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Long-Term Risk of Acute Coronary Syndrome in Splenectomized Patients Due to Splenic Injury

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Abstract: We aimed to assess the magnitude and duration of risk of acute coronary syndrome (ACS) associated with splenectomy for splenic injury.

We identified 5139 splenectomized patients (the splenectomy cohort) to compare with 2 other cohorts for assessing the magnitude and risk of ACS: the first cohort comprising subjects without splenic injury and without splenectomy (control cohort), and the second cohort comprising nonsplenectomized patients with splenic injury (nonsplenectomy cohort; n = 6391). For each splenic injury patient (n = 11530), 4 control comparisons were frequency-matched by the year of index date, age, and sex (n = 46120).

The adjusted risk of ACS was significantly higher in the splenectomy group than in the control group (2.08 vs 1.68 per 1000 person-years; adjusted hazard ratio [HR], 1.30; 95% confidence interval [CI], 1.01–1.68). The sex-specific data showed that the adjusted HR for the splenectomy group, compared with the control group, was 1.29 in men (95% CI, 0.97–1.73) and 1.36 in women (95% CI, 0.79–2.33). The age-specific analyses failed to demonstrate a significantly higher adjusted HR of ACS in the splenectomized patients in any age subgroup, compared with their counterparts in the control group. Furthermore, no difference in the risk of ACS was detected between the splenectomy and nonsplenectomy cohorts within the splenic injury patients.

In comparison with the control cohort, patients undergoing splenectomy for splenic injury exhibited an elevated risk of ACS.

(*Medicine* 94(9):e610)

Abbreviations: ACS = acute coronary syndrome, CI = confidence interval, COPD = chronic obstructive pulmonary disease, HR = hazard ratio, ICD-9-CM = International Classification of Diseases, Ninth Revision, Clinical Modification, NHIRD = National Health Insurance Research Database.

INTRODUCTION

The spleen, histologically divided into white pulp and red pulp, serves crucial hematological and immunological functions, such as the elimination of blood-borne pathogens and filtration of blood through splenic sinusoids. Splenectomy is associated with an increase in platelet count,[1–4] hemoglobin concentration,[3,5] white blood cell count,[4] plasma cholesterol,[6,7] and risk of infections.[8–11] All these factors are associated with prothrombotic states and increased risks of arteriothrombosis.[12–16]

The risk of thromboembolic diseases after splenectomy varies greatly, depending on the indication for splenectomy. The risk is also related to the patient's genetic and environmental risk factors. For example, thromboembolic events are mostly reported in splenectomized patients with thalassemia intermedia,[17] which is a characteristic of marked intravascular hemolysis. Splenectomy for other hematological diseases is also associated with various vascular complications.[18]

The association between splenectomy and thromboembolic events, particularly acute coronary syndrome (ACS), remains debatable. An early study concluded that splenectomy for trauma is associated with a significant excess mortality from pneumonia and ischemic heart disease.[19] Conversely, an animal study demonstrated that splenectomy effectively blocked myocardial infarction-induced atherosclerosis.[20] Moreover, myocardial infarction and ACS have rarely been reported in thalassemia or in any other hemolytic disorders after splenectomy.[18]

Given that trauma remains the primary indication for splenectomy,[21] determining whether splenectomy in patients with splenic injury is associated with an elevated risk of ACS is essential. Therefore, we conducted this 13-year follow-up study by analyzing a broadly representative population-based cohort from Taiwan's National Health Insurance Research Database (NHIRD).

Editor: Leonardo Roever.
Received: January 3, 2015; revised and accepted: February 10, 2015.
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This study is supported in part by Taiwan Ministry of Health and Welfare Clinical Trial and Research Center of Excellence (MOHW104-TDU-B-212-113002); China Medical University Hospital, Academia Sinica Taiwan Biobank, Stroke Biosignature Project (BM104010092); NRPB Stroke Clinical Trial Consortium (MOST 103-2325-B-039 -006); Tseng-Lien Lin Foundation, Taichung, Taiwan; Taiwan Brain Disease Foundation, Taipei, Taiwan; Katsuzo and Kiyo Aoshima Memorial Funds, Japan; and Health, and welfare surcharge of tobacco products, China Medical University Hospital Cancer Research Center of Excellence (MOHW104-TDU-B-212-124-002, Taiwan).

