding during a second (IPFD: OR 6.7, 95% CI 2.3-18.9, p=0.0004; IPND: OR 3.82, 95% CI 1.09-13.4, p=0.0357) or third procedure (IPFD: OR 10, 95% CI 1.1-90.6, p=0.04; IPND: OR 27, 95% CI 2.2-324.9, p=0.0094).

Characteristics associated with post surgical bleeding

A significant association was found between the frequency of AEB and clinical bleeding history assessed by the WHO bleeding score, both in the overall IPD population (WHO 1=OR 2.6; 95% CIs 1.0-6.9; WHO 2=OR 5.7; 95% CIs 2.4-13.6; WHO 3=OR 11.2; 95% CIs 4.7-26.7; WHO 4=OR 17.5; 95% CIs 5.6-54.7) and in the two populations analysed separately (**Figure 2A, Table 6**).The association between the WHO bleeding score and AEB remained also when procedures were subdivided in major, minor invasive and dental (**Figure 2B**).

Among IPFDs, a higher frequency of postsurgical bleeding was observed in females (**Table 6**). To exclude that this might be due to the relatively high bleeding rate associated with gynaecological procedures, we re-evaluated the association between sex and AEB after excluding gynaecological procedures. Results confirmed that female sex is a risk factor for postsurgical bleeding in IPFDs (OR 1.70 (1.05-2.77), p=0.03).

A higher frequency of postsurgical bleeding was observed in some disorders, like bBSS, GT and HPS (**supplementary Table 4**).

Finally, in IPND a platelet count below the median ($68x10^9$/L) and an age ≥70 were associated with a significantly higher frequency of post-surgical bleeding (**table 4**).

Efficacy of prophylactic treatments

The use of a prophylactic anti-hemorrhagic preparation was associated with a markedly reduced frequency of surgical bleeding in IPFDs (OR 0.38; 95% CIs 0.23-0.63) (**Table 6**).

Indeed, AEB was reported more frequently in patients not receiving a prophylactic treatment than in those receiving it (40.9% vs 21%, p<0.01).

Post-surgical bleeding was lowest in desmopressin-treated patients (AEB in 8.1% of procedures, OR 0.13; 95% CIs 0.04-0.45, as compared with no treatment), followed by desmopressin and antifibrinolytic agents (8.3%, OR 0.13; 95% CIs 0.04-0.46), antifibrinolytic agents alone (17.6%, OR 0.31; 95% CIs 0.13-0.71), antifibrinolytic agents and platelet transfusions (17.8%, OR 0.31; 95% CIs 0.14-0.70), and rFVIIa (18.5%, OR 0.33; 95% CIs 0.11-0.95). Platelet transfusions alone, the majority of which however were given to patients with WHO≥3 (86.8%) and/or undergoing major surgery (68.4%), were not associated with a lower frequency of AEB (31.1%).

Information about platelet transfusion modalities was obtained for 123 out of 276 procedures in which these were used. The median platelet transfusion dose was 4 units (2-8), significantly higher in IPFDs (5; 4-8) that in IPNDs (2.5; 1-4) (p=0.0007). The median time of administration before the procedure was 1 hour (range few minutes to 3 days). Among GT patients, the dose of platelet transfusions was recorded in 58 procedures: AEB was reported in 12 of them (20.7%) and occurred more frequently when the amount of platelets transfused was <6 units (9/12, 75%) than when it was >6 units (3/12; 25%) (p=0.04 by χ^2). Moreover, information about platelet refractioness and/or antiplatelet antibody positivity was obtained for 42 GT patients undergoing 143 invasive procedures prophylaxed with platelet transfusions. The bleeding rate (AEB) was 23.3% in those without and 37.5% in those with a history of platelet refractoriness or anti-platelet antibodies (p=ns).

Differently from IPFDs, prophylactic treatments did not seem to modify surgery-related bleeding frequency in IPNDs, since, indeed, AEB was reported in 12.7% of the procedures carried out without preparation (34/267) and in 14.9% of the procedures carried out with pre-operative prophylaxis (16/107). But actually, antifibrinolytic agents were associated with a lower post-surgical bleeding frequency in IPNDs (AEB in 6.7% of procedures), while other treatments were not. In particular, platelet transfusions were not associated with lower post-surgical bleeding, although it must be considered that they were mainly given to patients undergoing major surgery.

Treatment of bleeding and outcome

Surgical procedures followed by AEB received an emergency treatment in 86.7% of the cases (98/113) for IPFDs (platelet transfusions 60.2%, antifibrinolytic agents 17.3%, other 11.2%, FVIIa 6.1%), and in 62% for IPNDs (31/50) (other 41.9%, platelet transfusions 38.7%, and antifibrinolytic agents 19.3%). Treatment of bleeding according to disorder and type of surgery is reported in **supplementary Table 4**. Successful control was obtained in 73.4% of IPFDs and in 58% of IPNDs. The most effective treatments were antifibrinolytic agents (88.2% of bleedings controlled, 15/17), platelet transfusions (83% of bleedings controlled, 49/59), and other treatments (fresh frozen plasma, stitches, ice, compression and dressing) (100% of bleedings controlled, 10/10) for IPFDs, while they were platelet transfusions (100% of bleedings controlled, 12/12), followed by other treatments (surgical hemostasis, packing, compression, stitches) (92.3% of bleedings controlled, 12/13), and antifibrinolytic agents (83.3% of bleedings controlled, 5/6) for IPNDs.

In 21 procedures carried out in 18 patients (12.9% of the procedures with AEB) outcome of bleeding was unfavorable (19 re-bleeding, 2 not responding to treatment). Of these, 80.9% occurred in IPFD (12 GT, 1 bBSS, 1 primary secretion defect, 1 CalDAG-related platelet disorder, 1 GPS, 1 defect of TP receptor) and 19.1% in IPNDs (3 MYH9-RD, 1 ANKRD-26 related

thrombocytopenia). Among these patients, one had a WHO=0, nine a WHO =2, 10 a WHO= 3 and 1 a WHO=4. The majority of these procedures (15) were major surgeries, but 3 were colonoscopy with polypectomy, 2 dental procedures and one an enteroscopy for an angiodysplasia and in 76.2% of them prophylaxis had been administered before surgery. Re-bleeding was treated mainly with platelet transfusions and/or antifibrinolytic agents and resolved in all but two cases, a 32 year old man with GT undergoing partial lung resection for recurrent severe hemoptysis and a 51 year old man with MYH9-RD undergoing endovascular treatment of an intracranial aneurysm for whom the outcome was death.

DISCUSSION

Although IPDs are conventionally considered as rare, annually at least 14,000 patients worldwide undergo investigations for a suspected IPD and over 5,600 new diagnoses are made[2]. It is therefore not an unexpected evenience that a surgeon may deal with a patient with an IPD, and the knowledge of the bleeding risks associated with the distinct invasive procedures and the different platelet disorders may be of great help to guide surgical management.

Our study with 829 surgical procedures in 423 patients represents the largest experience reported so far on surgery in patients with IPDs.

