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ORIGINAL RESEARCH

The Economic Burden of Thromboembolic Events Among Patients with Immune-Mediated Diseases

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ABSTRACT

Introduction: Thromboembolic events (TEs) are associated with considerable costs. However, there is a paucity of evidence quantifying the economic burden associated with TEs among patients with immune-mediated diseases (IMDs).
Methods: This retrospective cohort study used the IBM MarketScan® Commercial and Medicare Supplemental Claims databases (2014–2018). Commercially insured adults with IMDs were classified into two cohorts based on diagnosis of TEs (deep vein thrombosis, pulmonary embolism, ischemic stroke, myocardial infarction). Patients in the TE cohort were matched on type of IMD, age, sex, and year of diagnosis to patients in the no TE cohort. In the TE cohort, the index date was the date of first TE following first IMD diagnosis. In the no TE cohort, the index date was assigned so the duration from first IMD diagnosis to index date matched the duration for the corresponding patient in the TE cohort. All-cause total healthcare costs were compared between cohorts in the 30-day and 1-year periods following the index date (inclusive). Unadjusted comparisons were conducted using Wilcoxon signed-rank tests. Adjusted results were estimated using generalized estimating equations with robust sandwich estimator.
Results: Overall, 9681 matched patients were included in each cohort (mean age 61.1 years; 63.7% female). The TE cohort had higher proportions of comorbidities than the no TE cohort (Charlson Comorbidity Index [1.5 vs. 0.9]; $p < 0.0001$). Adjusted all-cause total healthcare costs were significantly greater in the TE cohort versus no TE cohort in the 30-day and 1-year periods following the index date (cost difference: 30-day, $17,574; 1-year, $36,459; both $p < 0.0001$) and were driven by inpatient costs (cost difference: 30-day, $14,864; 1-year, $23,360; both $p < 0.0001$). TE-related healthcare costs were $15,955 and $20,239 in the 30-day and 1-year periods, respectively.
Conclusion: Among patients with IMDs, TEs are associated with substantial economic burden within 30-days and 1-year following the event.

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Keywords: Cost; Deep vein thrombosis; Economic burden; Immune-mediated diseases; Ischemic stroke; Myocardial infarction; Pulmonary embolism; Thromboembolic events

Key Summary Points

Why carry out this study?

Immune-mediated diseases (IMDs) are associated with an increased risk of thromboembolic events (TEs), which include venous events, such as deep vein thrombosis and pulmonary embolism, as well as arterial events, such as ischemic stroke and myocardial infarction.

IMDs and TEs are each associated with a substantial economic burden; however, limited evidence is available regarding the economic burden of TEs among patients with IMDs.

What was learned from this study?

Among adults with IMDs, the adjusted all-cause total healthcare costs incurred over the 30-day and 1-year periods following a TE were significantly greater among patients who experienced TEs than among patients who did not experience TEs (cost difference: 30-day, $17,574; 1-year, $36,459; both $p < 0.0001$); inpatient costs accounted for most of the cost differences.

Efforts aimed at reducing the risk of TEs among patients with IMDs may help lower the economic burden in this population.

INTRODUCTION

Immune-mediated diseases (IMDs) encompass a broad spectrum of unrelated conditions that involve dysregulation of the immune system leading to abnormal activation of inflammatory pathways [1]. IMDs can affect any organ in the body and typically result in debilitating symptoms that may be acute or chronic [2]. Over 100 conditions have been classified as IMDs; examples include rheumatoid arthritis, ankylosing spondylitis, psoriasis/psoriatic arthritis, systemic lupus erythematosus, atopic dermatitis, multiple sclerosis, and inflammatory bowel disease [2, 3]. Although the prevalence of IMDs is reported to vary from 3% to 8% in Western regions (e.g., approximately 10–-15 million Americans) [2, 4], these disabling conditions are among the leading causes of morbidity and mortality.

