Depression is associated with subsequent risk of pleural empyema

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Abstract

Background: Respiratory system infections are prevalent in patients with depression. However, it remains unclear if patients with depression are at an increased risk of developing pleural empyema.

Methods: We conducted a retrospective cohort study using data from the National Health Insurance Research Database of Taiwan. The depression group included 42,283 newly diagnosed patients between 2000 and 2012. The comparison group included the same number of individuals without depression, frequency matched for age, sex, comorbidities, and the year of diagnosis. The occurrence of pleural empyema was monitored until the end of 2013.

Results: The overall incidence of pleural empyema was 1.32-fold higher in the depression group than in the comparison group (3.94 *versus* 2.97 per 10,000 person-years), with an adjusted hazard ratio of 1.33 (95% confidence interval, 1.27–1.40). Stratified analyses by age, sex, and comorbidity revealed that the crude and adjusted hazard ratios of pleural empyema associated with depression were significant in all subgroups. The 30-day mortality for pleural empyema was higher, but not significantly, in the depression group compared to the comparison group (10.7% *versus* 6.4%, adjusted odds ratio = 2.23, 95% confidence interval, 0.77–6.49).

Conclusion: An association between depression and the development of pleural empyema may exist; however, more evidence is required to support this association.

The reviews of this paper are available via the supplemental material section.

Keywords: empyema, depression, pneumonia, retrospective cohort study

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Introduction

Pleural empyema refers to frank pus in the pleural space.[1] The most common etiology of pleural empyema is secondary to pneumonia, an infection of the lung tissue.[2] As expected, the mortality is much higher in pneumonia patients with pleural empyema than in those without pleural empyema.[3,4] The clinical significance of pleural empyema and the importance of its drainage have been identified for many centuries.[5] Delay diagnosis and inadequate drainage are associated with substantially higher mortality.[6] Alcoholism, drug abuse, diabetes mellitus, immunocompromised status, cancer, pre-existing pulmonary disease and pleural effusion are common risk factors for the development of pleural empyema.[7,8] Mental disorders, which play an essential role in developing pneumonia, may also contribute to the development of pleural empyema.[9]

Depression is a common mental disorder, characterized by sadness, loss of interest or pleasure, feelings of guilt or low self-worth, disturbed sleep or appetite, feelings of tiredness, and poor concentration.[10] Depression has become a severe public health and social problem all over the world. Evidence has shown a close association between depression and several systemic disorders.[11,12] In addition, depression could enhance susceptibility to various kinds of infections,[13] particularly respiratory tract infections and pneumonia.[9,14,15] Patients with pneumonia and underlying depression

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have been reported to have a higher mechanical ventilation use rate, a higher intensive care unit admission rate, a higher re-hospitalization rate, and a higher mortality rate.[16–18] In summary, patients with depression would have a poorer prognosis and a higher mortality when getting a pneumonia.

Several studies have investigated respiratory tract infections and pneumonia among patients with depression. However, none of these studies examined the occurrence and prognosis of pleural empyema in those patients. Since pleural empyema is a specific infection of the respiratory system and requires timely treatments such as antibiotic therapy, pleural space drainage, intrapleural fibrinolysis, and/or surgery, it is important to investigate the risk of pleural empyema in patients with depression. This study examined whether patients with depression are at an increased risk of subsequent occurrence of pleural empyema. Furthermore, it estimated the incidence of pleural empyema in patients with and without depression. Finally, a comparison of 30-day mortality from pleural empyema between the depression and the non-depression groups was conducted.

Materials and methods

Data source

The National Health Insurance (NHI) program was established in 1995. The National Health Insurance Research Database (NHIRD) is a nationwide database containing the medical claims data of more than 99.5% of Taiwan's residents. The National Health Research Institutes manages and updates the database. We used the Longitudinal Health Insurance Database 2000 (LHID2000) for this study, which included medical claims for 1,000,000 people randomly selected from all beneficiaries registered in 2000. All information regarding demographic status, diagnostic codes, procedure claims, and medication claims was available in the LHID2000. All identification numbers for insured people were scrambled to protect their privacy; therefore, written informed consent from the participants involved was unavailable and unnecessary. This study was granted the approval by the Research Ethics Committee of the China Medical University and Hospital (CMUH-104-REC2-115).

