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Platelet Function Disorders – Healthcare Utilization in Hospitalized Children

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Abstract

Health care resource utilization for children with platelet dysfunction is largely undescribed. This study aims to recognize the clinical characteristics in patients with platelet dysfunction, identify their rate of hospitalization to better understand the burden of illness for patients with platelet function disorders (PFD), as well as assess their healthcare utilization. We performed a cross-sectional analysis of all pediatric hospitalizations (age <21 years) of patients with platelet function disorders using the Kids' Inpatient Database (KID). The most common bleeding symptoms in hospitalized patients with PFDs are epistaxis (13.9%), menorrhagia (3.4%) and hemorrhage complicating a procedure (2.8%). Bronchial asthma (11.3%), esophageal reflux (10.4%) and anemia (8.4%) were the most common associated diagnoses. Ninety-five percent of all hospitalized children with PFD had some form of insurance coverage. Analysis of health care utilization between patients with PFD and without PFD showed no statistically significant difference in mean length of hospitalization, total hospital charges, length of hospital stay or mortality. Large prospective multi-center studies in both inpatient and outpatient settings are required to further assess health care utilization and help cater to the needs of these patients.

Abbreviations: *SD: Standard Deviation; A: simple Linear Regression*

Introduction

Platelets play a critical role in primary hemostasis and they are the first line of defense to "stop bleeding" [1]. Disorders of platelets typically present with mucocutaneous bleeding or significant hemorrhage after surgery or trauma, unlike deficiency of coagulation factors that typically manifest with deep tissue and joint bleeding [2]. Platelet abnormalities can either be quantitative, due to a decrease in platelet number, or qualitative, due to platelet dysfunction. Qualitative disorders of platelet function can be divided into two subgroups on a molecular level; disorders involving platelet surface markers versus disorders of platelet intracellular organelles or proteins. Glanzmann Thrombasthenia and Bernard Soulier are two well-known examples of platelet function disorders (PFDs) caused by dysfunction of platelet surface markers [3,4]. Less commonly, dysfunctional intracellular organelles or proteins are caused by defects in dense granules within platelets that contain elements such as alpha dehydrogenase (ADP), calcium, and serotonin [4]. Based on some prospective trials, each of these PFDs, in addition to several others, form a rare group of diseases with an unknown prevalence that may be similar to or slightly greater than that of Von Willebrand Disease itself [5]. They manifest with widespread clinical variability, ranging from mild bleeding to severe, life-threatening bleeding [4]. Moreover, they are challenging to diagnose due to technical difficulties in lab testing and the need for fresh samples for processing [6-8].

While healthcare utilization for bleeding disorders such as von Willebrand disease and Hemophilia has been looked at and has been helpful in improving care for these patients, resource utilization for children with platelet dysfunction is largely undescribed or quantified [9-12]. Without knowing the exact prevalence of PFDs, individual variations in severity of bleeding, treatment regimens and response to treatment, outcomes and costs cannot be effectively analyzed. This study aims to recognize the clinical characteristics in patients with platelet dysfunction, identify their rate of hospitalization to better understand the burden

of illness for patients with PFDs, as well as assess their healthcare utilization.

Material and Methods

Study Database

The Healthcare Cost and Utilization Project-Nationwide Inpatient Sample (HCUP-NIS) is the most comprehensive source of hospital care data and the Kids' Inpatient Database (KID) is the largest publicly available all-payer pediatric inpatient care database in the United States. This data is developed specifically for the purpose of analyzing nationwide trends in diseases and resource utilization. Unweighted, it contains data from approximately 3 million pediatric discharges each year. Weighted, it estimates roughly 7 million hospitalizations. Patient demographics, patient hospital admission information and hospital characteristics provided by these databases include patient age, sex, race, length of stay in days, death during hospitalization, elective admission, emergency department visit, admission month, hospital region, total charges for the admission, major operating room procedure and primary insurance status (Medicare, Medicaid, Private Insurance and Self-pay). The chief admission reason is provided as the primary diagnosis. All-listed diagnoses include both the principle diagnosis and any additional conditions that exist at the time of admission and/or develop during the hospital stay.