Patients with IMDs have increased risk of comorbidities, such as cardiovascular disease and thromboembolic events (TEs). TEs are potentially life-threatening events that include venous events, such as deep vein thrombosis (DVT) and pulmonary embolism (PE), as well as arterial events, such as ischemic stroke (IS) and myocardial infarction (MI) [5, 6]. TEs carry a significant economic burden [5]. Conservative estimates of the costs of incident venous TE (VTE) to the United States (US) healthcare system are approximately $7–10 billion each year [7]. TEs are also a strong predictor for unplanned readmissions in the US which can have a substantial economic impact on society [8].

While there have been studies on healthcare resource use and costs of TEs among the general population, for patients undergoing surgery and those diagnosed with cancer, less is known about the economic burden of TEs among patients with IMDs [9–11]. As the cost of TEs among patients with IMDs may differ from the costs of TEs in the general population or other patient populations, partly due to different comorbidity profiles, there is a need to quantify the economic burden in this patient population. To help address this knowledge gap, the current study quantified healthcare costs broadly among patients with IMDs who had evidence of a TE relative to patients with IMDs and no evidence of a TE.

METHODS

Data Source

Data from the IBM MarketScan® Commercial and Medicare Supplemental Databases (2014–2018) were used for this study. These databases contain information on employer-paid encounters for active employees, early retirees, Consolidated Omnibus Budget Reconciliation Act continuees and dependents, as well as employer-sponsored Medicare supplemental healthcare encounters. Detailed information on patient demographic characteristics (e.g., age, sex, and geographic region), enrollment history, dates of service, and claims for medical (e.g., professional and institutional) and pharmacy services are also included in these databases.

Compliance with Ethics Guidelines

Institutional review board approval was not required for this study. The pre-existing, retrospective data from the IBM MarketScan® Commercial and Medicare Supplemental Databases are represented by IBM MarketScan to be fully de-identified in accordance with the Health Insurance Portability and Accountability Act. The data were provided under license agreement with IBM.

Study Design and Sample Selection

To be eligible for inclusion in this retrospective cohort study, patients were required to have at least two diagnoses (on separate dates) for an IMD, which included ankylosing spondylitis, atopic dermatitis, inflammatory bowel disease, multiple sclerosis, psoriasis, psoriatic arthritis, rheumatoid arthritis, and systemic lupus erythematosus. Patients diagnosed with a TE following an IMD diagnosis were matched to patients with no evidence of a TE at any time on the following characteristics: first IMD diagnosis, age at first IMD diagnosis, sex, and year of first IMD diagnosis. In this study, TEs included DVT, PE, IS, and MI. For patients with TE (i.e., TE cohort), the first diagnosis for a TE following the first diagnosis of an IMD was defined as the index date to help ensure that patients had an IMD at the time of the index TE. For patients in the cohort without TEs (i.e., no TE cohort), the index date was assigned so that the duration of time from the first IMD diagnosis to index date matched the duration from matched patients with TE. In this study, patients were required to have at least 6 months of continuous enrollment prior to the index date, at least one year of continuous enrollment following the index date, and be at least 18 years old on the index date. Patients in the TE cohort with no eligible matched controls were excluded from the analysis. For patients in the TE cohort with at least one eligible matched patient without a TE, one eligible patient was randomly selected.

Study Measures and Outcomes

Patient Characteristics

The following patient characteristics were assessed during the baseline period: demographics (age on index date, sex), type of IMD and non-IMD-related medications, and select comorbidities/conditions of interest.

Healthcare Costs of TE

Unadjusted all-cause total healthcare costs (medical and pharmacy) and cost differences between the TE and no TE cohorts were assessed during the 30-day and 1-year periods following the index date. In addition, models adjusted for the following: age on index date, sex (female), index year, healthcare plan type (capitation), baseline comorbidities/conditions of interest, baseline non-IMD medications, and baseline IMD medications. TE-related healthcare costs (i.e., cost of medical visits with diagnosis of TE) were also reported during the 30-day and 1-year periods following the index date.

