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Splenectomy and risk of renal and perinephric abscesses

A population-based cohort study in Taiwan

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Abstract

Little epidemiological research is available on the relationship between splenectomy and renal and perinephric abscesses. The purpose of the study was to examine this issue in Taiwan.

We conducted a population-based retrospective cohort study using the hospitalization dataset of the Taiwan National Health Insurance Program. A total of 16,426 participants aged 20 and older who were newly diagnosed with splenectomy from 1998 to 2010 were assigned to the splenectomy group, whereas 65,653 sex-matched, age-matched, and comorbidity-matched, randomly selected participants without splenectomy were assigned to the nonsplenectomy group. The incidence of renal and perinephric abscesses at the end of 2011 was measured in both groups. The multivariable Cox proportional hazards regression model was used to measure the hazard ratio (HR) and 95% confidence interval (CI) for risk of renal and perinephric abscesses associated with splenectomy and other comorbidities including cystic kidney disease, diabetes mellitus, urinary tract infection, and urolithiasis.

The overall incidence rate of renal and perinephric abscesses was 2.14-fold greater in the splenectomy group than that in the nonsplenectomy group (2.24 per 10,000 person-years vs 1.05 per 10,000 person-years, 95% CI 2.02, 2.28). After controlling for sex, age, cystic kidney disease, diabetes mellitus, urinary tract infection, and urolithiasis, the multivariable regression analysis demonstrated that the adjusted HR of renal and perinephric abscesses was 2.24 for the splenectomy group (95 % CI 1.30, 3.88), when compared with the nonsplenectomy group. In further analysis, the adjusted HR markedly increased to 7.69 for those comorbid with splenectomy and diabetes mellitus (95% CI 3.31, 17.9).

Splenectomy is associated with renal and perinephric abscesses, particularly comorbid with diabetes mellitus. In view of its potential morbidity and mortality, clinicians should consider the possibility of renal and perinephric abscesses when patients with splenectomy present with fever of unknown origin.

Abbreviation: ICD-9-CM codes = International Classification of Diseases, 9th Revision, Clinical Modification.

Keywords: diabetes mellitus, perinephric abscess, renal abscess, splenectomy

1. Introduction

A renal abscess or perinephric abscess is defined as an accumulation of suppurative material in the renal parenchyma or perinephric space, which is usually caused by a variety of microorganisms.[1] Renal abscess or perinephric abscess could be a potentially serious condition due to its morbidity and mortality.

The morbidities could include percutaneous drainage, open surgical drainage, nephrocutaneous fistula, and nephrectomy.[2–4] The mortality rate could range from 6% to 25% in 4 case-series studies.[2–5] To date, some common predisposing factors of renal and perinephric abscesses have been observed, including diabetes mellitus, urolithiasis, urinary

tract infection, urinary tract infection, cancer, immunosuppression, and human immunodeficiency virus infection,[2–6] but splenectomy has not been studied.

As we know, splenectomized patients are at higher risk of infections by invasion of a variety of microorganisms due to immunocompromised status caused by splenectomy.[7–10] In addition to overwhelming postsplenectomy infection, numerous epidemiological studies have demonstrated that splenectomy could be associated with increased risk of other diseases, including pulmonary tuberculosis, type II diabetes mellitus, and pyogenic liver abscess,[11–13] but renal and perinephric abscesses has not yet been examined.

One the basis of immunocompromised status caused by splenectomy, we rationally make a hypothesis that patients with splenectomy could be at increased risk of renal infections, including renal and perinephric abscesses. If this link really exists, clinicians should consider the possibility of renal and perinephric abscesses when patients with splenectomy present with fever of unknown cause. To date, no formal epidemiological study based on systematic analysis focuses on this issue. Therefore, we conducted a population-based retrospective cohort study using the hospitalization dataset of the Taiwan National Health Insurance Program to examine whether there could be a relationship between splenectomy and renal and perinephric abscesses.