Data Abstraction

International Classification of Disease – Clinical Modification 9th revision (ICD- 9 CM) codes were used to identify admissions with platelet function defects. Specifically, ICD-9-CM 287.1 identified these patients under the term qualitative platelet defects. Patients over 20 years of age were excluded. We identified bleeding manifestations including epistaxis, excessive or frequent menstruation, hematoma complicating a procedure, and hemorrhage complicating a procedure using ICD 9 codes 7847, 6262, 99811 and 99812, respectively. We identified administration of packed cell transfusions, platelet transfusions, coagulation factor transfusions, and transfusion of other serum using ICD-9 procedure codes 9904, 9905, 9906, and 9909, respectively. We identified procedures performed for treatment of patients with PFDs with ICD 9 procedure codes 2101, 2103 and 2109, which indicated control of epistaxis by anterior nasal packing, control of epistaxis by cauterization and packing, control of epistaxis by other means, respectively.

Statistical Analysis

To reduce potential selection bias and confounding effects, we conducted propensity score matching. Using baseline characteristics (age, admission type, gender, race, number of diagnosis, number of procedures), matched controls were selected from HCUP KID 2006 and 2009 datasets using individuals who did not have a PFD. R programming language package "MatchIt" was used for propensity score matching using "nearest neighbor matching" technique with the matching ratio for cases and controls of 1:5. Matching was performed using a default distance measure (logit).

Demographic characteristics of the patients are described using mean and standard deviation for continuous variables, and frequencies and percentages for categorical variables, as appropriate. Continuous data is compared with the two-tailed independent sample t-test and simple linear regression while categorical data was compared with the Rao-Scott adjustment for chi square test. The Agency for Healthcare Research and Quality (AHRQ) provides sampling weights which allows researchers to report national and regional estimates. In order to describe the characteristics of the patients, weighted prevalence estimates were computed on the matched cases and controls. We reviewed appropriate documentation to ensure correct methodology for the analysis of HCUP-KID data. Multiple comparisons for bleeding manifestations, for procedures and for transfusions were performed between cases and controls to understand the burden of platelet function disorders. The primary outcome of the study was analyzing the total hospital charges during the hospitalization among PFD patients. For the analysis, the total charges variable was categorized as a binary outcome using median, thus multivariate logistic regression models were performed to examine the association. A P-value of less than 0.05 was considered statistically significant for the analysis. All the analysis was performed using MatchIt R package and SAS software, version 9.4 (SAS Institute, Cary, NC) using SAS survey procedures (PROC SURVEYFREQ, PROC SURVEYMEANS, PROC SURVEYLOGISTIC) to account for the complex sampling design.

Results

Patient Characteristics

Demographics: From 2006-2010, an estimated 6,554 patients were identified in the HCUP KIDS database. Of these, there were 1,099 pediatric hospital discharges with a platelet function disorder as one of all listed diagnoses (Table 1). describes age, gender, and race demographics for all patients, with further breakdown between the control population of patients without platelet function disorders versus patients with platelet function disorders. Approximately equal demographic distributions were observed for both populations.

Table 1: *Demographic, Admission and Hospital Characteristics in Patients with Platelet Function Disorders.*

Demographics	All Patients (n = 6554)	Patients with a platelet Function Disorder (n = 1099)	Patients without platelet Function Disorders (n = 5454)	p-value
Age, years, mean ± SD	10.16 ± 0.11	10.07 ± 0.28	10.18 ± 0.12	0.8676
Gender, n (%)				0.9474
Male	2908 (44.79)	486 (44.64)	2422 (44.82)	
Female	3585 (55.21)	603 (55.36)	2982 (55.18)	
Missing	42			
Race, n (%)				0.8612
White	3143 (47.95)	539 (49.04)	2604 (47.73)	
Black	729 (11.12)	110 (10.01)	619 (11.34)	
Hispanic	1207 (18.42)	194 (17.63)	1013 (18.57)	
Other	1475 (22.51)	256 (23.32)	1219 (22.34)	

Associated Diagnosis: (Table 2) lists the other associated diagnoses when a qualitative platelet defect was one of all listed diagnoses. These diagnoses are arranged in decreasing order of frequency. (Table 3) lists the most common bleeding manifestations documented for patients with platelet function defects in decreasing frequency. The most common bleeding manifestation associated with platelet function disorders was epistaxis (13.9%).

