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# Increased Risk of Hemorrhagic and Ischemic Strokes in Patients With Splenic Injury and Splenectomy

## A Nationwide Cohort Study

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**Abstract:** The spleen is a crucial organ in humans. Little is known about the association between stroke and splenic injury or splenectomy. The aim of this study was to determine the risk of stroke in patients with splenic injury and splenectomy.

A nationwide cohort study was conducted by analyzing the National Health Insurance Research Database in Taiwan. For comparison, control patients were selected and matched with splenic injury patients in a ratio of 4:1 according to age, sex, and the year of hospitalization. We analyzed the risks of stroke using a Cox proportional-hazards regression analysis.

A total of 11,273 splenic injury patients, including 5294 splenectomized and 5979 nonsplenectomized patients, and 45,092 control patients were included in this study. The incidence rates of stroke were 8.05, 6.53, and 4.25 per 1000 person-years in splenic injury patients with splenectomy, those without splenectomy, and the control cohort, respectively. Compared with the control cohort, splenic injury patients with splenectomy exhibited a 2.05-fold increased risk of stroke (95% confidence

interval [CI] 1.8–2.34), whereas those without splenectomy exhibited a 1.74-fold increased risk (95% CI 1.51–2). Splenectomy entailed an additional 1.21-fold increased risk of stroke compared with nonsplenectomy in patients with splenic injury.

This study revealed that splenic injury and splenectomy were significantly associated with an increased risk of hemorrhagic and ischemic strokes. The results of this study may alert physicians and patients to the complications of splenic injury and splenectomy.

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**Abbreviations:** CI = confidence interval, HR = hazard ratio, ICD-9-CM = International Classification of Diseases, Ninth Revision, Clinical Modification, IFN = interferon, NHI = National Health Insurance, NHIRD = National Health Insurance Research Database, NHRI = National Health Research Institutes, TNF = tumor necrosis factor, TOAST = Trial of Org 10172 in Acute Stroke Treatment.

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## INTRODUCTION

The spleen is a reticuloendothelial organ that constitutes a crucial part of the hematologic and immunologic system. Splenic injury is commonly associated with blunt abdominal trauma. The standard management of splenic injury has shifted from surgical splenectomy to spleen-preserving nonoperative procedures.<sup>1,2</sup> However, approximately 22,000 all-cause splenectomies are still performed per year in the United States.<sup>3–5</sup> The most common indications for splenectomy are hematologic disorders, such as hemolytic anemia, autoimmune hemolytic anemia, sickle cell disease,  $\beta$ -thalassemia, and immune thrombocytopenic purpura.<sup>3</sup> Although splenectomy in trauma patients has decreased in recent years, this procedure is still recommended for severe splenic injury (grade III–V) because of the high failure rate of nonoperative management.<sup>1,6,7</sup> Moreover, emergent splenectomy remains a life-saving technique for patients who exhibit life-threatening hemorrhage caused by splenic injury.<sup>6,7</sup>

Several complications of splenectomy, including bacterial infections, thrombosis, thromboembolism, pulmonary arterial hypertension, and cancer, have been described.<sup>3,8–11</sup> Thrombosis and thromboembolism may complicate ischemic heart disease, ischemic stroke, hemorrhagic stroke, pulmonary embolism, deep vein thrombosis, and portal vein thrombosis.<sup>3,8,10,11</sup> However, the association of thrombosis and thromboembolism with splenectomy has been inconsistently reported in previous studies.<sup>8,10,12,13</sup>

Splenic injury can impair the function of the spleen by causing the loss of functional splenic tissue.<sup>14</sup> However, no study has evaluated the increased risk of stroke in patients with splenic injury. In addition, most studies have investigated

vascular complications of splenectomy that was indicated for hematologic disorders.<sup>12,13,15–17</sup> Therefore, we conducted a nationwide retrospective cohort study to determine the risk of ischemic and hemorrhagic strokes in patients with splenic injury and splenectomy by analyzing the National Health Insurance Research Database (NHIRD) of Taiwan.