2. Methods

2.1. Data source

This was a population-based retrospective cohort study using the hospitalization dataset of the Taiwan National Health Insurance Program. In short, the Taiwan National Health Insurance Program was initiated in March 1995, which covered nearly 99% of the whole 23 million residents living in Taiwan.[14] The database contains patient's sex, date of birth, prescriptions, and medical services used. The details of the program have been well

recorded in previous studies.[15–21] This study was approved by the Ethics Review Board of China Medical University and Hospital in Taiwan (CMUH-104-REC2-115).

2.2. Study sample

Using the hospitalization dataset of the Taiwan National Health Insurance Program, all hospitalized participants aged 20 and older who received splenectomy from 1998 to 2010 were selected as the splenectomy group, according to the International Classification of Diseases, 9th Revision, Clinical Modification (ICD-9-CM procedure code 41.5). The index date was defined as the date of participants receiving splenectomy. For each participant with splenectomy, 4 participants without splenectomy were randomly selected from the same database as the nonsplenectomy group. The splenectomy and nonsplenectomy groups were matched by sex, age (every 5-year interval), baseline comorbidities, and the hospitalization year of receiving splenectomy. To validate the sequential causality between splenectomy and renal and perinephric abscesses, participants with history of renal and perinephric abscesses (ICD-9-CM code 590.2) or cancers (ICD-9-CM codes 140–208) before the index date were excluded from this study. Participants with diagnosis of renal abscess and perinephric abscesses within 1 month after performing splenectomy were also excluded (Fig. 1).

2.3. Outcome and baseline comorbidities

All study participants were followed until they were diagnosed with renal abscess and perinephric abscess or until the end of 2011.

Baseline comorbidities potentially related to renal and perinephric abscesses before the index date were included as follows: cystic kidney disease, diabetes mellitus, drug dependence, human immunodeficiency virus infection, urinary tract infection (including chronic pyelonephritis, acute pyelonephritis,
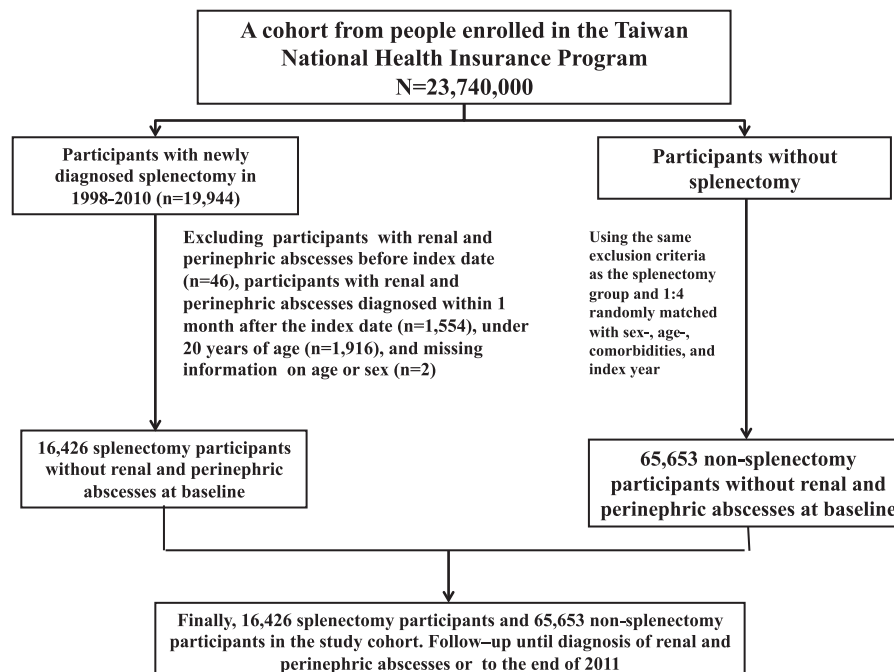

Figure 1. Flow chart showing selection process of study participants.

cystitis, and urethritis), and urolithiasis (including calculus of kidney, ureter, bladder, and urethra). All comorbidities were diagnosed with ICD-9-CM codes.

