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Risk of Pleural Empyema in Patients with Schizophrenia: A Nationwide Propensity-matched Cohort Study

— Original Article —

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Running head: *Risk of Empyema in Schizophrenia*

Keywords: empyema; schizophrenia; cohort study

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Abstract

Objective:

Thoracic infection and pneumonia are prevalent in patients with schizophrenia; however, it is unclear whether patients with schizophrenia are at an increased risk of developing pleural empyema.

Design:

A propensity-matched cohort study.

Setting:

National Health Insurance Research Database (NHIRD) of Taiwan.

Participants:

The schizophrenia group comprised 57,497 patients newly diagnosed between 2000 and 2011. The comparison group comprised individuals without schizophrenia selected at a 1:1 ratio and matched by a propensity score estimated according to age, sex, year of diagnosis, and comorbidities.

Primary and secondary outcome measures:

The occurrence of pleural empyema was monitored to the end of 2011. The hazard ratios of pleural empyema were estimated using the Cox proportional hazard model.

Results:

The overall incidence of pleural empyema was 2.69-fold higher in the schizophrenia

group than in the comparison group (4.32 versus 1.61 per 10,000 person-years), with an adjusted hazard ratio (HR) of 2.86 [95% confidence interval (CI) = 2.14−3.83]. Stratified analyses by age, sex, and comorbidity revealed significant HRs for pleural empyema associated with schizophrenia in all subgroups. In addition, the 30-day mortality rate for pleural empyema was higher in the schizophrenia group than in the comparison group (6.63% versus 4.76%, adjusted odds ratio = 1.56, 95% CI = 0.39−6.21).

Conclusions:

Patients with schizophrenia are associated with an increased risk of developing pleural empyema and require greater attention and appropriate support.

Strengths and limitations of this study

1. This is the first nationwide propensity-matched cohort study to evaluate the incidence of pleural empyema in patients with schizophrenia.

2. We have provided detailed epidemiological data for schizophrenia patients (n = 57,497).

3. The National Health Insurance program of Taiwan covers >99% of Taiwan's 23.74 million population. Universal coverage reduces barriers to health care access for all citizens, regardless of socioeconomic background and residential location.

4. The ICD-9-CM algorithm was used to define schizophrenia, pleural empyema, and comorbidities; however, an ad hoc committee was in charge of evaluating the claims data to prevent any errors and violation of confidentiality.

5. Relevant clinical variables such as serum laboratory data, image reports, and culture results were unavailable in the database.

Introduction

Empyema is a collection of pus within a naturally existing anatomical cavity, such as the pleural space. Pleural empyema is an important complication of thoracic infection and pneumonia that can arise from other rare causes.[1, 2] Patients with pleural empyema require prompt and timely treatments, such as antibiotic therapy, pleural space drainage, intrapleural fibrinolysis, and/or surgery.[3] Approximately 60,000 cases of pleural empyema are diagnosed annually in the United States, resulting in significant morbidity and mortality.[4] Certain risk factors for pleural empyema have been identified, which include alcoholism, intravenous drug use, aspiration or choking, diabetes mellitus, immunocompromised status, neoplasm, and preexistent pulmonary disease or pleural effusion.[5, 6] Patients with pleural empyema and comorbid chronic illness portend a poorer prognosis and a higher mortality.[7–9]

Schizophrenia is a severe mental disorder, characterized by profound disruptions in thinking, affecting language, perception, and the sense of self.[10] The hallmark symptom of schizophrenia is psychosis, such as experiencing auditory hallucinations and delusions. Approximately 0.3%–0.7% of individuals are affected by schizophrenia during their lifetime, and thus, schizophrenia affects more than 21 million people worldwide.[11] People with schizophrenia are at a markedly increased risk of premature death. Despite elevated rates of suicide and other unnatural causes

of death, most of the excess mortality has been attributed to cardiovascular disease, respiratory disease, and other natural causes.[12]

Patients with schizophrenia have been proven to be associated with a higher risk of thoracic infection and pneumonia.[13–16] An unhealthy lifestyle, lack of self-care, poorer physical circumstances, and health-risk activities may contribute to this condition.[13] Further, patients with schizophrenia suffering from these infections may have poorer clinical outcomes, such as acute respiratory failure, the use of mechanical ventilation, intensive care unit admission, and hospital death.[14, 17] However, the association between schizophrenia and the occurrence of pleural empyema, an advanced and specific thoracic infection, remains unclear.

The National Health Insurance Research Database (NHIRD) in Taiwan is a nationwide database containing the medical claims data of 23 million residents. These reliable data have been used in studies of various disorders, including schizophrenia and pleural empyema.[18–21] The present study aimed to investigate whether patients with schizophrenia are at an increased risk of subsequent occurrence of pleural empyema. We estimated the incidence of pleural empyema in patients with schizophrenia and compared it with that in individuals without schizophrenia. We also compared the 30-day mortality rate for pleural empyema between the schizophrenia and comparison groups.

Materials and Methods

Data source

The data for this cohort study were obtained from the NHIRD in Taiwan. The NHIRD covers more than 99% of the Taiwanese population and includes patient demographic and medical information. Patient identifiers were re-encoded before the National Health Research Institute released the NHIRD; thus, patient privacy was protected. This study was evaluated and approved by the Research Ethics Committee of China Medical University and Hospital (CMUH-104-REC2-115).

Sampled participants

This study aimed to evaluate the risk of pleural empyema in patients with schizophrenia, which is classified as a catastrophic illness in the NHIRD. The enrolled patients with schizophrenia were selected from the Registry of Catastrophic Illnesses Patient Database (RCIPD), a subset of the NHIRD. The schizophrenia group met the following criteria: patient age >20 years, new diagnosis of schizophrenia between 2000 and 2011 (ICD-9-CM code 295), and never been diagnosed with pleural empyema (ICD-9-CM code 510). The comparison individuals were selected from the Longitudinal Health Insurance Database 2000 (LHID2000), which randomly selected 1 million individuals from the NHIRD. The comparison group was 1:1 matched with the schizophrenia group by a propensity score. Using the propensity score reduces bias from baseline variables, including age; sex; and comorbidities of diabetes

(ICD-9-CM code 250), asthma (ICD-9-CM code 493), chronic obstructive pulmonary disease (COPD) (ICD-9-CM code 496), chronic liver disease and cirrhosis (CLD) (ICD-9-CM code 571), cancer (ICD-9-CM codes 140−208), SLE/RA/immune diseases (ICD-9-CM codes 710.0, 714.0, 279), organ transplant (ICD-9-CM code V42), malnutrition (ICD-9-CM codes 260−269), and obesity (ICD-9-CM code 278.0).

Outcome, relevant variables, and comorbidities

The main outcome of this study was pleural empyema. Person-years indicated the sum of the follow-up time for all participants, and the follow-up time was defined as the time from the index date to the diagnosis of pleural empyema, withdrawal from the insurance, or the end of 2011. Regarding demographic information, we considered age; sex; and comorbidities of diabetes, asthma, COPD, CLD, cancer, SLE/RA/immune diseases, organ transplant, malnutrition, and obesity.

Statistical analysis

The two groups were matched by the propensity score, and the standardized difference was used to quantify differences in mean or prevalence between the schizophrenia and comparison groups for continuous or categorical variables, respectively. The incidence rate of pleural empyema was estimated per person-years. The Kaplan–Meier curve showed the cumulative incidence of pleural empyema for each group and tested the difference between the two groups using a log-rank test.

Univariable and multivariable Cox proportional hazards regression models were used to estimate the hazard ratio (HR) and 95% confidence interval (CI) for the two groups. The multivariable model was adjusted by age; sex; and comorbidities of diabetes, asthma, COPD, CLD, and malnutrition. Data analysis for this study was performed using SAS statistical software (version 9.4 for Windows; SAS Institute, Inc., Cary, NC, USA). Statistical significance was determined at $p < 0.05$.

Results

Table 1 shows the baseline demographics and comorbidities of patients in the schizophrenia and comparison groups. The corresponding mean ages of the schizophrenia and comparison groups were 38.8 and 38.6 years, respectively. The mean follow-up times for the schizophrenia and comparison groups were 6.69 and 6.82 years, respectively.

The incidence of empyema was higher in the schizophrenia group than in the comparison group (4.32 vs. 1.61 per 10,000 person-years, crude HR = 2.69, 95% CI = 2.01−3.60), and the adjusted HR was 2.86 (95% CI = 2.14−3.83) (Table 2). The cumulative incidence was higher in the schizophrenia group than in the comparison group (Figure 1). Other risk factors for pleural empyema were identified. Older patients were at an increased risk of pleural empyema (adjusted HR = 2.89, 95% CI = 2.12−3.95 for the 50−64 age group; adjusted HR = 4.25, 95% CI = 2.79−6.46 for the ≥65 age group). Men had a higher incidence and risk of pleural empyema than women (4.29 vs. 1.46 per 10,000 person-years, adjusted HR = 3.40, 95% CI = 2.50−4.63). In the multivariable Cox regression model, when a patient with certain comorbidities had an increased risk of pleural empyema, including diabetes (adjusted HR = 2.54, 95% CI = 1.68−3.85), COPD (adjusted HR = 1.83, 95% CI = 1.22−2.75), and malnutrition (adjusted HR = 2.60, 95% CI = 1.06−6.37).

Table 3 shows the risk of empyema in patients with schizophrenia at different stratification levels. We found that patients with schizophrenia had an increased risk of empyema at all stratification levels, including those for age (adjusted HR = 2.77, 95% CI = 1.86−4.11 for the 20−49 age group; adjusted HR = 3.00, 95% CI = 1.70−5.28 for the 50−64 age group; adjusted HR = 2.70, 95% CI = 1.35−5.44 for the ≥65 age group) and sex (adjusted HR = 3.18, 95% CI = 1.70−5.95 for women; adjusted HR = 2.82, 95% CI = 2.02−3.93 for men). Patients with schizophrenia with any comorbidity had a 2.54-fold increased risk of pleural empyema, whereas those without comorbidities had a 3.09-fold increased risk of pleural empyema.

We further compared the 30-day mortality rate for pleural empyema between the schizophrenic and comparison groups (Table 4). The odds ratio of mortality rate for empyema between the schizophrenic group and the comparison group was 1.56 (95% CI = 0.39−6.21).

Discussion

To the best of our knowledge, this is the first nationwide propensity-matched cohort study evaluating the incidence of pleural empyema in patients with schizophrenia. Results revealed that patients with schizophrenia had an increased risk of pleural empyema compared to those without schizophrenia. Stratified analyses by age, sex, and presence of comorbidities also showed that the incidence rates of pleural empyema were consistently higher in the schizophrenia group than in the comparison group, and the adjusted HRs for pleural empyema associated with schizophrenia were significant for all subgroups. In addition, the incidences of pleural empyema were higher in older people than in young people, in men than in women, and in individuals with comorbidities than in those without comorbidities. These findings are in accordance with the general concepts. Furthermore, we found that the 30-day mortality rate of pleural empyema was higher in the schizophrenia group than in the comparison group.