## METHODS

### Data Source

The Taiwan National Health Insurance (NHI) program is a single-payer universal insurance program that was initiated in 1995 and covers approximately 99% of the Taiwanese population (>25 million people; <http://www.nhi.gov.tw/english/index.aspx>). The government of Taiwan has authorized the National Health Research Institutes (NHRI) to establish the NHIRD and release decoded and scrambled data for research purposes. In this study, we analyzed the hospitalization claims data, which constitute a subdataset of the NHIRD, containing information on sex, age, dates of admission and discharge, diagnoses, surgical procedures, discharge status, and medical expenditures. Diagnoses and management were classified according to the International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) codes. This study was approved by the Ethics Review Board of China Medical University (CMU-REC-101–012).

### Sampled Patients

The study patients were selected from the inpatients claims of patients who were diagnosed with splenic injury (ICD-9-CM code 865) between 1998 and 2010. Patients aged 20 years or older with splenic injury who underwent splenectomy (ICD-9-CM procedure codes 41.2, 41.3, 41.5) were classified as the splenectomized cohort, and patients with splenic injury who did not undergo splenectomy were classified as the nonsplenectomized cohort. The dates of the first hospitalization for splenic injury were defined as the index dates. To create a control cohort, patients without splenic injury and splenectomy were randomly selected and matched with splenic injury patients in a 4:1 ratio according to age group with a 5-year interval, sex, and the year of the index date. The exclusion criteria were age <20 years, a history of stroke (ICD-9-CM codes 430–438) before the index date, and a lack of complete information.

### Outcome and Comorbidities

Hemorrhagic (ICD-9-CM codes 430–432) and ischemic strokes (ICD-9-CM codes 433–438) were defined as the endpoint of this study. All of the included patients were followed from the index date to the occurrence of the endpoint, withdrawal from the NHI, or the end of 2011. To evaluate the potential risk and account for confounding factors, we explored the comorbidities of each patient, namely hypertension (ICD-9-CM codes 401–405), diabetes mellitus (ICD-9-CM code 250), chronic obstructive pulmonary disease (ICD-9-CM codes 491, 492, 496), hyperlipidemia (ICD-9-CM code 272), liver cirrhosis (ICD-9-CM code 571), chronic renal failure (ICD-9-CM code 585), autoimmune diseases (ICD-9-CM codes 710.0, 710.1, 710.2, 710.3, 714), cancer (ICD-9-CM codes 140–208), atrial fibrillation (ICD-9-CM code 427.31), and coronary artery disease (ICD-9-CM codes 410–414).

### Statistical Analysis

The  $\chi^2$  test was used for categorical variables, whereas the Student *t* test was used for continuous variables. Cumulative

incidences of stroke in the splenectomized, nonsplenectomized, and control cohorts were explored using the Kaplan–Meier method, and the differences were determined using log-rank tests. The incidence rates of stroke stratified by sex, age, and comorbidity were calculated for the splenectomized, nonsplenectomized, and control cohorts, respectively. Univariable and multivariable Cox proportional hazard regression models were used to determine the risk for stroke, shown as a hazard ratio (HR) with a 95% confidence interval (CI). All *P* values were 2-tailed, and a *P* value <0.05 was considered significant. Data management and analyses were performed using SAS 9.3 software (SAS Institute, Cary, NC).

## RESULTS

A total of 11,273 patients with splenic injury and 45,092 control patients were included in this study (Table 1). In the splenic injury cohort, 5294 patients received splenectomy, and 5979 patients did not receive splenectomy. The age of the patients with splenic injury was  $41.9 \pm 16.3$  years (mean  $\pm$  standard deviation). Most patients were aged 49 years or younger. Males accounted for approximately 71% of the patients in each cohort. Compared with the control cohort, hypertension, diabetes mellitus, chronic obstructive pulmonary disease, hyperlipidemia, chronic renal failure, atrial fibrillation, and coronary artery disease were more prevalent in the splenic injury cohort. The average follow-up durations were 6.08, 6.26, and 6.71 years in splenic injury patients without splenectomy, those with splenectomy, and the control cohort, respectively.

