

Age-adjusted Charlson comorbidity score is associated with the risk of empyema in patients with COPD

Chung-Han Ho, PhD^{a,b}, Yi-Chen Chen, MS^a, Chin-Chen Chu, MD, PhD^c, Jhi-Joung Wang, MD, PhD^a, Kuang-Ming Liao, MD^{d,*}

Abstract

Patients with chronic obstructive pulmonary disease (COPD) have a higher risk of pneumonia than the general population due to their impaired lung defense. They also have a higher risk of empyema and more comorbidities than patients without COPD. This study aimed to evaluate the risk of empyema in patients with COPD after adjusting for age and comorbidities using the age-adjusted Charlson comorbidity index (ACCI).

Data were retrieved from the National Health Insurance Research Database. COPD patients were defined as inpatients aged >40 years with an International Classification of Diseases, Ninth Revision, Clinical Modification diagnosis code for COPD. In total, 558,660 COPD patients were enrolled and separated into 3 groups by ACCI score to represent the severity of comorbidity (≤ 2 , 3–5, and > 5). Other comorbidities assessed included autoimmune diseases, gastroesophageal reflux disease, dyslipidemia, chest wall injury, and thoracostomy.

Of the 558,660 patients, 36,556 (6.54%) had low ACCI scores (≤ 2), 208,292 (37.28%) had moderate ACCI scores (3–5), and 313,812 (56.17%) had high ACCI scores (> 5). The mean ages of the low, moderate, and high groups were 50.66, 70.62, and 78.05 years, respectively. The hazard ratio (HRs) for empyema were 1.26 (95% confidence interval (CI) = 1.13–1.40) in the moderate ACCI group and 1.55 (95% CI = 1.39–1.72) in the high ACCI group compared with the low ACCI group. The overall incidence of empyema in COPD patients was 2.57 per 1000 person-years.

This is the first study to use ACCI scores to analyze the risk of empyema in patients with COPD. Patients with high ACCI scores were older and had more complicated comorbidities, resulting in a higher risk of empyema and poor prognosis. The subgroup analysis indicated that COPD patients with comorbid autoimmune disease, gastroesophageal reflux disease, chest wall injury, or history of thoracostomy did not have a higher risk of empyema than patients without these comorbidities.

Empyema is an important issue in patients with COPD and is associated with significant morbidity and mortality. Awareness of the risk factors for empyema, close monitoring, and early intervention may improve patient outcomes and decrease mortality.

Abbreviations: ACCI = age-adjusted Charlson comorbidity index, COPD = chronic obstructive pulmonary disease, GERD = gastroesophageal reflux disease, HR = hazard ratio, NHIRD = National Health Insurance Research Database.

Keywords: age-adjusted Charlson comorbidity index, chronic obstructive pulmonary disease, empyema

1. Introduction

Chronic obstructive pulmonary disease (COPD) is a chronic lung disease causing airflow limitation that is not fully reversible by medication. COPD is characterized by acute exacerbations and a decline in lung function over time.^[1] In a previous study, empyema

was associated with an increased risk of aortic aneurysm after adjusting for age, sex, and the comorbidities of diabetes, hypertension, hyperlipidemia, COPD, heart failure, coronary artery disease, stroke, bacterial endocarditis, and rheumatic endocarditis.^[2] COPD can lead to the impairment of pulmonary defense and an increased risk of pneumonia.^[3] Empyema is a complication of pneumonia in which pus and fluid from infected lung tissue collect in the pleural cavity, although empyema may arise from other infections as well.^[4] The risk factors for empyema include alcoholism, malignancy, and diabetes mellitus.^[5] Patients with empyema require tube thoracostomy or surgical management, which leads to prolonged antibiotic treatment and longer hospital stays. Few studies have assessed the incidence and risk of empyema in COPD. Accordingly, this study aimed to determine the incidence of empyema after an initial COPD diagnosis and to identify the risk of empyema in patients with COPD using the age-adjusted Charlson comorbidity index (ACCI).

