Intracerebral Hemorrhage in Multiple Sclerosis: A Retrospective Cohort Study

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Background: To identify the vascular risk factors associated with the occurrence of intracerebral hemorrhage (ICH) in Multiple Sclerosis (MS) patients. *Methods:* This is an observational, retrospective cohort study using the nationwide electronic medical records (EMR) database. Patients with the diagnosis of MS were extracted from inpatient and outpatient EMR using the international classification of diseases, ninth/tenth revisions, clinical modification codes. We excluded patients younger than 18 years, and those where gender was not specified. Patients were further stratified based on their demographics, risk factors, medications, and comorbidities. Tobacco, diabetes, hypertension, and alcohol were the predicting variables; antiplatelet medication, and anticoagulant agents were the primary exposures for the development of ICH. A validated diagnosis code algorithm defined the diagnosis of ICH. Multivariable logistic regression models were utilized to assess the risk of ICH in MS patients. *Results:* Of the total 57,099 MS patients (women: 75%, n = 41,517), 107 (.19%) sustained an ICH. Age (OR = 2.74, CI = 1.13-6.62), use of anticoagulants (OR = 2.15, 95% CI = 1.30-3.56, $P = .0028$), and history of tobacco exposure (OR = 2.44, CI = 1.37-4.36, $P = .0025$) were associated with increased risk of ICH. Use of antiplatelet and disease-modifying drugs (DMDs) showed a protective trend against ICH. *Conclusions:* Tobacco exposure and anticoagulant use were strongly associated with increased risk of ICH in patients with MS. There might be a protective effect that antiplatelet and DMDs have in the pathophysiology of this disease. Further prospective investigations are warranted to establish these associations.

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Introduction

Multiple sclerosis (MS) is a chronic autoimmune inflammatory disorder characterized by demyelination and neurodegeneration of the central nervous system.[1] Jean-Martin Charcot first described the disease course as recurrent bouts of "reversible" neurological deficits, leading to progressive neurological deterioration.[2] MS is a leading cause of nontraumatic disability in young adults with a prevalence in the United States of about 1 million and an incidence of 12,000 cases each year.[3,4] Reactive lymphocytes and the cytokines released by them are deemed to play a role in its pathophysiology, in addition to certain genetic and environmental factors.[5] The pathology of MS is characterized by white matter lesions with loss of myelin, axons, oligodendrocytes, and activation of leukocytes, penetrating the severed blood brain barrier to initiate the inflam-matory process.[6,7]

Presence of comorbid conditions in MS patients are of increasing interest.[8,9] According to the North American Research Committee on MS registry, new symptoms may be misattributed to a preexisting condition rather than to a new diagnosis of MS.[8,9] The resulting delay in diagnosis of MS may cause worsened outcomes such as poor quality of life and disability.[10] Comorbid conditions could also be associated with accelerated progression of MS like hyperlipidemia, alcohol, obesity, tobacco exposure, and hypertension (HTN).[11] These vascular risk factors are also linked to cerebrovascular complications including intracerebral hemorrhage (ICH) in the non-MS population. ICH accounts for 10%-20% of all strokes and generally has poorer outcomes and increased mortality compared to ischemic stroke (IS).[12,13] It is well-known that the integrity of the blood-brain barrier (BBB) in MS is affected in the process of demyelination, increasing the permeability of the vessels.[14] Immunologic studies also point to the possibility that the inflammatory cascade of MS may incite a nidus for focal hemorrhage.[15] Zöller et al. demonstrated that hospitalization for immune-mediated diseases is associated with increased risk of ischemic and hemorrhagic stroke.[16] Clinical deterioration, physical, and cognitive disability in MS patients are worse if they have a spontaneous ICH.[15,17]

We studied detailed hospital admission data using a nationwide retrospective cohort of over 57,000 MS patients that allowed us to assess vascular risk factors, medications, and comorbidities associated with ICH in MS. Our hypothesis is that MS patients on disease-modifying therapies (DMT) have less likelihood of ICH due to its anti-inflammatory effect, which in turn should counteract the increased vascular permeability associated with MS.