The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript. No additional external funding received for this study.

Authorship Contributions: conception and design: M-ST, C-HK; administrative support: C-HK; collection and assembly of data: all authors; data analysis and interpretation: all authors; manuscript writing: all authors; final approval of manuscript: all authors.

All authors report no conflicts of interest.

ISSN: 0025-7974
DOI: 10.1097/MD.0000000000000610

METHODS

Data Source

The National Health Insurance (NHI) program is a government-operated single-payer health insurance program, which was established in 1995. It covered approximately 99% of the 23.72 million residents of Taiwan by 2009 (http://www.nhi.gov.tw/english/index.aspx). The National Health Research Institutes (NHRI) maintains the claims data of the NHI program. NHRI established the NHIRD and releases it annually to the public for research purposes. All the data related to personal identification are encrypted by the Bureau of National Health Insurance before the dataset is released. Data files are linked with scrambled patient identification numbers to protect the privacy of the patients. The diagnostic codes in the NHIRD are in the format of the International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM). This study was approved by the Ethics Review Board of China Medical University (CMU-REC-101–012).

Sampled Participants

We used data from the NHIRD to identify inpatients between 1998 and 2010 who were diagnosed with splenic injury (ICD-9-CM 865). Patients older than 20 years with splenic injury who underwent splenectomy (ICD-9-OP 41.5) were considered as the splenectomy group, and patients with splenic injury who did not undergo splenectomy were considered as the nonsplenectomy group. The index date was the date on which the splenic injury occurred. The exclusion criteria were: age <20 years (n = 3560), a history of ACS (ICD-9-CM 410, 411.1, 411.8) at any time before the index date (n = 106), or missing data regarding date of birth or sex (n = 240). For each splenic injury patient, 4 comparisons were randomly selected from the pool of participants without splenic injury and ACS at the baseline, frequency-matched by the year of index date, age (every 5-year span), and sex. The workflow of patient selection was summarized as Figure 1, and the patients' age distribution was described in supplementary Table 1, http://links.lww.com/MD/A223.

Outcome and Comorbidities

The outcome of interest was a new diagnosis of ACS between 1998 and 2011, the data of which were obtained from hospital records. All the participants were followed up from the index date until the date of the diagnosis of ACS, the date of withdrawal from the database, or the date of the end of follow-up (December 31, 2011), whichever occurred first. Similar to the analyses in our published articles,[22–24] we adjusted several well-known risk factors or confounders of ACS risk in the present study, such as hypertension (ICD-9-CM 401–405), diabetes (ICD-9-CM 250), hyperlipidemia (ICD-9-CM 272), stroke (ICD-9-CM 430–438), chronic obstructive pulmonary disease (COPD) (ICD-9-CM 490–496), heart failure (ICD-9-CM 428), ischemic heart disease (ICD-9-CM 410–414, except 410, 411.1, 411.8), and menopause (ICD-9-CM V49.81, 627.2, 627.8, and 627.9).[25,26] All these comorbidities were determined from inpatient claims data for each participant and defined as preexisting comorbidities if they were claimed before the index date.

Statistical Analysis

We compared the distribution of demographic factors and the proportions of comorbidities between the splenectomy, nonsplenectomy, and control groups by using a chi-square test, Fisher exact test, and Student *t* test. The incidence density rate of ACS in the 3 groups was calculated in the follow-up period until the end of the study (2011). The univariable and multivariable Cox proportional hazards regression models were used to determine the risk of developing ACS. The multivariate