Statistical Analysis

Study measures were described using means and standard deviations for continuous variables and counts and percentages for categorical variables. Unadjusted statistical comparisons for matched samples were conducted using Wilcoxon signed-rank tests for continuous

variables and McNemar tests for categorical variables. The unadjusted results included mean (standard deviation) costs and differences in mean costs. Adjusted results included mean costs and *p* values that were estimated and compared using generalized estimating equations with a robust sandwich estimator. Data processing and statistical analyses were performed using SAS Enterprise Guide version 7.15 (SAS Institute Inc., Cary, NC).

RESULTS

Patient Characteristics

After the sample selection criteria were applied, a total of 9681 matched patients were included in each cohort (Fig. 1). Across both cohorts, rheumatoid arthritis (31.6%) was the most prevalent type of first IMD, followed by inflammatory bowel disease (19.5%), psoriasis (16.5%), systemic lupus erythematosus (12.4%), multiple sclerosis (8.7%), atopic dermatitis (7.5%), psoriatic arthritis (3.1%), and ankylosing spondylitis (1.5%). The most common index event in the TE cohort was DVT (39.6%) followed by IS (31.8%), MI (18.9%), and PE (14.3%) (Table 1). In general, the TE cohort had higher rates of comorbidities than the no TE cohort, as reflected by the significant difference in the Charlson Comorbidity Index (1.5 vs. 0.9; $p < 0.0001$) and proportion of patients with comorbidities/conditions of interest (cardiovascular diseases, 68.0% vs. 52.8%; type 2 diabetes, 22.8% vs. 14.1%; both $p < 0.0001$) (Table 1). The three most common medications in the TE cohort were glucocorticoids (35.6%),