The mechanism associating schizophrenia and pleural empyema remains largely unknown. As mentioned above, an unhealthy lifestyle, lack of self-care, poorer physical circumstances, and health-risk activities may contribute to this condition.[13] Frequent medical visits and a prolonged hospital stay may also be contributing factors.[16] Moreover, patients with schizophrenia may reside in a long-term care

facility. Pneumonia in these residents has been defined as a specific type, healthcare associated pneumonia (HCAP).[22] The pathogens of HCAP are often multidrug-resistant bacteria, which are potential risk factors for developing pleural empyema. Furthermore, patients with schizophrenia are at a higher risk of developing swallowing disorders, leading to aspiration pneumonia.[23] Pleural empyema is easily caused by the aspiration of mixed bacterial flora and other materials from the oropharyngeal cavity and even from the upper gastrointestinal tract. Lastly, previous studies have suggested that certain medications may increase the risk of pneumonia in patients with schizophrenia.[24–26]

Patients with schizophrenia are at a markedly increased risk of premature mortality, particularly from thoracic infection and pneumonia. In the United States, a large-scale study showed that the overall mortality rate for patients with schizophrenia was 3.7 times higher than that of the general population. Among them, the risk of death from respiratory diseases increased the most, that of COPD increased 9.9 times, and that of influenza and pneumonia increased 7.0 times.[27] In another Taiwanese study, patients with schizophrenia experienced a 3.09-fold increased risk of developing pneumonia. After adjusting for possible variables, the mortality HR for patients with schizophrenia was 1.39.[14] In another study, autopsy findings in sudden unexpected death of inpatients with schizophrenia revealed that the top three specific causes were

myocardial infarction (52.9%), pneumonia (11.8%), and airway obstruction (7.8%).[28] In the present study, we found that the 30-day mortality rate for empyema was higher in patients with schizophrenia than in individuals without schizophrenia.

The strength of this study is that we performed a nationwide propensity-matched evaluation of patients with schizophrenia and assessed their risk of developing pleural empyema. It is expensive to conduct a prospective cohort study; thus, a retrospective cohort study using insurance data is a suitable and economical alternative. The National Health Insurance program has covered >99.5% of the Taiwanese population since 2010. Universal coverage reduces barriers to healthcare access for all citizens, regardless of their socioeconomic background and/or residential location.[29] In the present study, by using the NHIRD, we were able to reflect a "real world" scenario wherein schizophrenia, pleural empyema, and all comorbidities were directly diagnosed during a medical consultation.

There are several limitations that should be considered when interpreting the results of the present study. First, the ICD-9-CM algorithm was used to define schizophrenia, pleural empyema, and comorbidities; thus, the diagnosis of schizophrenia was the most accurate because it required a carefully peer-reviewed process to confirm it as a catastrophic illness. All other diagnoses depended on the competence of clinical physicians. An ad hoc committee established by the insurance authority was charged

with evaluating the claims data to prevent errors and violations. In addition, we selected only those diagnoses that appeared at least twice within a year to increase the validity and accuracy. Second, the NHIRD does not provide detailed information about smoking or drinking habits and environmental factors, which may have been potentially confounding factors in the present study. In addition, relevant clinical variables such as serum laboratory data, image reports, and culture results were not available to our study.[30]

Conclusion

Patients with schizophrenia are at a significantly higher risk of developing empyema; therefore, we should pay attention to monitoring patients with schizophrenia for empyema development. These patients may require intensive monitoring throughout their clinical course by chest radiography and/or chest sonography because treatments for empyema are varied and complex. A delayed diagnosis of empyema is associated with severe symptoms, a prolonged hospital stay, and an increased fatality risk.

Contributor ship statement

T-CS, C-HC, Y-JH, T-CC, C-YT and C-MS conceived and designed the study.

T-CH, C-MS and W-HH provided administrative support.

T-CS, C-LL, C-MS and F-CS analysed and interpreted the data.

T-CS, C-LL, C-MS and F-CS contributed by writing the manuscript.

All authors were involved in collection and assembly of data.

All authors approved the final version of the manuscript to be published.

Competing interests

None declared.

Ethics approval

This study was approved by the Research Ethics Committee at the China Medical University and Hospital (CMUH-104-REC2-115).

Funding statement

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study design, data collection and analysis, decision to publish, or preparation of the manuscript. No additional external funding received for this study.

Data sharing statement:

No additional data available.

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Table 1. Baseline characteristics between individuals with and without schizophrenia

	Schizophrenia				
	No N = 57,497		Yes N = 57,497		
	n	%	n	%	Standard difference
Age					
20−49	46130	80.2	46227	80.4	0.004
50−64	8025	14.0	8705	15.1	0.034
≥ 65	3342	5.81	2565	4.46	0.061
Mean (SD)	38.6	(14.2)	38.8	(13.4)	0.014
Sex					
Women	27700	48.2	27194	47.3	0.02
Men	29797	51.8	30303	52.7	0.02
Comorbidity					
Diabetes	1938	3.37	2567	4.46	0.06
Asthma	1578	2.74	2329	4.05	0.07
COPD	2613	4.54	3356	5.84	0.06
CLD	6158	10.7	7613	13.2	0.08
Cancer	307	0.53	419	0.73	0.03
SLE/RA/immune disorders	9	0.02	32	0.06	0.02
Organ transplant	4	0.01	7	0.01	0.01
Malnutrition	283	0.49	342	0.59	0.01
Obesity	746	1.30	749	1.30	0.00

CLD, chronic liver disease and cirrhosis; COPD, chronic obstructive pulmonary disease; RA, rheumatoid arthritis; SD, standard deviation; SLE, systemic lupus erythematosus

Table 2. The incidence and risk factors for pleural empyema

	Event	PY	Rate†	Crude HR (95% CI)	Adjusted HR‡ (95% CI)
Schizophrenia					
No	63	392191	1.61	1.00	1.00
Yes	166	384415	4.32	2.69 (2.01, 3.60)***	2.86 (2.14, 3.83)***
Age					
20–49	131	638205	2.05	1.00	1.00
50–64	64	105224	6.08	2.98 (2.21, 4.02)***	2.89 (2.12, 3.95)***
≥ 65	34	33177	10.3	5.05 (3.46, 7.37)***	4.25 (2.79, 6.46)***
Sex					
Women	54	368905	1.46	1.00	1.00
Men	175	407701	4.29	2.93 (2.16, 3.98)***	3.40 (2.50, 4.63)***
Comorbidity					
Diabetes					
No	199	751738	2.65	1.00	1.00
Yes	30	24869	12.1	4.61 (3.14, 6.77)***	2.54 (1.68, 3.85)***
Asthma					
No	208	753918	2.76	1.00	1.00
Yes	21	22689	9.26	3.38 (2.16, 5.30)***	1.55 (0.94, 2.56)
COPD					
No	190	740617	2.57	1.00	1.00
Yes	39	35990	10.8	4.24 (3.01, 5.99)***	1.83 (1.22, 2.75)**
CLD					
No	194	689635	2.81	1.00	1.00
Yes	35	86971	4.02	1.44 (1.00, 2.06)*	0.86 (0.59, 1.25)
Cancer					
No	228	772739	2.95	1.00	1.00
Yes	1	3868	2.59	0.88 (0.12, 6.30)	-
SLE/RA/immune disorders					
No	229	776368	2.95	1.00	1.00
Yes	0	238	0.00	-	-
Organ transplant					
No	229	776525	2.95	1.00	1.00
Yes	0	81	0.00	-	-
Malnutrition					

No	224	772564	2.90	1.00	1.00
Yes	5	4042	12.4	4.28 (1.76, 10.4)**	2.60 (1.06, 6.37)*
Obesity					
No	227	768634	2.95	1.00	1.00
Yes	2	7973	2.51	0.86 (0.21, 3.46)	-

CI, confidence interval; CLD, chronic liver disease and cirrhosis; COPD, chronic obstructive pulmonary disease; HR, hazard ratio; PY, person-years; RA, rheumatoid arthritis; SLE, systemic lupus erythematosus;

† Incidence rate, per 10,000 person-years;

‡ Multivariable analysis including age, sex, and comorbidities of diabetes, asthma, COPD, CLD, and malnutrition;

* p <0.05, ** p <0.01, *** p <0.001.

Table 3. Incidence and hazard ratios of pleural empyema between individuals with and without schizophrenia

	Schizophrenia							
	No			Yes				
	Event	PY	Rate†	Event	PY	Rate†	Crude HR (95% CI)	Adjusted HR‡ (95% CI)
Age								
20−49	33	320560	1.03	98	317645	3.09	3.00 (2.02, 4.45)***	2.77 (1.86, 4.11)***
50−64	16	52065	3.07	48	53159	9.03	2.94 (1.67, 5.17)***	3.00 (1.70, 5.28)***
≥ 65	14	19566	7.16	20	13611	14.7	2.05 (1.03, 4.06)*	2.70 (1.35, 5.44)**
Sex								
Women	13	188593	0.69	41	180312	2.27	3.31 (1.77, 6.17)***	3.18 (1.70, 5.95)***
Men	50	203598	2.46	125	204103	6.12	2.49 (1.80, 3.46)***	2.82 (2.02, 3.93)***
Comorbidity§								
No	37	328798	1.13	106	302889	3.50	3.11 (2.14, 4.52)***	3.09 (2.13, 4.50)***
Yes	26	63394	4.10	60	81526	7.36	1.79 (1.13, 2.83)*	2.54 (1.58, 4.10)***

CI, confidence interval; HR, hazard ratio; PY, person-years;

† Incidence rate, per 10,000 person-years;

‡ Multivariable analysis including age, sex, and comorbidities of diabetes, asthma, COPD, CLD, and malnutrition;

§ Individuals with any comorbidity of diabetes, asthma, COPD, CLD, cancer, SLE/RA/immune disorders, organ transplant, malnutrition, and obesity were classified into the comorbidity group;

* p <0.05, ** p <0.01, *** p <0.001.

Table 4. Odds ratio of 30-day mortality rate for pleural empyema in individuals with schizophrenia compared to those without schizophrenia

	Schizophrenia	
	No	Yes
Deaths / Events	3/63	11/166
Mortality rate	4.76%	6.63%
Crude OR (95% CI)	1 (Reference)	1.42 (0.38, 5.26)
Adjusted OR[†] (95% CI)	1 (Reference)	1.56 (0.39, 6.21)

CI, confidence interval; OR, odds ratio;

[†] Multivariable analysis controlling for age, sex, and comorbidities of diabetes, asthma, COPD, CLD, and malnutrition;

* p <0.05, ** p <0.01, *** p <0.001.

Figure Legends

Figure 1. Cumulative incidence of pleural empyema in the schizophrenia group (dashed line) and comparison group (solid line).

