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Von Willebrand disease and gastrointestinal bleeding: A national inpatient sample study

Anastasia Tsagianni[a], Diane M. Comer[b], Jonathan G. Yabes[b,c], Margaret V. Ragni[d,e,*]

[a] Department of Medicine, University of Pittsburgh Medical Center, Pittsburgh, PA, United States of America
[b] Center for Research on Health Care Data Center, University of Pittsburgh, Pittsburgh, PA, United States of America
[c] Department of Biostatistics, University of Pittsburgh, Pittsburgh, PA, United States of America
[d] Department of Medicine and Clinical Translational Science, Division of Hematology/Oncology, University of Pittsburgh, Pittsburgh, PA, United States of America
[e] Hemophilia Center of Western Pennsylvania, Pittsburgh, PA, United States of America

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ABSTRACT

Introduction: Gastrointestinal tract bleeding (GIB) is a serious complication of von Willebrand Disease (VWD), but little is known regarding prevalence and risk factors. We, therefore, evaluated correlates of GIB among VWD using a large national database.

Methods: We conducted a retrospective analysis of adult discharges from the National Inpatient Sample (NIS) between 2009 and 2014. International Disease Classification codes were used to identify those with and without VWD with and without GIB. Prevalence estimates were weighted using NIS-provided discharge-level weights to reflect national estimates. Categorical variables were compared by Rao-Scott chi-square test, continuous variables by weighted simple linear regression, and independent factors associated with GIB in VWD were determined by weighted multivariable logistic regression.

Results: GIB is more prevalent in VWD, 3.70%, than those without VWD, 1.49%, $p < .0001$, and is more common in those who are younger, male, or Black than in VWD without GIB, each $p < .001$. Comorbidities of GIB in VWD include surgery, hypertension, hyperlipidemia, and smoking, each more common than in VWD without GIB, $p < .0001$. VWD with GIB also have higher length of stay and inpatient mortality, $p < .0001$. In a multivariable model, variables significantly associated with GIB in VWD were angiodysplasia, diverticulitis, hepatitis C, black race, male gender, and smoking, each $p < .001$.

Conclusions: GIB is more common in VWD who are young, black, or male, and the most significant predictors of GIB include angiodysplasia, diverticulitis, hepatitis C, and smoking. After a first GIB, such individuals should consider factor prophylaxis to prevent GIB recurrence and associated morbidity.

1. Introduction

VWD is the most common inherited bleeding disorder with a prevalence varying between 1 to 100 and 1 to 1000, with autosomal inheritance with variable penetrance [1,2]. It is caused by defective or deficient von Willebrand factor (VWF), a glycoprotein that plays a pivotal role in hemostasis by promoting platelet adhesion, platelet plug formation and stabilization of factor VIII [3]. Clinical manifestations include easy bruising, skin bleeding, mucosal and musculoskeletal bleeding including postoperative, oropharyngeal, gastrointestinal, and uterine bleeding which may affect quality-of-life and can be life-threatening [4,5]. While uncommon, bleeding from the gastrointestinal tract may be recurrent with significant morbidity and hospitalization, accounting for up to 53% of all bleeding-related hospitalizations in VWD [6–8]. The most common cause of recurrent GIB in VWD is angiodysplasia [6,9–11], which may occur in all types, but predominates in type 2 or 3 VWD with reduced high-molecular-weight (HMW) VWF multimers [12,13]. It is hypothesized that defective or deficient VWF may lead to endothelial cell proliferation, angiogenesis, and angiodysplasia [6], which, when located in the gastrointestinal tract, may lead to GIB. While acute GIB is standardly managed by VWF replacement with plasma-derived or recombinant VWF concentrates [14], these are seldom used as prophylaxis to prevent GIB as recurrence is unpredictable and long-term prophylaxis is costly and burdensome [7,12–16]. Little is known regarding the prevalence, epidemiology and risk factors associated with GIB in patients with VWD. We, therefore,

* Corresponding author at: Division Hematology/Oncology, University of Pittsburgh, Hemophilia Center of Western PA, 3636 Boulevard of the Allies, Pittsburgh, PA 15213-4306, United States of America.
E-mail address: ragni@pitt.edu (M.V. Ragni).