2.4. Statistical analysis

The differences of sex, age, and baseline comorbidities were compared between the splenectomy group and nonsplenectomy group using the Chi-square test for categorical variables and t test for continuous variables. Follow-up period (in person-years) was used to estimate the incidence rate and incidence rate ratio (IRR) with 95% confidence interval (CI) of splenectomy group to nonsplenectomy group using Poisson regression, stratified by sex, age, and follow-up period. The proportional hazard model assumption was also examined by using a test of scaled Schoenfeld residuals. In models evaluating risk of renal and perinephric abscesses throughout the follow-up period, results of the test revealed no significant relationship between Schoenfeld residuals for splenectomy and follow-up period (P value = 0.35). The multivariable Cox proportional hazards regression model was used to estimate the hazard ratio (HR) and 95% CI of renal and perinephric abscesses associated with splenectomy and other comorbidities after simultaneously controlling for variables found to be significant in a univariable Cox proportion hazard regression model. All statistical analyses were performed by SAS 9.2 (SAS Institute, Cary, NC). Two-tailed $P < 0.05$ was considered statistically significant.

3. Results

3.1. Baseline characteristics of the study population

Table 1 demonstrates the distributions of sex, age, and baseline comorbidities between the splenectomy group and nonsplenectomy group. There were 16,426 participants with splenectomy and 65,653 participants without splenectomy, with a similar sex distribution. The mean ages (standard deviation) of the study participants were 53.3 ± 17.6 years for the splenectomy group and 52.9 ± 17.7 years for the nonsplenectomy group (t test,

$P = 0.01$). The mean follow-up periods (standard deviation) of the study participants were 4.88 ± 4.00 years for the splenectomy group (range from 0.085 to 14) and 6.69 ± 3.83 years for the nonsplenectomy group (range from 0.085 to 14) (t test, $P < 0.001$). There was no significant difference in the prevalence rates of baseline comorbidities between the splenectomy group and nonsplenectomy group (Chi-square test, $P > 0.05$ for all).

3.2. Incidence of renal and perinephric abscesses in the study population

Table 2 demonstrates the incidence rates of renal and perinephric abscesses. At the end of follow-up, the overall incidence rate of renal and perinephric abscesses diagnosis was 2.14-fold greater in the splenectomy group than that in the nonsplenectomy group (2.24 per 10,000 person-years vs 1.05 per 10,000 person-years, 95% CI 2.02, 2.28). The incidence rates of renal and perinephric abscesses, as stratified by sex, age, and follow-up period, were all higher in the splenectomy group than those in the non-splenectomy group. The incidence rate of renal and perinephric abscesses was higher in female participants than that in male participants in both groups. The incidence rates of renal and perinephric abscesses increased with age in both groups, but the splenectomy group aged 65 to 84 years had the highest incidence rate of renal and perinephric abscesses (3.09 per 10,000 person-years). The analysis stratified by follow-up period revealed that the risk of renal and perinephric abscesses persisted over time, even after 5 year of diagnosing renal and perinephric abscesses. However, the risk seemed to be much higher during the 1st 3 years with an incidence rate ratio from 2.93 to 3.23.

3.3. Hazard ratio of renal and perinephric abscesses associated with splenectomy and other comorbidities

Table 3 demonstrates the HR of renal and perinephric abscesses associated with splenectomy and other comorbidities. After controlling for sex, age, cystic kidney disease, diabetes mellitus, urinary tract infection, and urolithiasis, the multivariable Cox proportional hazards regression model demonstrated that the

Table 1

Baseline characteristics between splenectomy group and nonsplenectomy group.