The cumulative incidences of stroke were the highest in splenic injury patients with splenectomy, followed by those without splenectomy and the control cohort. Significant differences in the cumulative incidences of stroke were observed among these 3 cohorts (Figure 1). The incidence rates of stroke were 8.05 per 1000 person-years in splenic injury patients with splenectomy and 6.53 per 1000 person-years in those without splenectomy; both were significantly higher than the incidence rate of the control cohort (4.25 per 1000 person-years; Table 2). Compared with the control cohort, splenic injury patients with splenectomy exhibited a 2.05-fold increased risk of stroke (95% CI 1.8–2.34), whereas those without splenectomy exhibited a 1.74-fold increased risk of stroke (95% CI 1.51–2).

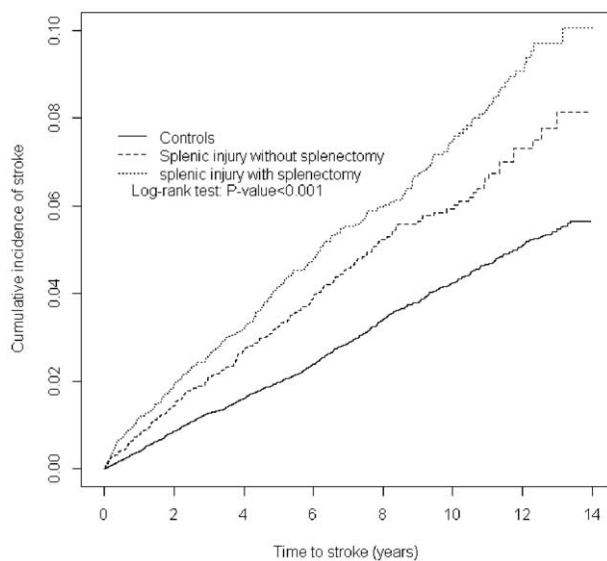
Among the splenic injury patients without splenectomy, the adjusted HRs for hemorrhagic and ischemic strokes were 2.66 (95% CI 1.97–3.58) and 1.57 (95% CI 1.34–1.84), respectively. Furthermore, splenic injury patients receiving splenectomy were 3.04-fold more likely to develop hemorrhagic stroke (95% CI 2.28–4.05) and 1.87-fold more likely to develop ischemic stroke (95% CI 1.61–2.18) than the control cohort after adjustment for age, sex, and comorbidities.

Stroke occurred more frequently in males in all 3 cohorts (Table 2). Although male patients exhibited a higher incidence rate of stroke in the nonsplenectomized cohort (male vs female, 1.79 vs 1.62), females exhibited a higher adjusted HR for stroke in the splenectomized cohort (male vs female, 1.99 vs 2.28). The incidence of stroke increased with age in the control, splenectomized, and nonsplenectomized patients. The increased risk of stroke relative to that of the control cohort was the highest in the younger age group of  $\leq 49$  years (adjusted HR in the nonsplenectomized cohort, 2.59; in the splenectomized cohort, 3.23). The comorbidity-stratified risk of stroke was increased in the patients with splenic injury, irrespective of whether they underwent splenectomy. We further analyzed the incidence of stroke associated with the follow-up duration and

**TABLE 1.** Comparison of Demographics and Comorbidity Between the Control Cohort and Splenic Injury Patients With and Without Splenectomy