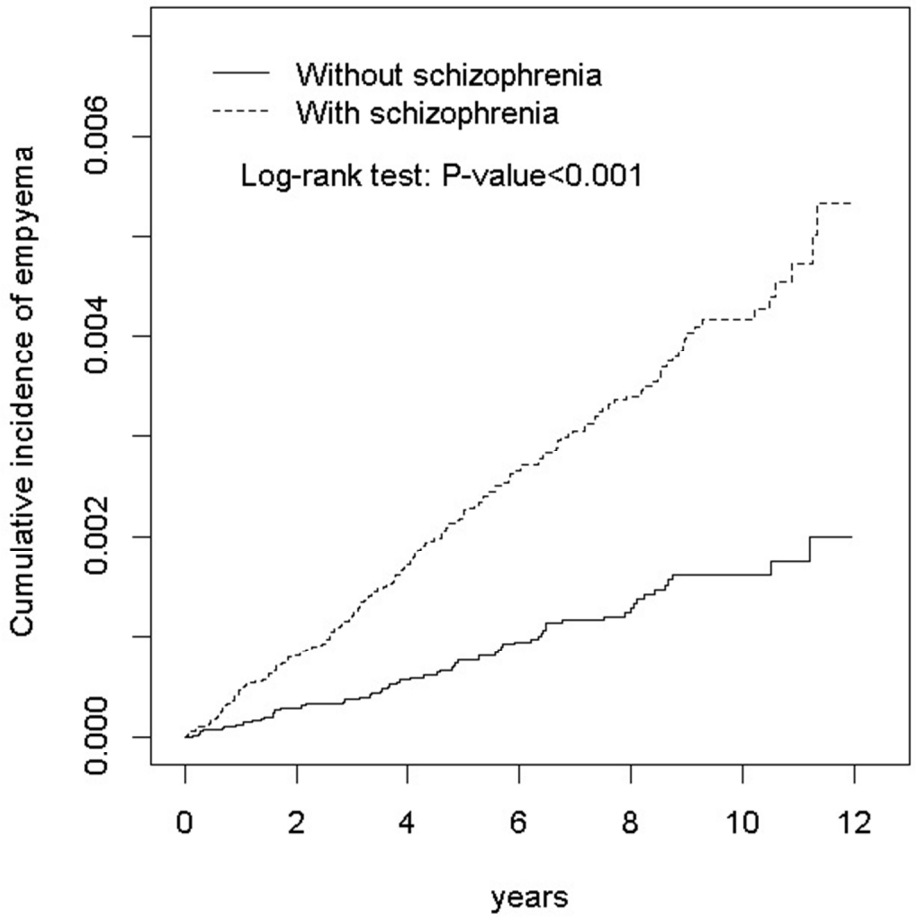

Figure 1. Cumulative incidence of pleural empyema in the schizophrenia group (dashed line) and comparison group (solid line).

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STROBE Statement

Checklist of items that should be included in reports of observational studies

Section/Topic	Item No	Recommendation	Reported on Page No
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1, 3-4
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	3-4
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	6-7
Objectives	3	State specific objectives, including any prespecified hypotheses	6-7
Methods			
Study design	4	Present key elements of study design early in the paper	8-9
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	8-9
Participants	6	(*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up *Case-control study*—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls *Cross-sectional study*—Give the eligibility criteria, and the sources and methods of selection of participants	8-9
		(*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed *Case-control study*—For matched studies, give matching criteria and the number of controls per case	8-9
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	9
Data sources/measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	8
Bias	9	Describe any efforts to address potential sources of bias	
Study size	10	Explain how the study size was arrived at	8
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	9-10
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	9-10
		(*b*) Describe any methods used to examine subgroups and interactions	9-10
		(*c*) Explain how missing data were addressed	
		(*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed *Case-control study*—If applicable, explain how matching of cases and controls was addressed *Cross-sectional study*—If applicable, describe analytical methods taking account of sampling strategy	
		(*e*) Describe any sensitivity analyses	9-10

Section/Topic	Item No	Recommendation	Reported on Page No
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	11
		(b) Give reasons for non-participation at each stage	
		(c) Consider use of a flow diagram	
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	11
		(b) Indicate number of participants with missing data for each variable of interest	
		(c) *Cohort study*—Summarise follow-up time (eg, average and total amount)	11
Outcome data	15*	*Cohort study*—Report numbers of outcome events or summary measures over time	11-12
		Case-control study—Report numbers in each exposure category, or summary measures of exposure	
		Cross-sectional study—Report numbers of outcome events or summary measures	
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	11-12
		(*b*) Report category boundaries when continuous variables were categorized	11-12
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	11-12
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	11-12
Discussion			
Key results	18	Summarise key results with reference to study objectives	13
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	15-16
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	13-16
Generalisability	21	Discuss the generalisability (external validity) of the study results	13-16
Other Information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	18-19

**Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.*

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Risk of Pleural Empyema in Patients with Schizophrenia: A Nationwide Propensity-matched Cohort Study in Taiwan

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Risk of Pleural Empyema in Patients with Schizophrenia: A Nationwide Propensity-matched Cohort Study in Taiwan

— Original Article —

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Running head: *Risk of Empyema in Schizophrenia*

Keywords: pleural empyema; schizophrenia; propensity score matched; retrospective cohort study

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Abstract

Objective:

Thoracic infection and pneumonia are prevalent in patients with schizophrenia; however, it is unclear whether patients with schizophrenia are at an increased risk of developing pleural empyema.

Design:

A retrospective cohort study with propensity-matched cohorts.

Setting:

National Health Insurance Research Database (NHIRD) of Taiwan.

Participants:

The schizophrenia group comprised 55,888 patients newly diagnosed between 2000 and 2011. The comparison group comprised individuals without schizophrenia selected at a 1:1 ratio and matched by propensity scores estimated according to age, sex, occupation, income, urbanization, year of diagnosis, and comorbidities.

Primary and secondary outcome measures:

The incidence of pleural empyema was monitored by the end of 2011. The adjusted hazard ratios (aHRs) of pleural empyema were estimated using the Cox proportional hazard model.

Results:

The overall incidence of pleural empyema was 2.44-fold higher in the schizophrenia group than in the comparison group (4.39 versus 1.80 per 10,000 person-years), with an aHR of 2.87 [95% confidence interval (CI) = 2.14−3.84]. Stratified analyses by age, sex, occupation, income, urbanization, and comorbidity revealed significant aHRs for pleural empyema associated with schizophrenia in all subgroups.

Conclusions:

Patients with schizophrenia are associated with an increased risk of developing pleural empyema and require greater attention and appropriate support.

Strengths and limitations of this study

1. This is the first nationwide propensity-matched cohort study to evaluate the risk of pleural empyema in patients with schizophrenia.

2. The National Health Insurance program of Taiwan covers >99% of Taiwan's 23.74 million population. Universal coverage reduces barriers to health care access for all citizens, regardless of socioeconomic background and residential location.

3. The ICD-9-CM algorithm was used to define schizophrenia, pleural empyema, and comorbidities and an ad hoc committee was in charge of evaluating the claims data to prevent errors and violation of confidentiality.

4. The database does not provide detailed information on smoking or drinking habits, nutrition status, and other psychosocial and environmental factors

5. Relevant clinical variables such as serum laboratory data, image reports, and culture results were unavailable in the database.

Introduction

Patients with pleural empyema require prompt and timely treatments, such as antibiotic therapy, pleural space drainage, intrapleural fibrinolysis, and/or surgery.[1, 2] Approximately 60,000 cases of pleural empyema are diagnosed annually in the United States.[3] The condition is more prevalent in Taiwan, with the incidence rate range from 0.96−8.19 per 10,000 person-year.[4–6] Certain risk factors for pleural empyema have been identified, which include alcoholism, intravenous drug use, aspiration or choking, diabetes mellitus, immunocompromised status, neoplasm, and preexistent pulmonary disease or pleural effusion.[7, 8] Patients with pleural empyema and comorbid chronic illness portend a poorer prognosis and a higher mortality.[9, 10]

Schizophrenia is a severe mental disorder, characterized by profound disruptions in thinking, affecting language, perception, and the sense of self.[11] The hallmark symptom of schizophrenia is psychosis, such as experiencing auditory hallucinations and delusions.[12] Approximately 0.3%–0.7% of individuals are affected by schizophrenia during their lifetime, and thus, schizophrenia affects more than 21 million people worldwide.[13] People with schizophrenia are at a markedly increased risk of premature death. Despite elevated rates of suicide and other unnatural causes of death, most of the excess mortality has been attributed to cardiovascular disease, respiratory disease, and other natural causes.[14]

Patients with schizophrenia have been found to be associated with a higher risk of thoracic infection and pneumonia.[15–18] The risk of having pneumonia is 3-fold greater in schizophrenic patients than in general population.[16, 18] An unhealthy lifestyle, lack of self-care, poorer physical circumstances, and health-risk activities may contribute to this condition.[13] Further, patients with schizophrenia suffering from these infections may have poorer clinical outcomes, such as acute respiratory failure, the use of mechanical ventilation, intensive care unit admission, and hospital death.[16, 19] Therefore, thoracic infection and pneumonia greatly increase morbidity and mortality in patients with schizophrenia and seriously threaten the health of these patients. However, the association between schizophrenia and the occurrence of pleural empyema, an advanced and specific thoracic infection, remains unclear.

The National Health Insurance Research Database (NHIRD) in Taiwan is a nationwide database containing the medical claims data of 23 million residents. These reliable data have been used in studies of various disorders, including schizophrenia and pleural empyema.[6, 20–22] The present study aimed to investigate whether patients with schizophrenia are at an increased risk of subsequent occurrence of pleural empyema. We estimated the incidence of pleural empyema in patients with schizophrenia and compared it with that in individuals without schizophrenia. We also compared the 30-day mortality rate for pleural empyema between the schizophrenia

and comparison groups.

Materials and Methods

Data source

The data for this cohort study were obtained from the NHIRD of Taiwan, including patient demographic and medical information. The insurance covers more than 99% of the Taiwanese population. Patient identifiers were re-encoded before the National Health Research Institute released the NHIRD; thus, patient privacy was protected. This study was evaluated and approved by the Research Ethics Committee of China Medical University and Hospital (CMUH-104-REC2-115).

Sampled participants

This study aimed to evaluate the risk of pleural empyema in patients with schizophrenia. The disease is classified as a catastrophic illness in the insurance system, similar to other 30 categories of diseases requiring long-term care, such as cancers, end-stage major organ diseases, systemic autoimmune diseases and major mental disorders. Patients with a catastrophic illness certificate are eligible for reduced financial burden for health care. Registry for the certificate requires a careful peer-review process in the insurance system. Schizophrenic patients aged 20 years and older newly diagnosed in 2000-2011 (ICD-9-CM code 295), without the history of pleural empyema (ICD-9-CM code 510) were identified as schizophrenia group. The comparison individuals were selected from the Longitudinal Health Insurance Database 2000 (LHID2000), which consisted of claims data of randomly selected 1

million individuals from the NHIRD. The schizophrenia group and the comparison group were established at 1:1 ratio, frequency matched by propensity scores. The propensity score was estimated to reduce bias from baseline variables, including age, sex, occupation, monthly income, urbanization level, and comorbidities of diabetes (ICD-9-CM code 250), asthma (ICD-9-CM code 493), chronic obstructive pulmonary disease (COPD) (ICD-9-CM code 496), chronic liver disease and cirrhosis (CLD) (ICD-9-CM code 571), cancer (ICD-9-CM codes 140−208), systemic lupus erythematosus (SLE)/rheumatoid arthritis (RA)/immune diseases (ICD-9-CM codes 710.0, 714.0, 279), organ transplant (ICD-9-CM code V42), malnutrition (ICD-9-CM codes 260−269), obesity (ICD-9-CM code 278.0), alcohol abuse (ICD-9-CM codes 291, 303, 305.0), drug abuse (ICD-9-CM codes 292, 304, 305.2, 305.9), and tobacco use disorder (ICD-9-CM code 305.1).

