Population-based cohort study investigating the correlation of diabetes mellitus with pleural empyema in adults in Taiwan

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Abstract

We assessed the association between diabetes mellitus and the risk of pleural empyema in Taiwan.

A population-based retrospective cohort study was conducted using the database of the Taiwan National Health Insurance Program. There were 28,802 subjects aged 20 to 84 years who were newly diagnosed with diabetes mellitus from 2000 to 2010 as the diabetes group and 114,916 randomly selected subjects without diabetes mellitus as the non-diabetes group. The diabetes group and the non-diabetes group were matched by sex, age, comorbidities, and the year of index date. The incidence of pleural empyema at the end of 2011 was estimated. A multivariable Cox proportional hazards regression model was used to estimate the hazard ratio (HR) and 95% confidence interval (95% CI) for pleural empyema associated with diabetes mellitus.

The overall incidence of pleural empyema was 1.65-fold higher in the diabetes group than that in the non-diabetes group (1.58 vs 0.96 per 10,000 person-years, 95% CI 1.57–1.72). After adjusting for confounders, a multivariable Cox proportional hazards regression model revealed that the adjusted HR of pleural empyema was 1.71 in subjects with diabetes mellitus (95% CI 1.16–2.51), compared with those without diabetes mellitus. In further analysis, even in the absence of any comorbidity, the adjusted HR was 1.99 for subjects with diabetes mellitus alone (95% CI 1.18–3.38).

Diabetic patients confer a 1.71-fold increased hazard of developing pleural empyema. Even in the absence of any comorbidity, the risk remains existent.

Abbreviation: ICD-9 code = International Classification of Diseases 9th Revision Clinical Modification.

Keywords: diabetes mellitus, pleural empyema, Taiwan National Health Insurance Program

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1. Introduction

Pleural empyema is defined as pus in the pleural space, which usually complicates pneumonia. In the review by Burgos et al,[1] the incidence of pleural empyema has tended to be increasing in the world in the past decades. The study by Grijalva et al[2] in USA showed that the hospitalization rates due to pleural empyema increased from 3.96 cases per 100,000 people in 1996 to 8.10 cases per 100,000 people in 2008 in adults aged 40 to 64 years. In addition, pleural empyema is associated with significant morbidity and mortality. Patients with pleural empyema often need prolonged management, longer hospital stay, intensive care unit admission, and more medical interventions.[3–6] The overall mortality rate of patients with pleural empyema ranged from 6.4% to 41% in Taiwan, depending on the patients selected.[7–9] The literature reveals that some factors, such as alcoholism and tobacco use, are associated with the development of pleural empyema among patients with pneumonia,[4,5,10] but the role of diabetes mellitus has not yet been confirmed.

Diabetes mellitus ranked as the fifth leading cause of deaths in Taiwan in 2016.[11] Abundant epidemiologic data support that patients with diabetes mellitus are at an increased risk for infections, such as lower respiratory tract infection, urinary tract infection, skin infection, and pyogenic liver abscess,[12,13] but the association of pleural empyema has not yet been fully elucidated.

To date, little information is available to assess the association between diabetes mellitus and the risk of pleural empyema in Taiwan. On the basis of the above review, because diabetes mellitus is associated with various infections and pleural empyema carries a potential mortality in Taiwan, we made a

rational link between diabetes mellitus and pleural empyema. If so, clinicians should pay more attention to the risk of pleural empyema among patients with diabetes mellitus. Therefore, we conducted a population-based retrospective cohort study using the database of the Taiwan National Health Insurance Program to assess whether there is an association between diabetes mellitus and the risk of pleural empyema.

2. Methods

2.1. Study design and data source

A population-based retrospective cohort study was conducted to analyze the database retrieved from claim data of the Taiwan National Health Insurance Program. Taiwan is an independent country with more than 23 million people.[14–26] The National Health Insurance Program has covered 99.6% of 23 million people living in Taiwan in 2015.[27] The claim data contained information on patient encrypted identification number, sex, date of birth, disease classification codes, medical facilities used, and so on. The details of the claim data have been well written down in previous studies.[28–32] The study was approved by the Research Ethics Committee of China Medical University and Hospital in Taiwan (CMUH-104-REC2-115).

2.2. Sampled participants

Using the database of the Taiwan National Health Insurance Program, subjects aged 20 to 84 years with newly diagnosed diabetes mellitus (International Classification of Diseases, Ninth Revision, Clinical Modification, ICD-9 code 250) between 2000 and 2010, were assigned as the diabetes mellitus group. The index date was defined as the date of subjects being diagnosed with diabetes mellitus. For each subject with diabetes mellitus, approximately 4 subjects without diabetes mellitus randomly selected from the same database were assigned as the nondiabetes group. The diabetes group and the nondiabetes group were matched by sex, age (every 5-year interval), comorbidities, and the year of index date.