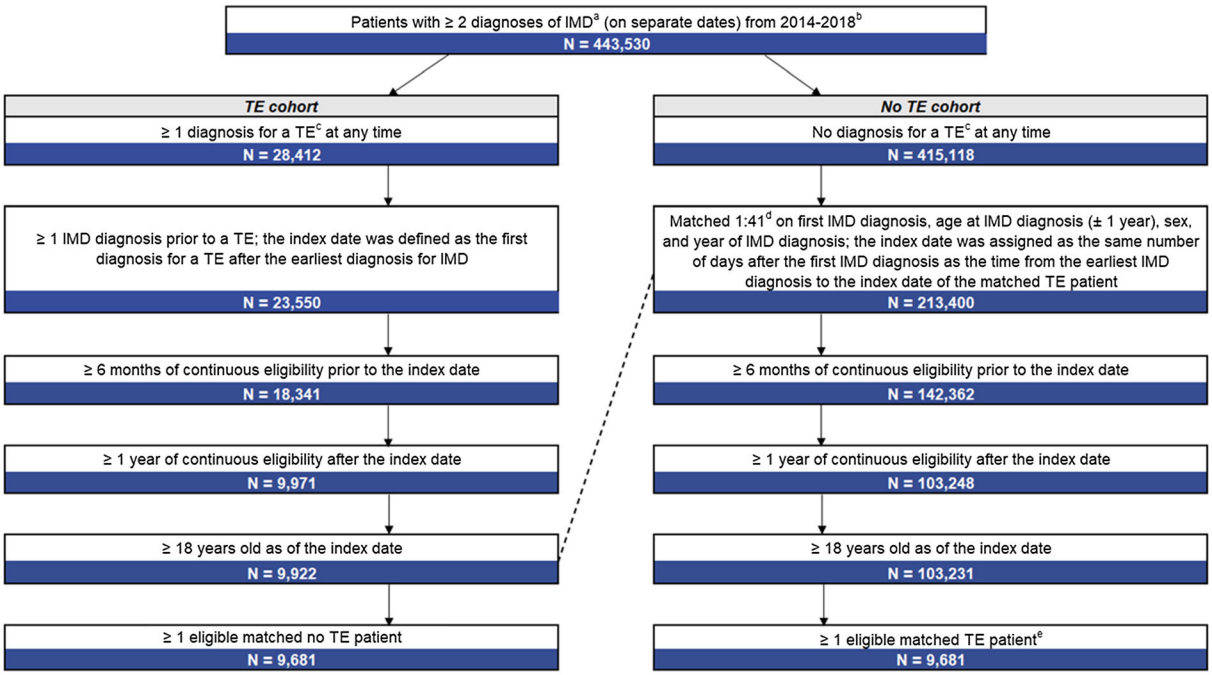

Fig. 1 Sample selection of patients with IMD with and without TEs. IMD immune-mediated disease, TE thromboembolic event. [a]IMDs included ankylosing spondylitis, atopic dermatitis, inflammatory bowel disease, multiple sclerosis, psoriasis, psoriatic arthritis, rheumatoid arthritis, and systemic lupus erythematosus. [b]Qualifying diagnoses for IMDs were identified on the inpatient and/or outpatient services claims datasets. All patients were required to have eligibility data. [c]TEs included deep vein thrombosis, pulmonary embolism, ischemic stroke, and myocardial infarction. [d]Matching between the thromboembolic event cohort and no TE cohort was done with a 1:41 ratio to keep as many eligible patients with thromboembolic events as possible. [e]For patients with TE with ≥ 1 eligible matched patient with no TE, 1 patient with no TE was randomly selected

Table 1 Demographics and clinical characteristics among patients with IMDs measured during the baseline period[a]

	TE cohort (n = 9681)	No TE cohort (n = 9681)	p value
Age at index date (years), mean ± SD	61.1 ± 14.6	61.0 ± 14.6	< 0.0001
Female, n (%)	6169 (63.7)	6169 (63.7)	–
Healthcare plan type, n (%)			
Plans with capitation	958 (9.9)	1077 (11.1)	0.0049
Plans without capitation	8616 (89.0)	8537 (88.2)	0.0715
Unknown	107 (1.1)	67 (0.7)	0.0023
Index year, n (%)			
2015	1704 (17.6)	1736 (17.9)	0.0845
2016	3251 (33.6)	3234 (33.4)	0.5404
2017	2625 (27.1)	2611 (27.0)	0.6245
2018	2101 (21.7)	2100 (21.7)	0.9597
Immune-mediated disease[b], n (%)			
Ankylosing spondylitis	179 (1.8)	161 (1.7)	0.0080
Atopic dermatitis	775 (8.0)	753 (7.8)	0.0164
Inflammatory bowel disease	1956 (20.2)	1932 (20.0)	0.0259
Multiple sclerosis	863 (8.9)	854 (8.8)	0.1060
Psoriasis	1750 (18.1)	1729 (17.9)	0.1707
Psoriatic arthritis	435 (4.5)	410 (4.2)	0.1073
Rheumatoid arthritis	3301 (34.1)	3201 (33.1)	< 0.0001
Systemic lupus erythematosus	1292 (13.3)	1256 (13.0)	0.0033
TEs during baseline, n (%)	1049 (10.8)	–	–
Deep vein thrombosis	491 (5.1)	–	–
Pulmonary embolism	289 (3.0)	–	–
Ischemic stroke	337 (3.5)	–	–
Myocardial infarction	119 (1.2)	–	–
TEs on index, n (%)			–
Deep vein thrombosis	3838 (39.6)	–	–
Pulmonary embolism	1385 (14.3)	–	–
Ischemic stroke	3080 (31.8)	–	–
Myocardial infarction	1826 (18.9)	–	–
Charlson comorbidity index, mean ± SD	1.5 ± 1.7	0.9 ± 1.2	< 0.0001