Variable	Nonsplenectomy N = 65,653		Splenectomy N = 16,426		P*
	n	(%)	n	(%)	
Sex					0.99
Female	24,967	38.0	6246	38.0	
Male	40,686	62.0	10,180	62.0	
Age group, year					0.99
20–39	16,739	25.5	4186	25.5	
40–64	29,362	44.7	7348	44.7	
65–84	19,552	29.8	4892	29.8	
Age, year, mean (standard deviation)†	52.9	17.7	53.3	17.6	0.01
Follow-up period, year, mean (standard deviation)†	6.69	3.83	4.88	4.00	<0.001
Baseline comorbidities					
Cystic kidney disease	935	1.42	242	1.47	0.64
Diabetes mellitus	9569	14.6	2397	14.6	0.95
Drug dependence	358	0.55	96	0.58	0.55
Human immunodeficiency virus diagnosis	26	0.04	8	0.05	0.61
Urinary tract infection	5961	9.08	1496	9.11	0.91
Urolithiasis	3211	4.89	806	4.91	0.93

Data are presented as the number of subjects in each group, with percentages given in parentheses, or mean with standard deviation given in parentheses.
* Chi-square test.
† t test comparing subjects with and without splenectomy.

Table 2

Cox proportional hazards regression analysis for incidence density and HR of renal and perinephric abscesses associated with splenectomy.

Variable	Nonsplenectomy				Splenectomy				IRR (95% CI)[†]
	N	Event	Person-years	Rate[*]	N	Event	Person-years	Rate[*]	
All	65,653	46	439,226	1.05	16,426	18	80,197	2.24	2.14 (2.02, 2.28)
Sex									
Female	24,967	29	167,056	1.74	6246	9	31,088	2.89	1.67 (1.51, 1.85)
Male	40,686	17	272,169	0.62	10,180	9	49,109	1.83	2.93 (2.72, 3.16)
Age group, year									
20–39	16,739	4	121,795	0.33	4186	2	28,335	0.71	2.15 (1.90, 2.44)
40–64	29,362	26	203,159	1.28	7348	11	35,684	3.08	2.41 (2.21, 2.63)
65–84	19,552	16	114,272	1.40	4892	5	16,178	3.09	2.21 (1.97, 2.48)
Follow-up period									
≤1 year	65,653	9	64,737	1.39	16,426	6	14,729	4.07	2.93 (2.76, 3.11)
2–3 years	63,666	8	114,470	0.70	13,338	5	22,152	2.26	3.23 (3.03, 3.45)
4–5 years	50,964	10	90,936	1.10	9285	2	15,973	1.25	1.14 (1.04, 1.25)
>5 years	40,072	19	169,083	1.12	6832	5	27,343	1.83	1.63 (1.48, 1.78)

95% CI = 95% confidence interval, HR = hazard ratio, IRR = incidence rate ratio.

[*] Incidence rate: per 10,000 person-years.

[†] IRR (incidence rate ratio): splenectomy versus nonsplenectomy (95% CI).

adjusted HR of renal and perinephric abscesses was 2.24 for the splenectomy group (95 % CI 1.30, 3.88), when compared with the nonsplenectomy group. Male (adjusted HR 2.24, 95 % CI 1.35, 3.72), age (per 1 year, adjusted HR 1.01, 95 % CI 1.00, 1.03), cystic kidney disease (adjusted HR 3.12, 95 % CI 1.10, 8.80), diabetes mellitus (adjusted HR 3.18, 95 % CI 1.85, 5.46), urinary tract infection (adjusted HR 2.13, 95 % CI 1.15, 3.94), and urolithiasis (adjusted HR 3.06, 95 % CI 1.54, 6.09) were other factors that were significantly related to renal and perinephric abscesses.