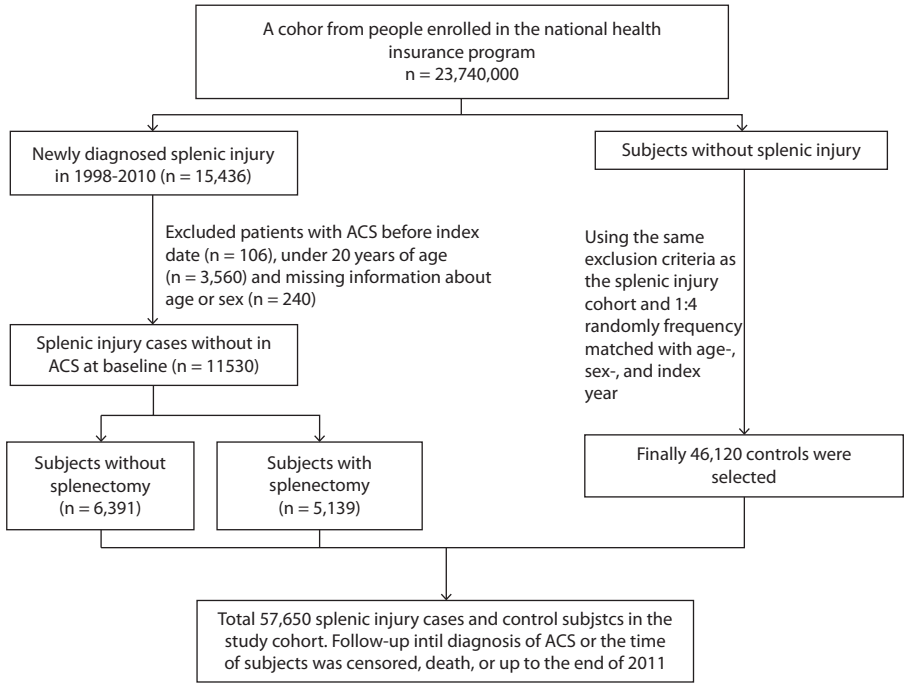


FIGURE 1. Flow diagram of study subjects.

TABLE 1. Comparison of Demographics and Comorbidity Between Patients With Splenic Injury and Controls

		splenic injury			
	Control (N = 46120) n (%)	Without splenectomy (N = 6391) n (%)	With splenectomy (N = 5139) n (%)	Total (N = 11530) n (%)	*P*
Age (year)					0.99
≤ 49	32012 (69.4)	4483 (70.2)	3520 (68.5)	8003 (69.4)	
50–65	8536 (18.5)	1204 (18.8)	930 (18.1)	2134 (18.5)	
≥65	5572 (12.1)	704 (11.0)	689 (13.4)	1393 (12.1)	
Mean (SD)*	42.1 (16.8)	41.9 (16.3)	42.9 (17.0)	42.3 (16.6)	0.22
Sex					0.99
Female	13396 (29.0)	1901 (29.7)	1448 (28.2)	3349 (71.0)	
Male	32724 (71.0)	4490 (70.3)	3691 (71.8)	8181 (71.0)	
Comorbidity					
Hypertension	1941 (4.21)	376 (5.88)	301 (5.86)	677 (5.87)	<0.001
Diabetes	1189 (2.58)	266 (4.16)	211 (4.11)	477 (4.14)	<0.001
Hyperlipidemia	546 (1.18)	179 (2.80)	112 (2.18)	291 (2.52)	<0.001
Stroke	870 (1.89)	165 (2.58)	122 (2.37)	287 (2.49)	<0.001
COPD	477 (1.03)	104 (1.63)	102 (1.98)	206 (1.79)	<0.001
Ischemic heart disease	702 (1.52)	135 (2.11)	115 (2.24)	250 (2.17)	<0.001
Heart failure	224 (0.49)	61 (0.95)	45 (0.88)	106 (0.92)	<0.001
Menopause†	10 (0.02)	2 (0.03)	1 (0.02)	3 (0.03)	0.73

COPD = chronic obstructive pulmonary disease.
* Two sample *t* test.
Chi-square test and † Fisher exact test compared with total gallstone.

models were adjusted for age, sex, and comorbidities of hypertension, diabetes, hyperlipidemia, stroke, COPD, heart failure, ischemic heart disease, and menopause. The related hazard ratio (HR) and 95% confidence interval (CI) were estimated in the Cox model.