It turns out that the frequency of excessive bleeding associated with surgery in patients with IPD is substantial, varying from 9.9% to 19.7% depending on the definition used. In particular, it strikingly emerges that bleeding frequency is almost double in platelet function disorders compared with thrombocytopenias, ranging from 15.4% to 24.8% depending on the definition used. The frequency of AEB appeared to be especially high for some disorders, including bBSS, FPD/AML, GT and HPS, with up to 44.4% of the procedures eliciting excessive bleeding.

Some of the findings of the present study provide novel and relevant clinical information on the bleeding risk associated with IPFDs. In fact, while a high bleeding risk of GT and bBSS is generally accepted, the high frequency of surgery-associated bleeding in HPS, FPD/AML, GPS and autosomal-dominant GT-variants was unexpected because they are commonly considered as non-severe. However, it can not be excluded that AEB in these patients was due to the infrequent use of a preoperative prophylactic treatment probably consequent to the assessment of these disorders as mild. Other IPFDs too, like PT-VWD, TXA_2 receptor defect and CalDAG-related platelet disorder, suffered frequent post-surgical bleedings, although this observation can be considered only as anecdotal given the scarce number of patients enrolled. On the other hand, other IPFDs showed a low bleeding risk, like collagen receptor defects, δ-granules deficiency and primary secretion

defects. Given that preoperative prophylaxis was administered in only 37.5% of the procedures in patients with collagen receptors defects, these seem indeed mild disorders.

IPNDs were associated with infrequent surgical bleeding, ranging from 5.4% to 13.3% depending on definition, with no significant differences among the different disorders.

Given that 21% of the enrolled patients were GT, and that a prophylactic treatment was administered in 90.7% of the procedures carried out in this patient subgroup, the impact of this on the overall analysis was evaluated by excluding the procedures carried out in GT. AEB in the remaining IPFD population was 21.9%, not significantly different from the 24.8% observed in the total IPFD population (p=ns by χ^2).

The same procedure was applied to IPNDs by excluding MYH9-RD: AEB in the remaining IPND population was 11.9%, not different from the 13.4% of the total IPND population (p=ns by χ^2).

In IPNDs 68 $x10^9$/L platelets was the threshold below which bleeding rate increased significantly, a value quite similar to that previously identified as predictive of bleeding at childbirth[8].

In the overall IPD population, bleeding history was highly predictive of surgical bleeding, in fact a WHO ≥2 was associated with an over than four-fold increased bleeding rate. Moreover, bleeding occurring after the first surgical procedure strongly predicted the rate of bleeding in subsequent procedures.

Of note, bleeding tendency was higher in IPFDs than in IPNDs, with 79.8% of patients with a WHO grade 3 and 64.3% with a WHO grade 4 being IPFD[8,9,32]. Similarly, in the subgroup of patients for whom the ISTH BAT bleeding score was available this was highly predictive of post-surgical bleeding, with a ISTH BAT ≥6 associated with a strongly increased bleeding risk.

Some types of surgery were associated with higher bleeding, like cardiovascular or urologic surgery. On the other hand, also minor invasive procedures were associated with bleeding, suggesting that prophylactic measures need to be applied also to procedures such as a gastroscopy with biopsy.

Administration of an anti-hemorrhagic prophylactic treatment was associated with a reduced bleeding frequency in the IPFD population but not in IPND. This seems to be reflected in the current practice, likely based on expert consultation, given that patients with IPFDs in our study were for the vast majority prophylaxed (80.6%), while patients with IPND were prophylaxed only occasionally (20.6%).

The apparent lower efficacy of preoperative prophylaxis in IPND patients may derive from the lower absolute bleeding risk in this subpopulation, with consequent lower statistical power to detect reduced bleeding in prophylaxed subjects, and/or by the use of milder prophylactic measures (lower dosage, shorter duration, etc..) due to the perception of a lower bleeding risk.

On the other hand, the choice of the preventive measures did not appear to be always appropriate,

since platelet transfusions, the most frequently used prophylactic treatment, revealed to be poorly effective, with bleeding occurring in 30.1% of the procedures in which they were used. These data are in agreement with previous findings in pregnancy[8,9]. However, it should be considered that platelet transfusions were most frequently used in patients with severe bleeding disorders and/or undergoing major surgery and that the mode of administration of platelet transfusions was rather heterogeneous and possibly sometimes incongruous. These observations suggest that the way platelet transfusions are employed (amount, type, timing) is often inappropriate[33,34]

The most effective prophylactic treatment was desmopressin, alone or in combination with antifibrinolytic agents, while antifibrinolytic agents used alone were less effective. In particular, desmopressin was prophylactically employed in 88 procedures (10.3% minor invasive, 26.1% dental and 63.6% major procedures) only 6 of which were followed by AEB (7%), 4 of which (66.7%) after major surgeries and 2 (33.3%) dental procedures. Interestingly, 31.9% (28/88) of patients in whom DDAVP was employed had a severe bleeding history (WHO=3) and only 3 of them suffered AEB, data supporting the efficacy of this pro-haemostatic treatment for IPFDs, even for the more severe conditions.

FVIIa, an approved treatment for GT, resulted to be a good prophylactic measure, in line with previous results[25]. In our cohort of patients FVIIa alone was prophylactically employed in 36 patients, 32 of whom were GT. 55% of these patients had a WHO = 1 or 2, 33% had a WHO=3 and 2.7% had a WHO=4 and underwent in 27.8% of cases to minor invasive procedures, 47.2% to dental procedures and in 25% to major procedures. These data suggest that FVIIa is efficacious also for severe cases and when used alone.

Although we do not have data from the current study on the safety of the prophylactic measures, previous experience suggests that they are generally well tolerated. Mild adverse effects of desmopressin may include headache, nausea and hypotension, although sometimes more serious side effects, such as hyponatremia and renal dysfunction, may occur. After antifybrinolytic agents allergic or anaphylactic reactions and sometimes headache may occur. Finally, pro-hemostatic agents, and in particular recombinant FVIIa, may predispose to thrombotic complications, however the latter are relatively rare and depend on the thrombotic risk profile of the patient and the procedure[5,35].

Finally, treatment of surgical bleeding was successful in most IPFD cases (73.4%), and in a slightly lower number of IPND cases (58%).

Our study has several limitations. First, it is retrospective, with all the inaccuracies in data collection that this may imply. However, the submitted questionnaire was strongly structured, with mandatory fields and pre-defined possible replies, ensuring a high degree of standardization;

moreover, the large number of patients and procedures collected strengthen the conclusions. Second, a comparative population of normal subjects undergoing the same invasive procedures would have provided a better quantification of the excess surgical bleeding risk. This was indeed planned in the study protocol, but it was impossible to collect enough control cases. However, for the few surgical procedures in healthy controls collected, frequency of post-surgical bleeding was strikingly lower (1/34; 3%), and similar to the estimated hemorrhagic complications rate of surgery (1.4% to 6%) in otherwise healthy subjects[30,36]. Third, for specific disorders, such as CalDAG-related platelet disorder, combined α/δ granule deficiency, and Scott syndrome, the exact bleeding risk could not be estimated, because only a few procedures were available, reflecting their rarity. However, our results provide a first useful hint of the surgical bleeding phenotype of these forms. Fourth, we do not have information about possible side effects of the pro-haemostatic procedures employed, about other concomitant factors that may have increased the risk of surgical bleeding (for example blood pressure, acquired coagulopathy, VWD, abnormalities of whole cell count).