Patient and public involvement

We conducted the retrospective cohort study from an insurance research database. Personal information in the database was anonymized and de-identified prior to analysis. Therefore, we considered that patients and public were not involved.

Outcome, relevant variables, and comorbidities

The main outcome of this study was pleural empyema. Person-years indicated the sum of the follow-up time for all participants, and the follow-up time was defined as

the time from the index date to the diagnosis of pleural empyema, withdrawal from the insurance, or the end of 2011. Regarding demographic information, we considered age, sex, occupation, monthly income, urbanization level, and comorbidities of diabetes, asthma, COPD, CLD, cancer, SLE/RA/immune diseases, organ transplant, malnutrition, obesity, alcohol abuse, drug abuse, and tobacco use disorder.

Statistical analysis

The two groups were matched by the propensity scores, and the standardized difference was used to quantify differences in means or prevalence rates between the schizophrenia and comparison groups for continuous or categorical variables, respectively. A standardized difference of 0.1 or less than 0.1 indicated a negligible difference in means between 2 cohorts.[23] The incidence rate of pleural empyema was estimated per 10,000 person-years. We used Poisson regression analysis to calculate the schizophrenia group to controls incidence rate ratio (IRR). The Kaplan-Meier method was then used to calculate the cumulative incidence of pleural empyema for each group and the difference between the two groups was examined using log-rank test. Multivariable Cox proportional hazards regression models was used to estimate the adjusted hazard ratio (aHR) and 95% confidence interval (CI) for the two groups. The multivariable model was adjusted by age, sex, occupation, monthly income, urbanization level, and comorbidities of diabetes, asthma, COPD, CLD, malnutrition,

and alcohol abuse. Data analysis for this study was performed using SAS statistical software (version 9.4 for Windows; SAS Institute, Inc., Cary, NC, USA). Statistical significance was determined at $p < 0.05$.

Results

Table 1 shows that schizophrenia and comparison groups were similar in distributions of baseline demographics and comorbidities with mean ages of 38.9 and 38.7 years, respectively.

After mean follow-up time of 6.7 year in both cohorts, Figure 1 shows that the cumulative incidence of pleural empyema was higher in the schizophrenia group than in the comparison group. The incidence was 2.4-fold greater in the schizophrenia group than in the comparison group (4.39 vs. 1.80 per 10,000 person-years), with an IRR of 2.44 (95% CI = 1.83−3.24) or an aHR of 2.87 (95% CI = 2.14−3.84) (Table 2). The pooled data showed that the overall incidence increased with age, and higher in men than in women. Study population of low income and living in rural area were at higher risk of empyema. Individuals with comorbidities are also at increased risk of pleural empyema, including those with diabetes (adjusted HR = 2.62, 95% CI = 1.77−3.87), asthma (adjusted HR = 1.98, 95% CI = 1.27−3.07), COPD (adjusted HR = 2.01, 95% CI = 1.38−2.95), malnutrition (adjusted HR = 3.60, 95% CI = 1.76−7.36), and alcohol abuse (adjusted HR = 1.74, 95% CI = 1.10−2.74).

Table 3 shows the incident empyema in patients with schizophrenia, comparing with the comparison group, by demographic status and comorbidity status. The incidence rate in each stratum was greater in the schizophrenia group than in the

comparison group. The schizophrenia group to the comparison group IRRs and aHRs were significant for all strata. Significant IRRs ranged from 1.51 to 3.63 and significant aHRs ranged from 2.45 to 3.70. Comorbidity increased the incidence of pleural empyema in both cohorts for 3.74 and 3.51 per 10,000 person-years, respectively. The schizophrenia group to comparison group aHR showed a relatively greater impact for study individuals without comorbidities than those with comorbidity.

Table 4 shows a lower 30-day mortality rate from pleural empyema for the schizophrenic group than the comparison group (6.71% vs. 8.96%), with an adjusted odds ratio of 0.95 (95% CI = 0.30−3.01).

Discussion

To the best of our knowledge, this is the first nationwide propensity-matched cohort study evaluating the incidence of pleural empyema in patients with schizophrenia. Results revealed that patients with schizophrenia had an increased risk of pleural empyema compared to those without schizophrenia. Stratified analyses by age, sex, occupation, income, urbanization, and presence of comorbidities also showed that the incidence rates of pleural empyema were consistently higher in the schizophrenia group than in the comparison group, and the aHRs for pleural empyema associated with schizophrenia were significant for all subgroups. In addition, the incidences of pleural empyema were higher in older people than in young people, in men than in women, and in individuals with comorbidities than in those without comorbidities. These findings are in accordance with the general concepts.

The mechanism associating schizophrenia to the risk of developing pleural empyema remains largely unknown. As mentioned above, an unhealthy lifestyle, lack of self-care, poorer physical circumstances, and health-risk activities may contribute to this condition.[15] Frequent medical visits and a prolonged hospital stay may also be contributing factors.[18] Moreover, patients with schizophrenia may reside in a long-term care facility. Pneumonia in these residents has been defined as a specific type, healthcare associated pneumonia (HCAP).[24] The pathogens of HCAP are often

multidrug-resistant bacteria, which are potential risk factors for developing pleural empyema. Furthermore, patients with schizophrenia are at a higher risk of developing swallowing disorders, leading to aspiration pneumonia.[25] Pleural empyema is easily caused by the aspiration of mixed bacterial flora and other materials from the oropharyngeal cavity and even from the upper gastrointestinal tract. In addition, previous studies have suggested that the use of second-generation antipsychotics, such as clozapine, may increase the risk of pneumonia in patients with schizophrenia.[26–28] Clozapine is known for associations with agranulocytosis, sialorrhea, and impairment of swallowing function; patients with this medication may thus take a greater risk for pneumonia.[29]

Patients with schizophrenia are at a markedly increased risk of premature mortality, particularly from thoracic infection and pneumonia. A large-scale study in the United States showed that the overall mortality rate was 3.7-time higher in patients with schizophrenia than in the general population.[30] The increased mortality was mainly from respiratory diseases: 9.9-time higher from COPD and 7.0-time higher from influenza and pneumonia. A study in Taiwan showed that patients with schizophrenia experienced a 3.09-fold increased risk of developing pneumonia, with an adjusted HR of 1.39 for deaths from pneumonia.[16] In an Romanian study, autopsy findings in sudden unexpected deaths of inpatients with schizophrenia revealed that the top three

specific causes were myocardial infarction (52.9%), pneumonia (11.8%), and airway obstruction (7.8%).[31] However, the result of present study did not show the difference of 30-day mortality between the schizophrenic group and the comparison group.

The strength of this study is that we performed a nationwide propensity-matched evaluation for patients with schizophrenia and assessed their risk of developing pleural empyema. It is expensive to conduct a prospective cohort study; thus, a retrospective cohort study using insurance data is a suitable and economical alternative. The National Health Insurance program has covered >99.5% of the Taiwanese population. The universal health coverage reduces barriers to healthcare access for all citizens, regardless of their socioeconomic background and/or residential location.[32] The present study reflected a "real world" scenario by using the claims data, as schizophrenia, pleural empyema, and comorbidities were diagnosed at clinics during medical consultations.

There are several limitations that should be considered when interpreting the study findings. First, we used the ICD-9-CM algorithm to define schizophrenia, pleural empyema, and comorbidities. The diagnosis of Schizophrenia is mostly accurate because it is a disease with catastrophic certificate. All other diagnoses depended on the competence of clinical physicians. An ad hoc committee established by the insurance authority was in charge of evaluating the claims data to prevent errors and

violations. In addition, we selected only those diagnoses that appeared at least twice within a year to increase the validity and accuracy. Second, the information on smoking, drinking, nutrition, and some psychosocial and environmental factors were unavailable, which may affect their risk of pulmonary infections and consequent complications. Instead, we have included the tobacco use disorder and COPD as variables to substitute smoking and included alcohol abuse to substitute drinking. Similarly, malnutrition is a crucial factor for pleural empyema development; however, it is unlikely to be identified adequately by relying on recorded diagnoses. In addition, institutional residence is a possible source of multiple-resistant infection, but the relevant data was unavailable. Furthermore, other clinical variables such as serum laboratory data, image reports, and culture results were not available to our study.[33]

Conclusion

This study suggests that patients with schizophrenia are at an elevated risk for developing pleural empyema. The risk increases further for those with comorbidity. It should be kept in mind that schizophrenic patients with pneumonia or other thoracic infection may be at potential risk for the development of pleural empyema and disease related mortality.

Contributor ship statement

T-CS, C-HC, Y-JH, T-CC, C-YT and C-MS conceived and designed the study.

T-CH, C-MS and W-HH provided administrative support.

T-CS, C-LL, C-MS and F-CS analysed and interpreted the data.

T-CS, C-LL, C-MS and F-CS developed and revised the manuscript.

All authors were involved in collection and assembly of data.

All authors approved the final version of the manuscript to be published.

Competing interests

None declared.

Ethics approval

This study was approved by the Research Ethics Committee at the China Medical University and Hospital (CMUH-104-REC2-115).

Funding statement

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study design, data collection and analysis, decision to publish, or preparation of the manuscript. No additional external funding received for this study.

Data sharing statement:

No additional data available.

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Table 1. Baseline characteristics compared between cohorts with and without schizophrenia

	Schizophrenia				
	No N = 55,888		Yes N = 55,888		
	n	%	n	%	Standardized difference
Age					
20−49	43651	78.1	44679	79.9	0.045
50−64	7083	12.7	8654	15.5	0.081
≥ 65	5154	9.22	2555	4.57	0.18
Mean (SD)	38.7	16.2	38.9	13.4	0.015
Sex					
Women	27036	48.4	26796	48.0	0.009
Men	28852	51.6	29092	52.1	0.009
Occupation [a]					
Office worker	24539	43.9	24844	44.5	0.011
Laborer	17604	31.5	17499	31.3	0.004
Other	13745	24.6	13545	24.2	0.008
Monthly income [b]					
< 15,000	25221	45.1	24985	44.7	0.008
15,000−19,999	23266	41.6	23696	42.4	0.016
≥ 20,000	7401	13.2	7207	12.9	0.01
Urbanization level [c]					
City	29894	53.5	30151	54.0	0.009
Rural area	25994	46.5	25737	46.1	0.009
Comorbidity					
Diabetes	2442	4.37	2485	4.45	0.004
Asthma	2204	3.94	2245	4.02	0.004
COPD	3168	5.67	3262	5.84	0.007
CLD	7134	12.8	7249	13.0	0.006
Cancer	430	0.77	417	0.75	0.003
SLE/RA/immune disorders	32	0.06	31	0.06	0.001
Organ transplant	7	0.01	7	0.01	0.000
Malnutrition	362	0.65	331	0.59	0.007

Obesity	719	1.29	724	1.30	0.001
Alcohol abuse	2922	5.23	2884	5.16	0.003
Drug abuse	1818	3.25	1986	3.55	0.017
Tobacco use disorder	843	1.51	789	1.41	0.008

CLD, chronic liver disease and cirrhosis; COPD, chronic obstructive pulmonary disease; RA, rheumatoid arthritis; SD, standard deviation; SLE, systemic lupus erythematosus;

[a] Other occupations include primarily retired, unemployed, and low-income populations;

[b] 1 new Taiwan dollar is equal to 0.03 US dollar;

[c] The urbanization level is categorized by the population density of the residential area into 2 levels: city and rural area.