We estimated the group-specific cumulative incidences by Kaplan–Meier survival curves for unadjusted and adjusted functions by considering age, sex, and the aforementioned comorbidities in the Cox model. The difference in cumulative incidence curves between the splenectomy and control groups was tested using the log-rank test and likelihood-ratio test, respectively. All statistical analyses were performed using SAS software Version 9.3 (SAS Institute, Inc, Cary, NC, USA). $P < 0.05$ was considered statistically significant.

TABLE 2. Hazard Ratios of ACS Between Splenic Injury Without Splenectomy and Control Subjects as well as Splenic Injury With Splenectomy and Control Subjects Stratified by Demographics and Comorbidity

	Control (N = 46120)			Without Splenectomy (N = 6391)					With Splenectomy (N = 5139)				
	Case	PY	Rate‡	Case	PY	Rate‡	Crude HR (95% CI)	Adjusted HR (95% CI)	Case	PY	Rate‡	Crude HR (95% CI)	Adjusted HR (95% CI)
All	520	309677	1.68	66	38875	1.70	1.01 (0.93, 1.10)	1.11 (0.86, 1.43)	67	32182	2.08	1.24 (1.14, 1.35)***	1.30 (1.01, 1.68)*
Sex													
Female	111	88860	1.25	11	11727	0.94	0.75 (0.62, 0.90)**	0.87 (0.47, 1.62)	15	9135	1.64	1.31 (1.12, 1.54)***	1.36 (0.79, 2.33)
Men	409	220818	1.85	55	27148	2.03	1.09 (0.99, 1.21)	1.18 (0.89, 1.57)	52	23046	2.26	1.22 (1.10, 1.35)***	1.29 (0.97, 1.73)
Age													
≤ 49	153	22523	0.69	20	28919	0.69	1.01 (0.90, 1.12)	0.91 (0.57, 1.46)	17	23933	0.71	1.03 (0.92, 1.16)	0.90 (0.54, 1.49)
50–65	157	55283	2.84	22	6743	3.26	1.15 (0.96, 1.38)	1.04 (0.66, 1.64)	23	5348	4.30	1.51 (1.26, 1.81)***	1.29 (0.83, 2.01)
≥65	210	31871	6.59	24	3213	7.47	1.13 (0.90, 1.42)	1.09 (0.71, 1.66)	27	2901	9.31	1.41 (1.14, 1.75)**	1.41 (0.94, 2.10)
Comorbidity													
No	354	292983	1.21	37	35571	1.04	0.86 (0.78, 0.95)**	1.00 (0.72, 1.41)	38	29586	1.28	1.06 (0.96, 1.17)	1.14 (0.82, 1.60)
Yes	166	16694	9.94	29	3303	8.78	0.88 (0.70, 1.12)	1.10 (0.74, 1.64)	29	2596	11.2	1.12 (0.89, 1.42)	1.33 (0.89, 1.98)

ACS = acute coronary syndrome; CI = confidence interval; Crude HR = relative hazard ratio; PY = person-years.
* $P < 0.05$
** $P < 0.01$
*** $P < 0.001$.
† Adjusted HR: multiple analysis including age, sex, and co-morbidities of hypertension, diabetes, hyperlipidemia, stroke, COPD, heart failure, ischemic heart disease and menopause.
‡ Rate, incidence rate, per 1000 person-years.