Methods

Data Source, Study Design, and Participants

This study is a retrospective review of data extracted from the CERNER Health Facts (HF) database (Cerner Corporation, Kansas City,MO), to examine risk factors associated with ICH in patients with MS. Use of the HF database was approved by the University of New Mexico Health Sciences Center institutional review board.

This contemporary database of subjects hospitalized at over 600 United States hospitals is composed of more than 62 million unique patient records. It is a deidentified Health Insurance Portability and Accountability Act of 1996 compliant electronic health record (EHR) database which contains longitudinal patient data. These data were captured, organized, and aggregated to facilitate analyses. Data incorporated demographics, comorbidities (determined from the international classification of diseases [ICD], ninth/tenth revision clinical modification diagnostic codes), medical history, laboratory data, in-hospital procedures, pharmacy data, in-hospital mortality, and hospital characteristics including presence of advanced facilities, number of beds, geographic region, and teaching versus nonteaching status.[18] Patients with a diagnosis of MS from January 2000 to March 2016 were identified *using ICD-9 (340.x) and ICD-10 (G35.x) −CM diagnostic codes*. Data acquisition and analysis were performed by the Clinical and Translational Science Center at the University of New Mexico Health Sciences Center. We gave particular attention to adherence to methodological standards in our research.

Outcome Variables

The total number of eligible patients with the diagnosis of MS was 57,099. Patients younger than 18 years of age and those who had no gender specified were excluded. ICH was identified (*using ICD-9 (431.x and 432.x) and ICD-10 (I61.x and I62.x) −CM diagnostic codes* from the pool of MS patients and subdivided into primary ICH, which was the outcome of interest, versus hemorrhagic transformations of IS. The latter was excluded from the analysis.

Covariates included baseline patient characteristics comprised of age, gender, ethnicity, EMR information related to tobacco exposure, alcohol use, and disease-modifying drugs (DMDs) therapy status. Risk factors

included in our analysis were: diabetes mellitus (DM), hypertension, use of antiplatelet, and anticoagulant agents. Four age categories were included in the analyses: 18-44 years, 45-64 years, 65-74 years, 75 years, and above. These cut-offs were categorized prior to analysis to facilitate age comparison. Ethnicity was classified into 5 categories: Whites, Asian/Pacific Islanders, Blacks, Others (Biracial, Hispanics, Middle-eastern, Native Americans), and Unknown. For tobacco exposure, we included all patients who had a history of current or past exposure as documented in the diagnosis or social history sections of the EMR. Similar methods were used to identify patients with alcohol intake. Alcohol use disorder was defined as a problematic pattern of alcohol use, leading to clinically significant impairment or distress over the past 12-month period. Diagnosis of DM was made *using ICD-9 (250.x), ICD-10 (E10.x, E11.x)-CM diagnostic codes* in EMR, insulin, and/or metformin use, or hemoglobin-A1c (HbA1c) ≥6.5%. HTN was identified *using ICD-9 (401.0x,401.1x,401.9x), ICD-10 (I10.x)-CM diagnostic codes* from the EMR. Use of antiplatelet and anticoagulant agents was confirmed from the medication data.

Aspirin, dipyramidole, or clopidogrel users were classified as an antiplatelet group. Warfarin, apixaban, rivaroxaban, dabigatran, or enoxaparin consumers were classified into an anticoagulants group. DMDs included interferon beta-1a, interferon beta-1b, glatiramer acetate, peginterferon beta-1a, daclizumab, teriflunomide, fingolimod, alemtuzumab, mitoxantrone, and natalizumab.

