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ORIGINAL RESEARCH

Economic Burden Associated with Major Surgery in Patients with von Willebrand Disease: A United States Retrospective Administrative Database Analysis

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Purpose: To estimate the incremental economic burden of major surgeries in patients with von Willebrand disease (VWD).

Patients and Methods: This was a retrospective analysis of the IBM Health MarketScan® database (2008–2018). Patients with at least two healthcare visits for VWD in the database who had undergone at least one major surgery unrelated to VWD (identified via International Classification of Diseases, Ninth and Tenth Revisions procedure codes) were included. Patients without VWD with major surgeries were selected from a 1% random database sample. All patients had ≥12 months of continuous healthcare plan enrollment before and following their first major surgery. Patients with VWD were matched (1:1) with patients without VWD using propensity score matching. Regression models compared healthcare resource utilization and costs between the matched cohorts over a 12-month period after patients' index major surgery.

Results: After propensity score matching, 2972 pairs were selected. Musculoskeletal and digestive surgeries were the two most common major surgeries (patients with VWD, 39.6% and 25.0%; without VWD, 37.1% and 23.4%, respectively). Patients with VWD were significantly more likely ($p<0.0001$) to have an inpatient admission (odds ratio = 1.71; 95% confidence interval [CI] 1.52–1.92) or emergency room visit (odds ratio = 1.41; 95% CI 1.25–1.59) than patients without VWD. The numbers of inpatient admissions (incidence rate ratio [IRR] = 1.47; 95% CI 1.35–1.60), emergency room visits (IRR = 1.44; 95% CI 1.31–1.59), and outpatient visits (IRR = 1.16; 95% CI 1.11–1.21) per patient were also significantly greater for patients with VWD than for those without VWD ($p<0.0001$). Patients with VWD incurred significantly higher ($p<0.0001$) total healthcare costs (medical and pharmacy) per patient than patients without VWD ($50,733.89 versus $30,154.84, respectively).

Conclusion: Healthcare resource utilization and associated costs among patients undergoing major surgeries were significantly higher for those with VWD than for patients without VWD.

Keywords: bleeding, healthcare costs, retrospective studies, healthcare resource utilization

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Introduction

von Willebrand disease (VWD) is an autosomal inherited blood clotting disorder that manifests most commonly as recurrent mild-to-moderate mucocutaneous

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bleeding and excessive bleeding after surgery or trauma.[1,2] Patients with VWD have impaired hemostasis owing to a quantitative or qualitative deficit in von Willebrand factor (VWF), a plasma glycoprotein that mediates platelet adhesion and aggregation and stabilizes coagulation factor VIII (FVIII) in the circulation.[1–4] Although VWD is classified as a rare disease, it is considered the most common bleeding disorder, with an estimated prevalence of between 0.01% and 1.00% depending on the population and diagnostic approach.[5–8]

The first-line treatment of bleeding events in patients with VWD is desmopressin, especially in those with type 1 disease, the mildest form.[1–3] Desmopressin increases plasma levels of endogenous VWF and FVIII by provoking the release of stored VWF.[3] For patients with more severe disease (such as those with type 2 subtypes or type 3), severe bleeding events, or an inadequate response to desmopressin, VWF replacement therapies are the mainstay of treatment.[9–11] In patients with VWD who undergo major surgical procedures, the risk of potentially life-threatening hemorrhage means that hemostatic measures to normalize functional VWF and FVIII levels are obligatory.[11–14]

Although major surgical procedures impose a clinical and economic burden on patients in general, patients with VWD who undergo major surgery may be exposed to the additional burden of impaired hemostasis.[15] There is a paucity of published data regarding the economic burden associated with major surgical procedures in patients with VWD in the United States, including gaps in knowledge regarding the extent of all-cause healthcare resource utilization and associated healthcare costs. A retrospective analysis of a large US database (the Healthcare Cost and Utilization Project National Inpatient Sample) detected a statistically significant higher risk of post-operative hemorrhage in patients with VWD undergoing major non-cardiac surgery relative to patients without VWD undergoing major surgery.[15] However, this study did not capture information on the costs and resources expended on managing these patients.

Therefore, the objective of this study was to estimate the overall economic burden associated with major surgeries in patients with VWD compared with matched patients without VWD who had major surgery in the United States.