2. Materials and methods

2.1. Data source

Taiwan launched a government-run single-payer National Health Insurance program in March 1995. The corresponding

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^a Department of Medical Research, Chi Mei Medical Center, ^b Department of Hospital and Health Care Administration, Chia-Nan University of Pharmacy and Science, ^c Department of Anesthesiology, Chi Mei Medical Center, ^d Department of Internal Medicine, Chi Mei Medical Center, Chiayi, Taiwan.

* Correspondence: Kuang-Ming Liao, Department of Internal Medicine, Chi Mei Medical Center, Chiayi, Taiwan (e-mail: abc8870@yahoo.com.tw).

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medical claims database, the National Health Insurance Research Database (NHIRD), was established for research purposes. In this study, data from January 1999 to December 2013 were obtained from Taiwan's NHIRD, which covers 99% of the inpatient and outpatient medical benefits claims for Taiwan's 23 million residents. To avoid potential ethical violations related to the data, patient confidentiality was protected using an encrypted personal identification system. The Institutional Review Board of Chi-Mei Medical Center approved this study (IRB: 10601-E01).

2.2. Patient selection and definition

All COPD patients in the inpatient claims databases of the NHIRD were selected. COPD patients were defined as inpatients aged >40 years with relevant International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) diagnosis codes (ICD-9-CM codes: 490–492 and 496). A total of 558,660 COPD patients were enrolled in this study. Patients with a prior medical history of COPD, based on a diagnosis recorded before December 31, 1999, were excluded to ensure that our population included those with new-onset COPD only. As our study aimed to estimate the incidence of new-onset empyema (ICD-9-CM code: 510), COPD patients with a history of diagnosed empyema were also excluded.

COPD patients were separated into 3 groups using ACCI scores to represent the severity of their comorbid conditions (≤ 2 , 3–5, and > 5). ACCI scores were based on the Charlson comorbidity index, which was developed by Charlson et al to measure baseline comorbid conditions.^[6,7] However, the ACCI scores adjust for age effects, with the comorbidity score of each patient aged >40 years increasing by 1 for each decade. Other related comorbidities were also measured, including autoimmune diseases (ICD-9-CM: 242, 242.01, 555.0, 555.1, 555.2, 555.9, 696, 696.1, 696.8, 710.0, 714, 720, 357.0, 710.2, 358, 281, 282, 446, 579, 364.00, 364.01, 725, 710.3, 245.2, 446.2, 446.29, 136.1, 710.4, 704.01, 446.4, 556.0, 556.6, 556.8, 556.9, 283, 694.4, 340, 710.1, 714.30, 714.33, 446.21, 446.5, 443.1, 446.7, and 446.1), gastroesophageal reflux disease (GERD, ICD-9-CM: 530.81), dyslipidemia (ICD-9-CM: 272.4), chest wall injury

(ICD-9-CM: 922.1 and 959.11), and thoracostomy (ICD-9-CM: 34.01, 34.04, 34.09).

2.3. Statistical analysis

Continuous variables were presented as the means and SD, and categorical variables were summarized as frequencies and percentages. An analysis of variance (ANOVA) was used to compare the differences between groups for continuous variables, and Pearson's χ^2 test was used for categorical variables.

A Cox proportional regression model was used to estimate the risk of new-onset empyema with adjustments for age, sex, and the listed comorbidities. The Kaplan–Meier method was used to describe the incidence of new-onset empyema, and differences between the 3 groups were compared using a log-rank test. All statistical analyses were conducted in SAS 9.4 (SAS Institute Inc., Cary, NC), and the Kaplan–Meier curves were plotted using STATA (version 12; Stata Corp., College Station, TX). Statistical significance was established as $P < .05$.