	Splenic Injury				P
	Control (N = 45092) (%)	Without Splenectomy (N = 5979) (%)	With Splenectomy (N = 5294) (%)	Total (N = 11273) (%)	
Age, y					0.99
≤49	31792 (70.5)	4254 (71.2)	3694 (69.8)	7948 (70.5)	
50–64	8272 (18.3)	1122 (18.8)	946 (17.9)	2068 (18.3)	
≥65	5028 (11.2)	603 (10.1)	654 (12.4)	1257 (11.2)	
Mean ± SD	41.7 ± 16.5	41.5 ± 16	42.4 ± 16.7	41.9 ± 16.3	0.28
Sex					0.99
Female	13100 (29.1)	1776 (29.7)	1499 (28.3)	3275 (29.1)	
Male	31992 (71)	4203 (70.3)	3795 (71.7)	7998 (71)	
Comorbidity					
Hypertension	1507 (3.34)	288 (4.82)	251 (4.74)	539 (4.78)	<0.001
Diabetes mellitus	1010 (2.24)	227 (3.8)	188 (3.55)	415 (3.68)	<0.001
Chronic obstructive pulmonary disease	375 (0.83)	81 (1.35)	89 (1.68)	170 (1.51)	<0.001
Hyperlipidemia	486 (1.08)	158 (2.64)	110 (2.08)	268 (2.38)	<0.001
Liver cirrhosis	780 (1.73)	364 (6.09)	338 (6.38)	702 (6.23)	<0.001
Chronic renal failure	147 (0.33)	27 (0.45)	31 (0.59)	58 (0.51)	0.003
Autoimmune diseases	65 (0.14)	13 (0.22)	8 (0.15)	21 (0.19)	0.31
Cancer	602 (1.34)	97 (1.62)	58 (1.1)	155 (1.37)	0.74
Atrial fibrillation	108 (0.24)	18 (0.3)	23 (0.43)	41 (0.36)	0.02
Coronary artery disease	801 (1.78)	131 (2.19)	128 (2.42)	259 (2.3)	<0.001

SD = standard deviation.



**FIGURE 1.** Cumulative incidences of stroke in the control cohort and splenic injury patients with and without splenectomy. The cumulative incidence of stroke was the highest in splenic injury patients with splenectomy, followed by those without splenectomy and the control cohort. Log-rank tests: splenic injury patients with splenectomy vs those without splenectomy,  $P=0.02$ ; splenic injury patients with splenectomy vs control cohort,  $P<0.001$ ; splenic injury patients with splenectomy vs control cohort,  $P<0.001$ .

demonstrated that the incidence and relative risk of stroke increased in both the splenectomized and nonsplenectomized cohorts when the follow-up duration was >1 year.

Table 3 shows a comparison of the risk of stroke between splenectomized and nonsplenectomized patients who had splenic trauma, revealing a 1.21-fold higher risk of stroke for patients who received splenectomy (95% CI 1.01–1.44). Females exhibited a significantly higher risk of stroke after splenectomy (adjusted HR 1.5; 95% CI 1.05–2.16). However, the increased risk of stroke in male patients receiving splenectomy compared with nonsplenectomy was nonsignificant (adjusted HR 1.13; 95% CI 0.92–1.39).

### DISCUSSION

This large nationwide cohort study confirmed the increased risk of hemorrhagic and ischemic strokes among patients with splenic injury. We observed that splenectomy increased the risk of stroke compared with nonsplenectomy in splenic injury patients.

The spleen is a reticuloendothelial organ that constitutes a vital part of the hematologic and immunologic systems. Multiple factors are likely to contribute to vascular events in patients with splenic injury and splenectomy, including platelet activation, hypercoagulability, activation of the endothelium, and altered lipid profiles.<sup>3</sup> Several studies have reported that splenectomy resulted in thrombocytosis, leukocytosis, concentrated hemoglobin, hyperlipidemia, and increased C-reactive protein levels.<sup>18–23</sup> All these alterations are independently associated with an increased risk of vascular complications in splenectomized patients.