2.3. Major outcome and potential comorbidities

The major outcome was a new diagnosis of pleural empyema based on diagnosis of hospital discharge during the follow-up period. Each subject was monitored from the index date until being diagnosed with pleural empyema, or until the end of 2011.

Potential comorbidities were included in the study as follows: alcohol-related disease, cancer, chronic kidney disease, chronic liver disease (including cirrhosis, hepatitis B, hepatitis C, and other chronic hepatitis), and chronic obstructive pulmonary disease. All comorbidities were diagnosed with ICD-9 codes, although ICD-9 code is only a diagnosing coding system, which has been fully discussed in previous studies.[33–43]

2.4. Statistical analysis

We used the Chi-square test to compare the distributions of sex and comorbidities between the diabetes group and the non-diabetes group. We used the t test to compare the differences of age and follow-up period between the diabetes group and the nondiabetes group. The incidence of pleural empyema was estimated as the event number of pleural empyema identified during the follow-up, divided by the total follow-up person-years for each group. To estimate the hazard ratio (HR) and 95% confidence interval (95% CI) of pleural empyema associated with diabetes mellitus and other comorbidities, initially, all covariables were included in a univariable Cox proportional hazards regression model. Variables found to be statistically significant in a univariable model were further examined in a multivariable Cox proportional hazards regression model. All statistical analyses were performed using SAS 9.2 (SAS Institute, Cary, NC). Two-tailed $P < .05$ was considered statistically significant.

3. Results

3.1. Baseline characteristics of the study population

Table 1 reveals the baseline characteristics of the study population. There were 28,802 subjects with diabetes mellitus and 114,916 subjects without diabetes mellitus during the study period, with similar distribution of sex. The mean ages (standard

Table 1

Baseline characteristics between diabetes group and nondiabetes group.

Variable	Nondiabetes N = 114,916 N (%)	Diabetes N = 28,802 n (%)	P*
Sex			.95
Female	51,800 (45.1)	12,989 (45.1)	
Male	63,116 (54.9)	15,813 (54.9)	
Age group, y			.17
20–39	9133 (8.0)	2194 (7.6)	
40–64	64,843 (56.4)	16,332 (56.7)	
65–84	40,940 (35.6)	10,276 (35.7)	
Age, y, mean (standard deviation)†	58.7 (13.8)	59.4 (13.4)	.001
Follow-up period, y, mean (standard deviation)†	8.35 (3.94)	7.93 (3.99)	.001
Baseline comorbidities			
Alcohol-related disease	6345 (5.52)	1632 (5.67)	.34
Cancer	3650 (3.18)	943 (3.27)	.40
Chronic kidney disease	3191 (2.78)	846 (2.94)	.14
Chronic liver disease	5497 (4.78)	1412 (4.90)	.40
Chronic obstructive pulmonary disease	21,916 (19.1)	5515 (19.2)	.77

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

Table 2

Incidence of pleural empyema estimated by sex and age between diabetes group and nondiabetes group.

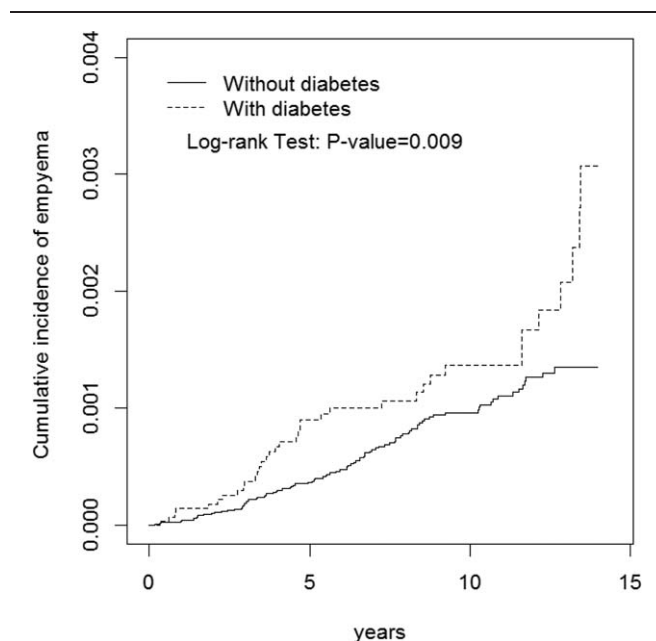| Variable	Nondiabetes				Diabetes				IRR[†]	(95% CI)
	N	Event	Person- years	Incidence[*]	N	Event	Person- years	Incidence[*]		
All	114,916	92	959,771	0.96	28,802	36	228,272	1.58	1.65	(1.57–1.72)
Sex										
Female	51,800	31	452,365	0.69	12,989	12	107,823	1.11	1.62	(1.52–1.74)
Male	63,116	61	507,406	1.20	15,813	24	120,449	1.99	1.66	(1.56–1.76)
Age group, y										
20–39	9133	0	75,366	0.00	2194	0	17,575	0.00	—	—
40–64	64,843	17	576,200	0.30	16,332	7	138,630	0.50	1.71	(1.61–1.82)
65–84	40,940	75	308,204	2.43	10,276	29	72,067	4.02	1.65	(1.54–1.77)