In conclusion, our study shows that surgery-related bleeding risk is substantial in IPDs, especially in IPFDs, that the bleeding history, some specific disorders and female gender are predictors of the bleeding risk, and that some types of invasive procedures are at particularly high risk. Importantly, prophylactic treatment is associated with a significant reduction of the bleeding frequency in IPFDs.

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AUTHORSHIP CONTRIBUTIONS

PG, MC, RF, PH, PN and NS conceived and designed the study; PN LB, PH, CS, RAK, NB, EF, ARC, FF, MF, KM, JR, PZ, CF, GP, NB, RF, YH, EDM, EDC, ADM, NO, IE, PN, SB, MPL, JB, BZ, AT, FM, CLB, MC, NS and PG collected cases and provided study materials; LB, SO and EF assembled data; SO analyzed data; LB, SO and PG wrote the manuscript. All authors revised and gave final approval of the manuscript.

CONFLICT OF INTEREST DISCLOSURES

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Table 1. Diagnosis and features of included patients

IPFD	N (% of total)	Females (%)	AGE (median-IQR)	Platelet count (x10^9/L) (median-IQR)	WHO (median-IQR)
Glanzmann thrombasthenia	89 (37.4)	53.9	33 (19-47)	245 (172-297)	3 (2-4)
Primary secretion defect	46 (19.3)	56.5	29 (14-46)	219 (160-272)	1.5 (1-3)
Bernard-Soulier Syndrome (biallelic)	17 (7.1)	58.8	34 (21-49)	33 (20-39)	3 (2-3)
Delta granule deficiency	17 (7.1)	82.3	50 (37-59)	197 (141-232)	2 (1.75-3)
Hermansky–Pudlak syndrome	11 (4.6)	54.5	31 (24-50)	261 (228-321)	2 (1-2.5)
Gray platelet syndrome	10 (4.2)	30	31 (21-58)	65 (56-85)	2 (2-2)
Autosomal dominant GT-variant	10 (4.2)	90	45 (42-53)	85 (62-110)	1 (0.25-2)
Familial platelet disorder and predisposition to acute myelogenous leukemia	8 (3.4)	50	38 (24-51)	102 (93-139)	2 (1.75-2.25)
Defects in α2-adrenergic receptor	6 (2.5)	33.3	19 (11-43)	178 (146-239)	1 (0.25-1.75)
Defects in collagen receptors	5 (2.1)	60	30 (23-59)	184 (126-256)	1 (0-2)
P2Y12 deficiency	5 (2.1)	40	36 (27-78)	190 (183-195)	2 (2-2)
Platelet-type Von Willebrand Disease	4 (1.7)	100	41 (31-52)	130 (113-168)	3 (2.75-3)
Defect of thromboxane A2 receptor	3 (1.3)	66.7	33 (29-52)	166 (129-169)	2 (2-2.5)
Scott syndrome	3 (1.3)	100	74 (58-75)	340 (-)*	1.5 (0.75-3)
CalDAG-related platelet disorder	2 (0.8)	50	54 (53-56)	267 (251-284)	3 (3-3)
Combined alpha-delta granule deficiency	2 (0.8)	50	52 (44-61)	85 (78-92)	0 (0-0)
TOTAL	**238 (56.3% of 423)**	**58**	**36 (20-50)**	**191.5 (113-266)**	**2 (1-3)**

IPND	N (% of total)	Females (%)	AGE (median-IQR)	Platelet count (x10^9/L) (median-IQR)	median (IQR)
MYH9-related disease	75 (40.5)	57.3	41 (31-56)	38 (22-50) [1]	1 (0-2)
ANKRD26-related thrombocytopenia	39 (21.1)	41	48 (38-67)	40 (29-54) [2]	1 (0-2)
Bernard-Soulier Syndrome (monoallelic)	34 (18.4)	61.7	49 (42-60)	82 (61-105) [3]	1 (0-2)
ACTN1-related thrombocytopenia	17 (9.2)	76.4	43 (35-51)	93 (72-118) [4]	1 (0-2)
X-linked thrombocytopenia	7 (3.8)	0	29 (16-36)	34 (24-34)	1 (1-2)
Thrombocytopenia with absent radii	5 (2.7)	40	26 (17-30)	20 (16-31)	2 (0-2)
Paris-Trousseau thrombocytopenia	4 (2.2)	25	12 (7-16)	52 (18-115)	0.5 (0-1)
Congenital amegakaryocytic thrombocytopenia	2 (1.1)	50	9 (6-11)	61 (61-61)	1 (1-1)
FLNA-related thrombocytopenia	2 (1.1)	100	40 (33-47)	34 (29-38) [5]	1 (0.5-1.5)
TOTAL	**185 (43.7% of 423)**	**53.5**	**43 (32-59)**	**50 (30-81)**	**1 (0-2)**

Platelet count microscopic (x10^9/L): [1]55 (36-72); [2]50 (33-70); [3]91 (82-121.5); [4]110 (93-129); [5]55.5 (47.25-63.75). * only one count available

Table 2. Characteristics of surgical procedures according to diagnosis.

IPFD	N (% of total)	AGE at surgery (median-IQR)	major surg (%)	minor surg (%)	dental proc (%)
Glanzmann thrombasthenia	182 (40)	31 (13-50)	43.9	15.4	40.7
Primary secretion defect	76 (16.7)	26 (8-40)	69.7	10.5	19.7
Bernard-Soulier Syndrome (biallelic)	36 (7.9)	30 (16-49)	52.8	19.4	27.8
Delta granule deficiency	36 (7.9)	50 (35-55)	72.2	13.9	13.9
Hermansky–Pudlak syndrome	22 (4.8)	16 (12-24)	63.6	18.2	18.2
Autosomal dominant GT-variant	22 (4.8)	23 (11-33)	63.6	0	36.4
Gray platelet syndrome	17 (3.7)	60 (22-69)	52.9	23.5	23.5
Defects in collagen receptors	16 (3.5)	10 (7-47)	56.2	12.5	31.2
Familial platelet disorder and predisposition to acute myelogenous leukemia	13 (2.8)	28 (20-48)	61.5	23.1	15.4
Defects in α2-adrenergic receptor	9 (1.9)	36 (22-44)	44.4	22.2	33.3
P2Y12 deficiency	9 (1.9)	73 (72-76)	33.3	66.7	0
Defect of thromboxane A2 receptor	5 (1.1)	24 (21-30)	80	0	20
Platelet-type Von Willebrand Disease	5 (1.1)	34 (30-38)	40	40	20
Scott syndrome	3 (0.7)	74 (73-76)	66.7	33.3	0
CalDAG-related platelet disorder	2 (0.4)	30 (28-31)	50	0	50
Combined alpha-delta granule deficiency	2 (0.4)	-	0	50	50
TOTAL	**455 (54.9% of 829)**	**31 (15-52)**	**54.5**	**16**	**29.5**

IPND	N (% of total)	AGE at surgery (median-IQR)	major surg (%)	minor surg (%)	dental proc (%)
MYH9-related disease	148 (39.6)	28 (12-47)	64.9	6.7	28.4
ANKRD26-related thrombocytopenia	89 (23.8)	35 (19-50)	70.8	2.2	26.9
Bernard-Soulier Syndrome (monoallelic)	74 (19.8)	34 (20-51)	67.6	12.2	20.3
ACTN1-related thrombocytopenia	39 (10.4)	30 (9-44)	66.7	10.3	23.1
X-linked thrombocytopenia	9 (2.4)	20 (17-26)	44.4	0	55.5
Thrombocytopenia with absent radii	6 (1.6)	16 (10-27)	50	33.3	16.7
Paris-Trousseau thrombocytopenia	5 (1.3)	1 (1-4)	80	0	20
Congenital amegakaryocytic thrombocytopenia	2 (0.5)	8 (6-11)	50	50	0
FLNA-related thrombocytopenia	2 (0.5)	23 (17-28)	0	0	100
TOTAL	**374 (45.1% of 829)**	**31 (14-47)**	**66**	**7.5**	**26.5**

Table 3. Prophylactic treatments according to disease category and type of surgery.