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evaluated prevalence and risk factors of GIB among individuals with and without VWD, using a large national database.

2. Materials and methods

2.1. Study design and data source

This was a retrospective study using data from the NIS spanning the time period from January 1, 2009 to December 31, 2014. The NIS database is the largest publicly available all-payer inpatient database in the United States developed by Healthcare Cost and Utilization Project (HCUP). It contains a stratified sample of 20% of all discharges from American community hospitals excluding rehabilitation and long-term acute care hospitals. It includes clinical and non-clinical elements, such as diagnoses, procedures, demographics, payment and hospital characteristics of about 7 million inpatient stays. Each observation is assigned a discharge weight which is projected to a nationally representative population and it represents a single hospital stay including one primary discharge diagnosis, up to 24 secondary diagnoses, patient demographics, procedures performed, in-hospital mortality status, insurance status and length of stay [17]. International Classification of Diseases, 9th edition, Clinical Modification (ICD9-CM) codes were used to collect records from the NIS [18]. The present study was approved by the Institutional Review Board (IRB) of the University of Pittsburgh.

2.2. Populations

Discharges aged 18 years and older with and without VWD, and with and without GIB were identified. The patients with VWD were identified by ICD9-CM code 286.4. In order to investigate the potential causes of GIB, which was further dichotomized into upper and lower, the following diagnostic codes were used: hematemesis (578), esophageal bleeding (530.82), Mallory-Weiss (530.7), and hemorrhage with angiodysplasia stomach/duodenum with hemorrhage (537.83), esophageal ulcer with hemorrhage (530.21), gastric ulcer with hemorrhage (531.00, 531.01, 531.20, 531.21, 531.40, 531.41, 531.60, 531.61), gastrointestinal ulcer with hemorrhage (534.00, 534.01, 534.20, 534.21, 534.40, 534.41, 534.60, 534.61), duodenal ulcer with hemorrhage (532.00, 532.01, 532.20, 532.21), gastritis/duodenitis with hemorrhage (535.01, 535.11, 535.31, 535.51, 535.71, 535.41, 535.61), angiodysplasia intestine with hemorrhage (569.85), diverticulitis colon with hemorrhage (562.12, 562.13), diverticulitis small intestine with hemorrhage (562.02, 562.03), rectal and anal hemorrhage (569.3), and Dieulafoy lesion (569.86).

2.3. Risk factors and comorbidities

Potential risk factors for GIB were identified and their frequency in VWD was evaluated using the following diagnosis codes: use of aspirin (V58.66, E850.3, E935.3, 965.1), use of antiplatelet agents (V58.63), NSAIDS (V58.64), anticoagulation (V58.61), chemotherapy (V58.1, V07.39, V07.3, V58.11, E933.1), steroids (V58.65, E932.0, 962.0), transfusion of platelets (99.05), transfusion of coagulation factors (99.06). Additional diagnosis codes included: general surgery procedures (01–86), hypertension (401, 405, 997.91, V81.1), hyperlipidemia (272.0, 272.2, 272.4), GERD (530.81), smoking (305.1), diabetes mellitus (250, 648.0, V18.0, V77.1), chronic kidney disease (585.9, 403, 404, 585, 586), hepatitis C (070.41, 070.44, 070.51, 070.54, 070.70, 070.71, 070.41), thrombocytopenia (287.4, 287.3, 287.39, 287.5, 287.30), liver disease (572.8, 571), aortic valve stenosis (424.1, 396.0, 396.8, 746.3, 093.22, 395.0, 747.22), vascular assist device (V43.21), obesity (278, V77.8) and sepsis (995.91, 995.92, 038). Deyo's modification of Charlson comorbidity index was used to define severity of illness between the groups [19]. The Charlson comorbidity index is a scoring system, constructed from mortality rates of 16 diseases, that controls for confounding by assigning weights based on the strength of their association with mortality [19].

2.4. Statistical analysis

We compared GIB prevalence between patients with and without VWD, and we also compared the demographics (age, gender, race), length of stay, inpatient mortality, payer, medical comorbidities, and potential causes of and risk factors for GIB, stratified by VWD and GIB status. Categorical variables were compared by Rao-Scott chi-square test, and continuous variables by weighted simple linear regression. Weighted multivariable logistic regression was performed to identify factors independently associated with GIB and calculate odds ratios (OR) stratified by VWD status. Covariates included in the multivariable model were selected based on clinical and statistical significance. A p-value $< .05$ was considered statistically significant.