Statistical Analysis

Frequencies and relative frequencies (*column percentages*) were used to describe the characteristics of patients in this study. The chi-square test was utilized to assess the *bivariate association* between ICH in MS patients, and other factors, *simple logistic regression* models were utilized to assess the unadjusted odds of ICH in MS patients for different categories of the predicting variables. Multivariable logistic regression models were consequently developed to assess if the association between ICH and covariates persists after adjustment for potential confounders and other patient characteristics. Patient characteristics previously described in the literature to be prognostically significant or considered clinically relevant, and covariates identified in analyses as predictors of ICH, were inserted into the models.[2,17,19] In particular, we have employed 4 multivariable logistic regression models for which ICH was the primary outcome; while gender, race, age, tobacco exposure, DM, HTN, DMDs, and alcohol use were the predicting variables; aspirin, antiplatelets, warfarin, and anticoagulants were the primary exposures for models I, II, III, and IV respectively. A significance level of 5% was used as a cut-off to identify statistically significant results. All statistical analyses were performed using the SAS system (Version 9.4; SAS, Cary, NC).

Results

A total of 57,099 MS patients (women: 75%, n = 41,517), from the HF database were grouped into 2 categories: MS with ICH (MS-ICH) and MS without ICH (MS-noICH). The prevalence of ICH in MS patients was found to be about .2% (107 patients), excluding the hemorrhagic transformation of IS. Out of 107 MS-ICH patients, females comprised of 73% (78 of 107) of the patient population. Among MS-ICH patients, race and ethnicity were distributed as follows: Whites, 76% (81 of 107), Blacks 12% (13 of 107), Asians/Pacific Islanders 2% and the remaining grouped as others (Hispanics, biracial, Native Americans, Middle Eastern). The distribution of age among MS-ICH patients was 16% (17 of 107), 39% (42 of 107), 29% (31 of 107), and 16% (17 of 107) for the age groups 18-44, 45-64, 65-74, and 75 years and above, respectively.

Risk Factors and Comorbid Conditions

Approximately 33% (35 of 107) of the MS-ICH patients had a history of tobacco exposure, compared to 15% (8651 of 56992) in the MS-noICH group. Similarly, 15% (16 of 107) of patients in the MS-ICH group were found to have a diagnosis of DM in contrast to 7% (4034 of 56992) in the MS-noICH group. Less than 5% (5 of 107) of patients in the MS-ICH group had HTN as compared to 1.6% (921 of 56992) in the MS-noICH group. Twenty-five percent (27 of 107) of patients in the MS-ICH group reported a history of alcohol use, compared to 10% (5934 of 56992) in the MS-noICH group. Table 1 shows socio-demographic and basic characteristics of the subjects stratified into MS-ICH patients versus MS-noICH patients, with depiction as column percentages.

The results of multivariable logistic regression analyses after controlling for all the variables are shown in Table 2. The analysis showed an increasing trend in the odds of having an ICH in MS patients with advancing age, whereas, the age group 65-74 years had the highest odds of ICH 2.74 (95% CI: 1.13-6.62, $P = .06$) when compared to the 18-44 years age group. But results were nonsignificant after adjusting for the variables.

A history of tobacco exposure has a statistically significant association with ICH (unadjusted OR: 2.66, 95% CI: 1.78-3.99, < .0001) and the same was noted with alcohol use (unadjusted OR: 2.86, 95% CI:1.85-4.43, $P < .0001$). When adjusted for age, gender, DM, HTN, diabetes, antiplatelet, anticoagulant, DMDs, and alcohol use; tobacco exposure still showed 2.4 times higher odds of having ICH in the MS population (adjusted OR: 2.44, 95% CI: 1.37-4.36, $P = .0025$). However, the association of alcohol was not statistically significant after adjusting for the covariates.

Patients with MS who had DM and HTN were more likely to develop ICH; the presence of HTN increased the odds of ICH 1.7 times in the MS population. However, when controlled for all the variables in the analysis, the

associations were not statistically significant. Regarding other comorbid conditions in the MS-ICH group, 10.2 % (11 of 107) had heart failure, 8.4% (9 of 107) had atrial fibrillation, 10.2 % (11 of 107) had renal disease, and 4.6% (5 of 107) had liver disease. These variables were not considered for adjustment analysis due to the limited sample size.