Study population

Patients with newly diagnosed depression between 1 January 2000 and 31 December 2012 were selected to the depression cohort, and the date of the diagnosis was defined as the index date. We excluded those who had been diagnosed with pleural empyema before the index date and those with incomplete age or sex information. The subjects in the comparison cohort included individuals free from depression. The exclusion criteria for the comparison cohort were the same as for the depression cohort. The comparison cohort was frequency matched with the depression cohort by age (every 5-year span), sex, comorbidities of diabetes mellitus, asthma and chronic obstructive pulmonary disease (COPD), chronic liver disease (CLD), chronic kidney disease (CKD), systemic lupus erythematosus (SLE), rheumatoid arthritis (RA) and immune disorders, cancer, organ transplant, malnutrition, and the index year. All subjects were monitored until any of the following occurred: development of pleural empyema, withdrawal from NHI system, death, or until 31 December 2013.

Disease definition

Diseases were recorded according to the International Classification of Disease, 9th Revision, Clinical Modification (ICD-9-CM) in the NHIRD. That is, the ICD-9-CM algorithm was used to define depression (ICD-9-CM codes 296.2, 296.3, 300.4, and 311), pleural empyema (ICD-9-CM code 510), and comorbidities [diabetes mellitus (ICD-9-CM code 250), asthma/COPD (ICD-9-CM codes 493 and 496), CLD (ICD-9-CM code 571), CKD (ICD-9-CM code 585), SLE/RA/immune disorders (ICD-9-CM codes 710.0, 714.0, and 279), cancer (ICD-9-CM codes 140–208), organ transplant (ICD-9-CM codes V42), malnutrition (ICD-9-CM codes 260–269)]. This method has been used for research into various disorders, including depression[19,20] and pleural empyema.[21,22] In addition, we selected only diagnoses that appeared at least twice within a year to increase the accuracy for depression and comorbidities.

Statistical analysis

We compared the distributions of baseline characteristics between the depression and the comparison cohorts by using the Chi-squared test for categorical variables and the Student's *t*-test for continuous variables. The Kaplan–Meier curve

Table 1. Baseline characteristics for individuals with and without depression.

	Depression				*p*-value
	No		Yes		
	N = 42,283		*N* = 42,283		
	n	%	*n*	%	
Age					0.99
20–49	23,284	55.1	23,284	55.1	
50–64	10,160	24.0	10,160	24.0	
⩾65	8839	20.9	8839	20.9	
Mean (SD)	48.7	(17.4)	49.0	(17.2)	0.01
Sex					0.99
Women	25,765	61.0	25,765	60.9	
Men	16,518	39.1	16,518	39.1	
Comorbidity					
Diabetes mellitus	3099	7.33	3099	7.33	0.99
Asthma/COPD	3882	9.18	3882	9.18	0.99
CLD	94	0.22	122	0.29	0.06
CKD	881	2.08	881	2.08	0.99
Cancer	11,005	26.0	11,005	26.0	0.99
SLE/RA/immune disorders	247	0.58	247	0.58	0.99
Organ transplant	10	0.02	10	0.02	0.99
Malnutrition	354	0.84	354	0.84	0.99

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

showed the cumulative incidence of pleural empyema for both cohorts and tested the difference by log-rank test. Among different risk factors stratified by age, sex, and comorbidities, the follow-up time in person-years estimated incidence density rates of pleural empyema. The hazard ratios (HRs) and 95% confidence intervals (CIs) for the risk of pleural empyema were estimated by univariable and multivariable Cox proportional hazard regression models. Variables in the multivariable model included age, sex, comorbidities of diabetes mellitus, asthma/COPD, CLD, CKD, cancer, and malnutrition and these showed significant difference in univariable Cox model. The data were further analyzed to compare the risk of mortality for pleural empyema between patients with and those without depression using logistic regression model. Data analysis for this study was conducted using the SAS statistical software (version 9.4 for Windows; SAS Institute, Inc., Cary, NC, USA). Statistical significance in this study was set as p-value <0.05.