	IPD		IPFD		IPND		Major surg		Minor surg		Dental proc	
Prophylaxis	**N (%)**	**% AEB**	**N (%)**	**% AEB**	**N (%)**	**% AEB**	**N (%)**	**% AEB**	**N (%)**	**% AEB**	**N (%)**	**% AEB**
None	355 (42.8)	19.7	88 (19.3)	40.9	267 (71.4)	12.7	232 (46.9)	20.8	27 (26.7)	21.4	96 (41.2)	16.7
Any:	474 (57.2)	19.6	367 (80.7)	20.9	107 (28.6)	14.9	263 (53.1)	22.8	74 (73.3)	24.3	137 (58.8)	10.9
- PT	199 (24)	26.3	122 (26.8)	31.4	77 (20.5)	18.2	137 (27.7)	29.2	33 (32.7)	33.3	29 (12.4)	3.6
- AA	66 (8)	15.1	51 (11.2)	17.6	15 (4)	6.7	15 (3.0)	6.7	12 (11.9)	33.3	39 (16.7)	12.8
- PT+AA	61 (7.4)	16.1	56 (12.3)	17.5	5 (1.3)	0	30 (6.1)	20.0	8 (7.9)	25.0	23 (9.9)	8.3
- DDAVP	41 (4.9)	7.3	37 (8.1)	8.1	4 (1.1)	0	17 (3.4)	17.6	8 (7.9)	0	16 (6.9)	0
- DDAVP+AA	36 (4.3)	8.3	36 (7.9)	8.3			31 (6.3)	3.2			5 (2.1)	40.0
- FVIIa	27 (3.3)	18.5	27 (5.9)	18.5			7 (1.4)	14.3	9 (8.9)	11.1	11 (4.7)	27.3
- Other	17 (2.1)	35.3	11 (2.4)	45.4	6 (1.6)	16.7	12 (2.4)	33.3	2 (2.0)	0	3 (1.3)	66.7
- PT+AA+DDAVP	8 (1)	0	8 (1.7)	0			6 (1.2)	0			2 (0.9)	0
- FVIIa+AA	7 (0.8)	14.3	7 (1.5)	14.3			1 (0.2)	100	1 (1.0)	0	5 (2.1)	0
- PT+ Other	4 (0.5)	50.0	4 (0.9)	50.0			3 (0.6)	66.7			1 (0.4)	0
- AA+Other	3 (0.4)	33.3	3 (0.7)	33.3			1 (0.2)	100				
- PT+DDAVP	2 (0.2)	0	2 (0.4)				2 (0.4)	0				
- FVIIa+AA+ Other	1 (0.1)	0	1 (0.2)						1 (1.0)	0		
- PT+DDAVP+ Other	1 (0.1)	0	1 (0.2)								1 (0.4)	0
- PT+FVIIa	1 (0.1)	0	1 (0.2)				1 (0.2)	0				
TOTAL	**829**	**19.66**	**455**	**24.84**	**374**	**13.37**	**495**	**21.86**	**101**	**23.53**	**233**	**13.30**

PT=Platelet transfusion; AA= Antifibrinolytic agents; Other: cryoprecipitate; fibrin-glue. fibrinogen. FFP. IVIG. local hemostatic agent. suture. local tranexamic acid (for IPFD); Eltrombopag. fresh frozen plasma. IVIG. local hemostatic agent. prophylactic surgical haemostasis (for IPND).

Table 4. Prophylactic treatments according to diagnosis.

IPFD	Prophylaxed/total (% of treated)	PT (%)	AA (%)	PT+AA (%)	DDAVP (%)	DDAVP +AA (%)	FVIIa (%)	Other (%)
Glanzmann thrombasthenia	155/182 (90.7)	54 (34.8)	30 (19.3)	35 (22.6)	6 (3.9)	(0)	24 (15.5)	6 (3.9)
Primary secretion defect	62/76 (85.5)	9 (14.5)	9 (14.5)	6 (9.7)	15 (24.2)	23 (37.1)	(0)	(0)
Bernard-Soulier Syndrome (biallelic)	34/36 (97.2)	26 (76.5)	1 (2.9)	3 (8.8)	1 (2.9)	2 (5.9)	(0)	1 (2.9)
Delta granule deficiency	25/36 (83.3)	2 (8)	3 (12)	6 (24)	5 (20)	9 (36)	(0)	(0)
Hermansky–Pudlak syndrome	11/22 (50)	4 (36.4)	1 (9.1)	1 (9.1)	4 (36.4)	(0)	1 (9.1)	(0)
ITGA2B/ITGB3-related thrombocytopenia	6/22 (36.4)	2 (33.3)	2 (33.3)	2 (33.3)	(0)	(0)	(0)	(0)
Gray platelet syndrome	12/17 (70.6)	8 (66.7)	2 (16.7)	(0)	(0)	1 (8.3)	(0)	1 (8.3)
Defects in collagen receptors	6/16 (37.5)	(0)	1 (16.7)	(0)	2 (33.3)	(0)	1 (16.7)	2 (33.3)
Familial platelet disorder and predisposition to acute myelogenous leukemia	6/13 (61.5)	4 (66.7)	1 (16.7)	1 (16.7)	(0)	(0)	(0)	(0)
Defects in α2-adrenergic receptor	7/9 (77.8)	3 (42.9)	1 (14.3)	1 (14.3)	2 (28.6)	(0)	(0)	(0)
P2Y12 deficiency	7/9 (77.8)	5 (71.4)	(0)	(0)	1 (14.3)	(0)	(0)	1 (14.3)
Defect of thromboxane A2 receptor	3/5 (60)	(0)	(0)	1 (33.3)	1 (33.3)	1 (33.3)	(0)	(0)
Platelet-type Von Willebrand Disease	1/5 (40)	1 (100)	(0)	(0)	(0)	(0)	(0)	(0)
Scott syndrome	3/3 (100)	2 (66.7)	(0)	(0)	(0)	(0)	1 (33.3)	(0)
CalDAG	2/2 (100)	2 (100)	(0)	(0)	(0)	(0)	(0)	(0)
Combined alpha-delta granule deficiency	0/2 (0)							
TOTAL	**455 (80.7)**	**122**	**51**	**56**	**37**	**36**	**27**	**11**