**TABLE 2.** HRs of Hemorrhagic and Ischemic Strokes Among the Control Cohort and Splenic Injury Patients With and Without Splenectomy Stratified by Demographics, Comorbidity, and Follow-Up Duration

	Control (N = 45092)			Without Splenectomy (N = 5979)			With Splenectomy (N = 5294)				
	Case	Rate <sup>†</sup>		Case	Rate <sup>†</sup>	Crude HR (95% CI)	Adjusted HR <sup>‡</sup> (95% CI)	Case	Rate <sup>†</sup>	Crude HR (95% CI)	Adjusted HR <sup>‡</sup> (95% CI)
All	1281	4.25		232	6.53	1.54 (1.34–1.77)***	1.74 (1.51–2)***	267	8.05	1.89 (1.66–2.16)***	2.05 (1.8–2.34)***
Hemorrhagic	195	0.65		56	1.58	2.45 (1.82–3.3)***	2.66 (1.97–3.58)***	62	1.87	2.88 (2.16–3.83)***	3.04 (2.28–4.05)***
Ischemic	1086	3.60		176	4.95	1.38 (1.17–1.61)***	1.57 (1.34–1.84)***	205	6.18	1.72 (1.48–1.99)***	1.87 (1.61–2.18)***
Sex											
Female	320	3.68		54	5.02	1.35 (1.02–1.81)*	1.62 (1.21–2.17)**	73	7.73	2.10 (1.63–2.71)***	2.28 (1.77–2.95)***
Male	961	4.48		178	7.18	1.61 (1.37–1.89)***	1.79 (1.52–2.1)***	194	8.17	1.82 (1.56–2.13)***	1.99 (1.7–2.32)***
Age, y											
≤49	240	1.08		82	3.05	2.85 (2.22–3.67)***	2.59 (2.01–3.35)***	96	3.81	3.50 (2.76–4.43)**	3.23 (2.54–4.1)***
50–65	394	7.48		76	12.6	1.71 (1.34–2.19)***	1.68 (1.31–2.14)***	80	15.1	2.03 (1.59–2.58)***	1.92 (1.51–2.44)***
≥65	647	23.6		74	28.0	1.19 (0.93–1.51)	1.16 (0.91–1.48)	91	33.8	1.43 (1.15–1.78)**	1.44 (1.16–1.8)**
Comorbidity											
No	939	3.31		159	4.98	1.52 (1.29–1.8)***	1.76 (1.49–2.08)***	193	6.41	1.93 (1.65–2.25)***	2.1 (1.8–2.45)***
Yes	342	19.5		73	20.1	1.03 (0.8–1.33)	1.44 (1.12–1.86)**	74	24.2	1.25 (0.97–1.6)	1.67 (1.29–2.15)***
Follow-up, y											
≤1	176	3.96		44	7.79	1.97 (1.41–2.74)***	1.47 (1.26–1.71)***	55	11.7	2.95 (2.18–4)***	1.73 (1.49–2)***
>1	1105	4.30		188	6.29	2.12 (1.52–2.95)***	1.68 (1.44–1.96)***	212	7.44	3.10 (2.29–4.21)***	1.89 (1.63–2.19)***

CI = confidence interval, HR = hazard ratio.

\*  $P < 0.05$ .

\*\*  $P < 0.01$ .

\*\*\*  $P < 0.001$ .

† Incidence rate per 1000 person-years.

‡ Including age, sex, and comorbidities of hypertension, diabetes mellitus, chronic obstructive pulmonary disease, hyperlipidemia, liver cirrhosis, chronic renal failure, autoimmune diseases, cancer, atrial fibrillation, and coronary artery disease.