Table 2. The incidence of pleural empyema incidence rate ratio and adjusted hazard ratio measured for pooled study population by study cohort, sociodemographic status and comorbidities

	Event	PY	Rate [a]	IRR (95% CI)	Adjusted HR [b] (95% CI)
Schizophrenia					
No	67	371984	1.80	1.00	1.00
Yes	164	373435	4.39	2.44 (1.83, 3.24)***	2.87 (2.14, 3.84)***
Age					
20−49	126	604297	2.09	1.00	1.00
50−64	65	97993	6.63	3.19 (2.36, 4.30)***	2.86 (2.09, 3.93)***
≥ 65	40	43129	9.27	4.46 (3.13, 6.37)***	3.45 (2.29, 5.19)***
Sex					
Women	52	360369	1.44	1.00	1.00
Men	179	385050	4.65	3.22 (2.37, 4.39)***	3.52 (2.57, 4.82)***
Occupation [c]					
Office worker	79	328927	2.40	1.00	1.00
Laborer	75	232762	3.22	1.34 (0.98, 1.84)	0.94 (0.67, 1.33)
Other	77	183730	4.19	1.75 (1.28, 2.39)***	1.19 (0.82, 1.71)
Monthly income [d]					
< 15,000	113	328597	3.44	2.00 (1.20, 3.33)**	1.92 (1.10, 3.33)*
15,000−19,999	101	318118	3.17	1.84 (1.10, 3.08)*	1.97 (1.15, 3.36)*
≥ 20,000	17	98704	1.72	1.00	1.00
Urbanization level [e]					
City	97	399858	2.43	1.00	1.00
Rural area	134	345561	3.88	1.60 (1.23, 2.08)***	1.46 (1.12, 1.90)**
Comorbidity					
Diabetes					
No	197	718779	2.74	1.00	1.00
Yes	34	26641	12.8	4.67 (3.24, 6.73)***	2.62 (1.77, 3.87)***
Asthma					
No	202	719903	2.81	1.00	1.00
Yes	29	25516	11.4	4.06 (2.75, 5.99)***	1.98 (1.27, 3.07)**
COPD					
No	182	707738	2.57	1.00	1.00
Yes	49	37681	13.0	5.07 (3.69, 6.95)***	2.01 (1.38, 2.95)***
CLD					

No	186	655200	2.84	1.00	1.00
Yes	45	90219	4.99	1.76 (1.27, 2.43)***	1.00 (0.71, 1.42)
Cancer					
No	228	741180	3.08	1.00	
Yes	3	4239	7.08	2.30 (0.74, 7.19)	
SLE/RA/immune disorders					
No	231	745075	3.10	1.00	
Yes	0	345	0.00	-	
Organ transplant					
No	231	745312	3.10	1.00	
Yes	0	107	0.00	-	
Malnutrition					
No	223	741266	3.01	1.00	1.00
Yes	8	4154	19.3	6.38 (3.15, 12.9)***	3.60 (1.76, 7.36)***
Obesity					
No	229	737942	3.10	1.00	
Yes	2	7478	2.67	0.86 (0.21, 3.46)	
Alcohol abuse					
No	209	714370	2.93	1.00	1.00
Yes	22	31049	7.09	2.42 (1.56, 3.77)***	1.74 (1.10, 2.74)*
Drug abuse					
No	220	724902	3.03	1.00	
Yes	11	20517	5.36	1.77 (0.96, 3.24)	
Tobacco use disorder					
No	227	739856	3.07	1.00	
Yes	4	5564	7.19	2.37 (0.88, 6.39)	

CI, confidence interval; CLD, chronic liver disease and cirrhosis; COPD, chronic obstructive pulmonary disease; HR, hazard ratio; IRR, incidence rate ratio; PY, person-years; RA, rheumatoid arthritis; SLE, systemic lupus erythematosus;

[a] Incidence rate per 10,000 person-years;

[b] Multivariable analysis controlling for age, sex, occupation, income, urbanization, and comorbidities of diabetes, asthma, chronic obstructive pulmonary disease, chronic liver disease and cirrhosis, malnutrition, and alcohol abuse;

[c] Other occupations include primarily retired, unemployed, and low-income populations;

[d] 1 new Taiwan dollar is equal to 0.03 US dollar;

[e] The urbanization level is categorized by the population density of the residential area into 2 levels: city and rural area;

* p <0.05, ** p <0.01, *** p <0.001.

Table 3. Incidence of pleural empyema and schizophrenia group to comparison group incidence rate ratio and hazard ratio

	Schizophrenia							
	No			Yes				
	Event	PY	Rate [a]	Event	PY	Rate [a]	IRR (95% CI)	Adjusted HR [b] (95% CI)
Age								
20−49	30	297238	1.01	96	307059	3.13	3.10 (2.06, 4.67)***	2.77 (1.84, 4.18)***
50−64	17	45162	3.76	48	52831	9.09	2.41 (1.39, 4.19)**	2.55 (1.45, 4.49)**
≥ 65	20	29584	6.76	20	13546	14.8	2.15 (1.16, 3.99)*	2.68 (1.43, 5.05)**
Sex								
Women	12	182640	0.66	40	177729	2.25	3.43 (1.80, 6.53)***	3.70 (1.93, 7.11)***
Men	55	189345	2.90	124	195706	6.34	2.18 (1.59, 2.99)***	2.63 (1.90, 3.65)***
Occupation [c]								
Office worker	20	164783	1.21	59	164144	3.59	2.99 (1.80, 4.96)***	3.05 (1.83, 5.11)***
Laborer	28	115910	2.42	47	116852	4.02	1.67 (1.04, 2.66)*	2.50 (1.53, 4.08)***
Other	19	91291	2.08	58	92439	6.27	3.01 (1.79, 5.05)***	3.41 (1.97, 5.93)***
Monthly income [d]								
< 15,000	28	162081	1.73	85	166516	5.10	2.95 (1.93, 4.53)***	3.20 (2.07, 4.94)***
15,000−19,999	35	158330	2.21	66	159788	4.13	1.87 (1.24, 2.82)**	2.49 (1.62, 3.82)***
≥ 20,000	4	51573	0.78	13	47131	2.76	3.63 (1.18, 11.1)*	3.64 (1.17, 11.4)*
Urbanization level [e]								
City	24	199255	1.20	73	200604	3.64	3.03 (1.91, 4.80)***	3.67 (2.29, 5.90)***
Rural area	43	172729	2.49	91	172832	5.27	2.11 (1.47, 3.04)***	2.45 (1.69, 3.56)***
Comorbidity [f]								
No	26	283934	0.92	96	276098	3.48	3.81(2.47, 5.87)***	3.73 (2.42, 5.76)***
Yes	41	88050	4.66	68	97338	6.99	1.51(1.02, 2.22)*	2.27 (1.50, 3.42)***

CI, confidence interval; HR, hazard ratio; IRR, incidence rate ratio; PY, person-years;

[a] Incidence rate per 10,000 person-years;

[b] Multivariable analysis controlling for age, sex, occupation, income, urbanization, and comorbidities of diabetes, asthma, chronic obstructive pulmonary disease, chronic liver disease and cirrhosis, malnutrition, and alcohol abuse;

[c] Other occupations include primarily retired, unemployed, and low-income populations;

[d] 1 new Taiwan dollar is equal to 0.03 US dollar;

[e] The urbanization level is categorized by the population density of the residential area into 2 levels: city and rural area;

[f] Individuals with any comorbidity of diabetes, asthma, chronic obstructive pulmonary disease, chronic liver disease and cirrhosis, cancer, systemic lupus erythematosus/rheumatoid arthritis/immune disorders, organ transplant, malnutrition, obesity, alcohol abuse, drug abuse, and tobacco use disorder were classified into the comorbidity group;

* p <0.05, ** p <0.01, *** p <0.001.

Table 4. 30-day mortality from pleural empyema in individuals with schizophrenia compared to those without schizophrenia

	Schizophrenia	
	No	Yes
Deaths / Events	6 / 67	11 / 164
Mortality rate	8.96%	6.71%
Crude OR (95% CI)	1 (Reference)	0.73 (0.26, 2.06)
Adjusted OR [a] (95% CI)	1 (Reference)	0.95 (0.30, 3.01)

CI, confidence interval; OR, odds ratio;

[a] Multivariable analysis controlling for age, sex, occupation, income, urbanization, and comorbidities of diabetes, asthma, chronic obstructive pulmonary disease, chronic liver disease and cirrhosis, malnutrition, and alcohol abuse.

Figure Legends

Figure 1. Cumulative incidence of pleural empyema in the schizophrenia group (dashed line) and the comparison group (solid line).

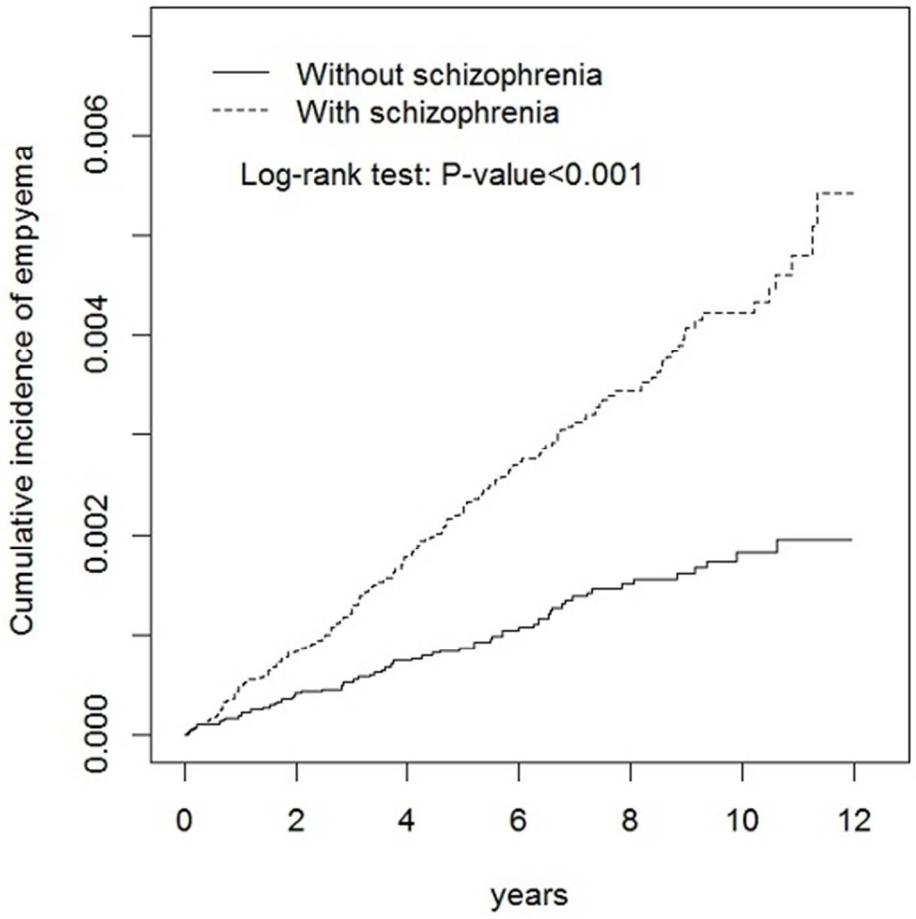

Figure 1. Cumulative incidence of pleural empyema in the schizophrenia group (dashed line) and the comparison group (solid line).