Table 1 continued

	TE cohort (n = 9681)	No TE cohort (n = 9681)	p value
Conditions/comorbidities of interest, n (%)			
Cancer	1300 (13.4)	861 (8.9)	< 0.0001
Cardiovascular diseases	6584 (68.0)	5113 (52.8)	< 0.0001
Atherosclerosis	1911 (19.7)	844 (8.7)	< 0.0001
Atrial fibrillation	850 (8.8)	390 (4.0)	< 0.0001
Heart failure	791 (8.2)	238 (2.5)	< 0.0001
Hyperlipidemia	3878 (40.1)	3205 (33.1)	< 0.0001
Hypertension	5354 (55.3)	3930 (40.6)	< 0.0001
Chronic kidney disease	888 (9.2)	402 (4.2)	< 0.0001
Chronic obstructive pulmonary disease	1059 (10.9)	469 (4.8)	< 0.0001
Diabetes			
Type 1	315 (3.3)	138 (1.4)	< 0.0001
Type 2	2204 (22.8)	1364 (14.1)	< 0.0001
Fracture (hip or leg)	149 (1.5)	50 (0.5)	< 0.0001
Peripheral vascular disease	1135 (11.7)	513 (5.3)	< 0.0001
Pregnancy[c]	86 (1.4)	65 (1.1)	0.0665
Common classes of medications, n (%)			
Non-immunomodulatory			
Anticoagulants	1669 (17.2)	330 (3.4)	< 0.0001
Hormone replacement therapies[c]	345 (5.6)	397 (6.4)	0.0481
Testosterone replacement therapies[c]	110 (3.1)	102 (2.9)	0.5809
Oral contraceptives[c]	208 (3.4)	248 (4.0)	0.0386
Immunomodulatory			
Biologics	1006 (10.4)	1122 (11.6)	0.0038
TNF inhibitors	766 (7.9)	908 (9.4)	< 0.0001
Interferon-β1a	83 (0.9)	101 (1.0)	0.1521
Interleukin inhibitors	114 (1.2)	78 (0.8)	0.0080
Other biologics	62 (0.6)	50 (0.5)	0.2568
JAK inhibitors	58 (0.6)	41 (0.4)	0.0843
Non-biologic immunomodulators	2813 (29.1)	2936 (30.3)	0.0287
Methotrexate	1117 (11.5)	1246 (12.9)	0.0017
S1P receptor modulators	34 (0.4)	56 (0.6)	0.0151

Table 1 continued

	TE cohort (n = 9681)	No TE cohort (n = 9681)	p value
Other non-biologic immunomodulators	1941 (20.0)	1978 (20.4)	0.4725
5-Aminosalicyclic acid derivative agents	1033 (10.7)	1059 (10.9)	0.4843
Glucocorticoids	3443 (35.6)	2412 (24.9)	< 0.0001
NSAIDs	2087 (21.6)	2014 (20.8)	0.1851

[a]The baseline period was defined as the 1-year period prior to the index date

IMD immune-mediated disease, *JAK* Janus kinase, *NSAIDs* nonsteroidal anti-inflammatory drugs, *S1P* sphingosine 1-phosphate, *SD* standard deviation, *TEs* thromboembolic events, *TNF* tumor necrosis factor

[b]IMDs were reported at any time prior to the index date

[c]The proportions of patients with pregnancy, hormone replacement therapies, and oral contraceptives were reported out of the total number of female patients in each group. The proportion of patients with testosterone replacement therapies was reported out of the total number of male patients in each group

Table 2 Unadjusted cost differences during the 30-day and 1-year periods among patients with IMDs

	30-day period				1-year period			
	TE cohort (n = 9681)	No TE cohort (n = 9681)	Cost difference	p value	TE cohort	No TE cohort	Cost difference	p value
All-cause healthcare costs ($)[a,b]								
Total costs	19,681	1631	18,050	< 0.0001	58,474	19,824	38,650	< 0.0001
Medical costs	18,640	777	17,863	< 0.0001	45,710	8956	36,753	< 0.0001
Inpatient	15,812	184	15,628	< 0.0001	27,432	2387	25,046	< 0.0001
Outpatient	1990	551	1440	< 0.0001	15,708	6079	9628	< 0.0001
Emergency department	838	42	796	< 0.0001	2,570	490	2079	< 0.0001
Pharmacy costs	1041	854	187	< 0.0001	12,764	10,867	1896	< 0.0001

IMDs immune-mediated diseases, *TE* thromboembolic event

[a]Unadjusted results include predicted costs and p values, estimated using generalized estimating equations with a robust sandwich estimator

[b]All costs were inflated to 2019 United States dollar

non-biologic immunomodulators (29.1%), and nonsteroidal anti-inflammatory drugs (21.6%). Use of anticoagulants was significantly higher in the TE cohort vs. the no TE cohort (17.2% vs. 3.4%; $p < 0.0001$) (Table 1).