Methods

Data Source

In this retrospective administration data analysis, we utilized data from the commercial IBM® MarketScan® Commercial Claims and Encounters (denoted MarketScan) database and the Medicare Supplemental and Coordination of Benefits database for the period of January 2008 to June 2018. The MarketScan database includes medical and procedural claims for outpatients and inpatients, and outpatient pharmaceutical claims for millions of individuals with employer-sponsored health insurance, including their spouses and dependents.[16] All VWD-related diagnoses (for patient identification) and procedures (for patient identification and economic analysis) were identified by medical claims with codes from the International Classification of Diseases, Ninth/Tenth Revision, Clinical Modification (ICD-9-CM/ICD-10-CM), Current Procedural Terminology (CPT), Healthcare Common Procedure Coding System, and National Drug Code.

As this analysis used de-identified patient data from the MarketScan® database, ethical approval was not required. The MarketScan® database is designed to meet the requirements of the Health Insurance Portability act (HIPAA) of 1996 for a limited-use dataset, and has also undergone statistical analysis by a third party to confirm that the data meet HIPAA requirements for fully de-identified datasets.

Patient Identification

Patients in the VWD cohort were identified from the MarketScan database using the following eligibility criteria: VWD diagnoses (ICD-9-CM = 286.4; ICD-10-CM = D68.0) from two separate healthcare visits (≥1 day apart and excluding laboratory and radiology orders), no diagnosis of acquired coagulation factor deficiency, including acquired VWD (ICD-9-CM = 286.7; ICD-10-CM = D68.32, D68.4) at any time, and major surgery on or after the first diagnosis of VWD (ie, after the first VWD claim and before the end of the observation period).

Patients in the non-VWD cohort with major surgeries were selected from a 1% random sample from the database and had no diagnosis of VWD or acquired coagulation factor deficiency at any time. To control for potential selection bias, patients with VWD were matched 1:1 with patients without VWD on the basis of baseline demographic and clinical characteristics (age, sex, US region, comorbidities

[anemia, anxiety, depression, fatigue, and obesity], and Charlson Comorbidity Index [CCI] scores[17]) using a propensity score matching method. Matching was performed using a preset caliper size of 0.01 to maintain the maximum sample size using the smallest caliper width.

A major surgery was defined as a medical claim associated either with an ICD-9/10 procedure coding system (PCS) code classified by the Healthcare Cost and Utilization Project as a major therapeutic operating room procedure (Procedure Class 4) or with a CPT code classified by the Centers for Medicare & Medicaid Services as a major procedure (Global Surgical Indicator = 090). Types of major surgical procedures are listed in Supplementary Table 1. In both the VWD and non-VWD cohorts, major surgeries associated with VWD treatment (ie, hysterectomy, nasal ablation, or uterine ablation; ICD-9-PCS = 21.69, 68.0, 68.23; ICD-10-PCS = 09BL*ZZ, 09TL*ZZ, 0U99**Z, 0UC9*ZZ, 0UJD*ZZ, 0U5B*ZZ, 0UDB*ZZ; CPT = 30801, 30802, 58150–58294, 58353, 58541–58554, 58563, 58570–58573) that were conducted at any time during the observation period were excluded.

The first medical claim for a major surgery during the identification period was designated the index date, defined as 1 day before the inpatient admission date (if the claim was identified in an inpatient setting) or 1 day before the procedure date (if the claim was identified in an outpatient setting). An emergency room (ER) visit also served to define the index date (ie, 1 day before ER visit) if the patient's visit was associated with a medical claim for a major surgical event. Patients in both groups were required to have had continuous healthcare plan enrollment for ≥12 months before the index date (baseline period) and after the index date (observation period following and including their first major surgery) and no capitated healthcare plan in the 12-month observation period.

Patient demographics (age, sex, and geographic region) as of the index date were extracted for the VWD cohort with major surgeries and the non-VWD cohort with major surgeries. Patient-related clinical characteristics, including CCI scores and comorbidities (anemia, anxiety, depression, fatigue, and obesity; identified using ICD-9-CM and ICD-10-CM codes; Supplementary Table 2 [18]), were extracted for the 12-month baseline period.

Outcome Measures

All types of major surgery performed during the 12-month observation period, including the index surgery, were evaluated in both cohorts, with the three most common types of surgery reported.