3. Results

3.1. Admission characteristics

During the 6-year period between January 1, 2009, and December 31, 2014, of 16,640 (weighted 82,809) admissions with von Willlebrand disease (VWD), 618 (weighted 3070) (3.71%) were admitted with gastrointestinal bleeding (GIB), a rate about 2.5-fold greater than the 45,106,446 (weighted 224,392,634) (1.48%) in non VWD-related patients, $p < .0001$ (Table 1). Among individuals with VWD, those who developed GIB were more likely to be older, 58.46 ± 0.88 vs. 45.19 ± 0.18 years, African-American, 12.34% vs. 7.53%, and male, 42.35% vs. 25.91%, than those with VWD who did not develop GIB, each $p < .0001$.

3.2. Univariate analysis

Among patients with VWD, univariate analyses revealed that those with GIB also had a higher Charlson comorbidity score, 1.47 ± 0.07 vs. 0.93 ± 0.01 ($p < .0001$), and were more likely to have surgery, 73.37% vs. 57.63%; hypertension, 36.72% vs. 29.06%; hyperlipidemia, 24.59% vs. 16.89%; smoking, 17.07% vs. 10.69%; chronic renal disease, 12.21% vs. 6.26%; hepatitis C, 9.19% vs. 3.23%; thrombocytopenia, 7.57% vs. 3.92%; liver disease, 7.47% vs. 2.56%; aortic valve stenosis, 5.49% vs. 2.00%; and a vascular assist device, 2.15% vs. 0.38%, each $p < .0001$, than patients without GIB (Table 1). Use of anticoagulants medication ($p = .0016$), antiplatelet agents ($p = .0112$), NSAIDS ($p = .0078$), and transfusion with coagulation factors ($p = .0003$) and platelets ($p = .0012$) were uncommon, but significantly greater in patients with GIB than patients without GIB. Patients with GIB also had a significantly longer length of stay, 5.49 ± 0.43 vs. 4.69 ± 0.05 ($p = .0042$) and higher mortality, 2.41% vs. 1.24% ($p = .0114$) than patients without GIB.

Among patients with GIB, patients with VWD had greater rates of hepatitis C, 9.19% vs. 5.32% ($p < .0001$); aortic valve stenosis, 5.49% vs. 2.57%, $p < .0001$; vascular assist device, 2.15% vs. 0.08%; and coagulation factor transfusion, 7.77% vs. 0.09%, each $p < .0001$; and lower rates of diabetes, 15.02% vs. 23.37%; chronic renal disease, 12.21% vs. 19.66%; liver disease, 7.47% vs. 14.04%; sepsis, 1.93% vs. 6.34%; aspirin use, 3.30% vs. 8.25%; and Charlson comorbidity scores, 1.47 ± 0.07 vs. 2.23 ± 0.00, as compared to those without VWD, each $p < .0001$ (Table 1).

In those with VWD with GIB, upper GI (UGI) bleeding was 1.3-fold more common than lower GI (LGI) bleeding (57.4% vs 44.4%), while among non-VWD patients with GIB, UGI bleeding was 1.8-fold more common than LGI bleeding, (65.5% vs 35.6%) (Table 2). The most common cause of GIB in VWD was angiodysplasia (UGI 16.3%, LGI 19.7%), which was significantly more common than in those without VWD (UGI 4.9%, LGI 4.1%) $p < .0001$. By contrast, the next most

Table 1
Incidence and Risk Factors for GIB in Patients with and without Von Willebrand Disease.