IPND	Prophylaxed/total (% of treated)	PT (%)	AA (%)	PT+AA (%)	DDAVP (%)	DDAVP +AA (%)	FVIIa (%)	Other (%)
MYH9-related disease	53/148 (35.8)	42 (79.2)	8 (15.1)					3 (5.6)
ANKRD26-related thrombocytopenia	24/89 (27)	18 (75)	1 (0.4)	1 (0.4)	3 (12.5)			1 (0.4)
Bernard-Soulier Syndrome (monoallelic)	13/74 (17.6)	7 (53.8)	5 (38.5)					1 (7.7)
ACTN1-related thrombocytopenia	0/39 (0)							
X-linked thrombocytopenia	6/9 (66.7)	2 (33.3)		3 (50)				1 (16.7)
Thrombocytopenia with absent radii	4/6 (66.7)	3 (75)		1 (25)				
Paris-Trousseau thrombocytopenia	5/5 (100)	3 (60)	1 (20)		1 (20)			
Congenital amegakaryocytic thrombocytopenia	2/2 (100)	2 (100)						
FLNA-related thrombocytopenia	0/2 (0)							
TOT	**374 (28.6)**	**77**	**15**	**5**	**4**			**6**

Prophylactic treatments with sample size <10 not shown. PT=Platelet transfusion; AA=Antifibrinolytic agents; Other: cryoprecipitate; fibrin-glue. fibrinogen. FFP. IVIG. local hemostatic agent. suture. local tranexamic acid (for IPFD); Eltrombopag. fresh frozen plasma. IVIG. local hemostatic agent. prophylactic surgical haemostasis (for IPND).

Table 5. Incidence of bleeding in the different IPD populations according to the type of surgery.

	IPD	IPFD	IPND	IPFD vs IPND X^2
Procedure	**N (% AEB)**	**N (% AEB)**	**N (% AEB)**	**p-value**
DENTAL PROCEDURES	**233 (13.3)**	**134 (15.7)**	**99 (10.1)**	
MINOR SURGERY:				
Cyst/abscess drainage	5 (60)	3 (66.7)	2 (50)	ns
Central catheter placement	11 (36.4)	9 (44.4)	2 (0)	ns
Hemorrhoidectomy	8 (25)	3 (33.3)	5 (20)	ns
Invasive Procedure	25 (20)	15 (26.7)	10 (10)	ns
Colonoscopy	25 (20)	21 (23.8)	4 (0)	ns
Gastroscopy	11 (18.2)	10 (20)	1 (0)	ns
Biopsy	17 (17.6)	13 (23.1)	4 (0)	ns
TOT minor surgery	**102 (23.5)**	**74 (28.4)**	**28 (10.7)**	
MAJOR SURGERY:				
Thoracic Surgery	2 (50)	2 (50)		ns
Cardiovascular Surgery	17 (47.1)	9 (77.8)	8 (12.5)	0.02
Urological Surgery	38 (34.2)	24 (37.5)	14 (28.6)	ns
Neurological Surgery	7 (28.6)	5 (20)	2 (50)	ns
Gynecological Surgery	56 (26.8)	31 (35.5)	25 (16)	ns
Otorinolaringologic Surgery	106 (24.5)	49 (24.5)	57 (24.6)	ns
Plastic Surgery	14 (21.4)	4 (25)	10 (20)	ns
Eye Surgery	25 (20)	12 (41.7)	13 (0)	0.03
Abdominal Surgery	126 (19.8)	52 (30.8)	74 (12.2)	0.01
Orthopedic Surgery	56 (12.5)	30 (16.7)	26 (7.7)	ns
Breast Surgery	13 (7.7)	7 (14.3)	6 (0)	ns
Dermatologic Surgery	34 (5.9)	22 (9.1)	12 (0)	ns
TOT major surgery	**494 (21.9)**	**247 (28.7)**	**247 (15)**	**0.0003**
TOT	**829 (19.7)**	**455 (24.8)**	**374 (13.4)**	**0.0001**

ns= not significant

Table 6. Univariate and multivariate logistic analyses of factors associated with surgical bleeding.

	IPFD (n=455)		IPND (n=374)	
	Univariate analysis OR (95% CI)	**Multivariate analysis OR (95% CI)**	**Univariate analysis OR (95% CI)**	**Multivariate analysis OR (95% CI)**
Female gender	1.8 (1.1-2.9)	1.28 (2.13-0.76)	-	-
WHO bleeding score				
- Grade 0	1.00	1.00	1.00	1.00
- Grade 1	0.91 (0.17-4.97)	1.29 (0.23-7.35)	4.27 (1.34-13.57)	
- Grade 2	3.87 (0.87-17.17)	4.96 (1.08-22.82)	5.16 (1.69-15.79)	
- Grade 3	6.62 (1.52-28.89)	8.47 (1.83-39.13)	10.9 (3.28-36.25)	
- Grade 4	10 (1.8-55.53)	19.23 (3.23-114.55)	20.44 (3.38-123.53)	
Platelet count $<68x10^9/L$	-	-	2.04 (1.01-4.12)	
Age ≥ 70 years			1.84 (1.009-3.37)	
Prophylaxis	0.38 (0.23-0.63)	0.24 (0.14-0.43)	-	-

FIGURE LEGENDS

Figure 1. Frequency of prophylactic treatments according to WHO bleeding score and platelet count.

A) Use of prophylactic preoperative treatments according to preoperative WHO bleeding score in the overall IPD population, in IPFDs and IPNDs.

B) Use of prophylactic preoperative treatments according to preoperative platelet count quartiles ($x10^9$/L) (microscopic) in IPNDs.

Figure 2. Post-surgical bleeding in IPD.

A) Incidence of bleeding (AEB) in the overall IPD population, in IPFD and in IPND according to pre-surgical WHO bleeding score.

B) Incidence of bleeding (AEB) in the different procedures according to pre-surgical WHO bleeding score.