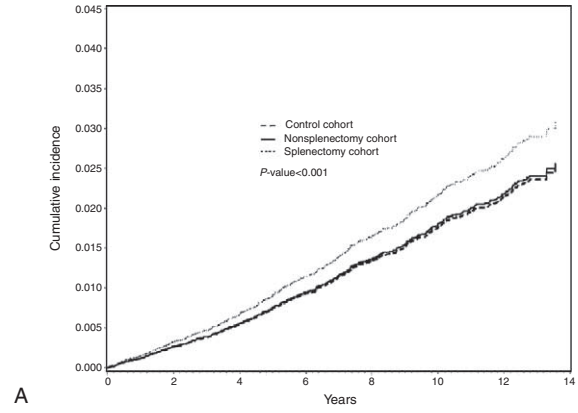
RESULTS

We identified 11530 patients with splenic injury (6391 subjects without splenectomy [nonsplenectomy group] and 5139 subjects with splenectomy [splenectomy group]) from the NHIRD. The control group consisted of 46120 subjects. The baseline characteristics of the patients in the 3 groups are presented in Table 1. Patients with splenic injury had higher prevalence of all comorbidities than the control group, except menopause. Because road accident is the main cause of major trauma, it is not surprising that the patients in the 3 groups were relatively young. The majority of patients were 49 years or younger (70.2%, 68.5%, and 69.4% in the nonsplenectomy, splenectomy, and control groups, respectively). Men accounted for approximately 70% of the patients in each group (70.3% in the nonsplenectomy group, 71.0% in the splenectomy group, and 71.0% in the control group).

The mean follow-up duration for the control group was 6.71 years, approximately 1 year more than that for the nonsplenectomy (6.08 years) and splenectomy (6.28 years) groups. During follow-up, the incidences of ACS were 2.08, 1.70, and 1.68 per 1000 person-years in the splenectomy, nonsplenectomy, and control groups respectively (Table 2). Compared with the control group, the patients who underwent splenectomy had a significantly higher risk of developing ACS (unadjusted HR, 1.24; 95% CI, 1.14–1.35 and adjusted HR, 1.30; 95% CI, 1.01–1.68) (Table 2). The sex- and age-specific analyses failed to demonstrate a significantly higher adjusted HR of ACS in the splenectomized patients in men, women, or any age subgroup, compared with their counterparts in the control group (Table 2).

Figure 2 presents the 14-year cumulative incidence curves of ACS in the splenectomy and control groups without any adjustment (Figure 2A), and with adjustment for age, sex, and comorbidities of hypertension, diabetes, hyperlipidemia, stroke, COPD, heart failure, ischemic heart disease, and menopause (Figure 2B). The difference in the cumulative incidence curves of ACS was higher in the splenectomy group than in the control group in unadjusted ($P < 0.001$) and the adjusted curves ($P = 0.01$). It should also be noted that the unadjusted and adjusted cumulative incidences of ACS between splenectomy and control groups became more and more divergent over the follow-up period (Figure 2). However, the overall risk of ACS was not significantly different between the splenectomy and nonsplenectomy groups (adjusted HR, 1.19; 95% CI, 0.84–1.67) (Table 3).

Trauma-associated hemodynamic instability and emotional reactions, such as fear and stress, may trigger myocardial ischemia, cardiac dysrhythmia, and thrombosis formation.[27,28] Usually, these factors only exist temporarily. More than two-thirds of patients who had posttraumatic syndrome after vehicle accidents would experience improvement within 1 year.[29] We therefore further explored the temporal relationship between risk of ACS and splenic injury/splenectomy, by using 1 year after splenic injury as a cutoff point. As shown in Table 4, we found that during the first year of follow-up, the nonsplenectomy group exhibited higher risk of ACS than the control group (adjusted HR, 2.43; 95% CI, 1.30–4.21) (Table 4). However, patients in the splenectomy group did not exhibit higher risk of ACS than subjects in the control group either within 1 year or a year after splenic injury/splenectomy (Table 4).



Splenic injury patients with splenectomy, No. at risk	5139	4050	3318	2637	1904	1231	597
ACS events	0	18	11	13	10	110	3
Splenic injury patients with splenectomy, No. at risk	6391	5287	4123	3016	2025	1285	628
ACS events	0	17	13	13	14	5	64
Control subjects, No. at risk	46120	40140	32014	24670	17332	11336	5832
ACS events	0	112	104	110	84	62	35

FIGURE 2. The unadjusted (A) and adjusted (B) cumulative incidence curves of ACS between the splenic injury patients with splenectomy (dotted line), the splenic injury patients without splenectomy (solid line) and comparison subjects (dashed line). ACS = acute coronary syndrome.