3.4. Interaction effect on risk of renal and perinephric abscesses between splenectomy and diabetes

Table 4 demonstrates interaction effect on risk of renal and perinephric abscesses between splenectomy and diabetes mellitus. As a reference of participants without splenectomy and without diabetes mellitus, the adjusted HR of renal and perinephric abscesses was 2.09 for participants with splenectomy alone and without diabetes mellitus (95% CI 1.04, 4.17). The adjusted HR was 3.02 for participants with diabetes mellitus and without splenectomy (95% CI 1.61, 5.67). The adjusted HR markedly

increased to 7.69 for those comorbid with splenectomy and diabetes mellitus (95% CI 3.31, 17.9).

4. Discussion

In the past, most studies of renal and perinephric abscesses were case-series studies. No formal systematic study has ever investigated the relationship between splenectomy and renal and perinephric abscesses. To the best of our knowledge, this is the 1st population-based cohort study to examine this issue. We noticed that the incidence rate of renal and perinephric abscesses was higher in patients with splenectomy than that in those without splenectomy. After statistical correction for potential confounding factors, the adjusted HR of renal and perinephric abscesses was 2.24 for the splenectomy group. In addition, Ko et al noticed that the incidence rate of renal and perinephric abscesses was 4.6 per 10,000 person-years among the diabetic participants, which seems to be higher than that in splenectomized participants of our study (2.24 per 10,000 person-years, Table 2).[22] In order to test whether the association between splenectomy and renal and perinephric abscesses is confounded by diabetes or not, we made an additional analysis. We noticed

Table 3

Adjusted HR and 95% CI of renal and perinephric abscesses associated with splenectomy and other comorbidities.

Variable	Crude		Adjusted[*]	
	HR	(95% CI)	HR	(95% CI)
Sex (male vs female)	2.37	(1.44, 3.91)	2.24	(1.35, 3.72)
Age (per 1 year)	1.02	(1.01, 1.04)	1.01	(1.00, 1.03)
Splenectomy (yes vs no)	2.11	(1.22, 3.64)	2.24	(1.30, 3.88)
Baseline comorbidities (yes vs no)				
Cystic kidney disease	5.23	(1.90, 14.4)	3.12	(1.10, 8.80)
Human immunodeficiency virus diagnosis[†]	—	—	—	—
Diabetes mellitus	4.28	(2.56, 7.15)	3.18	(1.85, 5.46)
Drug dependence[†]	—	—	—	—
Urinary tract infection	4.25	(2.41, 7.49)	2.13	(1.15, 3.94)
Urolithiasis	4.61	(2.41, 8.83)	3.06	(1.54, 6.09)

Only those found to be significant in the univariable analysis were further examined in the multivariable analysis. 95% CI = 95% confidence interval, HR = hazard ratio.

[*] Additionally adjusted for sex, age, cystic kidney disease, diabetes mellitus, urinary tract infection, and urolithiasis.

[†] Because of no event of renal and perinephric abscesses, the HR could not be estimated.

Table 4

Cox proportional hazard regression analysis for risk of renal and perinephric abscesses stratified by splenectomy and diabetes.

Variable		Event	Rate*	Adjusted HR (95% CI)†
Splenectomy	Diabetes mellitus			
No	No	30	0.77	1 (Reference)
No	Yes	16	3.13	3.02 (1.61, 5.67)
Yes	No	11	1.54	2.09 (1.04, 4.17)
Yes	Yes	7	8.13	7.69 (3.31, 17.9)

95% CI = 95% confidence interval, HR = hazard ratio.
* Incidence rate: per 10,000 person-years.
† Adjusted HR: HR adjusted for sex, age, cystic kidney disease, urinary tract infection, and urolithiasis.

that the adjusted HR of renal and perinephric abscesses was 2.09 for participants with splenectomy alone and without diabetes mellitus (Table 4). It indicates that splenectomy alone has a unique effect on risk of renal and perinephric abscesses that is independent of diabetes mellitus. If participants were comorbid with splenectomy and diabetes mellitus, the adjusted HR markedly increased to 7.69. It suggests that there could be a synergistic effect between splenectomy and diabetes mellitus on risk of renal and perinephric abscesses. These findings are consistent with the evidence that patients with splenectomy are not only more likely to develop overwhelming postsplenectomy infection,[7–10] but also are at higher risk of developing renal and perinephric abscesses.