Healthcare Utilization

Insurance Coverage: Of all patients with a PFD diagnosis, 95% had at least one form of insurance coverage. Medicaid and private insurance together comprised of the biggest payers with the distribution as follows: Medicare: 2.2%, Medicaid: 47.4%, Private: 45.6%, other sources or uninsured: 4.8%. The distribution was similar for patients without PFD diagnosis, as follows: Medicare: 0.9%, Medicaid: 48.5%,

Table 2*: Top Ten Associated Diagnoses in Decreasing Order of Frequency in Hospitalizations with Qualitative Platelet Defects.*

	ICD9 Code	Diagnosis	Percentage
1	49390	Bronchial asthma	11.3
2	53081	Esophageal reflux	10.4
3	2859	Anemia, unspecified	8.4
4	34590	Epilepsy, unspecified	6.8
5	56400	Constipation	6.7
6	78340	Lack of normal physiological development, unspecified	6.4
7	2851	Acute post hemorrhagic anemia	6.2
8	31401	Attention deficit hyperactivity disorder	5.9
9	4019	Essential hypertension	5.2
10	27651	Dehydration	4.4

Table 3: Top 10 Associated Bleeding Symptoms in Decreasing Order of Frequency in Hospitalizations with Qualitative Platelet Defects.

	ICD9 Code	Bleeding symptom	Percentage
1	7847	Epistaxis	13.9
2	6262	Excessive or frequent menstruation	3.4
3	99811	Hemorrhage complicating a procedure	2.8
4	5780	Hematemesis	1.9
5	5781	Blood in Stool	1.3
6	59970	Hematuria, unspecified	1
7	5693	Hemorrhage of rectum/anus	0.9
8	5789	Hemorrhage of GI tract	0.9
9	6268	Other disorders of menstruation and other abnormal bleeding from female genital tract	0.8
10	99812	Hematoma complicating a procedure	0.8

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Private: 42.9%, other sources or uninsured: 7.8%. A similar distribution was also noted for overall insurance coverage for all hospitalizations as seen in (Table 4).

Table 4: Hospital Admission Characteristics, Mortality and Cost in Hospitalizations with Qualitative Platelet Defects.

	All Patients (n = 6554)	Patients with a platelet function disorder (n = 1099)	Patients without platelet function disorders (n = 5454)	p-value
Length of stay, days, mean ± SD	8.51 ± 0.30	7.00 ± 0.65	8.81 ± 0.33	0.6548
Died during hospitalization, n (%)				
(%)	6452	1090 (99.18)	5361 (98.30)	
No	-98.44	9 (0.81)	93 (1.70)	0.1708
Yes	102 (1.55)			
Total charges, $, mean ± SD	$73,847 ± $3,692	$79,990 ± $7,748	$72,603 ± $3,881	0.8457
Payer, n (%)				0.048
Medicare	68 (1.04)	24 (2.22)	44 (0.88)	
Medicaid	3160 (48.30)	519 (47.36)	2640 (48.49)	
Private	2838 (43.38)	500 (45.61)	2337 (42.93)	
Other	475 (7.27)	53 (4.80)	423 (7.76)	
Required major operating room procedure, n (%)				
No	4616 (70.43)	784 (71.29)	3832 (70.26)	0.5834
Yes	1938 (29.57)	316 (28.71)	1622 (29.73)	
Admission month, n (%)				0.3156
January	557 (8.77)	94 (8.80)	463 (8.77)	
February	530 (8.35)	96 (8.97)	434 (8.22)	
March	580 (9.13)	104 (9.68)	476 (9.01)	
April	540 (8.50)	66 (6.15)	474 (8.97)	
May	550 (8.66)	100 (9.36)	450 (8.52)	
June	503 (7.92)	101 (0.40)	403 (7.62)	
July	487 (7.67)	75 (7.01)	412 (7.81)	
August	520 (8.19)	94 (8.77)	426 (8.07)	
September	519 (8.18)	97 (9.02)	423 (8.00)	
October	547 (8.61)	74 (6.94)	472 (8.95)	
November	518 (8.16)	85 (7.96)	433 (8.20)	
December	499 (7.86)	85 (7.94)	414 (7.84)	
Missing	131			
Hospital region, n (%)				<.0001
Northeast	630 (17.61)	103 (17.48)	526 (17.64)	
Midwest	987 (27.62)	260 (44.07)	727 (24.37)	
South	1230	153 (25.83)	1078 (36.12)	
West	-34.42	74 (12.62)	652 (21.86)	
Missing	727 (20.33)			
	2008			