The economic burden of major surgery in patients with and without VWD was evaluated by comparing healthcare resource utilization (HCRU) and costs in VWD cases with matched controls during the 12-month observation period from the index date. HCRU included the proportion of patients with inpatient admissions, ER visits, or any outpatient visits, as well as the number of visits per patient by visit type. Total healthcare costs represented the sum of pharmacy and medical costs (sum of inpatient, ER, and outpatient costs). All costs reflected reimbursed amounts from payers to healthcare providers and were adjusted to 2018 US dollars using the medical component of the Consumer Price Index.

Statistical Methods

Baseline patient demographics, clinical attributes, and outcome measures were summarized descriptively as the mean ± standard deviation (SD) and median (range) for continuous variables and frequency (percentage) for categorical variables.

After propensity score matching, comparisons between the VWD and non-VWD cohorts were conducted for each of the study endpoints (proportion and frequency of inpatient, outpatient, and ER visits and medical and pharmacy costs) using generalized linear regression models with the appropriate link function (eg, identity, log, and logit), controlling for age, sex, region, health plan, index year, CCI, comorbidities (anemia, anxiety, depression, fatigue, and obesity), and HCRU (inpatient, ER, and outpatient) during the baseline period. Comparisons were made on the basis of the type (categorical or continuous) and data distribution of the study endpoints (eg, normal, Poisson, binomial, categorical, and gamma). The Pearson scale was utilized when applying the Poisson model to account for over-distribution of the data.

All statistical analyses were performed using SAS (version 9.3; SAS Institute Inc., Cary, NC).

Results

Patient Disposition and Baseline Characteristics

Overall, 25,653 patients with VWD and 1,638,475 patients without VWD were identified from the MarketScan database (Figure 1). Of these, 2973 and 65,627 patients with and without VWD, respectively, met the inclusion criteria for this retrospective analysis.