The spleen is well recognized as an organ of regulating immune functions, which can induce various immune responses, including macrophage-mediated phagocytosis and antibody production, to protect the host against invasion of blood-borne microorganisms.[8–10] The impaired immune functions caused by splenectomy might contribute to not only increased risk of developing overwhelming postsplenectomy infection, but also increased risk of renal and perinephric abscesses.

A case-series study by Waghorn[7] noticed that the interval between splenectomy and onset of overwhelming postsplenectomy infection could range from 24 days to 65 years. According to the medical accessibility and quality in Taiwan, it does not need to take 1 month to diagnose renal and perinephric abscesses since the onset of related symptoms. To validate the sequential causality between splenectomy and renal and perinephric abscesses, participants with history of renal and perinephric abscesses before the index date were excluded from this study. It is rational that participants with diagnosis of renal abscess and perinephric abscesses within 1 month after performing splenectomy were also excluded. These points have been mentioned in method section. We also found that the interval between splenectomy and diagnosis of renal and perinephric abscesses would range from 31 days to 14 years. Therefore, we think that splenectomy really proceeded to diagnosis of renal and perinephric abscesses. We also noticed that the risk of renal and perinephric abscesses persisted over time, even after 5 year of diagnosing renal and perinephric abscesses (Table 2), which is consistent with Waghorn study.[7]

Several limitations should be addressed. First, the dataset used did not contain the medications information. We could not include glucocorticoids use or other immune-related medications for analysis. Second, due to the same limitation, renal and perinephric abscesses could be related to a specific history, such as stone obstruction, antiinflammatory agents, delay in care, neurogenic dysfunction of the urinary tract, or antibiotics prevention. These factors could not be evaluated here and the results might be influenced. Third, although the diagnosis of renal

and perinephric abscesses is not based directly on clinical data, it is based on the ICD-9-CM codes adapted from the hospitalization dataset. The accuracy of hospitalization diagnosis can be trusted from a view of excellent medical quality in Taiwan. Similarly, the diagnosis accuracy of the ICD-9-CM codes has been carefully examined in previous studies.[11,13,23,24] Fourth, the indications of splenectomy were unavailable due to the inherent limitation of this dataset. Cancers were found in some cases of perinephric abscess.[2,3] Some cancers might need splenectomy so that these backgrounds could potentially confound the results. In order to diminish the confounding effect of cancers, participants with history of cancers before the index date were excluded from this study. Therefore, the confounding potential caused by cancers could be minimized. Fifth, due to the strict inclusion and exclusion criteria used, the event number of renal and perinephric abscesses was too small (18 in splenectomy group and 46 in nonsplenectomy group). The event number could not convince the readers on the association between splenectomy and renal and perinephric abscesses. It remains to be an important issue. Sixth, such a study design does not permit to conclude a substantial causality. Further prospective studies with more events of renal and perinephric abscesses are needed to confirm our findings.

Some strengths of this study deserve discussion. The diagnosis of splenectomy and renal and perinephric abscesses is based on hospitalization diagnosis. The reliability is relatively high. The viewpoints of this study seem to be unique. The multivariable analysis was carried out logically and each factor was thoroughly examined. The results were not previously mentioned so far. The relationship between splenectomy and renal and perinephric abscesses was theoretically discussed. Therefore, these results themselves are worth reporting.

We conclude that splenectomy is associated with renal and perinephric abscesses, particularly comorbid with diabetes mellitus. In view of its potential morbidity and mortality, clinicians should consider the possibility of renal and perinephric abscesses when patients with splenectomy present with fever of unknown origin. Thus, clinicians can treat renal and perinephric abscesses as early as possible.

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