Hospital Admission Characteristics and Cost: The mean length of hospital stay per admission for patients without a PFD was 8.8 ± 0.3 days. This was not significantly different from patients with a PFD whose mean length of stay was 7.0 ± 0.7 days. More specifically, for patients with a PFD but no bleeding manifestations, the mean LOS 8.0 ± 1.0 days. For PFD patients with epistaxis, the mean LOS was 4.0 ± 1.0 days, 3.0 ± 0.5 for PFD patients with excessive or frequent menstruation, and 10.0 ± 2.0 days for PFD patients with hematoma(s) or hemorrhage. The mean total hospital charge for a patient with a PFD was $79,990 ± $7,748. This was not significantly different from patients without a PFD whose mean total charge of $72,603 ± $3,881. Both were similar to a mean total hospital charge of $73,847 ± $3,692 for all-cause hospital admissions. [Table 5] shows the results from univariate and multivariate logistic regression analysis for hospital charges higher than median. Overall, any major operating room procedure was statistically associated with higher cost on both the univariate and multivariate analysis (Adjusted OR: 4.98 [95% CI: 3.24-7.64]). In addition, for patients with a PFD, receiving one platelet transfusion significantly increased the cost of hospitalization from receiving no transfusion support. Receiving more than one platelet transfusion significantly increased this cost further. Further analysis compared each bleeding symptom (epistaxis, excessive menstruation, hematoma or hemorrhage) with the same following hospital characteristics: length of stay, mortality and total hospital charges. This was compared between patients with a PFD diagnosis and without a PFD diagnosis listed at discharge as seen in (Table 5). No significant difference was observed for each type of clinical manifestation. Specifically, honing in on the subset of patients with PFD and epistaxis diagnoses, no significant difference was observed in length of stay or hospital charges for those who underwent a procedure to control bleeding (23.5%) and those who did not (76.5%). In this same subset group (reported PFD and epistaxis diagnoses), no significant difference was observed in a comparison between hospital characteristics for those who received a transfusion as part of treatment (36.1%) and those who did not (63.9%). This was also true for patients with a PFD and hematoma or hemorrhage diagnoses. No significant difference was observed in a comparison between length of stay and hospital charges for those who received a transfusion as part of treatment (23.7%) and those who did not (76.3%).

Regional Variation in Hospitalizations: We analyzed the data to assess rate of hospitalizations in different regions in the country. All states were divided into the following four regions as defined by the KID Database: West, Midwest,

Table 5: Comparison of Bleeding Manifestations among Hospitalizations with Qualitative Platelet Defects.

PFD CASES (total = 1099)	Epistaxis (n = 153)	Excessive Menstruation (n = 35)	Hematoma, Hemorrhage (n = 38)	No bleeding (n = 874)	p-value
LOS, mean ± SD	4.17 ± 1.05	2.91 ± 0.54	10.05 ± 1.99	7.53 ± 0.77	0.0072a
Total charges, mean ± SD	$72,042 ± $17,021	$37,074 ± $13,143	$1,67,364± $50,033	$79,112 ± $8,082	0.0596 a

Northeast, and South. West included Alaska, Arizona, California, Colorado, Hawaii, Idaho, Montana, Nevada, New Mexico, Oregon, Utah, and Washington, Wyoming. Midwest included Illinois, Indiana, Iowa, Kansas, Michigan, Minnesota, Missouri, Nebraska, North Dakota, Ohio, South Dakota, Wisconsin. South included Connecticut, Maine, Massachusetts, New Hampshire, New Jersey, New York, Pennsylvania, Rhode Island, Vermont. Northeast included Connecticut, Maine, Massachusetts, New Hampshire, New Jersey, New York, Pennsylvania, Rhode Island, Vermont. The South had the most documented percentage of all hospital admissions (34.4%, n = 1230). This region also admitted the most patients without a PFD diagnosis as one of all listed diagnoses at discharge (36.1%, n = 1078), whereas the Midwest hospital region admitted the most patients with a PFD diagnosis (44.1%, n = 260). These results were statically significant (Chi square = 29.0145, df = 3, p < 0.0001).