[*] Incidence rate: per 10,000 person-years.
[†] IRR (incidence rate ratio): diabetes vs nondiabetes (95% confidence interval).

deviation) were 59.4 (13.4) years in the diabetes group and 58.7 (13.8) years in the nondiabetes group (t test, $P = .001$). The mean follow-up periods (standard deviation) were 7.93 (3.99) years in the diabetes group and 8.35 (3.94) years in the nondiabetes group (t test, $P = .001$). There was no significant difference in the prevalence of comorbidities between the diabetes group and the nondiabetes group (Chi-square test, $P > .05$ for all).

3.2. Incidence of pleural empyema stratified by sex and age

Table 2 reveals the incidence of pleural empyema of the study population. At the end of follow-up, the overall incidence of pleural empyema was 1.65-fold higher in the diabetes group than that in the nondiabetes group (1.58 vs 0.96 per 10,000 person-years, 95% CI 1.57–1.72). The incidences of pleural empyema, as stratified by sex and age, were all higher in the diabetes group than those in the nondiabetes group. There was no event of pleural empyema in both groups aged 20 to 39 years. Subjects aged 65 to 84 years in the diabetes group had the highest incidence rate (4.02 per 10,000 person-years).

In Fig. 1, the Kaplan–Meier model reveals that the diabetes group had a higher cumulative incidence of pleural empyema than the nondiabetes group (0.307% vs 0.135% at the end of follow-up; $P = .009$).

3.3. Hazard ratio of pleural empyema associated with diabetes mellitus and other comorbidities

Variables found to be statistically significant in a univariable model were further included in a multivariable model (Table 3). After multivariable adjustments, a multivariable Cox proportional hazards regression model revealed that the adjusted HR of pleural empyema was 1.71 in subjects with diabetes mellitus (95% CI 1.16–2.51), compared with those without diabetes mellitus. Male (adjusted HR 2.22, 95% CI 1.54–3.22) and chronic obstructive pulmonary disease (adjusted HR 1.95, 95% CI 1.35–2.80) were also significantly related to pleural empyema. Every 1-year increase in age was significantly related to pleural empyema (adjusted HR 1.13, 95% CI 1.11–1.15).

3.4. Interaction effects on risk of pleural empyema between diabetes mellitus and other comorbidities

As a reference of subjects without diabetes mellitus and without comorbidities including cancer, chronic kidney disease, and chronic obstructive pulmonary disease (Table 4), the adjusted

Figure 1. Kaplan–Meier model reveals that the diabetes group had a higher cumulative incidence of pleural empyema than the nondiabetes group (0.307% vs 0.135% at the end of follow-up; $P = .009$).

Table 3

Adjusted hazard ratio and 95% confidence interval of pleural empyema associated with diabetes mellitus and other comorbidities.

Variable	Crude		Adjusted[*]	
	HR	(95% CI)	HR	(95% CI)
Sex (male vs female)	1.80	(1.24–2.59)	2.22	(1.54–3.22)
Age (per one year)	1.14	(1.12–1.16)	1.13	(1.11–1.15)
Baseline comorbidities (yes vs no)				
Diabetes mellitus	1.66	(1.13–2.44)	1.71	(1.16–2.51)
Alcohol-related disease	0.58	(0.19–1.83)	—	—
Cancer	2.73	(1.27–5.86)	1.72	(0.80–3.71)
Chronic kidney disease	2.76	(1.29–5.91)	1.49	(0.69–3.20)
Chronic liver disease	0.65	(0.21–2.05)	—	—
Chronic obstructive pulmonary disease	4.21	(2.96–5.97)	1.95	(1.35–2.80)

CI = confidence interval, HR = hazard ratio.
[*] Variables found to be statistically significant in a univariable model were further examined in a multivariable model. Adjusted for sex, age, cancer, chronic kidney disease, and chronic obstructive pulmonary disease.

Table 4

Cox proportional hazard regression analysis for risk of pleural empyema stratified by diabetes mellitus and comorbidities.