Figure 1

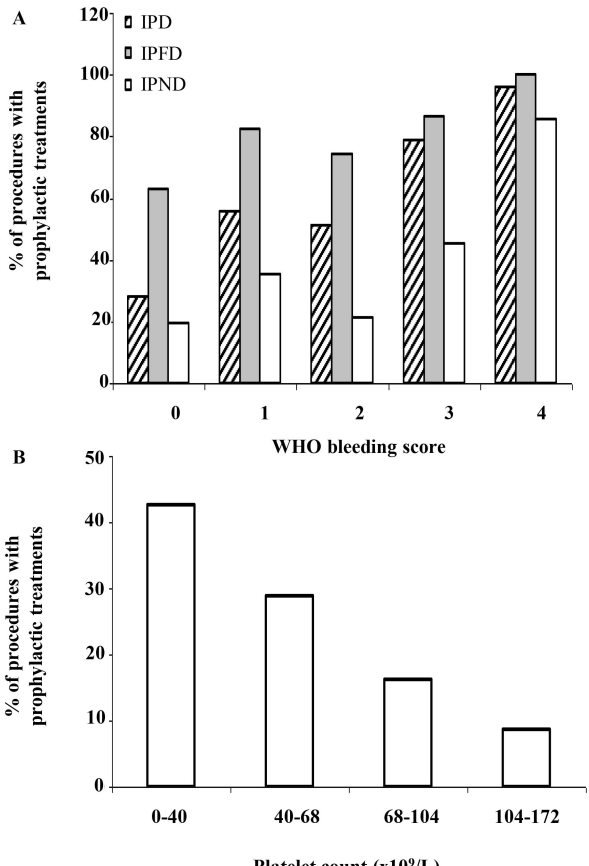
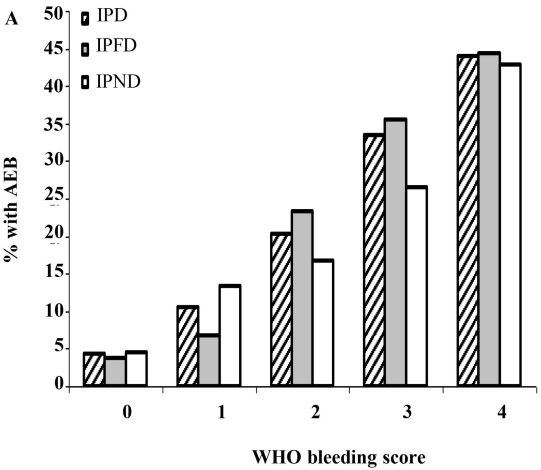
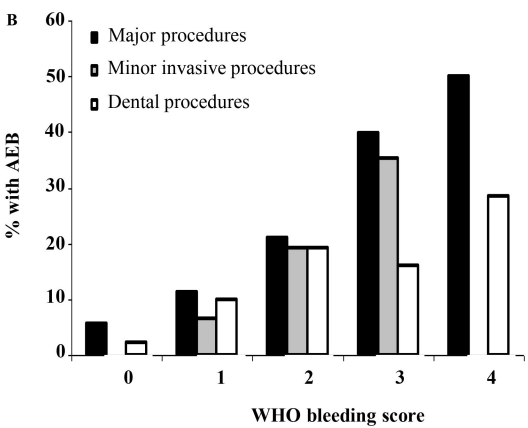

A
120
100
80
60
40
20
0
IPD
IPFD
IPND
% of procedures with prophylactic treatments
0
1
2
3
4
WHO bleeding score
B
50
40
30
20
10
0
% of procedures with prophylactic treatments
0-40
40-68
68-104
104-172
Platelet count (x10⁹/L)

Figure 2


A
IPD
IPFD
IPND
% with AEB
50
45
40
35
30
25
20
15
10
5
0
0
1
2
3
4
WHO bleeding score


B
Major procedures
Minor invasive procedures
Dental procedures
% with AEB
60
50
40
30
20
10
0
0
1
2
3
4
WHO bleeding score

SUPPLEMENTARY MATERIAL

SUPPLEMENTARY METHODS

Study population

This study was promoted by the Scientific Working Group (SWG) on Thrombocytopenias and Platelet Function Disorders of the European Hematology Association (EHA). The Institutional Review Board of the coordinating center (CEAS Umbria, Italy) approved the study, the study was performed in accordance with the Declaration of Helsinki, each center complied with local ethical rules and all patients or their legal representatives signed a written informed consent.

Clinical centers that, based on scientific publications and/or personal knowledge, represent reference centers for IPDs were invited to participate. Moreover, the EHA launched a public call to participate in the study in April 2014 and all the investigators that previously participated in two large international studies on the diagnosis of platelet function disorders were also personally contacted[3,8,9]. Participating investigators were asked to review their records and extract data on surgery and invasive procedures carried out in patients with IPDs over the last years (median 8; IQR 4-18 years) and to obtain additional data directly from the surgeon who carried out the intervention or, in case this was not possible, from the patient or his/her relatives. A series of structured questions had to be answered for each enrolled case concerning the characteristics of the patient, type of surgery, and preparation to and outcome of surgery, with particular attention to post surgical bleeding, its management and outcome. Only patients with a definite diagnosis of IPD confirmed according to well-defined laboratory and/or molecular genetic criteria[6,8,9], (**supplementary table 1-2)** were eligible for the study. IPDs were subdivided in IPNDs, when low platelet count was the main phenotypic characteristic (e.g. MYH9-RD), and IPFDs, when platelet dysfunction was the dominant phenotypic feature, independently of platelet count (e.g. autosomal dominant GT-variant) **(Table 1).** Patients with acquired platelet disorders of any etiology were excluded. All types of surgical procedures, including invasive diagnostic procedures (e.g. angiography, endoscopic and tissue biopsies) and dental extractions, were included. Caesarian sections were excluded because analyzed in a previous study[8,9].

Surgical procedures were categorized post hoc as major surgery, minor invasive procedures and dental procedures according to the following criteria: major, any procedure in which a body cavity was entered, a mesenchymal barrier was crossed, a facial plane was opened, an organ was removed or normal anatomy was altered; minor invasive, any operative procedure in which only skin, mucous membranes or superficial connective tissue were manipulated, gastroscopy, colonoscopy and similar; dental, i.e. extraction, abscess removal, apicectomy and similar[25].

Classification of bleeding

Bleeding history was assessed by the World Health Organization (WHO) bleeding assessment scale[29] and, when available, by the ISTH bleeding score scale[30]. Severity of surgical bleeding was defined according to three different criteria. One was the bleeding academic research consortium (BARC) classification, which is based on a score from 0 to 5 where 0 indicates absence of bleeding and 5 fatal bleeding. We considered as excessive any bleeding to which a BARC $\geq$ 2 was assigned[31]. Another was the classification of bleeding based on a subjective evaluation from the surgeon or, when not available, from the patient as "excessive" or "normal [8,9]. The third the duration (from less than 6 hours to more than 3 days), considered as excessive when >6 hours. Procedures associated with excessive bleeding according to any of the above three criteria, were classified as any excessive bleeding (AEB).

When available, maximal drop of hemoglobin after surgery (g/dl) and volume of blood lost (ml/24hours) were registered. Finally, outcome of treatment of surgical bleeding was classified as successfully controlled, not responsive or re-bleeding.

Supplemental Table 1. Laboratory and/or molecular genetic criteria required for a definite diagnosis of IPND.