3. Results

Table 1 provides the characteristics and distribution of ACCI scores in patients with COPD. Of the 558,660 patients, 36,556 (6.54%) had low ACCI scores (≤ 2), 208,292 (37.28%) had moderate ACCI scores (3–5), and 313,812 (56.17%) had high ACCI scores (> 5). The mean ages (\pm SD) of the low, moderate, and high ACCI groups were 50.66 (± 5.92), 70.62 (± 9.45), and 78.05 (± 9.65) years, respectively. The 3 groups were predominantly male, with proportions ranging from 65% to 72%. The rate of mortality was higher in the groups with higher ACCI scores. Comorbid autoimmune disease, GERD, dyslipidemia, and a previous history of thoracostomy were significantly more common in the high ACCI group than in the low ACCI group.

Table 2 shows the hazard ratios (HRs) for empyema in patients with different ACCI scores. The adjusted HR was 1.26 [95% confidence interval (CI) = 1.13–1.40] in the moderate ACCI group and 1.55 (95% CI = 1.39–1.72) in the higher ACCI group compared with the low ACCI group.

Table 1

Characteristics of COPD patients.

	Age-adjusted CCI score			P
	≤ 2 N = 36,556 (6.54%)	3–5 N = 208,292 (37.28%)	> 5 N = 313,812 (56.17%)	
Age (mean \pm SD)	50.66 \pm 5.92	70.62 \pm 9.45	78.05 \pm 9.65	<.0001*
Sex				
Male	23,599 (64.56%)	150,870 (72.43%)	214,037 (68.21%)	<.0001*
Female	12,957 (35.44%)	57,422 (27.57%)	99,775 (31.79%)	
Empyema				
Yes	548 (1.50%)	3231 (1.55%)	4560 (1.45%)	.0165*
No	36,008 (98.50%)	205,061 (98.45%)	309,252 (98.55%)	
Mortality				
Yes	3311 (9.06%)	59,135 (28.39%)	157,508 (50.19%)	<.0001*
No	33,245 (90.94%)	149,157 (71.61%)	156,304 (49.81%)	
Comorbidities				
Autoimmune disease	1097 (3.00%)	6226 (2.99%)	16,003 (5.10%)	<.0001*
GERD	603 (1.65%)	3452 (1.66%)	10,707 (3.41%)	<.0001*
Dyslipidemia	1887 (5.16%)	12,113 (5.82%)	27,012 (8.61%)	<.0001*
Chest wall injury	1439 (3.94%)	4958 (2.38%)	7135 (2.27%)	<.0001*
Thoracostomy	1095 (3.00%)	5480 (2.63%)	16,798 (5.35%)	<.0001*

COPD = chronic obstructive pulmonary disease, CCI = Charlson comorbidity index, GERD = gastroesophageal reflux disease.

* $P < .05$.

Table 2
The comparison hazard ratio (HR) of empyema in patients with different age-adjusted Charlson comorbidity index (ACCI) scores.

	Empyema	Adjusted HR (95% CI)	P
Overall (n = 558,660)			
≤2	548 (1.50)	Ref.	
3–5	3231 (1.55)	1.26 (1.13–1.40)	<.0001*
>5	4560 (1.45)	1.55 (1.39–1.72)	<.0001*
Sex			
Male (n = 388,506)			
≤2	479 (2.03)	Ref.	
3–5	2836 (1.88)	1.22 (1.08–1.37)	.0014*
>5	3821 (1.79)	1.49 (1.33–1.68)	<.0001*
Female (n = 170,154)			
≤2	69 (0.53)	Ref.	
3–5	395 (0.69)	1.50 (1.13–2.00)	.0057*
>5	739 (0.74)	1.81 (1.37–2.40)	<.0001*
Comorbidities			
Autoimmune disease (n = 23,326)			
≤2	19 (1.73)	Ref.	
3–5	85 (1.37)	1.16 (0.63–2.13)	.6378
>5	197 (1.23)	1.18 (0.65–2.12)	.5878
GERD (n = 14,762)			
≤2	4 (0.66)	Ref.	
3–5	58 (1.68)	1.60 (0.57–4.46)	.3697
>5	159 (1.49)	1.73 (0.64–4.69)	.2821
Dyslipidemia (n = 41,012)			
≤2	13 (0.69)	Ref.	
3–5	115 (0.95)	1.33 (0.73–2.42)	.3514
>5	323 (1.20)	2.13 (1.19–3.80)	.0106*
Chest wall injury (n = 13,532)			
≤2	18 (1.25)	Ref.	
3–5	86 (1.73)	1.44 (0.81–2.56)	.2124
>5	110 (1.54)	1.65 (0.94–2.92)	.0825
Thoracostomy (n = 23,373)			
≤2	169 (15.43)	Ref.	
3–5	717 (29.79)	1.01 (0.79–1.30)	.9369
>5	1521 (9.05)	1.21 (0.96–1.53)	.1142