	Variable	Event	Incidence*	Adjusted HR† (95% CI)
Diabetes mellitus	Any comorbidity‡			
No	No	45	0.58	(Reference)
No	Yes	47	2.48	2.20 (1.45–3.35)
Yes	No	20	1.10	1.99 (1.18–3.38)
Yes	Yes	16	3.46	3.18 (1.79–5.67)

CI = confidence interval, HR = hazard ratio.
* Incidence rate: per 10,000 person-years.
† Adjusted for sex and age.
‡ Comorbidities including cancer, chronic kidney disease, and chronic obstructive pulmonary disease.

HR of pleural empyema was 1.99 for subjects with diabetes mellitus alone and without any comorbidity (95% CI 1.18–3.38). The adjusted HR markedly increased to 3.18 for subjects with diabetes mellitus and with any comorbidity (95% CI 1.79–5.67).

4. Discussion

In this population-based retrospective cohort study, we found that the incidence of pleural empyema was 1.65-fold higher in the diabetes group than that in the nondiabetes group (Table 2). Because of no other incidence data available in Taiwan, we cannot compare them with each other. However, we found that the incidence of pleural empyema in diabetic patients in Taiwan seemed to be much higher than that in general population in USA (15.8 vs 8.10 per 100,000 person-years).[2] We found that the diabetes group had a higher cumulative incidence of pleural empyema than the nondiabetes group (0.307% vs 0.135% at the end of follow-up; $P = .009$). In further analysis, the risk of pleural empyema in the diabetes group was much higher in the first 5 years of follow-up (incidence rate ratio 2.50, 95% CI 2.39–2.62). Moreover, the risk seemed to be persistent in the diabetes group even after 5 years of follow-up (incidence rate ratio 1.07, 95% CI 1.02–1.13, Table not shown).

After multivariable adjustments, we found that diabetic patients were associated with 1.71-fold increased hazard of pleural empyema, compared with those without diabetes mellitus (Table 3). Three clinical studies of case series revealed that among patients with pleural empyema, 7.5% to 30.7% had diabetes mellitus.[44–46] Therefore, pleural empyema and diabetes mellitus were 2 common comorbid conditions.[44–46] However, other studies revealed that diabetes mellitus was not associated with pleural empyema.[6,10,47] We think that the different populations studied could partially explain the conflicting results.

We found that even in the absence of any comorbidity, patients with diabetes mellitus alone remained to have a higher risk of pleural empyema (adjusted HR 1.99, Table 4). In the meanwhile, there was no significant difference in the prevalence of comorbidities between the diabetes group and the nondiabetes group in the present study (Table 1). These findings suggest that the increased hazard of pleural empyema seems to be not confounded by comorbidities. That is, the increased hazard of pleural empyema in diabetic patients cannot be totally caused by the impact of comorbidities. Diabetes mellitus should have a vital role on the risk of development of pleural empyema. In addition, we found that the adjusted HR markedly increased to 3.18 for subjects with diabetes mellitus and with any comorbidity. There seems to be an interaction effect on the risk of pleural empyema between diabetes mellitus and any comorbidity (Table 4). That is,

if patients have diabetes mellitus and any comorbidity, the risk of pleural empyema will substantially increase.

Some limitations in this present study should be discussed. First, due to the inherent limitation of the database, HbA1c was not recorded in the database. As we know, HbA1c is used to assess diabetes control. Without HbA1c data, we cannot determine whether the risk of pleural empyema is associated with good control or poor control of diabetes mellitus. Second, due to the same limitation, the causative pathogens of pleural empyema were outside the scope of the discussion. We could not determine what pathogens of pleural empyema were more likely to be detected in diabetic patients. Third, due to the same limitation, pneumococcal vaccination was not recorded. We could not determine whether pneumococcal vaccination could reduce the risk of pleural empyema in diabetic patients. Fourth, the underlying biological mechanism of the diabetes-pleural empyema association could not be fully clarified in an observational study. However, extensive evidence has shown that the hyperglycemic status would cause dysfunctions of neutrophil, T lymphocyte, B lymphocyte, and humoral immunity.[48–50] Therefore, diabetic patients are more likely to increase susceptibility to various infectious diseases maybe including pleural empyema, mostly due to impaired immunity.

Some strengths of this present study should be mentioned. This study is based on the systematic analysis of the nation-wide insurance claim data, assessing the potential association between diabetes mellitus and pleural empyema. Such a novel finding is interesting and has an important clinical implication. The present study carries powerful updated information on this issue.

We conclude that diabetic patients confer a 1.71-fold increased hazard of developing pleural empyema. Even in the absence of any comorbidity, the risk remains existent. Further prospective research is needed to definitely prove this issue.

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