

Gastrectomy correlates with increased risk of pulmonary tuberculosis

A population-based cohort study in Taiwan

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Abstract

The objective to assess the association between gastrectomy and the risk of pulmonary tuberculosis among patients without gastric cancer in Taiwan.

There were 762 subjects with newly performing gastrectomy as the gastrectomy group since 2000 to 2012, and 2963 randomly selected subjects without gastrectomy as the non-gastrectomy group. Subjects with history of pulmonary tuberculosis or gastric cancer before the index date were excluded. Both gastrectomy and non-gastrectomy groups were matched with sex, age, and comorbidities. The incidence of pulmonary tuberculosis was assessed in both groups. The multivariable Cox proportional hazards regression model was used to assess the hazard ratio and 95% confidence interval for risk of pulmonary tuberculosis associated with gastrectomy.

The overall incidence of pulmonary tuberculosis was 1.97-fold greater in the gastrectomy group than that in the non-gastrectomy group. The multivariable Cox proportional hazards regression analysis demonstrated that the adjusted HR of pulmonary tuberculosis was 1.97 for the gastrectomy group, compared with the non-gastrectomy group. Male sex, age (increase per 1 year), chronic obstructive pulmonary disease, and splenectomy were other factors that could be related to pulmonary tuberculosis.

Gastrectomy is associated with 1.97-fold increased risk of pulmonary tuberculosis among patients without gastric cancer.

Abbreviations: CKD = chronic kidney disease, COPD = chronic obstructive pulmonary disease, DM = diabetes mellitus, HIV = human immunodeficiency virus, ICD-9 code = International Classification of Diseases, 9th Revision, Clinical Modification, pulmonary, TB = pulmonary tuberculosis, WHO = World Health Organization.

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1. Introduction

For several decades, the high extent of tuberculosis (TB) prevalence and its socioeconomic impact via associated health

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care costs have made it a major public health concern. World Health Organization (WHO) statistics indicated that in 2014 alone there was an estimated 10.4 million new cases.^[1] Prevalence varies significantly between countries across the world and, for example, in Taiwan data from 2006 showed the incidence was 63 individual cases per 100,000 population.^[2] Upon TB infection, the most prominent tissue affected are the lungs and a cluster of various risk factors for pulmonary TB are well characterized. These include characteristics such as aging, male sex, and lifestyle choices including tobacco smoking and excess alcohol consumption.^[3,4] Other diseases are also associated with TB, including chronic obstructive pulmonary disease (COPD), pneumoconiosis,^[5,6] chronic kidney disease (CKD), diabetes mellitus (DM), and human immunodeficiency virus (HIV).^[7]

In addition to the risk factors stated above, gastrectomy in patients with peptic ulcers is a potential risk for TB, particularly pulmonary TB.^[8-10] The articles mentioned the association between pulmonary TB and any degree of gastrectomy were scanty and most of them were time-honored and did not meet the trend. Based on these findings, the present study investigated the association of gastrectomy and increased risk of pulmonary TB using the Taiwan National Health Insurance Program database.

2. Methods

2.1. Study design and source of information

This population-based cohort study utilized material from the Taiwan National Health Insurance Program database which

allowed access to information from approximately 99% of the population of 23 million individuals^[11–23] since March 01, 1995. This database is well established and more detailed information can be found in previous studies.^[24–29] The present study was approved by the Ethics Review Board of China Medical University in Taiwan (CMUH-104-REC2–115).

2.2. Participants

The gastrectomy group was included as subjects aged 20 to 84 years with newly performing gastrectomy between 2000 and 2012 (International Classification of Diseases [ICD] 9th Revision, ICD-9 procedure codes 43.5, 43.6, 43.7, 43.8, 43.81, 43.82, 43.89, 43.91, and 43.99). To increase the statistical power of the study, for each subject with gastrectomy, 4 subjects without gastrectomy were randomly selected as the non-gastrectomy group. The index date was defined as the date of performing gastrectomy. Both gastrectomy and non-gastrectomy groups were matched by sex, age (every 5-year span) and comorbidities. Subjects with a history of pulmonary TB, or gastric cancer prior to the index date were excluded from the study.