50x50mm (300 x 300 DPI)

STROBE Statement

Checklist of items that should be included in reports of observational studies

Section/Topic	Item No	Recommendation	Reported on Page No
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1, 3-4
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	3-4
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	6-7
Objectives	3	State specific objectives, including any prespecified hypotheses	6-7
Methods			
Study design	4	Present key elements of study design early in the paper	8-9
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	8-9
Participants	6	(*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up *Case-control study*—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls *Cross-sectional study*—Give the eligibility criteria, and the sources and methods of selection of participants	8-9
		(*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed *Case-control study*—For matched studies, give matching criteria and the number of controls per case	8-9
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	9
Data sources/measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	8
Bias	9	Describe any efforts to address potential sources of bias	
Study size	10	Explain how the study size was arrived at	8
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	9-10
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	9-10
		(*b*) Describe any methods used to examine subgroups and interactions	9-10
		(*c*) Explain how missing data were addressed	
		(*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed *Case-control study*—If applicable, explain how matching of cases and controls was addressed *Cross-sectional study*—If applicable, describe analytical methods taking account of sampling strategy	
		(*e*) Describe any sensitivity analyses	9-10

Section/Topic	Item No	Recommendation	Reported on Page No
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	11
		(b) Give reasons for non-participation at each stage	
		(c) Consider use of a flow diagram	
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	11
		(b) Indicate number of participants with missing data for each variable of interest	
		(c) *Cohort study*—Summarise follow-up time (eg, average and total amount)	11
Outcome data	15*	*Cohort study*—Report numbers of outcome events or summary measures over time	11-12
		Case-control study—Report numbers in each exposure category, or summary measures of exposure	
		Cross-sectional study—Report numbers of outcome events or summary measures	
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	11-12
		(*b*) Report category boundaries when continuous variables were categorized	11-12
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	11-12
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	11-12
Discussion			
Key results	18	Summarise key results with reference to study objectives	13
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	15-16
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	13-16
Generalisability	21	Discuss the generalisability (external validity) of the study results	13-16
Other Information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	18-19

**Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.*

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Risk of Pleural Empyema in Patients with Schizophrenia: A Nationwide Propensity-matched Cohort Study in Taiwan

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Keywords:	schizophrenia, pleural empyema, retrospective cohort study, propensity score matched

Risk of Pleural Empyema in Patients with Schizophrenia: A Nationwide Propensity-matched Cohort Study in Taiwan

— Original Article —

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Running head: *Risk of Empyema in Schizophrenia*

Keywords: pleural empyema; schizophrenia; propensity score matched; retrospective cohort study

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Abstract

Objective:

Thoracic infection and pneumonia are prevalent in patients with schizophrenia; however, it is unclear whether patients with schizophrenia are at an increased risk of developing pleural empyema.

Design:

A retrospective cohort study with propensity-matched cohorts with and without schizophrenia.

Setting:

Using National Health Insurance Research Database (NHIRD) of Taiwan.

Participants:

We identified 55,888 schizophrenic patients newly diagnosed in 2000−2011 and same number of individuals without schizophrenia as the comparison cohort, frequency matched by propensity scores estimated using age, sex, occupation, income, urbanization, year of diagnosis, and comorbidities.

Primary outcome measures:

We assessed incident pleural empyema by the end of 2011 and used the Cox proportional hazards model to calculate the schizophrenia cohort to comparison cohort hazard ratio (HR) of pleural empyema.

Results:

The overall incidence of pleural empyema was 2.44-fold greater in the schizophrenia cohort than in the comparison cohort (4.39 versus 1.80 per 10,000 person-years), with an adjusted HR of 2.87 [95% confidence interval (CI) = 2.14−3.84]. Stratified analyses by age, sex, occupation, income, urbanization, and comorbidity revealed significant hazards for pleural empyema associated with schizophrenia in all subgroups.

Conclusions:

Patients with schizophrenia are at an increased risk of developing pleural empyema and require greater attention and appropriate support.

Strengths and limitations of this study

1. This is the first nationwide propensity score matched cohort study to evaluate the risk of pleural empyema in patients with schizophrenia.

2. The National Health Insurance program of Taiwan have covered >99% of 23.74 million people. Universal coverage reduces barriers to health care access for all citizens.

3. The ICD-9-CM algorithm was used to define diseases and an ad hoc committee was in charge of monitor the claims data to prevent errors and violation of confidentiality.

4. The database does not provide detailed information on lifestyles and other psychosocial and environmental factors

5. Relevant clinical variables such as serum laboratory data and image reports were unavailable in the database.

Introduction

Patients with pleural empyema require prompt and timely treatments, such as antibiotic therapy, pleural space drainage, intrapleural fibrinolysis, and/or surgery.[1, 2] Approximately 60,000 cases of pleural empyema are diagnosed annually in the United States.[3] The condition is more prevalent in Taiwan, with the incidence rates ranging from 0.96−8.19 per 10,000 person-year.[4–6] Alcoholism, drug abuse, diabetes mellitus, immunocompromised status, neoplasm, and preexistent pulmonary disease or pleural effusion are risk factors for the development of pleural empyema.[7, 8] Patients with pleural empyema and comorbid with chronic illness are at a poorer prognosis and a greater risk of mortality.[9, 10]

Schizophrenia is a severe mental disorder, characterized by profound disruptions in thinking, affecting language, perception, and the sense of self.[11] The hallmark symptom of schizophrenia is psychosis, such as experiencing auditory hallucinations and delusions.[12] Approximately 0.3%–0.7% of individuals are affected by schizophrenia during their lifetime, and thus, schizophrenia affects more than 21 million people worldwide.[13] People with schizophrenia are at a markedly increased risk of premature death. Despite elevated rates of suicide and other unnatural causes of death, most of the excess mortality has been attributed to cardiovascular disease, respiratory disease, and other natural causes.[14]

Patients with schizophrenia have been associated with a higher risk of thoracic infections.[15–18] The risk of having pneumonia is 3-fold greater in schizophrenic patients than in general population.[16,18] Unhealthy lifestyle, lack of self-care, poorer physical circumstances, and health-risk activities may contribute to this condition.[13] Further, schizophrenic patients suffering from these infections may have poorer clinical outcomes, such as acute respiratory failure, the use of mechanical ventilation, intensive care unit admission, and hospital death.[16, 19] Thoracic infection and pneumonia greatly increase morbidity and mortality in patients with schizophrenia and seriously threaten the health of these patients. However, the association between schizophrenia and the occurrence of pleural empyema, an advanced and specific thoracic infection, remains unclear.

The National Health Insurance Research Database (NHIRD) in Taiwan is a nationwide database containing the medical claims data of 23 million residents. These reliable data have been used in studies on various disorders, including schizophrenia and pleural empyema.[6, 20–22] The present study aims to investigate whether patients with schizophrenia are at an increased risk of subsequent occurrence of pleural empyema. In addition to estimate the incidence of pleural empyema in persons with and without schizophrenia, we also compared the 30-day mortality from pleural empyema between the two cohorts.

Materials and Methods

Data source

The universal health insurance of Taiwan covers more than 99% of the Taiwanese population. Information on demographic status of insured people and their medical services received were available in the NHIRD obtained from the National Health Research Institutes. Patient identifiers were re-encoded before the release of NHIRD to protect the patient privacy. This study has received approval from the Research Ethics Committee of China Medical University and Hospital (CMUH-104-REC2-115).

Study population

Pleural empyema is one of diseases among 30 categories of catastrophic illnesses classified in the insurance system, requiring long-term and/or extensive care, similar to cancers, end-stage major organ diseases, systemic autoimmune diseases and major mental disorders. After a careful peer-review process, patients registered with a catastrophic illness certificate are eligible for reduced financial burden for health care.

For the present study, we used a subset data of NHIRD, the Longitudinal Health Insurance Database 2000 (LHID2000), which contains health data of one million people randomly selected from 23 million people. From the database, we identified schizophrenic patients aged 20 years and older newly diagnosed in 2000-2011 (ICD-9-CM code 295), without the history of pleural empyema (ICD-9-CM code 510)

as the schizophrenia cohort. The comparison cohort were randomly selected from individuals without schizophrenia and pleural empyema from the LHID2000 file, using a 1:1 ratio, frequency matched by propensity scores. The propensity score was estimated to reduce bias from baseline variables, including age, sex, occupation, monthly income, urbanization level, and comorbidities of diabetes (ICD-9-CM code 250), asthma (ICD-9-CM code 493), chronic obstructive pulmonary disease (COPD) (ICD-9-CM code 496), chronic liver disease and cirrhosis (CLD) (ICD-9-CM code 571), cancer (ICD-9-CM codes 140−208), systemic lupus erythematosus (SLE)/rheumatoid arthritis (RA)/immune diseases (ICD-9-CM codes 710.0, 714.0, 279), organ transplant (ICD-9-CM code V42), malnutrition (ICD-9-CM codes 260−269), obesity (ICD-9-CM code 278.0), alcohol abuse (ICD-9-CM codes 291, 303, 305.0), drug abuse (ICD-9-CM codes 292, 304, 305.2, 305.9), and tobacco use disorder (ICD-9-CM code 305.1).

Patient and public involvement

This retrospective cohort study used the secondary data of insurance claims with anonymized identifications. Therefore, we considered that patients and public were not involved.

Outcome

The main outcome of this study was pleural empyema. Person-years indicated the

sum of the follow-up time for all participants, and the follow-up time was defined as the time from the index date to the diagnosis of pleural empyema, death, withdrawal from the insurance, or the end of 2011.

Statistical analysis

The two study groups were matched by the propensity scores, and the standardized difference was used to quantify differences in means or prevalence rates between schizophrenia and comparison cohorts for continuous or categorical variables, respectively. A standardized difference of 0.1 or less indicated a negligible difference between 2 cohorts.[23] The incidence rate of pleural empyema was estimated per 10,000 person-years. We used Poisson regression analysis to calculate the schizophrenic patients to controls incidence rate ratio (IRR). The Kaplan-Meier method was then used to calculate and plot the cumulative incidence of pleural empyema for each cohort and the difference between the two curves was examined using log-rank test. Multivariable Cox proportional hazards regression analysis was used to estimate the adjusted hazard ratio (aHR) and 95% confidence interval (CI) for the two groups. The multivariable model included variables of age, sex, occupation, monthly income, urbanization level, and comorbidities of diabetes, asthma, COPD, CLD, malnutrition, and alcohol abuse. Data analysis for this study was performed using SAS statistical software (version 9.4 for Windows; SAS Institute, Inc., Cary, NC, USA). Statistical

significance was determined at $p < 0.05$.

Results

Table 1 shows that schizophrenia and comparison cohorts were similar in distributions of baseline demographics and comorbidities with mean ages of 38.9 and 38.7 years, respectively.