Variable	VWD & GIB	VWD & GIB	No VWD & No GIB	No VWD & No GIB	Group 1 vs 2	Group 1 vs 3
		Percent or mean ± SE			p-Value	
Admissions						
Raw	618	16,022	669,990	44,436,456	–	–
Weighted	3070	79,739	3,331,237	221,061,397		
Age	58.46 ± 0.88	45.19 ± 0.18	65.31 ± 0.02	48.43 ± 0.00	< .0001	< .0001
< 18 yr	5.09%	10.30%	1.17%	15.91%	< .0001	< .0001
18-40 yr	14.52%	35.76%	8.90%	21.60%		
> 40 yr	80.40%	53.94%	89.94%	62.50%		
Race						
Caucasian	77.58%	79.45%	68.71%	65.82%	< .0001	< .0001
African-American	12.34%	7.53%	15.75%	14.93%		
Asian	1.78%	1.59%	2.44%	2.69%		
Other	8.30%	11.44%	13.10%	16.56%		
Gender						
Female	57.65%	74.09%	48.13	57.86	< .0001	< .0001
Male	42.35%	25.91%	51.87	42.14		
Risk Factor/Comorbidity						
Surgery	73.37%	57.63%	78.22%	49.82%	< .0001	.0036
Hypertension	36.72%	29.06%	42.89%	32.34%	< .0001	.0020
Hyperlipidemia	24.59%	16.89%	29.85%	22.98%	< .0001	.0043
GERD	19.27%	16.15%	17.65%	12.80%	.0392	.2919
Smoking	17.07%	10.69%	15.25%	11.77%	< .0001	.2093
Diabetes mellitus	15.02%	10.92%	23.37%	16.47%	.0015	< .0001
Chronic renal disease	12.21%	6.26%	19.66%	10.96%	< .0001	< .0001
Hepatitis C	9.19%	3.23%	5.32%	1.55%	< .0001	< .0001
Obesity	7.59%	10.06%	8.61%	9.62%	.0447	.3694
Thrombocytopenia	7.57%	3.92%	7.80%	2.71%	< .0001	.8312
Liver disease	7.47%	2.56%	14.04%	2.27%	< .0001	< .0001
Aortic valve stenosis	5.49%	2.00%	2.57%	1.51%	< .0001	< .0001
Vascular assist device	2.15%	0.38%	0.08%	0.01%	< .0001	< .0001
Sepsis	1.93%	3.33%	6.34%	4.24%	.0561	< .0001
Medication						
Anticoagulation	4.40%	2.39%	7.37%	3.86%	.0016	.0049
ASA	3.30%	2.02%	8.25%	4.99%	.0296	< .0001
Steroids	1.94%	1.25%	1.26%	1.03%	.1329	.1324
Antiplatelet agents	1.33%	0.54%	2.56%	1.21%	.0112	.0563
NSAIDS	0.67%	0.18%	1.05%	0.14%	.0078	.3541
Chemotherapy	0.16%	0.32%	0.08%	0.43%	.4947	.4865
Transfusion						
Coagulation factor	7.77%	4.59%	0.09%	0.03%	.0003	< .0001
Platelets	4.04%	2.10%	3.20%	0.65%	.0012	.2353
Charlson Score	1.47 ± 0.07	0.93 ± 0.01	2.23 ± 0.00	1.23 ± 0.00	< .0001	< .0001
Length of Stay	5.94 ± 0.43	4.69 ± 0.05	6.08 ± 0.01	4.56 ± 0.00	.0042	.7482
Mortality	2.41%	1.24%	4.12%	1.86%	.0114	.0327

GIB is gastrointestinal bleeding; VWD is von Willebrand disease; GERD is gastroesophageal reflux disease; ASA is aspirin; NSAIDS is nonsteroidal anti-inflammatory drugs.

Table 2
Causes of Gastrointestinal Bleeding in Patients with and without Von Willebrand Disease.

Causes of GIB	VWD and GIB Percent	No VWD and GIB Percent	p-Value
Upper GIB	57.4	65.5	< .0001
Angiodysplasia	16.3	4.9	< .0001
Hematemesis	13.8	16.3	.0934
Gastritis, duodenitis	8.9	12.5	.0077
Gastric ulcer	6.5	14.1	< .0001
Mallory-Weiss	5.6	5.7	.8484
Esophageal bleeding	3.8	9.9	< .0001
Gastrointestinal ulcer	2.6	1.3	.0070
Esophageal ulcer	0.8	2.6	< .0040
Diverticulitis, small intestine	0.7	0.2	.0238
Duodenal ulcer	0.3	1.4	.0304
Lower GIB	44.4	35.5	< .0001
Angiodysplasia intestine	19.7	4.1	< .0001
Rectal hemorrhage	15.2	15.1	.9655
Diverticulitis colon	9.0	16.6	< .0001
Dieulafoy lesion, intestine	1.3	0.2	< .0001