Medications and ICH

Medications including aspirin, other antiplatelet (clopidogrel or dipryamidole), anticoagulants, and DMDs were only analyzed where data was available (Table 1). Twenty percent (14 of 69) of the MS-ICH patients were taking aspirin and 23% (16 of 69) were taking aspirin or other antiplatelet agents. The regression analysis further showed that the MS patients who were using aspirin and/or other antiplatelet drugs were less likely to develop ICH when controlling for other variables. However, these associations were not statistically significant (Table 2).

Anticoagulants were grouped into warfarin alone and all anticoagulants (warfarin, apixaban, rivaroxaban, dabigatran, and enoxaparin). There were 8.7% (6 of 69) and 45% (31 of 69) patients with MS-ICH who were taking warfarin alone or all anticoagulants, respectively (Table 1). Regression analysis showed that MS patients who were taking warfarin or other anticoagulants were twice as likely to develop ICH when compared to patients who were not taking anticoagulants (Table 2). After adjusting for covariates, ICH risk remained higher in MS patients taking anticoagulants (adjusted OR: 2.15, 95% CI: 1.30-3.56, $P = .0028$), whereas, warfarin when analyzed alone showed no significant difference (adjusted OR: 1.52, 95% CI: .64-3.59, $P = .3366$).

Of the 107 MS-ICH patients, information regarding DMDs was available for 85 patients: 18% were on DMDs while 82% were untreated (Table 1). In the MS-noICH group, 22% were on DMDs while 78% were untreated and similarly patients with the missing data were excluded from the adjusted analysis. Further analysis showed that MS-ICH patients who were using DMDs were less likely to develop ICH compared with MS-ICH patients who were not using DMDs when controlled for all the variables in the study analysis (adjusted OR: .86, 95% CI: .44-1.65, $P = .6485$) (Table 2). However, the association was not statistically significant, most likely due to the limited sample size.

Discussion

This is the first EHR-based, national study of MS patients (from January 2000 to March 2016) examining risk factors, medications, and comorbidities associated with ICH in MS patients in the United States. Several studies reported the risk factors of ICH in the general population[19,20]; however, there is a little data focusing on ICH in MS patients, its risk factors, and other characteristics. This novel investigation describes a large MS cohort of 57,099 patients, out of which 107 (.2%) had the diagnosis of primary ICH whereas the crude incidence in general population was reported to be 15 per 100,000.[21] We found conventional risk factors such as tobacco exposure, older age, and use of anticoagulant medications contribute to ICH risk in MS similar to general population. Interestingly, we found a potential protective effect of antiplatelet medications and DMDs on risk of ICH.

ICH is the second most common type of stroke and has an increased morbidity and mortality as compared with IS.[22] Risk factors for ICH include advanced age, Asian ethnicity, HTN, amyloid angiopathy, impaired coagulation with or without the associated use of anticoagulant and antiplatelet treatments, vascular malformations, tobacco and alcohol abuse, sympathomimetic drugs, and tumors.[19,22] There are very few treatments for hemorrhagic stroke despite advances in IS treatment, hence clarification of risk factors in different patient populations is warranted and comorbidities have not been well studied for ICH in the MS population.[23] Due to disparate designs and lack of population based studies, the prevalence of comorbidities varies significantly in MS patient population.[24] Our study found that MS-ICH patients had similar comorbidities and risk factors that are associated with ICH in non-MS patients (older age, HTN, use of alcohol and tobacco, and anticoagulants).