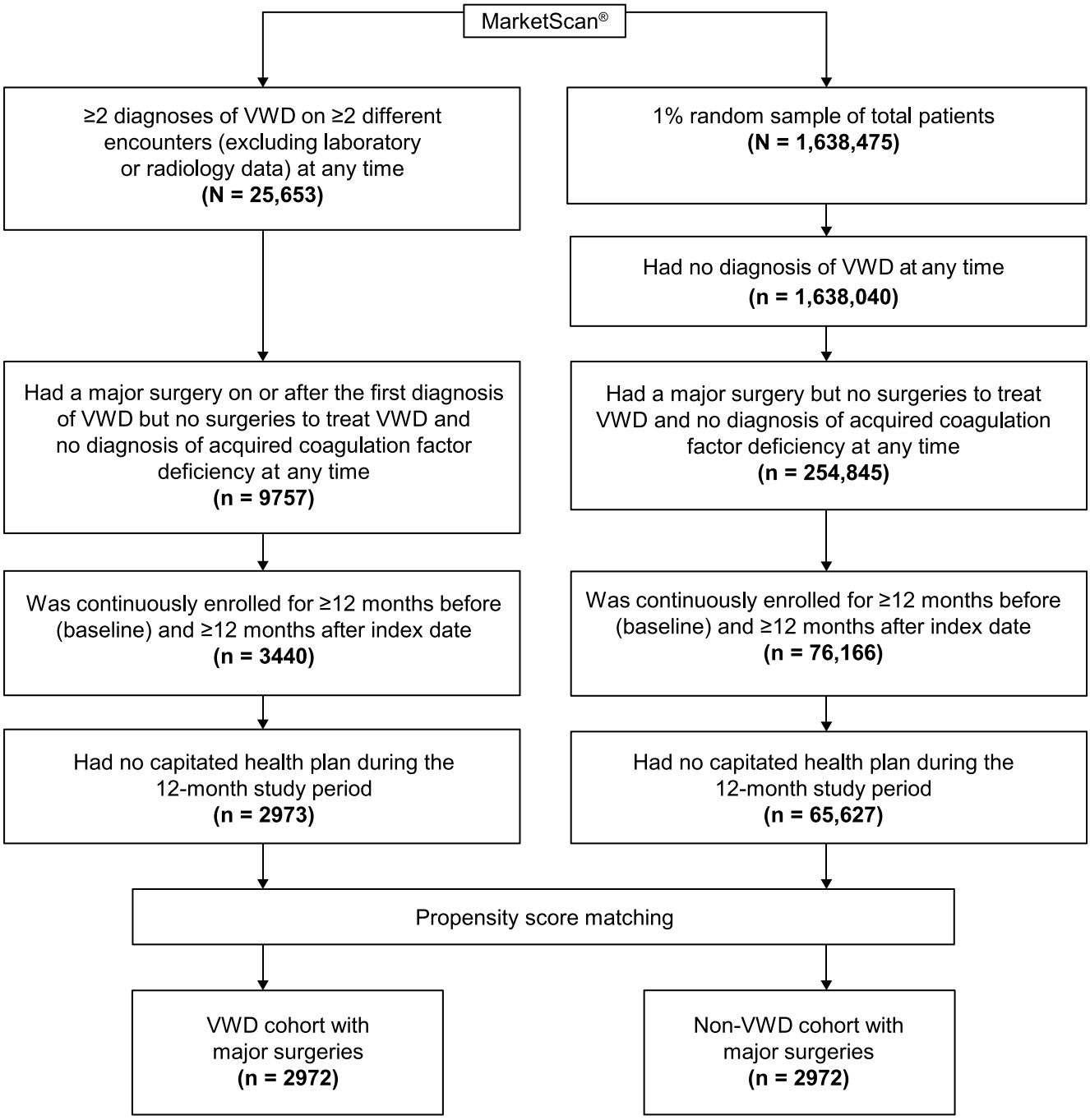

Figure 1 Patient selection for the VWD and non-VWD study cohorts with major surgeries.
Notes: Surgeries to treat VWD included uterine ablation, nasal ablation, and hysterectomy. The index date was defined as the date preceding the admission date for the first major surgery for cases identified in the hospital or as the date preceding the date of the first procedure for major surgery for cases identified in other settings.
Abbreviation: VWD, von Willebrand disease.

Baseline Characteristics

After propensity score matching, 2972 patients with VWD and 2972 patients without VWD who had undergone at least one major surgery were selected for analysis (Table 1). Mean (SD) age was 40.5 (20.6) and 40.9 (20.3) years in the VWD and non-VWD matched cohorts, respectively. The matched study population was predominantly female, with female patients accounting for nearly three-quarters of the patients in each cohort (73.3% and 73.6% for the VWD and non-VWD cohorts, respectively). Mean (SD) CCI score was 0.7 (1.3) in the VWD cohort and 0.6 (1.3) in the non-

Table 1 Baseline Demographic and Clinical Characteristics of the VWD and Non-VWD Cohorts

Status	Before Propensity Score Matching			After Propensity Score Matching		
	VWD Cohort (n = 2973)	Non-VWD Cohort (n = 65,627)	p-value	VWD Cohort (n = 2972)	Non-VWD Cohort (n = 2972)	p-value
Age, years			<0.0001			0.4267
Mean (SD) Median (range)	40.5 (20.6) 42 (1–94)	45.8 (21.0) 49 (0–103)		40.5 (20.6) 42 (1–94)	40.9 (20.3) 42 (0–96)	
Age group, years, n (%)			<0.0001			0.6448
0–11 12–17 18–54 >55	240 (8.1) 274 (9.2) 1582 (53.2) 877 (29.5)	4656 (7.1) 3980 (6.1) 31,458 (47.9) 25,553 (38.9)		240 (8.1) 274 (9.2) 1581 (53.2) 877 (29.5)	235 (7.9) 247 (8.3) 1599 (53.8) 891 (30.0)	
Sex, n (%)			<0.0001			0.769
Female Male	2178 (73.3) 795 (26.7)	35,026 (53.4) 30,601 (46.6)		2177 (73.3) 795 (26.7)	2188 (73.6) 784 (26.4)	
US geographic region, n (%)			<0.0001			0.7946
Midwest Northeast South West Unknown	762 (25.6) 906 (30.5) 858 (28.9) 399 (13.4) 48 (1.6)	17,097 (26.1) 12,750 (19.4) 25,632 (39.1) 9260 (14.1) 888 (1.4)		761 (25.6) 906 (30.5) 858 (28.9) 399 (13.4) 48 (1.6)	761 (25.6) 946 (31.8) 842 (28.3) 378 (12.7) 45 (1.5)	
CCI			<0.0001			0.1067
Mean (SD) Median (range)	0.7 (1.3) 0 (0–12)	0.5 (1.0) 0 (0–13)		0.7 (1.3) 0 (0–12)	0.6 (1.3) 0 (0–10)	
Comorbidity, n (%)						
Anemia	296 (10.0)	2677 (4.1)	<0.0001	295 (9.9)	282 (9.5)	0.5991
Anxiety	351 (11.8)	3882 (5.9)	<0.0001	350 (11.8)	362 (12.2)	0.6604
Depression	360 (12.1)	4414 (6.7)	<0.0001	359 (12.1)	365 (12.3)	0.8428
Fatigue	537 (18.1)	6758 (10.3)	<0.0001	536 (18.0)	546 (18.4)	0.7623
Obesity	227 (7.6)	3904 (5.9)	0.0002	227 (7.6)	212 (7.1)	0.4875