After a mean follow-up time of 6.7 year in both cohorts, Figure 1 shows that the cumulative incidence of pleural empyema was 0.34% higher in the schizophrenia cohort than in the comparison cohort. The incidence was 2.4-fold greater in schizophrenic patients than in comparisons (4.39 vs. 1.80 per 10,000 person-years), with an IRR of 2.44 (95% CI = 1.83−3.24) or an aHR of 2.87 (95% CI = 2.14−3.84) (Table 2). The pooled data showed that the overall incidence increased with age, and higher in men than in women. Study population of low income and living in rural area were at higher risk of empyema. Individuals with comorbidities are also at increased risk of pleural empyema, including those with diabetes (adjusted HR = 2.62, 95% CI = 1.77−3.87), asthma (adjusted HR = 1.98, 95% CI = 1.27−3.07), COPD (adjusted HR = 2.01, 95% CI = 1.38−2.95), malnutrition (adjusted HR = 3.60, 95% CI = 1.76−7.36), and alcohol abuse (adjusted HR = 1.74, 95% CI = 1.10−2.74).

Table 3 shows the incident empyema developed in the 2 cohorts by demographic status and comorbidity status. The incidence rates in each stratum were greater in the schizophrenia subgroups than in the comparison subgroups. The schizophrenia group

to the comparison group IRRs and aHRs were significant for all strata. Significant IRRs ranged from 1.51 to 3.63 and significant aHRs ranged from 2.45 to 3.70. Comorbidity increased the incidence of pleural empyema in both cohorts for 3.74 and 3.51 per 10,000 person-years, respectively. The schizophrenia group to comparison group aHR showed a relatively greater impact for study individuals without comorbidities than those with comorbidity.

Table 4 shows a lower 30-day mortality rate from pleural empyema for the schizophrenic cohort than for the comparison cohort (6.71% vs. 8.96%), with an adjusted odds ratio of 0.95 (95% CI = 0.30−3.01).

Discussion

To the best of our knowledge, this is the first propensity-matched cohort study using population data to evaluate the risk of developing pleural empyema in patients with schizophrenia. The risk of pleural empyema is more than 2-fold greater than those without schizophrenia. Stratified analyses by age, sex, occupation, income, urbanization, and presence of comorbidities also showed that the incidence rates of pleural empyema were consistently higher in the schizophrenia cohort than in comparisons, and the aHRs for pleural empyema associated with schizophrenia were significant for all subgroups. In addition, the incidences of pleural empyema were higher in older people than in young people, higher in men than in women, and in individuals with comorbidities than in those without comorbidities. These findings are in accordance with the general concepts.

The mechanism associating schizophrenia to the risk of developing pleural empyema remains largely unknown. Smoking is a well-known behavior prevalent in schizophrenic patients and has association with the development of pleural empyema. In addition, an unhealthy lifestyle, lack of self-care, poorer physical circumstances, and health-risk activities may contribute to this condition.[15] Frequent medical visits and a prolonged hospital stay may also be contributing factors.[18] Moreover, patients with schizophrenia may reside in a long-term care facility. Pneumonia in these

residents has been defined as a specific type, healthcare associated pneumonia (HCAP).[24] The pathogens of HCAP are often multidrug-resistant bacteria, which is a potential risk factor for developing pleural empyema. Furthermore, patients with schizophrenia are at a higher risk of developing swallowing disorders, leading to aspiration pneumonia.[25] Pleural empyema is easily caused by the aspiration of mixed bacterial flora and other materials from the oropharyngeal cavity and even from the upper gastrointestinal tract. In addition, previous studies have suggested that the use of second-generation antipsychotics, such as clozapine, may increase the risk of pneumonia in patients with schizophrenia.[26–28] Clozapine has been associated with agranulocytosis, sialorrhea, and impaired swallowing function; patients with this medication may thus have a greater risk for pneumonia.[29]

Patients with schizophrenia are at a markedly increased risk of premature death, particularly from thoracic infection and pneumonia. A large-scale study in the United States showed that the overall mortality rate was 3.7-time higher in patients with schizophrenia than in the general population.[30] The increased mortality was mainly from respiratory diseases: 9.9-time higher from COPD and 7.0-time higher from influenza and pneumonia. A study in Taiwan showed that patients with schizophrenia experienced a 3.09-fold increased risk of developing pneumonia, with an adjusted HR of 1.39 for deaths from pneumonia.[16] In a Romanian study, autopsy findings in sudden

unexpected deaths in schizophrenia inpatients revealed that the top three specific causes were myocardial infarction (52.9%), pneumonia (11.8%), and airway obstruction (7.8%).[31] However, the present study showed no significant disparity in the 30-day mortality between the schizophrenic and comparison cohorts.

The strength of this study was using a large nationwide data to perform the propensity-matched evaluation assessing the pleural empyema risk for schizophrenia patients. Confounding bias has been thus reduced in this inexpensive retrospective cohort study. The National Health Insurance program has covered >99.0% of the Taiwanese population. The universal health coverage reduces barriers to healthcare access for all citizens, regardless of their socioeconomic background and/or residential location.[32] The present study reflected a "real world" scenario by using the claims data, as schizophrenia, pleural empyema, and comorbidities were diagnosed at clinics during medical consultations.

There are several limitations that should be considered when interpreting the study findings. First, we used the ICD-9-CM algorithm to define schizophrenia, pleural empyema, and comorbidities. The diagnosis of Schizophrenia is mostly accurate because it is a disease with catastrophic certificate. All other diagnoses depended on the competence of clinical physicians. An ad hoc committee established by the insurance authority was in charge of evaluating the claims data to prevent errors and

violations. In addition, only the disease with at least two diagnosis codes identified within a year was included to increase the validity and accuracy. Second, the information on smoking, drinking, nutrition, and other psychosocial and environmental factors were unavailable, which may affect the risk of pulmonary infections and consequent complications. Instead, we used the tobacco use disorder and alcohol abuse to substitute smoking and drinking, respectively, in the multivariable analysis for adjustment. Similarly, malnutrition is a crucial factor for pleural empyema development; however, it is unlikely to be identified adequately by relying on recorded diagnoses. In addition, institutional residence is a possible source of multiple-resistant infection, but the relevant data was unavailable. Furthermore, other clinical variables such as serum laboratory data, image reports, and culture results were not available to our study.[33]

Conclusion

This study provides evidence that patients with schizophrenia are at an elevated risk of developing pleural empyema. The risk increases further for those with comorbidity. Schizophrenic patients with pneumonia or other thoracic infection need close surveillance for potential risk of development of pleural empyema and disease related mortality.

Contributor ship statement

T-CS, C-HC, Y-JH, T-CC, C-YT and C-MS conceived and designed the study.

T-CH, C-MS and W-HH provided administrative support.

T-CS, C-LL, C-MS and F-CS analysed and interpreted the data.

T-CS, C-LL, C-MS and F-CS developed and revised the manuscript.

All authors were involved in collection and assembly of data.

All authors approved the final version of the manuscript to be published.

Competing interests

None declared.

Ethics approval

This study was approved by the Research Ethics Committee at the China Medical University and Hospital (CMUH-104-REC2-115).

Funding statement

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Aoshima Memorial Funds, Japan. 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.

Data sharing statement:

No additional data available.

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Table 1. Baseline characteristics compared between cohorts with and without schizophrenia

	Schizophrenia				
	No N = 55,888		Yes N = 55,888		
	n	%	n	%	Standardized difference
Age					
20−49	43651	78.1	44679	79.9	0.045
50−64	7083	12.7	8654	15.5	0.081
≥ 65	5154	9.22	2555	4.57	0.18
Mean (SD)	38.7	16.2	38.9	13.4	0.015
Sex					
Women	27036	48.4	26796	48.0	0.009
Men	28852	51.6	29092	52.1	0.009
Occupation [a]					
Office worker	24539	43.9	24844	44.5	0.011
Laborer	17604	31.5	17499	31.3	0.004
Other	13745	24.6	13545	24.2	0.008
Monthly income [b]					
< 15,000	25221	45.1	24985	44.7	0.008
15,000−19,999	23266	41.6	23696	42.4	0.016
≥ 20,000	7401	13.2	7207	12.9	0.01
Urbanization level [c]					
City	29894	53.5	30151	54.0	0.009
Rural area	25994	46.5	25737	46.1	0.009
Comorbidity					
Diabetes	2442	4.37	2485	4.45	0.004
Asthma	2204	3.94	2245	4.02	0.004
COPD	3168	5.67	3262	5.84	0.007
CLD	7134	12.8	7249	13.0	0.006
Cancer	430	0.77	417	0.75	0.003
SLE/RA/immune disorders	32	0.06	31	0.06	0.001
Organ transplant	7	0.01	7	0.01	0.000
Malnutrition	362	0.65	331	0.59	0.007
Obesity	719	1.29	724	1.30	0.001
Alcohol abuse	2922	5.23	2884	5.16	0.003

Drug abuse	1818	3.25	1986	3.55	0.017
Tobacco use disorder	843	1.51	789	1.41	0.008

CLD, chronic liver disease and cirrhosis; COPD, chronic obstructive pulmonary disease; RA, rheumatoid arthritis; SD, standard deviation; SLE, systemic lupus erythematosus;

[a] Other occupations include primarily retired, unemployed, and low-income populations;

[b] 1 new Taiwan dollar is equal to 0.03 US dollar;

[c] The urbanization level is categorized by the population density of the residential area into 2 levels: city and rural area.

Table 2. Incidence of pleural empyema, incidence rate ratio and adjusted hazard ratio measured for pooled study population by study cohort, sociodemographic status and comorbidities

	Event	PY	Rate [a]	IRR (95% CI)	Adjusted HR [b] (95% CI)
Schizophrenia					
No	67	371984	1.80	1.00	1.00
Yes	164	373435	4.39	2.44 (1.83, 3.24)***	2.87 (2.14, 3.84)***
Age					
20–49	126	604297	2.09	1.00	1.00
50–64	65	97993	6.63	3.19 (2.36, 4.30)***	2.86 (2.09, 3.93)***
≥ 65	40	43129	9.27	4.46 (3.13, 6.37)***	3.45 (2.29, 5.19)***
Sex					
Women	52	360369	1.44	1.00	1.00
Men	179	385050	4.65	3.22 (2.37, 4.39)***	3.52 (2.57, 4.82)***
Occupation [c]					
Office worker	79	328927	2.40	1.00	1.00
Laborer	75	232762	3.22	1.34 (0.98, 1.84)	0.94 (0.67, 1.33)
Other	77	183730	4.19	1.75 (1.28, 2.39)***	1.19 (0.82, 1.71)
Monthly income [d]					
< 15,000	113	328597	3.44	2.00 (1.20, 3.33)**	1.92 (1.10, 3.33)*
15,000–19,999	101	318118	3.17	1.84 (1.10, 3.08)*	1.97 (1.15, 3.36)*
≥ 20,000	17	98704	1.72	1.00	1.00
Urbanization level [e]					
City	97	399858	2.43	1.00	1.00
Rural area	134	345561	3.88	1.60 (1.23, 2.08)***	1.46 (1.12, 1.90)**
Comorbidity					
Diabetes					
No	197	718779	2.74	1.00	1.00
Yes	34	26641	12.8	4.67 (3.24, 6.73)***	2.62 (1.77, 3.87)***
Asthma					
No	202	719903	2.81	1.00	1.00
Yes	29	25516	11.4	4.06 (2.75, 5.99)***	1.98 (1.27, 3.07)**
COPD					
No	182	707738	2.57	1.00	1.00
Yes	49	37681	13.0	5.07 (3.69, 6.95)***	2.01 (1.38, 2.95)***
CLD					