common causes of GIB in VWD were rectal hemorrhage, 15.2%, and hematemesis, 13.8%, each similar to rates in non-VWD patients, followed by gastroduodenal ulcer 10.9%, diverticulitis, 9.0%, gastritis/duodenitis, 8.9%, and gastric ulcer 6.5%, which were significantly less common than in non-VWD patients (Table 2). Length of hospitalization did not differ significantly between the two groups, 5.94 ± 0.43 vs 6.08 ± 0.01 days, $p = .748$, whereas inpatient mortality was lower than in VWD, 2.41% vs 4.12%, $p = .0327$ (Table 1).

3.3. Multivariable logistic regression

After fitting a multivariate logistic regression model, variables significantly associated with GIB in VWD were angiodysplasia (OR 104.06, 95% CI 75.14–144.11), colonic diverticulitis (OR 16.66, 95% CI 11.85–23.42), hepatitis C (OR 2.17, 95% CI 1.40–3.36), African-American race(OR1.80, 95% CI 1.31–2.47), male gender (OR 1.61, 95% CI 1.30–2.00), and smoking (OR 1.40, 95% CI 1.04–1.88), which were similar to risk factors identified in the non-VWD group (Table 3). Although significant, age did not appear to be a strong risk factor for either group. Steroids were not associated with increased risk for GIB in either group.

Table 3
Multivariable logistic regression odds ratio for GIB by VWD status.

Covariate	VWD		Non-VWD	
	Odds ratio (95% CI)	p-Value	Odds ratio (95% CI)	p-Value
Angiodysplasia[a]	104.06 (75.14–144.11)	< .0001	111.19 (109.50–112.89)	< .0001
Diverticulitis[b]	16.66 (11.85–23.42)	< .0001	22.58 (22.41–22.75)	< .0001
Hepatitis C	2.17 (1.40–3.36)	.0005	3.70 (3.65–3.74)	< .0001
African-American race	1.80 (1.31–2.47)	.0003	1.24 (1.23–1.25)	< .0001
Male gender	1.61 (1.30–2.00)	< .0001	1.45 (1.44–1.46)	< .0001
Steroids	1.43 (0.69–2.99)	.337	0.94 (0.92–0.96)	< .0001
Smoking	1.40 (1.04–1.88)	.0245	1.31 (1.30–1.32)	< .0001
Vascular assist device	1.27 (0.46–3.54)	.6428	1.98 (1.75–2.24)	< .0001
Aortic valve stenosis	1.15 (0.71–1.86)	.5626	0.88 (0.87–0.90)	< .0001
GERD	1.14 (0.87–1.50)	.3249	1.04 (1.04–1.05)	< .0001
Age	1.01 (1.01–1.02)	< .0001	1.02 (1.02–1.02)	< .0001

[a] Includes angiodysplasia in the upper and lower GI tract.
[b] Includes diverticulitis in the small intestine and colon.

4. Discussion

This retrospective cross-sectional study of discharges from the NIS registry demonstrated that the prevalence of GIB in patients with VWD is 2.5 times higher than in non-VWD patients (3.7% vs 1.49%). These findings are consistent with previous published rates of GIB in von Willebrand disease [7,8,13], and among the most common causes of hospitalization in VWD [8,14]. The frequency of GIB in VWD in this NIS study was also noted to be higher with increasing age, as noted in other series [7, 21, 30].

The most significant cause of GIB in VWD was angiodysplasia, a well-recognized cause of bleeding morbidity and hospitalization [7,8], and, in our series, accounted for approximately one-third of all GIB in VWD, or about three-fold more common than in non-VWD. Other causes such as ulcer, gastritis and diverticulitis were less common compared to non-VWD population, consistent with previous studies [6,7,13,20]. Angiodysplasia is known to occur primarily in VWD patients with more severe types, e.g. types 2 and 3 [7,13,26], but in our series, however, it was not possible to determine VWD type in this NIS study. It is noteworthy that even after extensive imaging, a diagnosis of angiodysplasia may be challenging, as lesions may occur in several sites in the GI tract, some or all of which may be missed [7].