DISCUSSION

This nationwide cohort study provided strong evidence of an elevated long-term risk of ACS in patients who underwent splenectomy for splenic injury (splenectomy group). Our results demonstrated that this group exhibited an adjusted HR of 1.34 (95% CI, 1.04–1.73) for ACS compared with the control group, after accounting for mortality as the competing cause of risk and adjusting for multiple known confounding factors. However, no significant difference in risk of ACS was observed between the control and nonsplenectomy groups or between the splenectomy and nonsplenectomy groups. These results suggested that the elevated risk of ACS cannot be attributed to splenectomy alone, and that some of the risk may be attributable to the splenic injury. Therefore, elevated risks of ACS indicate a crucial concern that could be neglected in managing this group of patients. Additional clinical and basic studies investigating the underlying pathophysiological association are warranted.

Trauma and surgery are known to increase risk of ACS.[30] Therefore, it is not surprising that the patients with splenic injury but not splenectomy exhibited an elevated ACS risk

TABLE 3. Hazard Ratios of ACS Between all Splenic Injury Patients With and Without Splenectomy Stratified by Demographic Characteristics and Comorbidity

	Splenectomy			
	No		Yes	
	Crude HR (95% CI)	Adjusted HR† (95% CI)	Crude HR (95% CI)	Adjusted HR† (95% CI)
All	1(Reference)	1(Reference)	1.23 (1.09, 1.38)***	1.19 (0.84, 1.67)
Sex				
Female	1(Reference)	1(Reference)	1.75 (1.40, 2.19)***	1.66 (0.75, 3.70)
Men	1(Reference)	1(Reference)	1.11 (0.97, 1.28)	1.10 (0.75, 1.62)
Age				
≤ 49	1(Reference)	1(Reference)	1.03 (0.88, 1.19)	0.96 (0.50, 1.84)
50–65	1(Reference)	1(Reference)	1.32 (1.02, 1.70)*	1.25 (0.69, 2.26)
≥65	1(Reference)	1(Reference)	1.25 (0.93, 1.67)	1.29 (0.74, 2.25)
Comorbidity				
No	1(Reference)	1(Reference)	1.23 (1.09, 1.40)**	1.12 (0.71, 1.76)
Yes	1(Reference)	1(Reference)	1.27 (0.94, 1.72)	1.21 (0.72, 2.03)

ACS = acute coronary syndrome; CI = confidence interval; Crude HR = relative hazard ratio.
* $P < 0.05$
** $P < 0.01$
*** $P < 0.001$.
† Adjusted HR: multiple analysis including age, sex, and co-morbidities of hypertension, diabetes, hyperlipidemia, stroke, COPD, heart failure, ischemic heart disease and menopause.

within 1 year after splenic injury (Table 4). We also observed the excessive ACS risk no longer existed during the long-term follow up (>1 year after injury). Our finding suggested that a temporarily elevated risk of ACS in nonsplenectomy group was likely due to perioperative complications or the trauma event itself, as reported previously.[31,32] The temporal relationship implied that the trauma-associated excessive ACS risk was possibly related to some reversible factors, such as bleeding[27] and emotional stress.[28] As these physiological and psychological conditions improved over time, the patients with splenic injury, but not splenectomy, were not associated with an elevated ACS risk 1 year after trauma.

Splenectomy has been associated with increased arteriothrombotic risks in various hematological diseases, such as thalassemia,[17] sickle-cell diseases,[33] and hereditary spherocytosis.[34] However, patients with these hematological diseases exhibited risks of arteriothrombosis that were different from those in the general population. For example, hereditary spherocytosis patients with a spleen have significantly fewer adverse vascular events than their unaffected family members.[35] Conversely, patients with sickle cell diseases have higher risks of stroke.[33] Thalassemia intermedia is related to pulmonary hypertension and congestive heart failure.[36] The present study also showed that splenectomy for splenic injury is associated with increased risks of ACS in patients without underlying hematological diseases.