Healthcare Costs

In both the unadjusted and adjusted analyses, the TE cohort incurred significantly greater total healthcare costs in the 30-day and 1-year periods following the index event versus the no TE cohort IMD (unadjusted cost difference: 30-day,

Table 3 Adjusted cost differences during the 30-day and 1-year periods among patients with IMDs

	30-day period				1-year period			
	TE cohort (n = 9681)	No TE cohort (n = 9681)	Cost difference	p value	TE cohort	No TE cohort	Cost difference	p value
All-cause healthcare costs ($)[a,b]								
Total costs	19,306	1731	17,574	< 0.0001	57,374	20,915	36,459	< 0.0001
Medical costs	17,849	872	16,977	< 0.0001	42,742	9987	32,755	< 0.0001
Inpatient	15,081	217	14,864	< 0.0001	25,945	2585	23,360	< 0.0001
Outpatient	1923	576	1347	< 0.0001	14,666	6710	7956	< 0.0001
Emergency department	854	42	812	< 0.0001	2383	547	1836	< 0.0001
Pharmacy costs	1191	827	364	< 0.0001	14,066	10,909	3157	< 0.0001

IMDs immune-mediated disease, *TE* thromboembolic event

[a]Adjusted results include predicted costs and p values, estimated using generalized estimating equations with a robust sandwich estimator. The adjusted models controlled for the following: cohort assignment, age at index date, sex (female), index year, healthcare plan type (capitation), baseline comorbidities/conditions of interest, baseline non-immune-mediating medications, and select baseline immune-mediating medications

[b]All costs were inflated to 2019 United States dollar

$18,050; 1-year, $38,650; adjusted cost difference: 30-day, $17,574; 1-year, $36,459; all $p < 0.0001$) (Tables 2 and 3). Overall, the adjusted cost differences in the 30-day and 1-year periods were slightly less than the unadjusted cost differences but remained statistically significant after adjusting for potential confounders. The total healthcare cost differences were largely driven by differences in inpatient costs (unadjusted cost difference: 30-day, $15,628; 1-year, $25,046; adjusted cost difference: 30-day, $14,864; 1-year, $23,360; all $p < 0.0001$) (Table 2). In the TE cohort, TE-related healthcare costs were $15,955 and $20,239 in the 30-day and 1-year periods, respectively.

DISCUSSION

This retrospective cohort study quantified the healthcare costs among adults with IMDs who had evidence of a TE relative to patients with IMDs and no evidence of a TE. Overall, our results showed that patients with IMDs with a TE incurred greater total healthcare costs relative to those without a TE. Moreover, the main driver of this high-cost burden was inpatient costs. Taken together, results from this study have the potential to provide healthcare stakeholders with insights regarding decisions to prioritize efforts aimed at reducing the high economic burden of TEs among patients with IMDs.

To date, few studies have examined healthcare costs associated with TEs among patients with IMDs [7, 12]. As a result, insights regarding the cost burden in the IMD population have been limited. Previously, cost studies of TE have focused on specific subtypes of TE, IMDs, or the cost burden of TEs among the general population or in populations without IMDs [7, 12–14]. For example, a retrospective study published in 2019 based on data from 2003 to 2011 found that hospitalization costs among patients with systemic lupus erythematosus who experienced VTEs were greater by $25,400 compared with those who did not experience VTEs [7]. The current study not only included patients with