Abbreviations: CCI, Charlson Comorbidity Index; SD, standard deviation; VWD, von Willebrand disease.

VWD cohort. Baseline comorbidities were comparable between the two matched cohorts.

Clinical Outcomes

The most common major surgeries over the observation period were musculoskeletal, digestive, and integumentary in both patients with VWD and without VWD (39.6%, 25.0%, and 8.6% versus 37.1%, 23.4%, and 9.0%, respectively). The percentages of major surgeries that were related to the female genital organs or were obstetric procedures (including Cesarean sections) were 7.0% and 6.1%, respectively, in the matched VWD cohort and 7.7% and 7.6% in the non-VWD cohort. Further details on the types of major surgery undertaken in the matched cohorts are provided in Supplementary Table 3.

Economic Outcomes

HCRU

During the 12-month observation period, patients with VWD had significantly greater HCRU than those without VWD (Figure 2A and B). The proportions of patients having an inpatient admission (43.0% versus 29.4%; p<0.0001), ER visit (34.5% versus 25.7%; p<0.0001), and outpatient visit (99.5% versus 99.1%; p=0.0302)

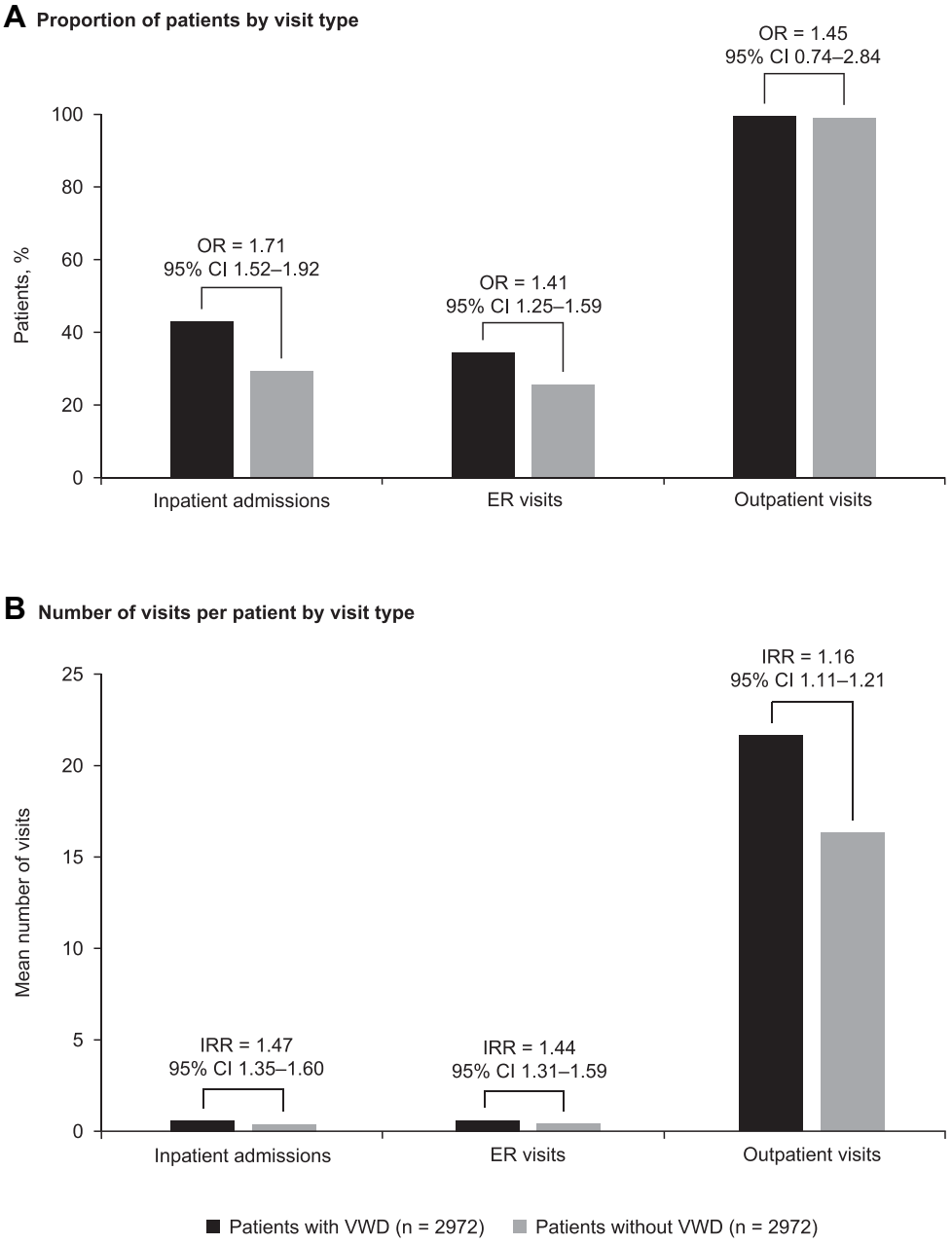

Figure 2 Comparison of all-cause HCRU in the 12-month observation period between matched cohorts of patients with and without VWD who had major surgery, showing (**A**) proportion of patients by visit type and (**B**) number of visits per patient by visit type.

Notes: HCRU was measured during the observation period, defined as the 12-month period beginning from the index date. ORs were evaluated for binary variables (ie, at least one visit) using logistic regression. IRRs were evaluated for count variables (ie, number of visits and total length of inpatient stay) using Poisson regression. Models were controlled for age, sex, region, health plan, index year, CCI, comorbidity (anemia, anxiety, depression, fatigue, and obesity), and HCRU (inpatient, ER, and outpatient) during the baseline period. ORs >1 indicate higher odds for patients with VWD and major surgeries compared with propensity score matched patients without VWD who had major surgeries. IRRs >1 indicate