Results

We recruited a depression cohort consisting of 42,283 patients and a comparison cohort comprising also 42,283 individuals (Table 1). The distributions of age, sex, and comorbidity did not differ significantly between the depression and the

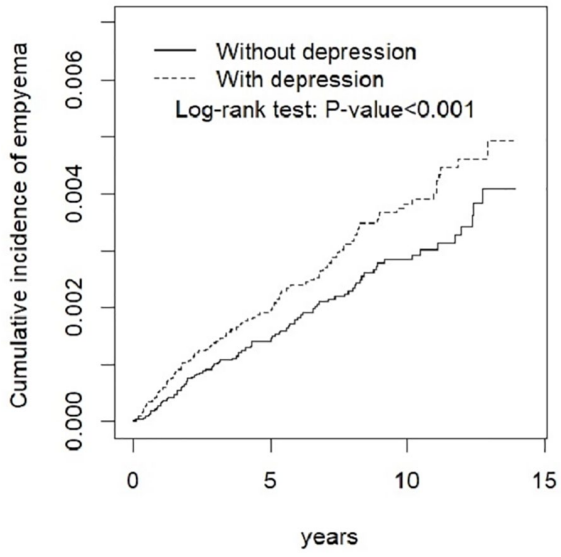

Figure 1. Cumulative incidence of pleural empyema in the depression group (dashed line) and in the comparison group (solid line).

comparison cohorts. The mean age ± standard deviation of the depression cohort and the comparison cohort was 49.0 ± 17.2 and 48.7 ± 17.4 years, respectively. In both cohorts, approximately 61% of the subjects were women. The major comorbidities were cancers (26.0%), followed by asthma/COPD (9.18%), diabetes mellitus (7.33%), and CKD (2.08%). The average follow-up duration was 7.33 ± 3.85 years for the depression cohort and 7.47 ± 3.78 years for the comparison cohort. Figure 1 showed that throughout the 14-year study period, patients with depression had higher cumulative incidence of pleural empyema than the individuals without depression.

The overall incidence density rates of pleural empyema were 3.94 and 2.97 per 10,000 person-years in the depression cohort and in the comparison cohort, respectively (Table 2). Compared to the comparison cohort, the corresponding adjusted HR (aHR) for pleural empyema was 1.33 (95% CI, 1.27–1.40) in the depression cohort, after adjusting for age, sex, and comorbidities of diabetes mellitus, asthma/COPD, CLD, CKD, and malnutrition. Compared to persons aged 20–49 years, the risk of pleural empyema was 2.41-fold higher in those aged 50−64 years (95% CI, 2.25–2.58) and 4.64-fold higher in those aged ⩾65 years (95% CI, 4.36–4.95). The aHR of pleural empyema was 2.87-fold higher for men relative to women (95% CI, 2.72−3.01). Moreover, the risk of empyema was higher in persons with diabetes mellitus (aHR, 2.80; 95% CI, 2.65–2.97), asthma/COPD (aHR, 1.59; 95% CI = 1.49–1.69), CLD (aHR, 1.35; 95% CI, 1.29–1.42), CKD (aHR, 1.66; 95% CI, 1.50–1.84), and malnutrition (aHR, 2.42; 95% CI, 2.09–2.80), compared to subjects without these comorbidities.

In further analyses, after stratification for age, sex, and presence of comorbidities, the aHRs for pleural empyema in the depression cohort were all significantly higher than the aHRs in the comparison cohort (Table 3). In our analysis of prognosis, we found that the 30-day mortality for pleural empyema was higher, but not significantly, in the depression cohort than in the comparison cohort [10.66% *versus* 6.38%, adjusted odds ratio (OR), 2.33; 95% CI, 0.77–6.49; Table 4].

Discussion

To the best of our knowledge, this is the first population-based retrospective cohort study to evaluate the occurrence of pleural empyema in patients with depression. Our results showed that patients with depression have a significantly elevated risk of developing pleural empyema than those without depression. In accordance with general concepts, the risk of pleural empyema was also greater in older subjects, in males, and in those with comorbidities. Furthermore, the hazards of pleural empyema were significantly greater in subjects of the depression group compared to those in the comparison group whenever stratified by age, sex, and comorbidity. Moreover, we found that the 30-day mortality rate of pleural empyema was higher in the depression group than in the comparison group, although the difference was not statistically significant.