Disease (abbreviation. OMIM entry)		Inheritance	Gene (chromosome localization)	Diagnostic criteria
SYNDROMIC FORMS				
X-linked thrombocytopenia (XLT. 313900)		XL	*WAS* (Xp11)	Genetic analysis
MYH9-related disease (*MYH9*-RD. nd)		AD	*MYH9* (22q12-13)	Genetic analysis or positive immunofluoresce screening test or Döhle-like bodies
Paris-Trousseau thrombocytopenia (TCPT. 188025/600588). Jacobsen syndrome (JBS. 147791)		AD	Large deletion (11q23-ter)	Genetic analysis
Thrombocytopenia with absent radii (TAR. 274000)		AR	*RBM8A* (1q21.1)	Genetic analysis or typical phenotype
Congenital thrombocytopenia with radio-ulnar synostosis (CTRUS. 605432)		AD	*HOXA11* (7p15-14)	Genetic analysis or typical phenotype
Thrombocytopenia associated with sitosterolaemia (STSL. 210250)		AR	*ABCG5*. *ABCG8* (2p21)	Genetic analysis
NON-SYNDROMIC FORMS				
Bernard-Soulier syndrome (BSS. 231200)	Biallelic	AR	*GP1BA* (17p13). *GP1BB* (22q11). *GP9* (3q21)	Genetic analysis or absent GPIb/IX/V or absent RIPA
	Monoallelic	AD		Genetic analysis
Familial platelet disorder and predisposition to acute myelogenous leukemia (FPD/AML. 601399)		AD	*RUNX1* (21q22)	Genetic analysis
ANKRD26-related thrombocytopenia (THC2. 313900)		AD	*ANKRD26* (10p2)	Genetic analysis
ITGA2B/*ITGB3*-related thrombocytopenia (*ITGA2B*/*ITGB3-RT*. 187800)		AD	*ITGA2B* (17q21.31). *ITGB3* (17q21.32)	Genetic analysis
TUBB1-related thrombocytopenia (TUBB1-RT. 613112)		AD	*TUBB1* (6p21.3)	Genetic analysis
CYCS-related thrombocytopenia (THC4. 612004)		AD	*CYCS* (7p15.3)	Genetic analysis
Congenital amegakaryocytic thrombocytopenia *(CAMT. 604498)*		AR	*MPL* (1p34)	Genetic analysis or typical phenotype
GATA1-related diseases *(GATA1-RDs.* Dyserythropoietic anemia with thrombocytopenia. 300367 – X-linked thrombocytopenia with thalassemia. 314050)		XL	*GATA1* (Xp11)	Genetic analysis
ACTN1-related thrombocytopenia *(ACTN1-RT. nd)*		AD	*ACTN1* (14q24)	Genetic analysis
FLNA-related thrombocytopenia *(FLNA-RT. nd)*		XL	*FLNA* (Xq28)	Genetic analysis

Supplemental Table 2. **Laboratory and/or molecular genetic criteria required for a definite diagnosis of IPFD.**

Disease (abbreviation. OMIM entry)	***Inheritance***	***Gene (chromosome localization)***	**Diagnostic criteria**
SYNDROMIC FORMS			
Hermansky–Pudlak syndrome (HPS. 203300)	AR	*HPS1. ADTB3A. HPS3. HPS4. HPS5.HPS6. DTNBP1. BLOC1S3*	Genetic analysis or typical phenotype + delta granule deficiency or decrease in platelet nucleotide content and increased ATP/ADP ratio (+decreased 5HT content)
Cediak-Higashi Syndrome (CHS. 214500)	AR	*CHS1 (1q42.1-42.2)*	
NON SYNDROMIC FORMS			
Glanzmann thrombasthenia (GT. 273800)	AR	*ITGA2B. ITGB3* (17q21.32)	Genetic analysis or absent platelet aggregation or absent GPIIb-IIIa
P2Y12 deficiency (nd. 609821)	AR	*P2RY12* (3q24-q25)	Genetic analysis or selective. severe defect of platelet aggregation by ADP. defect of inhibition o adenylyl cyclase by ADP (VASP phosphorylation assay)
Defect of thromboxane A2 receptor (nd. 188070)	AD	*TBXA2R* (19p13.3)	Genetic analysis or defective platelet aggregation induced by U46619 and by arachidonic acid
Scott syndrome (SCTS. 262890)	AR	*TMEM16F* (12q12)	Genetic analysis
Quebec platelet disorder (QPD. 601709)	AD	*PLAU* (10q24)	Genetic analysis
Delta granule deficiency	AR/AD	*Unknown*	Absence of delta-granules (TEM) or decrease in platelet nucleotide content and increased ATP/ADP ratio (+decreased 5HT content)
Combined alpha-delta granule deficiency (nd. 185050)	AR/AD	Unknown	Severe deficiency of alpha and delta granules
Platelet-type Von Willebrand Disease (VWDP. 177820)	AD	*GP1BA (17p13.2)*	Genetic analysis
Gray platelet syndrome (GPS. 139090)	AR	*NBEAL2* (3p21.1)	Genetic analysis or absence of alpha-granules
Gray platelet syndrome with mutation in GFI1B	AD	*GFI1B* (9q34.13)	Genetic analysis
Primary secretion defect (nd. nd)	AR/AD	*Unknown*	Reduced primary platelet granule secretion upon stimulation by different platelet aggregation agonists. normal TxB2 production induced by AA (or serum TxB2) and normal granule content.
Defects in collagen receptors (nd. nd)	AR	*Unknown*	Defective platelet aggregation in the response to collagen
Stormorken syndrome (nd. 185070)	*AD*	*ORAI1 (12q24.31) STIM1 (11p15.5)*	*Genetic analysis*
COX-1 deficiency	*AD*	*Unknown*	*Defective aggregation in response to arachidonic acid; defective serum TXB2;*
cPLA2 deficiency	*AR*	*PLA2G4A (1q31.1)*	*Genetic analysis*
Tx synthase deficiency	*AD*	*TBXAS1 (7q34)*	*Genetic analysis*
PKC deficiency	*unknown*	*Unknown*	*Defective aggregation in response to Thrombin and PAF; defective GPIIb/IIIa activation*

Supplemental Table 3. Incidence of bleeding according to definition and diagnosis.

IPFD	AEB	BARC									Subjective evaluation	Duration >6h
Diagnosis	**AEB/total (% of total)**	**0**	**1**	**2**	**3a**	**3b**	**4**	**5a**	**5b**	**% >=2**	**N (% of total)**	**N (% of total)**
Defect of thromboxane A2 receptor	4/5 (80)	2	0	1	2	0	0	0	0	60	3 (60)	5 (60)
Platelet-type Von Willebrand Disease	4/5 (80)	1	0	2	2	0	0	0	0	80	3 (60)	5 (40)
CalDAG-related platelet disorder	1/2 (50)	0	1	1	0	0	0	0	0	50	1 (50)	2 (50)
Bernard-Soulier Syndrome (biallelic)*	16/36 (44)	15	9	11	1	0	0	0	0	33.3	7 (19.4)	36 (41.7)
Familial platelet disorder and predisposition to acute myelogenous leukemia*	4/13 (30.8)	8	3	2	0	0	0	0	0	15.4	4 (30.8)	13 (15.4)
Glanzmann thrombasthenia*	53/182 (29.1)	102	34	19	19	5	2	0	0	24.7	37 (20.3)	167 (15)
Hermansky–Pudlak syndrome*	6/22 (27.3)	13	3	3	1	2	0	0	0	27.3	5 (22.7)	21 (19)
Gray platelet syndrome*	4/17 (23.5)	12	2	2	1	0	0	0	0	17.6	2 (11.7)	17 (0)
Autosomal dominant GT-variant*	5/22 (22.7)	15	2	2	2	0	0	0	0	18.2	5 (22.7)	19 (10.5)
Defects in α2-adrenergic receptor	2/9 (22.2)	7	0	1	0	1	0	0	0	22.2	2 (12.5)	16 (0)
Defects in collagen receptors*	2/16 (12.5)	13	2	1	0	0	0	0	0	6.2	2 (22.2)	9 (22.2)
Delta granule deficiency*	4/36 (11.1)	29	3	2	1	0	0	0	0	8.3	4 (11.1)	36 (11.1)
Primary secretion defect*	8/76 (10.5)	66	3	5	1	1	0	0	0	9.2	7 (9.2)	76 (9.2)
Combined alpha-delta granule deficiency	0/2 (0)	2	0	0	0	0	0	0	0	0	0 (0)	2 (0)
P2Y12 deficiency	0/9 (0)	8	0	0	0	0	0	0	0	0	0 (0)	9 (0)
Scott syndrome	0/3 (0)	3	0	0	0	0	0	0	0	0	0 (0)	3 (0)
TOTAL	**113 (24.8)**	**296**	**62**	**52**	**30**	**9**	**2**	**0**	**0**	**20.4**	**82 (18)**	**436 (15.4)**