increased incidence rate for patients with VWD and major surgeries compared with propensity score matched patients without VWD who had major surgeries. Inpatient visits were identified with a service location of inpatient hospital; ER visits were identified with a service location of emergency department; and outpatient visits were identified with a service location of clinic, office, or outpatient hospital.

Abbreviations: CCI, Charlson Comorbidity Index; CI, confidence interval; ER, emergency room; HCRU, healthcare resource utilization; IRR, incidence rate ratio; OR, odds ratio; VWD, von Willebrand disease.

were significantly higher in the VWD cohort than in the non-VWD cohort, respectively. Patients with VWD were 71.0% and 41.0% more likely ($p<0.0001$) to have an inpatient admission (odds ratio [OR] = 1.71; 95% confidence interval [CI] 1.52–1.92) and/or ER visit (OR = 1.41; 95% CI 1.25–1.59), respectively, compared with those without VWD. No statistically significant between-cohort difference was detected regarding the odds of

having an outpatient visit (OR = 1.45; 95% CI 0.74–2.84; p=0.2824) (Figure 2A).

Patients with VWD had significantly more healthcare visits than those without VWD (p<0.0001): inpatient admissions (mean [SD] = 0.59 [0.93] vs 0.38 [0.73]; incidence rate ratio [IRR] = 1.47; 95% CI 1.35–1.60), ER visits (mean [SD] = 0.58 [1.14] vs 0.40 [1.21]; IRR = 1.44; 95% CI 1.31–1.59), and outpatient visits (mean [SD], 21.6 [18.75] vs 16.3 [16.22]; IRR = 1.16; 95% CI 1.11–1.21) (Figure 2B).

Healthcare Costs

Over the 12-month observation period, patients with VWD incurred significantly higher adjusted total healthcare costs ($50,734 versus $30,155; p<0.0001), pharmacy costs ($10,581 versus $4632; p<0.0001), and medical costs ($41,943 versus $26,234; p<0.0001) than patients without VWD, respectively, after adjusting for baseline covariates: age, sex, region, health plan, index year, CCI, comorbidity profile (anemia, anxiety, depression, fatigue, and obesity), and HCRU (inpatient, ER, and outpatient; Figure 3). Medical costs accounted for the greatest proportion (83% and 87%) of overall costs in both cohorts.