The mechanism that governs the link between depression and pleural empyema remains largely unknown. Unhealthy lifestyle, lack of self-care, poor physical health, and risky activities are commonly observed in patients with depression. These factors are associated with the development of pneumonia and pleural empyema.[9] Risk factors for respiratory system infections such as smoking, alcohol consumption, and substance abuse are prevalent in patients with depression.[23,24] Most important of all, depression and psychological stress can induce dysfunction of the immune system and modulate the production of proinflammatory cytokines such as

Table 2. The incidence and risk factors for pleural empyema.

	Event	PY	Rate[a]	Crude HR (95% CI)	Adjusted HR[b] (95% CI)
Depression					
No	94	316,019	2.97	1.00	1.00
Yes	122	310,001	3.94	1.32 (1.26–1.39)***	1.33 (1.27–1.40)***
Age					
20–49	51	368,429	1.38	1.00	1.00
50–64	61	149,131	4.09	2.95 (2.76–3.16)***	2.41 (2.25–2.58)***
⩾65	104	108,460	9.59	6.93 (6.51–7.37)***	4.64 (4.36–4.95)***
Sex					
Women	77	391,746	1.97	1.00	1.00
Men	139	234,274	5.93	3.02 (2.87–3.18)***	2.87 (2.72–3.01)***
Comorbidity					
Diabetes mellitus					
No	161	587,651	2.74	1.00	1.00
Yes	55	38,369	14.3	5.23 (4.94–5.54)***	2.80 (2.65–2.97)***
Asthma/COPD					
No	178	575,830	3.09	1.00	1.00
Yes	38	50,190	7.57	2.45 (2.29–2.62)***	1.59 (1.49–1.69)***
CLD					
No	129	463,081	2.79	1.00	1.00
Yes	87	162,939	5.34	1.92 (1.82–2.02)***	1.35 (1.29–1.42)***
CKD					
No	203	617,033	3.29	1.00	1.00
Yes	13	8988	14.5	4.39 (3.95–4.88)***	1.66 (1.50–1.84)***
Cancer					
No	159	469,657	3.39	1.00	1.00
Yes	57	156,363	3.65	1.08 (1.02–1.14)*	1.05 (0.99–1.11)
SLE/RA/immune disorders					
No	215	622,926	3.45	1.00	1.00
Yes	1	3094	3.23	0.94 (0.65–1.36)	
Organ transplant					
No	216	625,918	3.45	1.00	1.00
Yes	0	102	0.00	-	
Malnutrition					
No	210	621,180	3.38	1.00	1.00
Yes	6	4840	12.4	3.67 (3.15–4.27)***	2.42 (2.09–2.80)***

CI, confidence interval; CKD, chronic kidney disease; CLD, chronic liver disease and cirrhosis; COPD, chronic obstructive pulmonary disease; HR, hazard ratio; PY, person-years; RA, rheumatoid arthritis; SLE, systemic lupus erythematosus.
[a]Incidence rate per 10,000 person-years.
[b]Multivariable analysis including age, sex, and comorbidities of diabetes mellitus, asthma/COPD, CLD, CKD, and malnutrition.
*$p < 0.05$, ***$p < 0.001$.

Table 3. Incidence and hazard ratio of pleural empyema for individuals with and without depression.

	Depression						Crude HR (95% CI)	Adjusted HR[b] (95% CI)
	No			Yes				
	Event	PY	Rate [a]	Event	PY	Rate [a]		
Age								
20–49	20	185,237	1.08	31	183,102	1.69	1.57 (1.46–1.69)***	1.60 (1.49–1.71)***
50–64	28	75,435	3.71	33	73,695	4.48	1.21 (1.09–1.33)***	1.23 (1.12–1.36)***
⩾65	46	55,257	8.32	58	53,203	10.9	1.31 (1.18–1.45)***	1.32 (1.19–1.46)***
Sex								
Women	36	196,789	1.83	41	194,958	2.10	1.15 (1.08–1.23)***	1.15 (1.08–1.22)***
Men	58	119,231	4.86	81	115,043	7.04	1.45 (1.34–1.57)***	1.47 (1.36–1.58)***
Comorbidity [c]								
No	24	159,048	1.51	39	156,629	2.49	1.65 (1.53–1.78)***	1.68 (1.56–1.81)***
Yes	70	156,972	4.46	83	153,372	5.41	1.21 (1.13–1.30)***	1.23 (1.15–1.31)***