Risk factors and Comorbid Conditions

Age is a significant risk factor for ICH in the general population.[19] Our study confirms increased risk of developing ICH with increasing age. For other nonmodifiable risk factors, we did not find a gender specific predisposition to ICH, even accounting for the fact that MS is more common in females. Likewise, ethnicity and race were not identified as risk factors, although the majority of MS-ICH patients in this study were Whites. However, earlier studies in the general population suggest an increased ICH risk in non-Whites (especially Asians).[25,26] Regarding modifiable risk factors, 1.62 % of the entire cohort carried a diagnosis of HTN, in contrast to other studies where the prevalence of HTN was about 8% among the MS patients.[27,28] This may be due to inconsistent reporting of HTN in this deidentified dataset. Although not statistically significant when adjusted for predicting variables, MS patients with HTN, as anticipated, had higher odds of developing ICH. Therefore, blood pressure management should be a priority in MS patients just as in the population as a whole. Hypertensive MS patients are also less prone to developing neurologic deficits compared to their normotensive counterparts. It is theorized that antihypertensive medications may have a protective role and also

Table 1. *Characteristics of patients*

Variables	MS-ICH n (%*)	MS-no ICH n (%*)	Total n (%†)	*P* value
Total	107 (.19)	56992 (99.81)	57099 (100.00)	<.0001
Demographics				
Gender				
Male	29 (27.1)	13,891 (25.1)	13,920 (25.07)	.5871
Female	78 (72.9)	41,517 (74.9)	41,594 (74.93)	
Age[#]				
18-44	17 (15.9)	12,746 (22.4)	12,763 (22.35)	.0013
45-64	42 (39.3)	28,433 (49.9)	28,475 (49.87)	
65-74	31 (29.0)	10,472 (18.4)	10,503 (18.39)	
75+	17 (15.9)	5341 (9.4)	5358 (9.38)	
Race				
Asian/PI**	2 (1.9)	423 (.7)	425 (.74)	.7377
Black	13 (12.2)	7320 (12.9)	7333 (12.84)	
White	81 (75.7)	43,633 (76.6)	43,714 (76.56)	
Others[‡]	3 (2.8)	1,772 (3.1)	1,775 (3.11)	
Unknown	8 (7.5)	3844 (6.7)	3852 (6.75)	
Risk Factors				
Tobacco exposure[#]				
Yes	35 (32.7)	8651 (15.2)	8686 (15.21)	<.0001
No	72 (67.3)	48,341 (84.8)	48,413 (84.79)	
Diabetes[#]				
Yes	16 (14.95)	4034 (7.1)	4050 (7.09)	.0015
No	91 (85.05)	52,958 (92.9)	53,049 (92.91)	
Hypertension[#]				
Yes	5 (4.7)	921 (1.6)	926 (1.62)	.0124
No	102 (95.3)	56,071 (98.4)	56,173 (98.38)	
Alcohol[#]				
Yes	27 (25.2)	5934 (10.4)	5961 (10.44)	<.0001
No	80 (74.8)	51,058 (89.6)	51,138 (89.56)	
Medications				
Aspirin				
Yes	14 (20.3)	3984 (17.2)	3998 (17.23)	.5004
No	55 (79.7)	19,150 (82.8)	19,205 (82.77)	
Antiplatelet group[§]				
Yes	16 (23.2)	4186 (18.1)	4202 (18.11)	.2726
No	53 (76.8)	18,948 (81.9)	19,001 (81.89)	
Warfarin				
Yes	6 (8.7)	1006 (4.4)	1012 (4.36)	.0775
No	63 (91.3)	22,128 (95.7)	22,191 (95.64)	
Anticoagulant group[#,‖]				
Yes	31 (44.9)	5294 (22.9)	5325 (22.95)	<.0001
No	38 (55.1)	17,840 (77.1)	17,878 (77.05)	
DMDs (MS drugs)[¶]				
Yes	15 (17.7)	9640 (22.2)	9655 (22.22)	.3103
No	70 (82.4)	33,732 (77.8)	33,802 (77.78)	

Abbreviations: DMDs, disease-modifying Drugs; MS, multiple sclerosis; MS-ICH, MS-Intracerebral hemorrhage.
*% represent a column percent.
†% represent a total percent.
‡Biracial, Hispanic, Middle Eastern, Native American, and others.
§Aspirin, dipyramidole, or clopidogrel.
‖Warfarin, apixaban, rivaroxaban, dabigatran, or enoxaparin.
¶Disease-modifying Drugs (DMDs): Interferon beta 1a, interferon beta 1b, Glatiramer acetate, peginterferon beta 1a, daclizumab, teriflunomide, fingolimod, alemtuzumab, mitoxantrone, and natalizumab. (Please note that the MS patients who had no DMD therapy data available were not included in this analysis).
#Statistically significant at the 5% significance level.
**Pacific Islanders.