I. Seasonal Variation: When comparing the month of admission in patients with PFD to those without as associated PFD, there was no statistically significant difference in the rates of admission during a specific month [Table 4]. This was performed to assess whether seasonal changes (i.e. weather differences, development of allergies) predisposed to a greater incidence of bleeds such as epistaxis.

II. Mortality: The all cause in-hospital mortality among discharges with PFD diagnosis was 0.81% (n=9) and for patients without a documented PFD was 1.7% (n=93). However, the difference was not found to be statistically significant.

Discussion

Optimal management of patients with platelet function disorders requires understanding the burden of illness associated with treating the various diseases. Identifying a patient with a platelet function disorder can be difficult. Bleeding manifestations vary and even if concern is raised that patient has a PFD, making the diagnosis is difficult in itself. Despite development of tools such as the ISTH-BAT, which has helped capture and document lifelong bleeding history, it is not predictive of platelet function disorders [13]. Moreover, testing itself can be expensive, time-consuming, and generally requires that it is carried out in specialized hematologic laboratories. If diagnosed, treatment further depends on assessment of the patient's clinical bleeding severity in the context of his or her specific underlying PFD [3].

Associated Diagnosis

There are no specific reports of most common associated diagnosis in patients with a PFD when hospitalized. Our study reports the top 10 associated diagnosis among patients hospitalized with platelet function disorders. There are several reports of platelet function disorders associated with a number of syndromes such as Hermansky Pudlak Syndrome, MYH9-related disorders, X-linked thrombocytopenia, Wiskott Aldrich syndrome, Thrombocytopenia absent radius (TAR) syndrome, Chediak Higashi Syndrome [5]. 1.9% of our patients had an associated diagnosis of Wiskott Aldrich syndrome. 1.4% of patients had as associated ICD9 code of 270.2, which includes Hermansky Pudlak Syndrome grouped with multiple other disorders of aromatic amino acid metabolism. None of the patients in our study were noted to have associated MYH9 related disorders or Chediak Higashi Syndrome. Multiple disorders with thrombocytopenia such as TAR Syndrome and X-Linked Thrombocytopenia are grouped under ICD9 code 287.5. Approximately 3.6% of patients in our study had this associated ICD9 code.

Bleeding Manifestations

The frequencies of bleeding manifestations in each type of mild platelet function disorder has not been defined [5]. It is known that patients with disorders such as Bernard Soulier syndrome experience severe bleeding manifestations, while patients with MYH9 related disorders have minimal to no bleeding at all [14,15]. It is also well established that patients with mild bleeding symptoms are more difficult to diagnosis, especially due to challenges in diagnostic testing for platelet function disorders [7]. In a study from India, out

of 164 patients with mild bleeding symptoms, PFDs were the least common (9 out of 164), which included 1 case of Bernard Soulier syndrome, 3 cases of unclassifiable PFDs, and 5 cases of isolated PF3 screen positive patients [7].

Epistaxis (13.9%) was the leading bleeding manifestation in patients hospitalized with PFD in our study. This was consistent with results from the THROMKID study which showed that among 123 patients with hereditary PFDs, epistaxis was the most common manifestation (54%), followed by easy bruising (20%) and oral cavity or mucus membrane bleeding (11%) [16,17]. A study by Biss et al reported that in their study of 23 patients with PFD, the most common clinically significant bleeding manifestation was bleeding after tooth extraction (75%), surgical bleeding (73%), epistaxis (43%), prolonged bleeding from minor wounds, (43%) [14]. However, these studies consist of small patient populations and are reflective of more than only patients who are hospitalized. In a recent 2018 study evaluating inpatient pediatric epistaxis, "having a procedure to control epistaxis did not significantly impact cost," which was also seen in our study [18].

The reported rates of menorrhagia in patients with PFD are very variable and range from 5% to 70% [17,19,20]. However, the variability also signifies the difficulty in exactly assessing menorrhagia, and tools such as the pictorial blood assessment chart (PBAC), though available and helpful, are not in routine use in the pediatric population [21]. In our study, among hospitalizations associated with PFD, only 3.4% were noted to have menorrhagia. Though much lower than reported rates, this indicates that menorrhagia due to platelet function disorder is likely not a common reason for hospitalization and is more likely managed outpatient.