Discussion

This retrospective cohort analysis of claims data assessed the economic impact of VWD among patients undergoing major surgery in a real-world US setting. Our study results suggest that HCRU and total healthcare costs in the 12-month period following and including the index major surgical procedure were significantly higher for the VWD cohort than for the non-VWD cohort. Among patients undergoing major surgery, those with VWD were significantly more likely to have an inpatient admission and ER visit and required significantly more inpatient admissions and ER visits. As would be expected in patients undergoing major surgery, most (99%) patients in both the VWD and non-VWD cohorts had at least one outpatient visit; however, the number of outpatient visits per patient was significantly higher in patients with VWD than in patients without VWD. Not surprisingly, the increased level of post-surgical healthcare engagement by patients with VWD relative to patients without VWD translated primarily into increased medical costs. Given that the mean age of patients with VWD included in this analysis was 40.5 years, it may be expected that the greater burden faced by patients with VWD will have

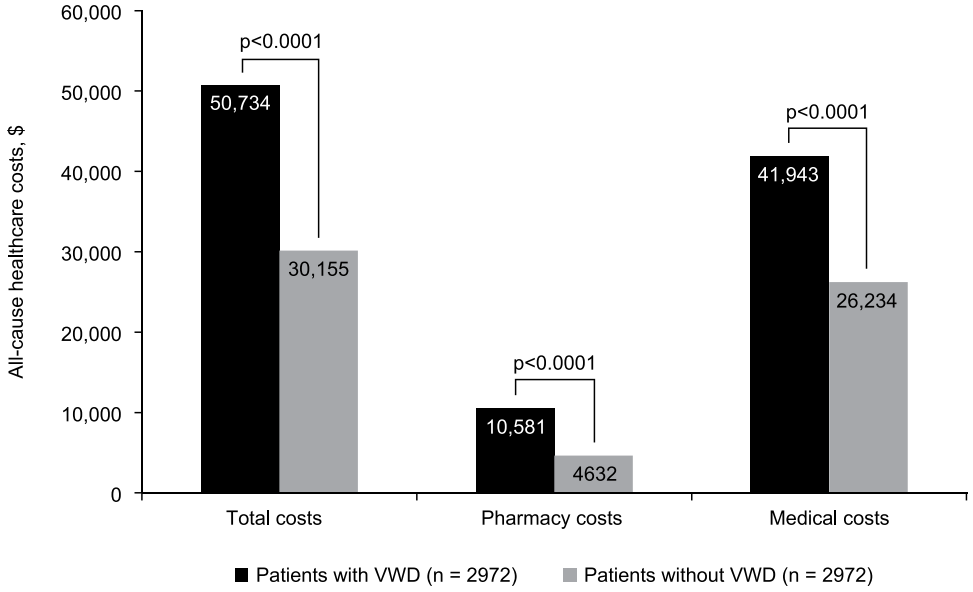

Figure 3 Comparison of adjusted healthcare costs in the 12-month observation period between matched cohorts of patients with and without VWD who had major surgery.

Notes: Healthcare costs were measured during the observation period, defined as the 12-month period beginning from the index date. All costs were measured as reimbursed amounts from payers to healthcare providers and adjusted to 2018 US dollars using the medical component of the Consumer Price Index. Predicted means for all costs were estimated using a generalized linear model with a gamma distribution and log link. All models were controlled for age, sex, region, health plan, index year, CCI, comorbidity (anemia, anxiety, depression, fatigue, and obesity), and HCRU (inpatient, ER, and outpatient) during the baseline period.

Abbreviations: CCI, Charlson Comorbidity Index; ER, emergency room; HCRU, healthcare resource utilization; VWD, von Willebrand disease.

a major social and economic impact on individuals' productivity and family life.