IPND	AEB/total (% of total)	BARC									Subjective evaluation	Duration >6h
Diagnosis	**N (% of total)**	**0**	**1**	**2**	**3a**	**3b**	**4**	**5a**	**5b**	**% >=2**	**N (% of total)**	**N (% of total)**
FLNA-related thrombocytopenia	1/2 (50)	1	1	0	0	0	0	0	0	0	1/2 (50)	1/2 (50)
X-linked thrombocytopenia	2/92 (22.2)	5	2	1	0	0	0	0	0	11.1	2/92 (22.2)	2/92 (22.2)
Paris-Trousseau thrombocytopenia	1/5 (20)	4	0	0	1	0	0	0	0	20	1/5 (20)	1/5 (20)
MYH9-related disease*	23/148 (15.5)	119	13	11	3	0	0	0	1	10.1	20/148 (13.5)	3/148 (2.1)
ACTN1-related thrombocytopenia*	5/39 (12.8)	34	1	3	0	1	0	0	0	10.3	5/39 (12.8)	2/39 (5.1)
ANKRD26-related thrombocytopenia*	10/89 (11.2)	74	5	7	1	0	0	0	0	9	10/89 (11.2)	7/89 (7.9)
Bernard-Soulier Syndrome (monoallelic) *	8/74 (10.8)	65	4	3	1	1	0	0	0	6.7	6/74 (8.1)	4/74 (5.4)
Congenital amegakaryocytic thrombocytopenia	0/2 (0)	1	1	0	0	0	0	0	0	0	0/2 (0)	0/2 (0)
Thrombocytopenia with absent radii	0/6 (0)	4	2	0	0	0	0	0	0	0	0/6 (0)	0/6 (0)
TOTAL	**50 (13.4)**	**307**	**29**	**25**	**6**	**2**	**0**	0	**1**	**9.1**	**45 (12)**	**370 (5.4)**

*Disorders with more than 10 procedures

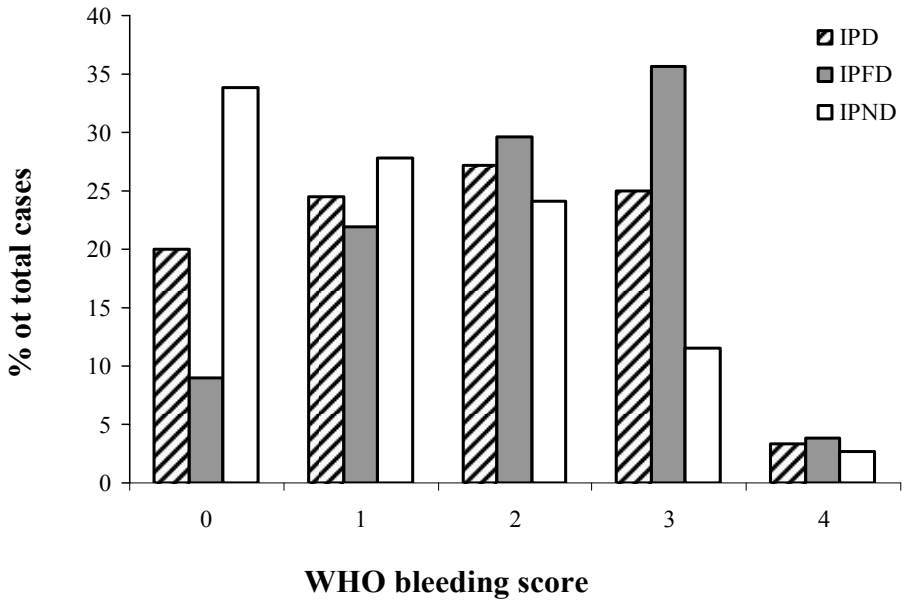
Supplemental table 4. Treatment of post-surgical bleeding according to disease group and type of surgery.

	IPD	IPFD	IPND	Major surg	Minor surg	Dental proc
Treatment	**N/total (% of total)**	**N (% of total)**	**N (% of total)**	**N (% of total)**	**N (% of total)**	**N (% of total)**
PT	56 (34.4)	44 (38.9)	12 (24)	43 (39.8)	8 (33.3)	5 (16.1)
Ot	23 (14.1)	10 (8.8)	13 (26)	12 (11.1)	2 (8.3)	9 (29)
AA	22 (13.5)	16 (14.2)	6 (12)	10 (9.3)	3 (12.5)	9 (29)
PT+FVIIa	10 (6.1)	10 (8.8)		8 (7.4)	2 (8.3)	
FVIIa	6 (3.7)	6 (5.3)		2 (1.9)	2 (8.3)	2 (6.5)
PT+AA	5 (3.1)	5 (4.4)		4 (3.7)	1 (4.2)	
AA+DDAVP	2 (1.2)	2 (1.8)			1 (4.2)	1 (3.2)
PT+FVIIa+AA	2 (1.2)	2 (1.8)			2 (8.3)	
AA+Ot	1 (0.6)	1 (0.9)			1 (4.2)	
AA+PT+Ot	1 (0.6)	1 (0.9)		1 (0.9)		
DDAVP	1 (0.6)	1 (0.9)		1 (0.9)		
none	34 (20.9)	15 (13.3)	19 (38)	27 (25.0)	2 (8.3)	5 (16.1)
TOTAL	163	113	50	108	24	31

PT=Platelet transfusion; AA=Antifibrinolytic agents; Ot=other: cryoprecipitate; fibrin-glue. fibrinogen. FFP. IVIG. local hemostatic agent. suture. local tranexamic acid (for IPFD); Eltrombopag. fresh frozen plasma. IVIG. local hemostatic agent. prophylactic surgical haemostasis (for IPND).

Supplemental Figure 1. WHO bleeding score distribution of the enrolled IPD population.

The WHO bleeding score is reported for the overall IPD population and separately for IPFDs and IPNDs (IPDs; n=423; IPFDs; n=238; IPNDs; n=185).



Supplemental Figure 2. Post-surgical bleeding in IPD.

Percentage of total procedures (IPD=829; IPFD=455; IPND=374) followed by excessive bleeding according to the different definition criteria: AEB= any excessive bleeding; BARC≥2= any bleeding to which a BARC≥2 was assigned; subjective evaluation= bleeding classified as "excessive" or "normal" based on a subjective evaluation by the surgeon or when this was not available by the patient; duration ≥6h= a bleeding with a duration ≥ 6 hours.