2.3. Comorbidities

Comorbidities which could be potentially related to pulmonary TB were included, as follows: alcohol-related disease, COPD, CKD, DM, pneumoconiosis, splenectomy, chronic liver disease including cirrhosis, hepatitis B infection, hepatitis C infection, and other chronic hepatitis. All comorbidities were diagnosed in accordance to the ICD-9 codes. The accuracy of ICD-9 codes has been examined in previous studies.^[30–33]

2.4. Major outcome

In this study we monitored individuals until the end of 2013, with or without diagnosis of pulmonary TB. A principal and novel observation was diagnosis of pulmonary TB (ICD-9 codes 010, 011, 012, and 018) during the course of the follow-up period.

2.5. Statistical analysis

To statistically analyze changes between the gastrectomy and non-gastrectomy groups, we used the Chi-square test for categorized variables and the *t* test for continuous variables. These included sex, age, and various comorbidities as listed above. We defined incidence of pulmonary TB within each group as the number of pulmonary TB events identified during the follow-up period, divided by the total follow-up person-years. The univariable model was first used to analyze all variables and, subsequently, only those found to be significant were chosen for additional analysis using the multivariable model. To do so, multivariable Cox proportional hazards regression was used to assess the hazard ratio (HR) and 95% confidence interval (CI) for risk of pulmonary TB. All analyses were performed by the SAS software version 9.2 (SAS Institute, Inc., Cary, NC).

3. Results

3.1. Baseline characteristics of the study population

Table 1 demonstrates the baseline characteristics of the study population. There were 762 subjects in the gastrectomy group and 2963 subjects in the non-gastrectomy group, with similar distributions of sex and age. The mean age of the study subjects was 59.0 years (± 16.2 years) for the gastrectomy group and 58.4 years (± 16.2 years) for the non-gastrectomy group (*t* test; *P* = .4). The gastrectomy group had a higher proportion of splenectomy than the non-gastrectomy group (4.72% vs 2.4%; Chi-square test; *P* = .001). There was no significant difference in other comorbidities between the gastrectomy and non-gastrectomy groups (Chi-square test; *P* > .05).

3.2. Incidence of pulmonary TB in the study population stratified by sex and age

Table 2 demonstrates that the overall incidence of pulmonary TB was 1.97-fold greater in the gastrectomy group than that in the

Table 1
Baseline characteristics between gastrectomy group and non-gastrectomy group.

Variable	Non-gastrectomy N = 2963		Gastrectomy N = 762		P value*
	n	%	n	%	
Sex					.98
Female	1063	35.9	273	35.8	
Male	1900	64.1	489	64.2	
Age group, y					.93
20–39	875	29.5	220	28.9	
40–64	897	30.3	231	30.3	
65–84	1191	40.2	311	40.8	
Age, y, mean (standard deviation)†	58.4	16.2	59.0	16.2	.4
Follow-up period, y, mean (standard deviation)†	5.33	4.00	3.31	3.57	.001
Baseline comorbidities					
Alcohol-related disease	380	12.8	99	13.0	.90
Chronic liver disease	661	22.3	170	22.3	.99
Chronic obstructive pulmonary disease	522	17.6	137	18.0	.82
Chronic kidney disease	150	5.06	41	5.38	.72
Diabetes mellitus	492	16.6	129	16.9	.83
Pneumoconiosis	19	0.64	7	0.92	.41
Splenectomy	71	2.40	36	4.72	.001

Data are presented as the number of subjects in each group with percentages given in parentheses, or mean with standard deviation given in parentheses.

CKD = chronic kidney disease, COPD = chronic obstructive pulmonary disease, DM = diabetes mellitus (DM).

* Chi-square test.

† *t* test comparing subjects with and without gastrectomy.

Table 2**Incidence of pulmonary tuberculosis estimated by sex and age between gastrectomy group and non-gastrectomy group.**

Variable	Non-gastrectomy				Gastrectomy				IRR* (95% CI)
	N	Event	Person-years	Incidence [†]	N	Event	Person-years	Incidence [†]	
All	2963	54	15796	3.42	762	17	2521	6.74	1.97 (1.56, 2.49)
Sex									
Female	1063	9	5300	1.70	273	2	876	2.28	1.34 (0.83, 2.18)
Male	1900	45	10497	4.29	489	15	1645	9.12	2.13 (1.61, 2.81)
Age group, y									
20–39	875	4	4595	0.87	220	2	891	2.24	2.58 (1.62, 4.11)
40–64	897	10	4676	2.14	231	3	790	3.80	1.78 (1.13, 2.79)
65–84	1191	40	6524	6.13	311	12	840	14.3	2.33 (1.65, 3.29)

* IRR (incidence rate ratio): gastrectomy versus non-gastrectomy (95% confidence interval).