A probable explanation for the incremental economic burden associated with major surgery among patients with VWD is complications related to their bleeding propensity. In a separate analysis of the MarketScan database (2008–2016) that involved 19,785 patients with documented VWD, 15.1% of patients experienced at least one major bleeding event during a median 4-year observation period (mean [SD] rate = 0.11 [0.64] major bleeding events per year).[18] Furthermore, within this VWD cohort, patients with major bleeding events were significantly more likely to have an inpatient admission (OR = 4.1; 95% CI 3.4–5.0), ER visit (OR = 1.8; 95% CI 1.5–2.1), or outpatient visit (OR = 4.9; 95% CI 1.8–13.4); they also had more frequent inpatient admissions (OR = 3.2; 95% CI 2.8–3.8), ER visits (OR = 2.0; 95% CI 1.8–2.3), and outpatient visits (OR = 1.3; 95% CI 1.2–1.3) relative to patients without major bleeding events (all $p<0.01$).[18] As a result, patients with VWD and major bleeding events incurred significantly higher total healthcare costs (adjusted mean difference $20,890; 95% CI $15,524–29,254; $p<0.01$) than patients with VWD without major bleeding events.[18] These findings are also consistent with data from the Swedish VWD Prophylaxis Network, a population-based registry, which showed, between 1987 and 2009, a two-fold higher rate of inpatient hospitalizations among 2790 patients with VWD versus age- and sex-matched controls.[19]

The 2008 National Heart, Lung, and Blood Institute guidelines recommend various strategies for the treatment of VWD, with the appropriate therapy depending on the type and severity of VWD, the severity of the hemostatic challenge, and the nature of the actual or potential bleeding event.[3] The guidelines recommend evaluating the risks and benefits of prophylaxis with VWF replacement therapies when considering long-term therapy for VWD.[3] There is evidence from the observational VWD Prophylaxis Network supporting prophylaxis as a means to reduce hospitalizations in VWD patients with severe and frequent bleeds,[19–22] but data are limited regarding the use of prophylaxis among patients with VWD undergoing elective surgical procedures.[12]

Limitations

Our findings should be interpreted with due consideration to the methods used for data collection. Findings from an analysis by Sidonio et al[23] have raised questions concerning the reliability of using ICD-9 claims data alone to identify patients with VWD. Sidonio et al also utilized ICD-9 codes (at least two claims for VWD) to identify patients with VWD, and found that less than two-thirds of patients had a diagnostic laboratory test within the 2 years before or after diagnosis. Our analysis did include criteria such as exclusion of laboratory and radiology claims to minimize false positives; however, this may not have completely eliminated this issue.

As VWD was identified via ICD code, it was not possible to identify the specific type of VWD. Comorbidities were identified using ICD-9/10 diagnosis codes, which may be underestimated or mislabeled in administrative claims databases. Owing to the observational design, the analysis may have been affected by unobserved differences between comparison cohorts. As the data used in this analysis are limited to patients in a US commercial plan, findings may not be generalizable to populations beyond those covered by commercial medical insurance plans in the United States. Future research, however, could utilize the methodology described in this publication to undertake a similar analysis in other patient cohorts, including in other countries.

Conclusion

This retrospective analysis of a large US commercial healthcare database suggests that patients with VWD who had major surgeries incurred significantly higher HCRU and associated costs (particularly medical costs) compared with patients without VWD who had major surgeries.

Previous Presentation

Poster presentation (#4602) at 61st American Society of Hematology (ASH) Annual Meeting, December 7–10, 2019, Orlando, FL, USA.

Abbreviations

CCI, Charlson Comorbidity Index; CI, confidence interval; CPT, Current Procedural Terminology; ER, emergency room; FVIII, factor VIII; HCRU, healthcare resource utilization; IRR, incidence rate ratio; OR, odds ratio; PCS, procedure coding system; SD, standard deviation; VWD, von Willebrand disease; VWF, von Willebrand factor.

Data Sharing Statement

Data are the proprietary property of IBM.

Ethics Approval and Informed Consent

Not applicable; no institutional review board approval was required for this retrospective claims database analysis

because only de-identified data were used. All data analyzed in the present study complied with the requirements of the Health Insurance Portability and Accountability Act (HIPAA) of 1996 for fully de-identified datasets.

Consent for Publication

Not applicable.

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Author Contributions

All authors made a significant contribution to the work reported, whether that was in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas (AO, YW, ML, SF, and BE contributed to the study design, interpretation of the data, and preparation of the manuscript. YW analyzed the data); took part in drafting, revising, or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

Abiola Oladapo was an employee of Baxalta US Inc., a Takeda company, at the time the analysis was completed and the manuscript developed and is an owner of Takeda stock. Yanyu Wu, Mei Lu, Sepehr Farahbakhshian, and Bruce Ewenstein are employees of Takeda Development Center Americas, Inc., and are owners of Takeda stock.

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