CI, confidence interval; HR, hazard ratio; PY, person-years.
[a]Incidence rate per 10,000 person-years.
[b]Multivariable analysis including age, gender, and comorbidities of diabetes mellitus, asthma/chronic obstructive pulmonary disease, chronic liver disease, chronic kidney disease, and malnutrition.
[c]Individuals with any comorbidity of diabetes mellitus, asthma/chronic obstructive pulmonary disease, chronic liver disease, chronic kidney disease, cancer, systemic lupus erythematosus/rheumatoid arthritis/immune disorder, organ transplant, and malnutrition were classified into the comorbidity group.
***$p < 0.001$.

Table 4. 30-day mortality rate of pleural empyema for individuals with and without depression.

	Depression	
	No	Yes
Death/empyema events	6/94	13/122
Mortality rate	6.4%	10.7%
Crude OR (95% CI)	1 (Reference)	1.75 (0.64–4.79)
Adjusted OR [a] (95% CI)	1 (Reference)	2.23 (0.77–6.49)

CI, confidence interval; OR, odds ratio.
[a]Multivariable analysis controlling for age, sex, and comorbidities of diabetes mellitus, asthma/ chronic obstructive pulmonary disease, chronic liver disease, chronic kidney disease, and malnutrition.

interleukin-6, tumor necrosis factor, and C-reactive protein.[25–27] These factors might influence both susceptibility to and clinical outcomes of pleural empyema.

It is reasonable that patients with depression who develop pleural empyema may have a poorer prognosis. Evidence has shown that patients with depression who develop respiratory tract infections and pneumonia have worse clinical outcomes. Kao *et al.*[16] reported that patients with depression ($n = 2394$) had a significantly higher probability of an intensive care unit admission (18.1% *versus* 12.9%; $p < 0.001$), need for mechanical ventilation (21.9% *versus* 18.1%; $p < 0.001$) and in-hospital death (10.4% *versus* 9.0%; $p < 0.025$) attributable to pneumonia than those without depression ($n = 11,970$). Mather *et al.*[17] investigated 148 subjects who were re-admitted following pneumonia, they found a history of anxiety or depression was significantly associated with 30-day all-cause re-admission (OR, 1.62; 95% CI, 1.04–2.52). In addition, Davydow *et al.*[18] investigated 59,688 individuals who had a total of 703,158 hospitalizations for various infections. They found pre-existing depression was associated with an increased risk

of all-cause mortality within 30 days following pneumonia-related hospitalization (mortality rate ratio, 1.23; 95% CI, 1.16–1.29). The explanation for this is primarily rooted in the relationship between depression and increased systemic inflammation, as previously mentioned.[25–27] Other explanations are based on the negative effects of depression on self-care and adherence to treatment for medical conditions,[28,29] as well as the adverse effects of antidepressants or benzodiazepines.[30] However, in this study, the 30-day mortality for pleural empyema was higher, in the depression group, although not significantly, than in the comparison group. We must consider that limited event numbers may have limited the significance of our results.

Strength

The strength of this study is that we established a population-based depression cohort and we assessed the risk of developing pleural empyema. It is expensive to conduct a prospective cohort study. Therefore, a retrospective cohort study using insurance data is a suitable and economical alternative. The universal coverage of the provided by the NHI program reduces barriers to healthcare access for all citizens, regardless of socioeconomic background and/or residential location.[31] In this study, by using NHIRD, we were able to reflect a "real world" scenario in which depression, pleural empyema, and all comorbidities were directly diagnosed during medical consultation.