Comorbidities associated with greater GIB risk in individuals with VWD include past surgery, hypertension, hyperlipidemia, smoking, renal disease, hepatitis C, thrombocytopenia, or liver disease. These findings point to the potential worsening of bleeding risk in those with VWD by the concomitant bleeding risks of thrombocytopenia or platelet dysfunction in liver disease and chronic renal disease; and/or the bleeding risk associated with anticoagulants and antiplatelet agents in those at risk for chronic cardiovascular disease. It is also possible that antiplatelet or anticoagulant treatment could have been administered in patients with these disorders and bleeding from angiodysplasia subsequently identified as an association with acquired von Willebrand syndrome. Medications associated with greater GIB risk included aspirin, antiplatelet agents, NSAIDS, and anticoagulants. It was, however, surprising that patients with VWD received these agents, given their underlying bleeding risk and potential anatomic predisposition to bleed, e.g. angiodysplasia. Thus, it is important to monitor concomitant medications and additional conditions that could potential bleeding risk in patients with VWD who have GI bleeding. Whenever possible aspirin, antiplatelet agents, anticoagulants, and NSAIDs should be discontinued and supportive therapy considered, including platelet transfusion, if indicated, during acute GIB. Finally, other markers of overall health status, including Charlson comorbidity score, length of stay and inpatient mortality were significantly worse in VWD patients who developed GIB as compared to VWD without GIB, but were not as severe as patients without VWD and GIB, likely related to the significantly older age in the latter group.

There are several limitations to this study. First, since discharge diagnosis codes were used for patient inclusion in this study, there is the potential for coding inaccuracy and subsequent misclassification bias. In that regard, while previous studies have demonstrated that the accuracy of discharge data collected through diagnosis codes is of sufficient accuracy for research studies [22–24], it is recognized that with only admission level data in the NIS database, confirmation of VWD diagnosis is not possible. Second, the NIS database does not provide data on severity of VWD, specific types of the disease, whether it is inherited or acquired, or methods used to determine specific causes of GIB, or treatment modalities used. It is worth noting that the occurrence of aortic valve stenosis and vascular assist devices in VWD with GI bleed may suggest a possible diagnosis of acquired rather than inherited VWD, which cannot be determined in this database. Third, since the NIS database includes only admission level data, it is not possible to determine if VWD cases were miscoded. Fourth, the NIS is an inpatient database with a potential bias towards a sicker population, and, thus, selection bias is difficult to eliminate given that hospitalizations skew the population studied towards those with more severe disease. Fifth, hospital discharges rather than specific patient encounters are reported in NIS, and, thus, it is possible that multiple admissions for the same patient may be included. Sixth, as this is a retrospective study, it is impossible to prove causality. Finally, NIS contains about 20% of all U.S. hospital admissions, and, thus, it is possible that this sample is not representative. To limit this effect, we used discharge-level-weights.

In conclusion, our study demonstrates that the most significant correlates of GIB in VWD are angiodysplasia, diverticulitis, hepatitis C, black race, male gender, and smoking. After a first GIB, such individuals should consider factor prophylaxis, which has been shown to prevent GIB recurrence and hospital admissions [8,21,25,26]. Of course, cure of the cause of GI bleeding, except for the bleeding disorder, is an extremely important consideration. Further research is needed to investigate prospectively the optimal dose and duration of factor prophylaxis to reduce GIB recurrence in VWD, and to develop animal models to study the relationship between von Willebrand factor, angiogenesis, and angiodysplasia [27].

Author addendum

A. Tsagianni and M. Ragni contributed to the study design, data acquisition, interpretation of the data and writing of the manuscript. D. Comer contributed to the data acquisition, performance of the data analysis, and critical review of the manuscript. J. Yabes contributed to the study design, data acquisition, performance of the data analysis, and critical review of the manuscript. The data set and analysis of the selected years from the NIS can be obtained by contacting the

corresponding author.

Disclosures

A. Tsagianni, D. Comer, J. Yabes, and M. Ragni report no conflicts of interest.

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