Table 2. *Unadjusted and adjusted odds ratios of ICH for predicting variables in MS patients*

Variables	Unadjusted OR (95% C.I.)[†]	*P* value	Adjusted OR* (95% C.I.)[†]	*P* value
Gender				
Male	1.13 (.73-1.73)	.5873	1.20 (.71-2.00)	.4986
Female	Ref. = 1[‡]		Ref. = 1	
Age				
75+	2.27 (1.14-4.49)	.0632	2.34 (.88-6.25)	.3734
65-74	**2.25 (1.25-4.08)**[§]	**.0222**[§]	2.74 (1.13-6.62)	.0679
45-64	1.12 (.64-1.96)	.0320	1.83 (.80-4.20)	.9588
18-44	Ref. = 1		Ref. = 1	
Race				
Asian/PI	2.55 (.62-10.39)	.2513	2.33 (.31-17.22)	.4799
Black	.96 (.53-1.72)	.3047	.92 (.43-1.95)	.4400
Others	.91 (.29-2.89)	.4727	.52 (.07-3.78)	.2871
Unknown	1.67 (.77-3.61)	.4875	3.05 (.74-12.66)	.1752
White	Ref. = 1		Ref. = 1	
Tobacco exposure				
Yes	**2.66 (1.78-4.00)**[§]	**<.0001**[§]	**2.44 (1.37-4.36)**[§]	**.0025**[§]
No	Ref. = 1		Ref. = 1	
Diabetes				
Yes	**2.27 (1.33-3.87)**[§]	**.0026**[§]	1.10 (.61-1.98)	.7485
No	Ref. = 1		Ref. = 1	
Hypertension				
Yes	**2.93 (1.19-7.21)**[§]	**.0193**[§]	1.76 (.62-4.96)	.2857
No	Ref. = 1		Ref. = 1	
Aspirin				
Yes	1.22 (.68-2.20)	.5013	.79 (.42-1.47)	.4549
No	Ref. = 1		Ref. = 1	
Antiplatelet group				
Yes	1.37 (.78-2.39)	.2739	.89 (.49-1.62)	.7016
No	Ref = 1		Ref = 1	
Warfarin				
Yes	2.10 (.91-4.85)	.0840	1.52 (.65-3.60)	.3366
No	Ref. = 1		Ref. = 1	
Anticoagulant group				
Yes	**2.75 (1.71-4.42)**[§]	**<.0001**[§]	**2.15 (1.30-3.56)**[§]	**.0028**[§]
No	Ref. = 1		Ref. = 1	
DMDs (MS Drugs)				
Yes	.74 (.43-1.30)	.2997	.86 (.45-1.65)	.6485
No	Ref. = 1		Ref. = 1	
Alcohol				
Yes	**2.86 (1.85-4.43)**[§]	**<.0001**[§]	1.19 (.65-2.17)	.5809
No	Ref. = 1		Ref. = 1	

Abbreviations: DMDs, disease-modifying Drugs; MS, multiple sclerosis; PI, Pacific Islanders.

*Adjusted ORs for gender, race, age, tobacco exposure, diabetes, hypertension, DMDs, and alcohol were obtained from the logistic model with the anticoagulant group as the primary exposure (model IV). Adjusted ORs for Aspirin, anti-platelets and warfarin were obtained from models I, II, and III respectively.