Limitation

There were still several limitations that should be considered when interpreting the results from this study. First, the ICD-9-CM algorithm was used to define depression, pleural empyema, and comorbidities from information provided by clinical physicians. Coding-based studies may underestimate the prevalence of depression and pleural empyema. The comparison cohort might have occult depression; depression and pleural empyema might miss other conditions such as complicated parapneumonic effusion. However, an *ad hoc* committee established by the insurance authority oversaw the evaluation of claims data to prevent errors and violations and several common diseases recorded in the NHIRD have been carefully validated.[32,33] In addition, we selected only diagnoses that appeared at least twice within a year to increase the accuracy. Secondly, the NHIRD does not provide detailed information about smoking habits, drinking habits and other environmental factors, which are potentially confounding factors in our study. Thirdly, the disease status and treatment status of the depression group was unknown. This prevented us from further analyzing the impact of depression severity on the risk of pleural empyema. Moreover, relevant clinical variables such as serum laboratory data, image reports, and pathogen results were not available for our study.[34,35]

Conclusion

Although this study had several limitations as mentioned above, the results suggested that patients with depression could be at a higher risk of developing pleural empyema than those without depression. However, additional evidence is needed to support this association, and further investigations are required to clarify the detailed mechanisms involved.

Author contribution(s)

Yi-Chen Shen: Conceptualization; Data curation; Investigation; Writing-original draft; Writing-review & editing.

Kuang-Ming Liao: Conceptualization; Data curation; Investigation; Writing-original draft; Writing-review & editing.

Yen-Sung Lin: Conceptualization; Data curation; Investigation; Writing-original draft; Writing-review & editing.

Yu-Jhen Huang: Conceptualization; Data curation; Investigation; Writing-original draft.

Cheng-Li Lin: Data curation; Investigation; Writing-original draft; Writing-review & editing.

Chia-Wen Tsai: Data curation; Investigation; Writing-original draft.

Wen-Shin Chang: Data curation; Investigation; Writing-original draft.

Te-Chun Shen: Conceptualization; Data curation; Investigation; Writing-original draft; Writing-review & editing.

Da-Tian Bau: Data curation; Investigation; Writing-original draft.

Te-Chun Hsia: Data curation; Investigation; Writing-original draft.

Conflict of interest statement

The authors declare that there is no conflict of interest.

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Supplemental material

The reviews of this paper are available via the supplemental material section.

References

1. Redden MD, Chin TY and van Driel ML. Surgical versus non-surgical management for pleural empyema. *Cochrane Database Syst Rev* 2017; 3: CD010651.
2. Bedawi EO, Hassan M and Rahman NM. Recent developments in the management of pleural infection: a comprehensive review. *Clin Respir J* 2018; 12: 2309–2320.
3. Hasley PB, Albaum MN, Li YH, *et al.* Do pulmonary radiographic findings at presentation predict mortality in patients with community-acquired pneumonia? *Arch Intern Med* 1996; 156: 2206–2212.
4. Menéndez R, Torres A, Zalacaín R, *et al.* Risk factors of treatment failure in community acquired pneumonia: implications for disease outcome. *Thorax* 2004; 59: 960–965.
5. Feller-Kopman D and Light R. Pleural disease. *N Engl J Med* 2018; 378: 740–751.
6. Ashbaugh DG. Empyema thoracis. Factors influencing morbidity and mortality. *Chest* 1991; 99: 1162–1165.
7. Strange C and Sahn SA. The definitions and epidemiology of pleural space infection. *Semin Respir Infect* 1999; 14: 3–8.
8. Sahn SA. Diagnosis and management of parapneumonic effusions and empyema. *Clin Infect Dis* 2007; 45: 1480–1486.
9. Seminog OO and Goldacre MJ. Risk of pneumonia and pneumococcal disease in people with severe mental illness: English record linkage studies. *Thorax* 2013; 68: 171–176.
10. Ferrari AJ, Charlson F, Norman RE, *et al.* Burden of depressive disorders by country, sex, age, and year: findings from the global burden of disease study 2010. *PLoS Med* 2013; 10: e1001547.
11. Noël PH, Williams JW Jr, Unützer J, *et al.* Depression and comorbid illness in elderly primary care patients: impact on multiple domains of health status and well-being. *Ann Fam Med* 2004; 2: 555–562.
12. Iwata M, Ota KT and Duman RS. The inflammasome: pathways linking psychological stress, depression, and systemic illnesses. *Brain Behav Immun* 2013; 31: 105–114.
13. Andersson NW, Goodwin RD, Okkels N, *et al.* Depression and the risk of severe infections: prospective analyses on a nationwide representative sample. *Int J Epidemiol* 2016; 45: 131–139.
14. Falagas ME, Karamanidou C, Kastoris AC, *et al.* Psychosocial factors and susceptibility to or outcome of acute respiratory tract infections. *Int J Tuberc Lung Dis* 2010; 14: 141–148.
15. Davydow DS, Hough CL, Zivin K, *et al.* Depression and risk of hospitalization for pneumonia in a cohort study of older Americans. *J Psychosom Res* 2014; 77: 528–534.
16. Kao LT, Liu SP, Lin HC, *et al.* Poor clinical outcomes among pneumonia patients with depressive disorder. *PLoS ONE* 2014; 9: e116436.
17. Mather JF, Fortunato GJ, Ash JL, *et al.* Prediction of pneumonia 30-day readmissions: a single-center attempt to increase model performance. *Respir Care* 2014; 59: 199–208.
18. Davydow DS, Ribe AR, Pedersen HS, *et al.* The association of unipolar depression with thirty-day mortality after hospitalization for infection: a population-based cohort study in Denmark. *J Psychosom Res* 2016; 89: 32–38.
19. Hsu CL, Wang TC, Shen TC, *et al.* Risk of depression in patients with chronic rhinosinusitis: a nationwide population-based retrospective cohort study. *J Affect Disord* 2016; 206: 294–299.
20. Shen TC, Yang CY, Huang YJ, *et al.* Risk of depression in patients with uterine leiomyoma:

a nationwide population-based cohort study. *J Affect Disord* 2017; 213: 126–130.

21. Shen TC, Chen CH, Lai HC, *et al.* Risk of empyema in patients with chronic liver disease and cirrhosis: a nationwide, population-based cohort study. *Liver Int* 2017; 37: 862–870.
22. Shen TC, Chen CH, Wang IK, *et al.* Risk of empyema in patients with end-stage renal disease: a nationwide propensity-matched cohort study. *QJM* 2017; 110: 425–430.
23. Mégarbane B and Chevillard L. The large spectrum of pulmonary complications following illicit drug use: features and mechanisms. *Chem Biol Interact* 2013; 206: 444–451.
24. Grau I, Ardanuy C, Calatayud L, *et al.* Smoking and alcohol abuse are the most preventable risk factors for invasive pneumonia and other pneumococcal infections. *Int J Infect Dis* 2014; 25: 59–64.
25. Kiecolt-Glaser JK and Glaser R. Depression and immune function: central pathways to morbidity and mortality. *J Psychosom Res* 2002; 53: 873–876.
26. Penninx BW, Kritchevsky SB, Yaffe K, *et al.* Inflammatory markers and depressed mood in older persons: results from the Health, Aging and Body Composition study. *Biol Psychiatry* 2003; 54: 566–572.
27. Godbout JP and Glaser R. Stress-induced immune dysregulation: implications for wound healing, infectious disease and cancer. *J Neuroimmune Pharmacol* 2006; 1: 421–427.
28. Katon WJ. Clinical and health services relationships between major depression, depressive symptoms, and general medical illness. *Biol Psychiatry* 2003; 54: 216–226.
29. Schmitz N, Wang J, Malla A and Lesage A. Joint effect of depression and chronic conditions on disability: results from a population-based study. *Psychosom Med* 2007; 69: 332–338.
30. Hak E, Bont J, Hoes AW, *et al.* Prognostic factors for serious morbidity and mortality from community-acquired lower respiratory tract infections among the elderly in primary care. *Fam Pract* 2005; 22: 375–380.
31. Hsing AW and Ioannidis JP. Nationwide population science: lessons from the Taiwan national health insurance research database. *JAMA Intern Med* 2015; 175: 1527–1529.
32. Hsieh CY, Su CC, Shao SC, *et al.* Taiwan's National Health Insurance Research Database: past and future. *Clin Epidemiol* 2019; 11: 349–358.
33. Su VY, Su WJ, Yen YF, *et al.* Statin use is associated with a lower risk of TB. *Chest* 2017; 152: 598–606.
34. Lai SW, Lin CL and Liao KF. Population-based cohort study investigating the correlation of diabetes mellitus with pleural empyema in adults in Taiwan. *Medicine* 2017; 96: e7763.
35. Lin HF, Liao KF, Chang CM, *et al.* Population-based cohort study examining the association between splenectomy and empyema in adults in Taiwan. *BMJ Open* 2017; 24: e015101.