**TABLE 3.** HRs of Hemorrhagic and Ischemic Strokes Among Splenic Injury Patients With and Without Splenectomy Stratified by Demographics and Comorbidity

	Without Splenectomy		With Splenectomy	
	Crude HR (95% CI)	Adjusted HR (95% CI) <sup>†</sup>	Crude HR (95% CI)	Adjusted HR (95% CI) <sup>†</sup>
All	1 (Reference)	1 (Reference)	1.24 (1.04–1.48)*	1.21 (1.01–1.44)*
Hemorrhagic	1 (Reference)	1 (Reference)	1.19 (0.83–1.72)	1.18 (0.82–1.69)
Ischemic	1 (Reference)	1 (Reference)	1.26 (1.03–1.54)*	1.22 (0.99–1.49)
Sex				
Female	1 (Reference)	1 (Reference)	1.56 (1.09–2.21)*	1.5 (1.05–2.16)*
Male	1 (Reference)	1 (Reference)	1.15 (0.93–1.41)	1.13 (0.92–1.39)
Age, y				
≤49	1 (Reference)	1 (Reference)	1.26 (0.93–1.69)	1.26 (0.94–1.69)
50–64	1 (Reference)	1 (Reference)	1.19 (0.87–1.63)	1.16 (0.85–1.6)
≥65	1 (Reference)	1 (Reference)	1.21 (0.89–1.64)	1.24 (0.91–1.7)
Comorbidity				
No	1 (Reference)	1 (Reference)	1.28 (1.04–1.58)*	1.23 (0.99–1.51)
Yes	1 (Reference)	1 (Reference)	1.21 (0.87–1.67)	1.16 (0.84–1.61)

CI = confidence interval, HR = hazard ratio.

\* *P* < .05.

<sup>†</sup> Including age, sex, and comorbidities of hypertension, diabetes mellitus, chronic obstructive pulmonary disease, hyperlipidemia, liver cirrhosis, chronic renal failure, autoimmune diseases, cancer, atrial fibrillation, and coronary artery disease.

In addition to the aforementioned factors, bidirectional interaction between brain injury and spleen is proposed.<sup>24,25</sup> Brain injury, including trauma, hemorrhage, and ischemia, induces an immunoinflammatory response and release of inflammatory cytokines by macrophages in the spleen, the so-called “brain-spleen inflammatory coupling.”<sup>24,25</sup> The brain is susceptible to inflammatory substances activated by the immune-inflammatory processes.<sup>26</sup> For example, tumor necrosis factor (TNF)-α has been shown to result in exacerbation of brain ischemia. TNF-α inhibitors could improve the outcome of ischemic brain in animal models.<sup>25,26</sup> Immune alterations, including increased ratio of interferon (IFN)-γ to interleukin-10 and significant elevation of absolute lymphocyte, CD4+ T cell, and CD8+ T cell counts, have been described after splenectomy.<sup>27,28</sup> T lymphocytes are associated with the production of IFN-γ and TNF-α, which have shown a direct pathogenetic role in neuronal ischemic damage.<sup>29</sup> Tuttolo-mondo et al<sup>30</sup> reported a significant elevation in peripheral frequency of CD4+ cells and CD28 null cells (CD4+CD28- T cells) in patients with acute ischemic stroke, particularly in those with cardioembolic stroke. These complex multifactorial interactions could possibly play a critical role in the pathogenesis of stroke in splenectomized patients.

Our study revealed that the cumulative incidence of stroke was the highest in splenic trauma patients who underwent splenectomy, followed by those who did not receive splenectomy. Cox proportional hazard modeling showed that splenectomy and splenic injury were independently associated with an increased risk of stroke. Patients with splenic injury are typically young (approximately 70% were younger than 50 years in this study) and have few medical comorbidities. These young patients are at a lower risk of stroke. Recently, surgery and invasive procedures were shown to be associated with an increased risk of stroke within 30 days after the procedures

and operations.<sup>31</sup> However, the risk of stroke returned to the baseline if the surgery and invasive procedures were performed >30 days previously.<sup>31</sup> The increased risk of stroke after splenic injury and splenectomy may be a postprocedural or postoperative phenomenon. But our study showed that splenic trauma patients, both those who underwent splenectomy and those who did not, exhibited a higher HR of stroke during a follow-up period of >1 year than those who were observed during a follow-up duration of ≤1 year. Therefore, merely the postprocedural or postoperative attribution of increased risk of stroke cannot explain the results of our study. In other words, the increased risk is likely attributable to the splenic injury and splenectomy.