[†]Statistically significant ORs are identified by the 95% C.I. that do not overlap with 1 (highlighted in bold in the table).

[‡]Ref = 1 signifies the reference category.

[§]Statistically significant values.

these patients may have increased scrutiny by their primary care physician due to their MS diagnosis.[27] DM is another vascular comorbidity associated with cerebrovascular and cardiovascular disorders. In our cohort, around 15% of the people with ICH had diabetes, as compared to only 7.6% of patients who did not have ICH. Patients with diabetes were at higher odds of suffering from ICH compared to those who did not have diabetes.

Tobacco exposure is a risk factor for the MS progression[29]; although a few studies found no attributable difference.[30] Tobacco exposure doubles the chance of developing MS.[31] Tobacco also causes an increase in MRI

lesion burden and MS disease progression.[32] In our cohort, 15% of MS patients had tobacco exposure (past or current). The results show that MS patients who smoke are twice as likely to develop ICH as compared to nonsmokers. This is consistent with other studies on the general population indicating an increased risk of ICH with tobacco exposure.[31,33,34] Heavy alcohol use is also associated with an increased incidence of ICH in the general population.[19] In our study, more than 10% of the population were consuming alcohol or had a history of heavy alcohol consumption. We found that these MS patients who consume alcohol were more likely to sustain an ICH. The odds of ICH remained high; however, the association was statistically nonsignificant when the analysis was controlled for the covariates (Table 2).

Medications and ICH

The use of Vitamin K antagonists has been associated with an increased risk of ICH.[35] Although warfarin decreases the risk of IS, it increases the chances of having an ICH by 68% compared with nonusers.[36] Schulman & Majeed and Ansell suggested that patients on nonvitamin K oral anticoagulants tend to have larger bleeds and more unfavorable outcomes compared to patients taking warfarin.[37,38] In the current study, MS patients on anticoagulants (warfarin, apixaban, rivaroxaban, dabigatran, or enoxaparin) were twice as likely to develop ICH.

Interestingly, our study showed near significance of aspirin or other antiplatelet agents use against ICH indicating a possible beneficial effect. Previously, Tsau et al. elaborated on the benefits of aspirin use in MS patients for the prevention of IS but suggested ICH as a potential complication in aspirin users at the same time.[39] The Antithrombotic Trialists' Collaboration also supports the idea of increased incidence of hemorrhagic stroke in general population.[40] Despite the minimal increase in ICH risk with aspirin use in the general population, the possibility of hemorrhage might be even higher in a setting where the BBB is already compromised, such as in MS.[14,39] Our study shows a trend, though statistically insignificant, suggesting a plausible consideration of protective role for aspirin and antiplatelet agents against ICH in MS patients.

Although statistically insignificant, patients with MS on DMDs depicted a protective trend against ICH. The possible protective effect persisted even after adjusted analyses; however this was also statistically insignificant. It is theoretically possible that inflammation as a result of ICH which causes brain injury and contributes to the eventual clinical presentation in ICH patients, is suppressed by DMDs in MS patients. However, other factors may also contribute to MS pathogenesis including activated microglia, cerebrovascular changes, and mitochondrial dysfunction.[41-43] Matrix metalloproteinase inhibitors reduce the injury to BBB in various animal models.[44] Additionally, blood levels of vasoconstrictive peptide-endothelin have been found to impair cerebral blood flow in MS.[45,46] This, in turn, causes a compromise in cerebrovascular reactivity in MS affecting the neurovascular coupling.[47] A large Swedish study by Zöller et al. reported a doubled risk of ICH early after the diagnosis of systemic immune-mediated diseases (lupus, rheumatoid arthritis, ankylosing spondylitis, psoriasis, and other diseases); however, MS was not in the high-risk category.[16] On the other hand, a study examining the Danish registry found an increased risk of death in MS patients due to cerebrovascular or cardiovascular complications.[48] Of note, less than 25% of our MS patient population was noted to be taking a DMD. This is lower than the published DMD adherence rates that range from 53.1% to 72.8%.[49] Reasons for this discrepancy are unclear, but could include the possibility of inaccurate or unsure diagnosis of MS, leading to nontreatment. However, this is hypothetical, and further studies are needed to confirm and explain this phenomenon.