The exact mechanisms underlying the association between splenectomy and ACS are not completely clear. Infection might be a common pathway contributing to ACS in splenectomized patients without underlying hematological diseases. Several studies have shown that risk of ACS is elevated in various infections, such as cholangitis,[37] periodontal infection,[38] and chlamydial infection.[39] A previous group study comparing patients who underwent splenectomy for trauma with those who underwent laparotomy without splenectomy showed that splenectomized patients had a greater likelihood of early

TABLE 4. Trends of ACS Risks by Stratified Follow-up Years

	Control (N = 46120)		Without Splenectomy (N = 6391)				With Splenectomy (N = 5139)			
Follow-up Time, y	Case	Rate†	Case	Rate†	Crude HR (95% CI)	Adjusted HR‡ (95% CI)	Case	Rate†	Crude HR (95% CI)	Adjusted HR‡ (95% CI)
≤1	46	1.01	15	2.49	2.43 (1.30, 4.21)**	2.77 (1.54, 4.97)***	7	1.53	1.52 (1.36, 1.69)***	1.53 (0.69, 3.39)
>1	474	1.79	51	1.55	0.96 (0.72, 1.28)	1.01 (0.76, 1.36)	60	2.17	1.21 (1.11, 1.32)***	1.28 (0.98, 1.67)

ACS = acute coronary syndrome; CI = confidence interval; Crude HR = relative hazard ratio.
** $P < 0.01$
*** $P < 0.001$.
† Rate, incidence rate, per 1000 person-years.
‡ Adjusted HR: multiple analysis including age, sex, and co-morbidities of hypertension, diabetes, hyperlipidemia, stroke, COPD, heart failure, ischemic heart disease and menopause.

postoperative infection, particularly pneumonia.[40] Moreover, the increased risk of infection seemed to persist even a year after splenectomy.[9] In Taiwan, pneumococcal vaccination after splenectomy is uncommon. From the NHIRD, we could not accurately estimate the percentage of patients receiving vaccination, because vaccination is not completely covered by the NHI. On the basis of the findings in the present study, further investigation is warranted to determine whether vaccination can decrease the risks of not only infections but also ACS.

Controversy, however, remains regarding the association between splenectomy and the metabolic syndrome, which is diagnosed when patients present with $\geq$3 of the following indicators: obesity, hyperglycemia, hypertension, low high-density lipoprotein cholesterol levels, or hypertriglyceridemia.[41,42] Splenectomy has been associated with altered lipid profiles.[6,7] Moreover, it has been shown that splenectomy may accelerate the development of steatohepatitis in animals fed with a high-fat diet.[43] However, direct evidence that splenectomy predisposes a patient to diabetes and/or hyperglycemia is lacking. For treating chronic pancreatitis, spleen-preserving distal pancreatectomy might delay the onset of postoperative diabetes, in comparison with splenectomy groups.[44] The incidence of conventional cardiovascular risk factors should be further studied in splenectomized patients.

This nationwide observational study demonstrated the elevated risk of ACS in patients who underwent splenectomy for splenic injury. Based on the completeness of the NHIRD, we were able to adjust and control several confounding factors. However, some important limitations should be addressed here. First, we could not obtain some detailed information regarding tobacco use, alcohol consumption, physical activity level, obesity, socioeconomic status, or family history, all of which are potential confounding factors. Especially, lack of information regarding trauma severity and mechanisms might have biased the results. Second, we analyzed the incidence of ACS by investigating only the hospitalized patients. It is therefore possible that we neglected too severe or mild patients who could not or did not seek hospital care. Finally, we could not confirm the diagnoses of splenic injury and ACS by chart review. However, we were confident of the accuracy of these diagnoses because patient diagnoses are strictly audited for the purpose of reimbursement. Despite the existence of these limitations, they should not bias the results of the present study because of the high accessibility and nearly 100% coverage rate of the health insurance in Taiwan.[45]

In summary, this study demonstrates that splenectomized patients have a greater risk of developing ACS than the general population, but not those who experience splenic trauma but do not receive splenectomy. The results of the present study not only support the current principle of spleen preservation in patients of splenic injury, but also raise the neglected issue of ACS risk in splenctomized patients.

ACKNOWLEDGMENTS

None.

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