[†] Incidence: per 1000 person-years.

non-gastrectomy group (6.74 vs 3.42 per 1000 person-years, 95% CI 1.56, 2.49). In a sub-analysis, the partial gastrectomy group and the total gastrectomy group demonstrated higher incidences of pulmonary TB compared with the non-gastrectomy group (5.58 and 20.9 per 1000 person-years, respectively). The incidence of pulmonary TB, as stratified by sex and age, was higher in the gastrectomy group compared with the non-gastrectomy group. The gastrectomy group aged 65 to 84 years had the highest incidence of pulmonary TB (14.3 per 1000 person-years). Figure 1 demonstrates that the Kaplan–Meier cumulative incidence of pulmonary TB was higher in the gastrectomy group than that in the non-gastrectomy group (5.4% vs 4.0% at the end of follow-up; $P < .001$).

3.3. Pulmonary TB was associated with gastrectomy and comorbidities

Table 3 demonstrates the risk of pulmonary TB associated with gastrectomy and comorbidities. After analysis of all variables using the univariable model, only those found to be significant

were then analyzed further using the multivariable model. After appropriate correction for covariables, the adjusted HR of pulmonary TB for the gastrectomy group was calculated to be 1.97 (95% CI 1.13, 3.42), compared with the non-gastrectomy group. In addition, male sex (adjusted HR 2.5; 95% CI 1.31, 4.77), age (increase per 1 year; adjusted HR 1.05; 95% CI 1.03, 1.07), COPD (adjusted HR 2.52; 95% CI 1.50, 4.24), and splenectomy (adjusted HR 6.1; 95% CI 2.73, 13.7) were other factors that could be related to pulmonary TB.

3.4. Interaction effect on pulmonary TB between gastrectomy and splenectomy

As a reference of subjects without gastrectomy and without splenectomy, the adjusted HR of pulmonary TB was 1.92 (95% CI 1.06, 3.49) for those subjects with gastrectomy and without splenectomy. The adjusted HR increased to 13.1 (95% CI 4.03, 42.5) for those subjects with gastrectomy and splenectomy (Table 4).

4. Discussion

Previous literature revealed that there was a probable link between gastrectomy and pulmonary TB, on and off since 1954.^[34] The published literature may be divided into 3 stages. Before 1954, the retrospective studies were on small populations,^[35,36] therefore resulted in certain recall bias. Most authors were interested in the surgical sequel of post-gastrectomy resulting from any disease and provided only certain information in regards to the association of gastrectomy and pulmonary TB. Furthermore, Johnson^[37] was the first author to describe a search for pulmonary TB following partial gastrectomy, however, the results were not inclusive.

Between 1960 and 1990, certain literature was focused on the associations between gastrectomy and pulmonary TB, probably for the advanced treatment for active TB. The prevalence of gastrectomy among patients with pulmonary TB ranged from 1.7% to 12.3%^[38–40] and the sample size was increased compared with previous studies. Thorn et al^[10] indicated that the annual incidence of TB among these individuals was approximately 5 times the rate of same age in this area. In addition, the observation period ranged from 1.5 to 6.5 years in the present study, thus increased the specificity and sensitivity compared with other similar studies in this stage. After 1990, due to the rapid progress in statistics and related researches, certain studies were focused in Japan^[8,41] and Taiwan.^[2] A large scale