Strengths

The major strength of this study is its large sample of patients representing MS from many United States (U.S.) hospitals. This is important as previous small studies were either conducted outside the U.S., excluded relevant patient populations (more specifically ICH) or were conducted at single centers. Because this is a population-based U.S. study, MS patients in this cohort are similar to the United States' population in age, sex, socioeconomic groups, medications, comorbidity distributions, and other risk factors. Unlike other studies, this study focuses solely on ICH in MS, which is a primarily neurological inflammatory disorder. The cohort of MS patients in the current study, to the best of our knowledge, is the largest ever reported in the literature. Furthermore, this EHR based research analysis is comparable to other database such as the national inpatient sampling which have similar distribution patterns across the data elements.[18,50] However, an added unique feature of the EHR database is the availability of medication record.

Limitations

This study has some limitations. The diagnoses were based on using billing codes, leading to the possibility of error due to misdiagnosis during the hospital admission. The probability of under-reporting a comorbidity is also high and patients might also have undiagnosed HTN and diabetes which may not have been adequately captured. Also, it is not certain whether the diagnosis of MS was based on McDonald's criteria, on clinical exam, cerebrospinal fluid analysis, imaging, or combination of them. There is a probability that in some cases white matter disease from vascular causes was misdiagnosed as MS and were not put on DMDs, in addition to under reporting the

use of DMDs. This could be the reason that DMDs appear to have a protective trend, and that those patients not on DMDs, have vascular white matter disease rather than MS. Patients who had no gender information were excluded and we were only able to identify 107 patients who had primary ICH, therefore, small sample size itself may skew the results. This prevented us from incorporating potentially important comorbidities such as hepatic failure, obstructive sleep apnea, and congestive heart failure. The retrospective study design itself has some innate limitations. This design cannot infer causality nor explain if the exposure to comorbidities and risk factors occurred before or after the ICH. As this is an observational study, many relevant confounding effects may still be present in these estimates.

Conclusions

This study asserts the association of modifiable and nonmodifiable risk factors like old age, DM, HTN, alcohol consumption, tobacco exposure, use of antiplatelet, and anticoagulant agents with ICH in the MS patient population. Tobacco exposure and anticoagulant use are strongly associated with ICH in MS patients. This study revealed no beneficial effect of aspirin or DMDs on the incidence of ICH. However, the near significance of the statistical tests in this regard suggest the need for a larger study to better analyze this relationship. The anti-inflammatory effects of aspirin and/or DMDs could logically be expected to have a salutary effect on ICH.

Author Contribution

Maryam Zulfiqar, MD−Study design, data interpretation, drafting, and revising the manuscript for intellectual content. Fares Qeadan, PhD−Study design, data analysis, interpretation, and review of the manuscript. Asad Ikram, MD - Study design, data interpretation, drafting, and revising the manuscript for intellectual content. Mudassir Farooqui, MD−Study design, drafting, and critical review of the manuscript. Sarah Pirio Richardson, MD−Critical revision and review of the manuscript. Christopher S Calder, MD, PhD−Study design, drafting, and critical review of the manuscript. Syed A Quadri, MD−Study design, drafting, and critical review of the manuscript. Puja Mathur, MD − Manuscript revision. Corey Ford, MD, PhD−Study design, drafting, and critical review of the manuscript. Santiago Ortega-Gutierrez, MD, MSc−Critical revision and review of the manuscript. Enrique Liera, MD−Critical revision and review of the manuscript. Harry Snow−Data extraction. Joel Nunez-Gonzalez MD−Critical review of the manuscript. Atif Zafar, MD−Study idea, design, data mining, data analysis, interpretation, drafting, and revising the manuscript for intellectual content.

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