systemic lupus erythematosus but also with other IMDs, and found similar hospitalization costs. Other studies have shown that patients with TEs experience a significant economic burden compared with the general population. For example, one study estimated that annualized all-cause median costs were $17,512 and $18,901 for patients with DVTs and PEs, respectively, compared with $680 in the control group (general population) [14]. Results from another study estimated that among patients with a VTE, the total annual healthcare costs for a VTE ranged from $7594 to $16,644 [13]. While the current study also found an increased economic burden among patients with TEs, the incremental economic burden of TE in our study among patients with IMDs is greater than the incremental burden previously reported in the general population. This difference can be possibly attributed to more severe TEs among IMD populations, higher downstream costs due to long-term medical needs after an acute TE, and/or a more severe comorbidity profile that further complicates the management of TEs, compared to the general population. Our findings extend the literature by quantifying the healthcare costs of TEs among patients with a range of IMDs. Additionally, this study assessed the overall burden of TE by including both venous and arterial events while previous studies have focused on the burden associated with specific subtypes of TE, such as venous TE [7, 13, 14]. The current study did not assess the cost associated with each TE, but future studies could consider how costs may differ by subtype of TE.

Understanding the drivers of the increased healthcare costs can help stakeholders identify where to direct resources to mitigate costs. In this study, inpatient costs were the main driver behind the differences in healthcare costs between patients with IMDs with TEs and without TEs. The differences in inpatient costs accounted for 85% and 64% of the adjusted total cost difference in the 30-day and 1-year periods. This difference may be due to the acute TE on the index date and resulting inpatient stays. In this study, TE-related healthcare costs (i.e., cost of medical visits with diagnosis of TE) accounted for 88% and 52% of the unadjusted total cost difference in the 30-day and 1-year periods. It is important to note that the economic burden of TEs extends beyond the diagnosis and treatment of the initial event as costs of recurring TEs and associated longer-term effects can cumulatively add to the overall long-term cost burden, which is reflected in the 30-day vs. 1-year costs. Moreover, history of a TE is a significant risk factor for recurrent TEs [15, 16]. For example, the risk of recurrence of VTEs has been reported to be 5–7% per year, which is 50 times higher than the risk in patients without a history of VTE [17]. Certain medications, such as glucocorticoids, nonsteroidal anti-inflammatory drugs, and Janus kinase inhibitors, have been reported to increase the risk of TE [5]. Given the substantial clinical and economic burden of TE among patients with IMDs, the risks of TEs among patients with IMDs should be carefully considered when optimizing treatment for this patient population. In addition, it may be helpful for further studies to evaluate ways to reduce the burden of TE after its occurrence among patients with an IMD.

Limitations

This study should be considered within the context of specific limitations. First, as with any observational claims-based study, databases may be vulnerable to errors in coding and/or data omission. Second, the primary function of claims data is to capture diagnostic and procedure codes for reimbursement. Therefore, the impact of omitted variables on costs associated with TE outcomes (e.g., body mass index, smoking, and immobility) could not be considered in the adjusted analysis as these measures are not collected in claims data. Moreover, other unmeasured and unobserved confounders could not be adjusted for, although this study adjusted for factors that were as comprehensive as was feasible from claims data. Finally, this analysis was conducted using a commercially insured population in the US. As a result, the findings may not be generalizable to other populations such as the Medicaid population, which may have different patient profiles than

commercially insured patients, resulting in a cost estimate of the TE burden that could potentially be greater. Future studies using generalizable databases could provide insight into the economic burden among other segments of the population like Medicaid or uninsured/self-pay patients. As a result of these limitations, the results from this dataset may be a conservative estimate of the economic burden among patients with IMDs who experience TEs.

CONCLUSIONS

Among patients with IMDs, TEs are associated with substantial economic burden within the 30-day and 1-year periods after the event. Research focused on TE risk reduction among patients with IMDs may help to reduce their economic burden. Specifically, given the elevated risks of TEs and the high economic burden of TEs among patients with IMD, the risk of TEs should be carefully considered when optimizing treatment for this patient population.

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Compliance with Ethics Guidelines. Institutional review board approval was not required for this study. The pre-existing, retrospective data from the IBM MarketScan® Commercial and Medicare Supplemental Databases are represented by IBM MarketScan to be fully de-identified in accordance with the Health Insurance Portability and Accountability Act. The data were provided under license agreement with IBM.

Data Availability. The datasets generated during the current study are not publicly available due to licensing agreement with IBM.

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