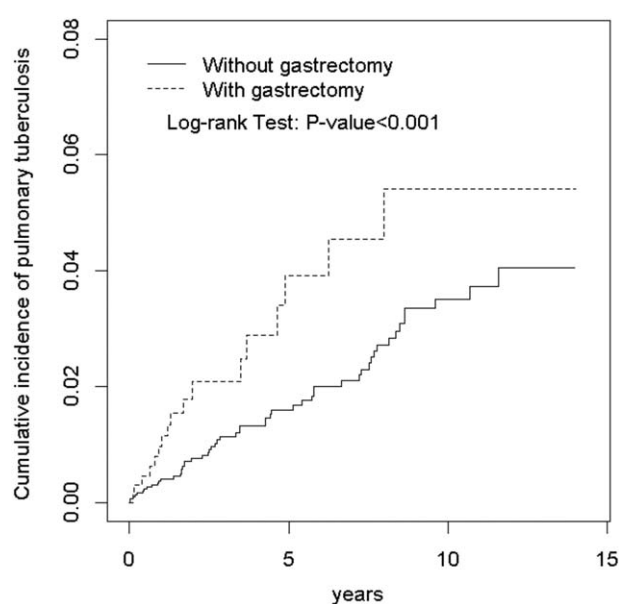


Figure 1. Cumulative incidence of pulmonary tuberculosis for subjects with gastrectomy and without gastrectomy (5.4% vs 4.0% at the end of follow-up; $P < .001$).

Table 3**Cox model measured hazard ratio and 95% confidence interval of pulmonary tuberculosis associated with gastrectomy and comorbidities.**

Variable	Crude HR (95% CI)	Adjusted* HR (95% CI)
Sex (male vs female)	2.80 (1.47, 5.33)	2.50 (1.31, 4.77)
Age (per 1 year)	1.06 (1.04, 1.08)	1.05 (1.03, 1.07)
Gastrectomy	1.92 (1.11, 3.32)	1.97 (1.13, 3.42)
Baseline comorbidities (yes vs no)		
Alcohol-related disease	0.78 (0.34, 1.81)	–
Asbestosis	–	–
Chronic liver disease	0.88 (0.48, 1.61)	–
Chronic obstructive pulmonary disease	4.42 (2.77, 7.05)	2.52 (1.50, 4.24)
Chronic kidney disease	1.37 (0.50, 3.77)	–
Diabetes mellitus	1.21 (0.66, 2.21)	–
Human immunodeficiency virus infection	–	–
Pneumoconiosis	2.04 (0.28, 14.7)	–
Splenectomy	3.71 (1.70, 8.09)	6.10 (2.73, 13.7)

Adjusted for sex, age, chronic obstructive pulmonary disease, and splenectomy.

CKD=chronic kidney disease, COPD=chronic obstructive pulmonary disease, DM=diabetes mellitus, HIV=human immunodeficiency virus.

* Variable found to be significant in the univariable analysis were further examined in the multivariable analysis.

randomized study was assigned and the results indicated that gastrectomy may be a risk factor for the reactivation of pulmonary TB. Huang et al^[2] concentrated on the incidence rate of any spectrum of TB with gastrectomy after gastric cancer predominantly, ignoring gastrectomy after other diseases. To the best of our knowledge, this is the first population-based study to investigate the relationship between gastrectomy after any disease and pulmonary TB.

The baseline characteristics of our study population demonstrated that the gastrectomy group had a higher proportion of splenectomy than the non-gastrectomy group. A decrease in immunity may be the explanation for this condition. Recent evidence revealed that humoral immunity and B-cells may play an independent role for the immune response to different microorganisms, including mycobacterium TB.^[42] In addition, the role of spleen as a protector of the human body against invading microorganisms is well established.^[43] A recent Taiwan population-based study also demonstrated the association between pulmonary TB and splenectomy in 2014.^[32] Gastrectomy causes a poor nutritional status leading to poor immunity, as demonstrated by a previous study.^[44] Due to reasons stated above, the patients' post-gastrectomy or post-splenectomy, disregarding resulted from any disease might be in lower resistance to mycobacterium TB. We also found that the groups with gastrectomy alone, splenectomy alone, and combination of gastrectomy and splenectomy all showed higher risk of

pulmonary tuberculosis than the group without gastrectomy and without splenectomy in Table 4. Furthermore, synergistic effect over the risk of pulmonary TB could be expected and surmised when patients with gastrectomy and splenectomy at the same time from our study, therefore, should be applied in the medical field in the future.