GERD = gastroesophageal reflux disease, CI = confidence interval.
 * P < .05.

In male patients, the adjusted HR for empyema was 1.22 (95% CI = 1.08–1.37) in the moderate ACCI group and 1.49 (95% CI = 1.33–1.68) in the high ACCI group compared with the low ACCI group. In female patients, the adjusted HR for empyema was 1.50 (95% CI = 1.13–2.00) in the moderate ACCI group and 1.81 (95% CI = 1.37–2.40) in the high ACCI group compared with the low ACCI group. The subgroup analysis by ACCI showed that COPD patients with comorbid autoimmune disease, GERD, chest wall injury, or history of thoracostomy did not have a higher risk of empyema. Patients with dyslipidemia had a higher risk of empyema when they had a high ACCI compared with a low ACCI, with an adjusted HR of 2.13 (95% CI = 1.19–3.80).

Figure 1 provides the incidence of empyema in patients with COPD by different age groups. The incidence in each age group was similar, and the overall incidence rate was 2.57 per 1000 person-years. Figure 2 depicts the prevalence of empyema in COPD patients in different age groups. The prevalence of empyema steadily decreased with the increasing age during the study period.

Figure 3 presents the Kaplan–Meier plot of patients with COPD in different ACCI groups and shows that patients with a higher ACCI had a significantly higher incidence of empyema.

4. Discussion

Empyema is an important disease that requires prompt treatment and aggressive intervention to prevent prolonged hospitalization and decreased lung function. Few studies have addressed the

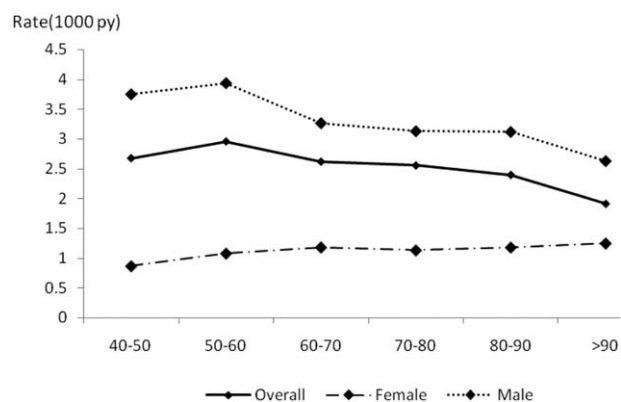


Figure 1. Incidence of empyema in patients with COPD; the overall incidence rate was 2.57 per 1000 person-years. COPD = chronic obstructive pulmonary disease.

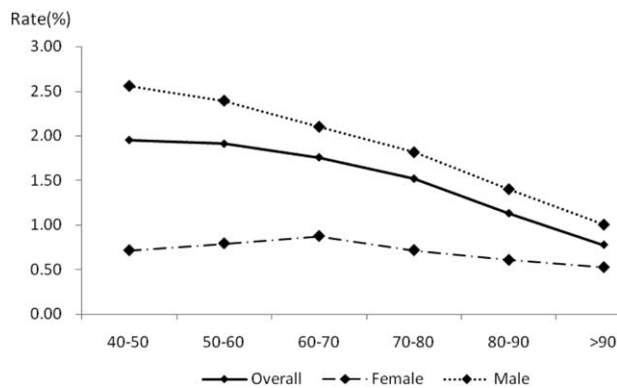


Figure 2. The prevalence of empyema in COPD patients. COPD = chronic obstructive pulmonary disease.

relationship between COPD and empyema and evaluated the risk of empyema in COPD after adjusting for comorbidities. In addition, no studies have monitored the incidence and prevalence of empyema after a COPD diagnosis. To our knowledge, this is the first study to use ACCI scores to analyze the risk of empyema in patients with COPD and to determine the incidence of empyema in COPD. Our study showed that COPD patients with higher ACCI scores had a higher incidence of empyema than those with moderate or low ACCI scores and that the overall incidence of empyema remained stable over the observed period. The prevalence decreased with increasing age due to high mortality in old age.