Kristinsson et al<sup>8</sup> reported the long-term complications of 8149 veterans who underwent splenectomy irrespective of indications. During a 27-year follow-up, they determined that splenectomized patients exhibited an increased risk of pulmonary embolism and deep vein thrombosis, but not ischemic stroke, coronary artery disease, or acute myocardial infarction.<sup>8</sup> By contrast, our study revealed that splenic trauma patients exhibited a 1.74-fold greater risk of stroke if they did not receive splenectomy and a 2.05-fold increased risk of stroke if they received splenectomy. The risk of thromboembolic events after splenectomy varies considerably in previous studies.<sup>8,10,12,13</sup> The conditions under which splenectomy is indicated and the presence or absence of ongoing intravascular hemolysis are likely to determine the risk of thromboembolic events after splenectomy.<sup>3</sup> Patients with thalassemia intermedia, Hgb E/β-thalassemia, sickle cell anemia, and hereditary stomatocytosis exhibit a greatly increased risk of vascular complications after splenectomy. Moreover, these hematologic disorders themselves could be associated with vascular complication.<sup>3</sup> Trauma patients with splenectomy are thought to have a baseline or increased risk.<sup>3</sup> In our study, all patients

underwent splenectomy because of splenic injury. The differences in indications for splenectomy may explain the conflicting results regarding the risk of thromboembolic events after splenectomy.

Our study revealed that both patients with splenic injury who underwent splenectomy and those who did not exhibited an increased risk of hemorrhagic and ischemic strokes. The increased HRs of hemorrhagic stroke were higher than those of ischemic stroke after adjustment for age, sex, and comorbidities. Based on our research, there has been no comprehensive study that evaluated the risk of hemorrhagic stroke after splenic injury and splenectomy.<sup>32</sup> Intracranial hemorrhage may be associated with cerebral venous thrombosis.<sup>33</sup> Ischemic stroke and hemorrhagic stroke also share several similar risk factors, including hypertension, atherosclerosis, coronary artery disease, heart failure, atrial fibrillation, hematologic disorders, hyperlipidemia, diabetes mellitus, obesity, and alcohol use.<sup>34</sup> Some factors, such as diabetic foot, increased CD4+CD28- T cells (CD28 null cells), arterial stiffness, and elevation of immuno-inflammatory markers, are found commonly in patients with stroke and coronary artery disease.<sup>30,35–39</sup> The mechanism of ischemic stroke in splenectomized patients could be also responsible for the increased incidence of hemorrhagic stroke in patients after splenectomy.

Although this study was a large nationwide study, several limitations remain. First, the lack of data on risk factors for stroke, such as smoking, obesity, and socioeconomic status, represents a major limitation. Second, the severity of stroke is not specified in the dataset. Therefore, we could not evaluate the association of the severity of stroke with splenic injury and splenectomy. Third, laboratory data are not included in the database. Fourth, information on the etiology and subtypes of ischemic stroke was not available in the NHIRD. We cannot discriminate the subtypes of ischemic stroke according to the Trial of Org 10172 in Acute Stroke Treatment (TOAST) classification.<sup>40</sup> Finally, the diagnoses of stroke, splenic injury, and splenectomy could not be validated using the NHIRD. Misclassification of diseases may cause bias in our study, although several studies have proven the accuracy of the NHIRD.<sup>41,42</sup>

In conclusion, our study results show that splenic injury and splenectomy are significantly associated with an increased risk of hemorrhagic and ischemic strokes. In addition, splenectomy additionally increased the risk of stroke in splenic injury patients. Higher HRs of hemorrhagic stroke than of ischemic stroke were observed among patients with splenic injury and splenectomy. The results of this study may alert physicians and patients to the severe complications of splenic injury and splenectomy. Additional trials may be required to investigate prophylactic management of these complications.

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