In the present study, the incidence of pulmonary TB, as stratified by sex and age, was higher in the gastrectomy group than the non-gastrectomy group. Gastrectomy indicates that a certain portion of the stomach was surgically removed due to gastric cancer, peptic ulcer, or other diseases. Folic acid, iron, minerals zinc, copper, and vitamins A, C, E, and B are mostly absorbed from the stomach or a certain part of the duodenum. Thus, decreasing absorption of micronutrients post-gastrectomy may result in abnormal cellular function and lower the resistance against invading microorganisms.^[45] An Indonesian study demonstrated that a lower concentration of micronutrients led to a decreased host defense to TB.^[46] Another meta-analysis review study revealed that long-term malnutrition was an important risk factors in developing pulmonary TB.^[47] In the sub-analysis of the present study, the partial gastrectomy group and the total gastrectomy group demonstrated higher incidence of pulmonary TB than the non-gastrectomy group (5.58 and 20.9 per 1000 person-years, respectively), compatible with the mechanism and explanation provided above.

Table 4**Interaction effect on pulmonary tuberculosis between gastrectomy and splenectomy.**

Variable						
Gastrectomy	Splenectomy	N	Event	Person-years	Incidence	Adjusted HR [†] (95% CI)
No	No	2892	50	15342	3.26	1.00 (Reference)
No	Yes	71	4	454	8.80	5.68 (1.99, 16.3)**
Yes	No	726	14	2446	5.72	1.92 (1.06, 3.49)*
Yes	Yes	36	3	75	40.0	13.1 (4.03, 42.5)***

The interaction between current use of Gastrectomy and Splenectomy was not significant (P value for interaction = .27).

* Significant.

** More significant.

*** Most significant.

† Adjusted for sex, age, and chronic obstructive pulmonary disease.

In the current study, male sex and old age were the potential risk factors related with pulmonary TB, following adjustment for covariables. These conditions were compatible with previous literature.^[2,8,10,34] A previous study demonstrated that the elderly are easily infected by pulmonary TB due to a decreased immune response.^[3] As for the male sex being another risk factor for pulmonary TB, this may be due to the fact that men are more involved with alcohol drinking and tobacco smoking than females. In addition, previous studies demonstrated that smoking, drinking silicosis, and air pollution were also associated with a high incidence of pulmonary TB,^[4,48] therefore further research is required to fully understand the reason of the male sex being a risk factor associating with pulmonary TB.

COPD was one of the factors that could be related to pulmonary TB noted in our study. Previous studies discussed the association between COPD and pulmonary TB directly. In one of the studies, cardiovascular, COPDs, and DM were the most frequent concomitant diseases after emergency surgery, including 19.5% gastrectomy (Billroth II resection) in perforated peptic ulcer patients.^[49] Furthermore, 6 patients who developed a postoperative abscess had a previous history of COPD. A possible explanation may be that the reduced tissue oxygenation resulted in the damage of postsurgical wound healing process.

This possibility was also supported by other recent studies.^[50] Physicians at local clinics should pay more attention to this the condition and prevent this comorbidity earlier.

5. Limitations

In the present study, various risk factors of pulmonary TB, such as alcohol consumption, tobacco smoking, socioeconomic status mentioned above^[7] and albumin, were not enrolled due to our database inherent limitations. Furthermore, the current study did not differentiate for the reason the patients received gastrectomy, such as gastric cancer or other gastrointestinal malignancies, and this may have served an independent role in the development of pulmonary TB. Finally, the present study had an inherent limitation, as the diagnosis of pulmonary TB and gastrectomy confirmed by ICD-9 only. A further definite evaluation for pulmonary TB, such as chest x-ray or sputum culture could be added for the reduction of confounding effects in future investigations.

6. Strength

One of the strengths of the present study is that the set of ICD-9 codes used has been validated in previous published studies.^[25,26,30–32] Under the normal physical mechanism and plausible hypothesis, the long-term observation period from 2000 to 2012 allowed for more credibility compared with other similar studies.

7. Conclusion

In conclusion, gastrectomy is associated with 1.97-fold increased risk of pulmonary TB in Taiwan compared with the non-gastrectomy group. Following adjustment for covariables, male sex, age, COPD, and splenectomy were other factors that could be associated with pulmonary TB. In light of this, regular and conventional surveillance for pulmonary TB should be emphasized and recommended for patients with gastrectomy. Future prospective and comprehensive studies are required to further support the results of the present study.

Author contributions

Kao-Chi Cheng and Kuan-Fu Liao initiated the draft of the article, revised the article, and contributed equally to the article. Cheng-Li Lin conducted the data analysis and revised the article. Shih-Wei Lai contributed to the conception of the article, initiated the draft of the article, and revised the article.

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