4.1. Risk factors for empyema

Chalmers et al^[8] performed a prospective observational study of 1269 patients and found that 92 patients (7.2%) developed complicated parapneumonic effusion or empyema. They identified some factors that predicted the development of these conditions, including hypoalbuminemia (<30 g/L), hyponatremia (<130 mmol/L), platelet count $>400 \times 10^9/L$, C-reactive protein $>100 \text{ mg/L}$, and a history of alcoholism or intravenous drug use. They also found that a history of COPD was associated with a decreased risk of empyema. The reason for the decreased risk of empyema in COPD in their study may have been due to the decreased local pulmonary inflammation produced in response to

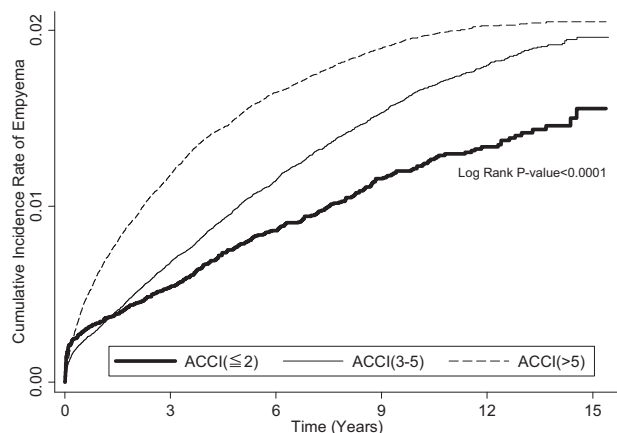


Figure 3. Kaplan-Meier plot of COPD patients in different ACCI groups. ACCI = age-adjusted Charlson comorbidity index, COPD = chronic obstructive pulmonary disease.

the acute bacterial challenge. Another reason could be that patients with COPD may receive steroids, which reduce pulmonary and systemic inflammation and mitigate pleural inflammation.^[8] In a previous study, 1269 patients were included, and only 92 developed complicated parapneumonic effusion or empyema. This case number was limited; thus, we need more prospective studies to determine the effect of COPD on empyema and the mechanism behind this relationship.

In our study, we analyzed the risk of empyema among patients with COPD, and showed that higher ACCI scores conferred the highest risk and mortality of empyema. Patients in the high ACCI group were older (mean age of 78 y) and had more complicated comorbidities than patients in the moderate and low ACCI groups, and these factors resulted in a poor prognosis.

4.2. Autoimmune disease and empyema

No previous studies have examined the relationship between autoimmune disease and empyema. In our study, autoimmune disease did not increase the risk of empyema in patients with COPD when considering ACCI scores. Patients with systemic lupus erythematosus (SLE) are predisposed to infections given their use of immunosuppressive medications and intrinsic immune dysregulation.^[9] Infections are also an important cause of morbidity and mortality in this population.^[10] Wiedemann and Matthey^[11] reported that one-third of patients with SLE have lung inflammation with no clinical symptoms. The most common pulmonary manifestation of SLE is pleuritis;^[12] 45% to 60% of patients with SLE present with pleuritic pain with or without pleural effusion.^[13] Although 50% of patients with SLE report pleural effusion,^[11] the risk of empyema is low in SLE, and the true incidence of empyema in SLE has not been examined. Another common autoimmune disease causing pleural effusion and pleuritis is rheumatoid arthritis. Pleural effusion in patients with rheumatoid arthritis often does not require treatment and can spontaneously resolve over time.^[14] Data on empyema in rheumatoid arthritis are also lacking. Our study showed that autoimmune diseases did not increase the risk of empyema in patients with COPD; however, our case number was small, and the true incidence should be further studied.