Hemorrhage After Surgery

One of the most common pediatric surgical procedures in the United States is a tonsillectomy. Up to 5% of patients develop post-tonsillectomy hemorrhage [11]. Per a 2013 study, the frequency of hemorrhage within one day of tonsillectomy in pediatric patients with VWD or hemophilia was found to be similar (1.6%) to rates in the general healthy population. However, the delayed hemorrhage rate was "substantially higher at 10% in children 5 years or younger, 15% in children 6 to 15 years old, and 35% in children at least 16 years old" [11]. This study also found the whole blood and red blood cell transfusion rate to be 2.4% during hospitalizations or upon readmission [11]. Although our data set did not define what procedure a patient had performed or the time frame of hemorrhage post-procedure (immediate versus delayed), we found that PFD patients had a frequency of post-procedure hemorrhage of 2.8%, similar to the rate of immediate post-tonsillectomy hemorrhage.

More information is needed on the frequency of each type of common platelet function disorder and associated bleeding phenotype [5]. This will help educate families on what to expect with their diagnosis.

Mortality

The overall morbidity and mortality secondary to inherited PFDs are difficult to assess because diagnosis is challenging in and of itself and severe PFDs are very rare. Moreover, although severe PFDs such as Glanzmann Thrombasthenia and Bernard Soulier Syndrome can cause life threatening hemorrhages, especially in the setting of trauma, their prognoses are excellent with prompt diagnosis and careful supportive care [22-24]. Our study only describes mortality associated with hospital stay and the rates were similar to control group. This most likely reflects the rarity of life-threatening bleeds and the effective care provided to patients with a PFD.

Treatment

Most episodes of local bleeding can be controlled with external pressure such as nose pads or fibrin sealants with fibrinogen, thrombin factor XIII, aprotinin, or fibrin-coated collagen fleece, antifibrinolytics agents [3]. However, for severe bleeding, platelet transfusions are still the primary therapy, with recombinant activated factor VIIa being an alternative treatment for bleeding that cannot be stopped with conventional treatments, with the best efficacy in thrombasthenic patients [3]. While information on drugs and local agents used to control bleeding is not available in our study database, we assessed the need for transfusions among patients with a PFD and also found no increased rate of platelet or packed red blood cell transfusions in hospitalization associated with PFD than in the general population.

Health Care Utilization

Health care utilization has been studied in other bleeding disorders, namely hemophilia and von Willebrand disease [10,25-27]. To the best of our knowledge, there is no available data on health care utilization by patients with a PFD. Based on our study, there are no differences in the number of Emergency Room for patients with PFDs compared to the general population. In addition, the costs of inpatient care in patients with a PFD are very comparable to the general population and there are no statistically significant differences. However, this reflects all

PFDs, including the mild to severe forms. In the future, to better understand hospital resource utilization it would be beneficial to specifically study patients with the more severe forms of PFDs that are likely to require hospitalization, such as Bernard Soulier or Glanzmann Thrombasthenia.

Insurance Coverage

Based on the United States Census Bureau data from 2018, 91.5% of the population had some form of insurance coverage. 67.3% had a private insurance and 34.4% had public insurance coverage [28]. It is notable that a majority of patients with PFDs have insurance coverage, which is in fact higher than national average at 95%, with 45.6% having private insurance, 49.6% having public insurance (2.2% medicare, 47.8% Medicaid) and 4.8% uninsured/self-pay. This is comparable to rate reported for other bleeding disorders like hemophilia and other hospitalized patients [10].

Strengths

KID inpatient database, is one of the largest databases covering 4200 hospitals with pediatric discharges in 47 states. This is approximately 84% of all hospitals in the United States (n = 5001). Hence it is ideal for studying a rare disorder, such as a PFD, as well as examining health care outcomes.

Limitations

There are several limitations to this study. Use of an administrative database for evaluation of clinical and health care utilization definitely has its own limitations. Laboratory data is not available. PFD are listed under one ICD code and different subtypes and their course is not identifiable. The precision of coding limits our result accuracy. The data is limited to inpatient hospitalizations only without information on outpatient visits.

Conclusion

Health care utilization in platelet function disorders is an important aspect to understand and analyze, since the milder forms of these disorders are not even diagnosed. While this study highlights the health care utilization in hospitalized patients with PFD, large prospective multi center studies in both the inpatient and outpatient setting are required to further understand the health care needs of these patients.

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