No	186	655200	2.84	1.00	1.00
Yes	45	90219	4.99	1.76 (1.27, 2.43)***	1.00 (0.71, 1.42)
Cancer					
No	228	741180	3.08	1.00	
Yes	3	4239	7.08	2.30 (0.74, 7.19)	
SLE/RA/immune disorders					
No	231	745075	3.10	1.00	
Yes	0	345	0.00	-	
Organ transplant					
No	231	745312	3.10	1.00	
Yes	0	107	0.00	-	
Malnutrition					
No	223	741266	3.01	1.00	1.00
Yes	8	4154	19.3	6.38 (3.15, 12.9)***	3.60 (1.76, 7.36)***
Obesity					
No	229	737942	3.10	1.00	
Yes	2	7478	2.67	0.86 (0.21, 3.46)	
Alcohol abuse					
No	209	714370	2.93	1.00	1.00
Yes	22	31049	7.09	2.42 (1.56, 3.77)***	1.74 (1.10, 2.74)*
Drug abuse					
No	220	724902	3.03	1.00	
Yes	11	20517	5.36	1.77 (0.96, 3.24)	
Tobacco use disorder					
No	227	739856	3.07	1.00	
Yes	4	5564	7.19	2.37 (0.88, 6.39)	

CI, confidence interval; CLD, chronic liver disease and cirrhosis; COPD, chronic obstructive pulmonary disease; HR, hazard ratio; IRR, incidence rate ratio; PY, person-years; RA, rheumatoid arthritis; SLE, systemic lupus erythematosus;

[a] Incidence rate per 10,000 person-years;

[b] Multivariable analysis controlling for age, sex, occupation, income, urbanization, and comorbidities of diabetes, asthma, chronic obstructive pulmonary disease, chronic liver disease and cirrhosis, malnutrition, and alcohol abuse;

[c] Other occupations include primarily retired, unemployed, and low-income populations;

[d] 1 new Taiwan dollar is equal to 0.03 US dollar;

[e] The urbanization level is categorized by the population density of the residential area into 2 levels: city and rural area;

* p <0.05, ** p <0.01, *** p <0.001.

Table 3. Incidence of pleural empyema and schizophrenia cohort to comparison cohort incidence rate ratio and adjusted hazard ratio

	Schizophrenia							
	No			Yes				
	Event	PY	Rate [a]	Event	PY	Rate [a]	IRR (95% CI)	Adjusted HR [b] (95% CI)
Age								
20−49	30	297238	1.01	96	307059	3.13	3.10 (2.06, 4.67)***	2.77 (1.84, 4.18)***
50−64	17	45162	3.76	48	52831	9.09	2.41 (1.39, 4.19)**	2.55 (1.45, 4.49)**
≥ 65	20	29584	6.76	20	13546	14.8	2.15 (1.16, 3.99)*	2.68 (1.43, 5.05)**
Sex								
Women	12	182640	0.66	40	177729	2.25	3.43 (1.80, 6.53)***	3.70 (1.93, 7.11)***
Men	55	189345	2.90	124	195706	6.34	2.18 (1.59, 2.99)***	2.63 (1.90, 3.65)***
Occupation [c]								
Office worker	20	164783	1.21	59	164144	3.59	2.99 (1.80, 4.96)***	3.05 (1.83, 5.11)***
Laborer	28	115910	2.42	47	116852	4.02	1.67 (1.04, 2.66)*	2.50 (1.53, 4.08)***
Other	19	91291	2.08	58	92439	6.27	3.01 (1.79, 5.05)***	3.41 (1.97, 5.93)***
Monthly income [d]								
< 15,000	28	162081	1.73	85	166516	5.10	2.95 (1.93, 4.53)***	3.20 (2.07, 4.94)***
15,000−19,999	35	158330	2.21	66	159788	4.13	1.87 (1.24, 2.82)**	2.49 (1.62, 3.82)***
≥ 20,000	4	51573	0.78	13	47131	2.76	3.63 (1.18, 11.1)*	3.64 (1.17, 11.4)*
Urbanization level [e]								
City	24	199255	1.20	73	200604	3.64	3.03 (1.91, 4.80)***	3.67 (2.29, 5.90)***
Rural area	43	172729	2.49	91	172832	5.27	2.11 (1.47, 3.04)***	2.45 (1.69, 3.56)***
Comorbidity [f]								
No	26	283934	0.92	96	276098	3.48	3.81(2.47, 5.87)***	3.73 (2.42, 5.76)***
Yes	41	88050	4.66	68	97338	6.99	1.51(1.02, 2.22)*	2.27 (1.50, 3.42)***

CI, confidence interval; HR, hazard ratio; IRR, incidence rate ratio; PY, person-years;

[a] Incidence rate per 10,000 person-years;

[b] Multivariable analysis controlling for age, sex, occupation, income, urbanization, and comorbidities of diabetes, asthma, chronic obstructive pulmonary disease, chronic liver disease and cirrhosis, malnutrition, and alcohol abuse;

[c] Other occupations include primarily retired, unemployed, and low-income populations;

[d] 1 new Taiwan dollar is equal to 0.03 US dollar;

[e] The urbanization level is categorized by the population density of the residential area into 2 levels: city and rural area;

[f] Individuals with any comorbidity of diabetes, asthma, chronic obstructive pulmonary disease, chronic liver disease and cirrhosis, cancer, systemic lupus erythematosus/rheumatoid arthritis/immune disorders, organ transplant, malnutrition, obesity, alcohol abuse, drug abuse, and tobacco use disorder were classified into the comorbidity group;

* p <0.05, ** p <0.01, *** p <0.001.

Table 4. 30-day mortality from pleural empyema in cohorts with and without schizophrenia and odds ratio of mortality

	Schizophrenia	
	No	Yes
Deaths / Events	6 / 67	11 / 164
Mortality per 100	8.96	6.71
Crude OR (95% CI)	1 (Reference)	0.73 (0.26, 2.06)
Adjusted OR [a] (95% CI)	1 (Reference)	0.95 (0.30, 3.01)

CI, confidence interval; OR, odds ratio;

[a] Multivariable analysis controlling for age, sex, occupation, income, urbanization, and comorbidities of diabetes, asthma, chronic obstructive pulmonary disease, chronic liver disease and cirrhosis, malnutrition, and alcohol abuse.

Figure Legends

Figure 1. Cumulative incidence of pleural empyema in the schizophrenia cohort (dashed line) and the comparison cohort (solid line).

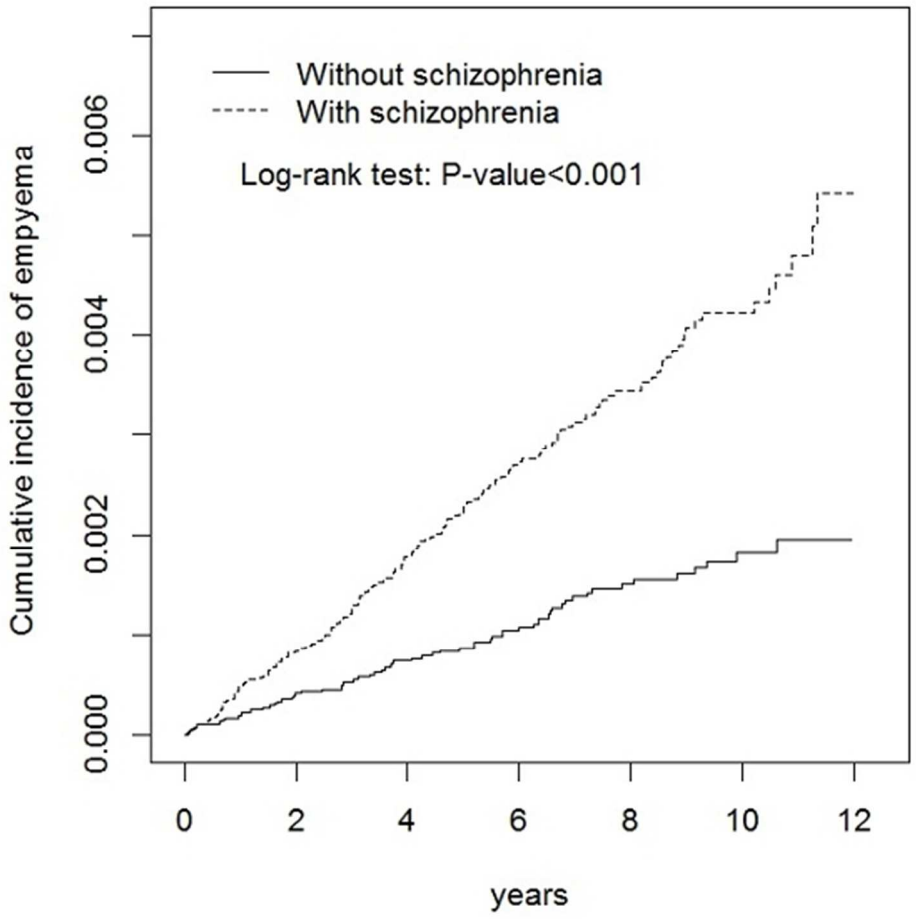

Figure 1. Cumulative incidence of pleural empyema in the schizophrenia group (dashed line) and the comparison group (solid line).

50x50mm (300 x 300 DPI)

STROBE Statement

Checklist of items that should be included in reports of observational studies

Section/Topic	Item No	Recommendation	Reported on Page No
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1, 3-4
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	3-4
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	6-7
Objectives	3	State specific objectives, including any prespecified hypotheses	6-7
Methods			
Study design	4	Present key elements of study design early in the paper	8-9
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	8-9
Participants	6	(*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up *Case-control study*—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls *Cross-sectional study*—Give the eligibility criteria, and the sources and methods of selection of participants	8-9
		(*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed *Case-control study*—For matched studies, give matching criteria and the number of controls per case	8-9
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	9
Data sources/measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	8
Bias	9	Describe any efforts to address potential sources of bias	
Study size	10	Explain how the study size was arrived at	8
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	9-10
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	9-10
		(*b*) Describe any methods used to examine subgroups and interactions	9-10
		(*c*) Explain how missing data were addressed	
		(*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed *Case-control study*—If applicable, explain how matching of cases and controls was addressed *Cross-sectional study*—If applicable, describe analytical methods taking account of sampling strategy	
		(*e*) Describe any sensitivity analyses	9-10

Section/Topic	Item No	Recommendation	Reported on Page No
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	11
		(b) Give reasons for non-participation at each stage	
		(c) Consider use of a flow diagram	
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	11
		(b) Indicate number of participants with missing data for each variable of interest	
		(c) *Cohort study*—Summarise follow-up time (eg, average and total amount)	11
Outcome data	15*	*Cohort study*—Report numbers of outcome events or summary measures over time	11-12
		Case-control study—Report numbers in each exposure category, or summary measures of exposure	
		Cross-sectional study—Report numbers of outcome events or summary measures	
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	11-12
		(*b*) Report category boundaries when continuous variables were categorized	11-12
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	11-12
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	11-12
Discussion			
Key results	18	Summarise key results with reference to study objectives	13
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	15-16
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	13-16
Generalisability	21	Discuss the generalisability (external validity) of the study results	13-16
Other Information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	18-19

**Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.*