4.3. GERD and empyema

One prospective study enrolled 119 patients with empyema and showed that aspiration and GERD were risk factors for empyema.^[15] GERD is a condition that involves regurgitation of stomach content into the esophagus, leading to mucosal erosion. GERD has been extensively studied in chronic cough and asthma. Micro- and macroaspiration of esophageal content into the airway may cause pneumonia. In some cases, parapneumonic effusion can occur after pneumonia and may progress to empyema. In our analysis, GERD was not a significant risk factor for empyema in patients with COPD. In addition to the small case number, our findings may have been limited by the prescription of proton pump inhibitors for GERD to reduce microaspiration in our clinical practice. A meta-analysis showed that there was no association between community pneumonia and proton pump inhibitor use for >180 days.^[16] The risk of empyema in GERD patients was not statistically significant.

4.4. Dyslipidemia and empyema

No studies have investigated the relationship between dyslipidemia and empyema. In animal studies, dyslipidemia was found

to impair chemokine-induced neutrophil migration and reduce neutrophil recruitment to the lung, which can result in decreased pulmonary bacterial clearance.^[17] In our study, COPD patients with dyslipidemia had an increased risk of empyema, with an HR of 2.13 (95% CI = 1.19–3.80) in the group of patients with ACCI scores >5. Dyslipidemia may impair host immunity and play an important role in controlling pulmonary infection, especially in patients with multiple comorbidities or old age. More evidence and studies are needed to determine the causal association between dyslipidemia and empyema.

4.5. ACCI and empyema

The combined age-comorbidity ACCI scores were shown to be valid in a separate cohort. This index is useful for reporting longitudinal outcomes stratified by a combined risk assessment that adds additional points for age. COPD could increase the risk of empyema, and patients with advanced age and more comorbidities usually show a higher rate of empyema and poor outcomes. In a previous study, COPD was one of the confounding factors used to analyze the association between other diseases and empyema. However, no studies have investigated the risk ratio of empyema in COPD patients. The estimated relative risk was considered to be a crude index that could be used by clinicians in health care systems to assess separate cohorts grouped by patients' age and comorbidities.

According to a previous study, most patients with empyema and complicated parapneumonic pleural effusion had a mean age of 53 years. Patients had at least 1 risk factor, such as neoplasia (37%), treatment with immunosuppressive medicine (15%), or alcohol abuse (15%).^[18] Another study identified risk factors for the development of empyema among patients admitted with community-acquired pneumonia.^[19] A history of alcohol abuse and intravenous drug use was associated with the development of complicated parapneumonic effusion or empyema. Our study is the first to investigate the association between ACCI scores and COPD.

4.6. Limitations

There are some limitations to our study. There were no laboratory or imaging data; thus, pulmonary function tests, pleural effusion data, roentgenograms, and chest computed tomography were not used to evaluate the severity of COPD or empyema. The definition of COPD according to the relevant ICD-9-CM codes and lack of COPD severity were other limitations. COPD severity is associated with increased risk of pneumonia, which is a common cause of empyema. Although COPD patients with more severe obstruction usually have higher ACCI scores, such information regarding COPD severity was lacking in our study.

The diagnosis of COPD was based on clinical physicians' assessments; however, the National Health Insurance Administration performs quarterly expert reviews on a random sample of ambulatory and inpatient claims. The nationwide population assessed can be generalized to represent the COPD population and has been used in many studies.^[20–23]

5. Conclusions

Empyema is a common problem encountered in clinical practice and is associated with significant morbidity and mortality. Early

and correct diagnoses can present a challenge and delay patient treatment, which can lead to morbidity and complications. The risk of empyema and mortality was highest among patients with high ACCI scores (>5). Prompt treatment with antibiotics, thoracentesis, or surgery is necessary for this population.

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