The Impact of Sepsis on the Outcomes of COPD Patients: A Population-Based Cohort Study

Cheng-Hsin Chen, Chih-Cheng Lai, Ya-Hui Wang, Cheng-Yi Wang, Hao-Chien Wang, Chong-Jen Yu, Likwang Chen and Taiwan Clinical Trial Consortium for Respiratory Diseases (TCORE)

Abstract: This study aims to identify the impact of new-onset sepsis in patients with chronic obstructive pulmonary disease (COPD) including the effects on acute exacerbations, pneumonia and mortality. Using the National Health Insurance Research Database of Taiwan, all patients with COPD older than 40 years between 1988 and 2010 were recruited. After propensity score matching, each of the 8774 COPD patients with and without sepsis were identified to have similar characteristics. The primary outcome was severe exacerbations of COPD, with a severe exacerbation being defined as a patient requiring hospital admission or an emergency department visit due to COPD. The secondary outcomes were pneumonia, serious pneumonia, and all-cause mortality. The post-index overall cumulative incidence rates of total acute exacerbations were 11.2/person-years in the sepsis group and 6.2/person-years in the non-sepsis group (adjusted hazard ratio (HR) = 1.38, 95% confidence interval (CI), 1.38–1.40). The sepsis group also had higher risks of severe exacerbations (adjusted HR = 2.05, 95% CI, 2.02–2.08), severe exacerbations requiring hospitalization (adjusted HR = 2.30, 95% CI, 2.24–2.36), and severe exacerbations leading to an emergency room visit (adjusted HR = 1.91, 95% CI, 1.87–1.94). Regarding the effect on secondary outcomes, the sepsis group had higher risks of mortality (incidence rate: 23.7/person-years vs. 11.34/person-years, adjusted HR = 2.27, 95% CI, 2.14–2.41), pneumonia (incidence rate: 26.41 per person-days vs. 10.34 per person-days, adjusted HR = 2.70, 95% CI, 2.5–2.91), and serious pneumonia (incidence rate: 5.84 per person-days vs. 1.98 per person-days, adjusted HR = 2.89, 95% CI, 2.5–3.33) compared with the non-sepsis group. Sepsis survivors among patients with COPD had a higher risk of severe exacerbations, pneumonia, serious pneumonia, and mortality compared to patients with COPD without sepsis.

Keywords: Chronic obstructive pulmonary disease (COPD); sepsis; exacerbation; pneumonia; mortality
1. Introduction

Chronic obstructive pulmonary disease (COPD) is a common disease characterized by persistent airflow limitation and associated respiratory symptoms. It is currently the fourth leading cause of death worldwide [1]. Globally, the prevalence of COPD is expected to increase due to a prolonged lifespan and increased exposure to the risk factors of COPD. An exacerbation of COPD is a critical acute event characterized by the worsening of respiratory symptoms, and it is associated with an accelerating decline in lung function. This has a negative effect on the quality of life and increases the rates of hospitalization and mortality [2]. Several factors may induce acute exacerbations in patients with COPD, including air pollution, poor compliance, and most commonly, respiratory tract infections [3,4]. The early identification of the predisposing factors is an important issue in the prevention of acute exacerbations and to improve outcomes in COPD.

Sepsis is a life-threatening condition defined by organ dysfunction caused by a dysregulated host response to infection [5]. Patients with COPD have been reported to be at a higher risk of developing sepsis due to the use of corticosteroids, underlying comorbidities, and possibly impaired barrier function [6,7]. However, the role of sepsis in increasing the risk of acute exacerbations and the effect on the outcomes in COPD has yet to be well defined.

The National Health Insurance (NHI) program in Taiwan was initiated in March 1995. It is a public health insurance system for the general population in Taiwan, and it provides medical care for up to 99% of the 23 million residents of Taiwan [8]. In this study, the National Health Insurance Research Database (NHIRD) of Taiwan was used to identify the impact of new-onset sepsis in patients with COPD including the effects on acute exacerbations, pneumonia and mortality.

2. Methods and Materials

2.1. Study Design and Patient Selection

This study was conducted using the NHIRD, which is a database constructed by the National Health Research Institutes (NHRI) and includes comprehensive medical care records of more than 97% of the hospitals and clinics in Taiwan [9]. All claims data of ambulatory care records, outpatient visits, prescriptions, inpatient care records, registration files, and disease and vital status data were retrieved from the NHIRD. Ethical approval was obtained from the Institutional Review Board of the Cardinal Tien Hospital (Number: CTH-106-3-5-060).

All patients with COPD older than 40 years between 2000 and 2010 were recruited for this study. The diagnosis of COPD was defined when the patients had an International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) diagnostic code for COPD (491, 492, or 496) in at least one hospital admission or three outpatient visits. Although the diagnosis of COPD is based on the clinical signs/symptoms and the findings of spirometry, these data are not available from NHIRD database. Therefore, like other researches based on health claims databases, we used ICD-9-CM codes of COPD and spirometry to identify patients with COPD [10]. To ensure the accuracy and reliability of the COPD diagnosis, the exclusion criteria were: (1) incomplete demographic data; (2) no pulmonary function test within one year before or after the diagnosis of COPD; and (3) COPD was not diagnosed after the lung function test. We also excluded those who died or were diagnosed with sepsis prior to being indexed.

The patients with sepsis were identified by ICD-9-CM codes for both an infectious process and acute organ dysfunction, which is similar to the method previously reported by Lai et al. [11]. For the patients with more than one episode of sepsis, only the first episode was included. The non-sepsis cohort was sampled as the reference group, and patients with a previous history of sepsis were excluded.
2.2. Demographic Characteristics and Comorbidities

The patients’ demographic characteristics including age, sex, monthly income (less than NT$ 19,100, NT$ 19,100-NT$ 41,999, and more than NT$ 42,000), hospital level at admission (medical center, regional, district, and others), number of severe exacerbations of COPD in the one year prior to the index date (never, 1, or ≥2 times/year), and the index year of sepsis (2000–2011) were extracted. Underlying comorbid conditions were identified according to ICD-9-CM codes and grouped into the following categories: myocardial infarction, congestive heart failure, peripheral vascular disease, cerebrovascular disease, dementia, rheumatologic disease, peptic ulcer disease, hemiplegia or paraplegia, renal disease, diabetes, moderate/severe liver disease, and tumors. The Charlson Comorbidity Index (CCI) was used to determine the severity of the comorbidities in each patient. Important medications including aspirin, statins, non-steroidal anti-inflammatory drugs (NSAIDs), anti-hyperglycemic drugs, proton-pump inhibitors (PPIs), medications for hypertension and for COPD (long-acting beta agonist (LABAs), short-acting beta agonists (SABAs), long-acting muscarinic antagonists (LAMAs), and inhaled corticosteroids (ICSs)), were recorded.

2.3. Outcomes

The primary outcome was severe exacerbations of COPD, which was defined as a patient requiring hospital admission or an emergency department visit due to COPD. The secondary outcomes were pneumonia, serious pneumonia, and all-cause mortality. Pneumonia is identified according to ICD-9-CM codes 480-486, and 507. Serious pneumonia was defined as pneumonia requiring invasive or non-invasive mechanical ventilation. Because of the high mortality rate and older-age in COPD patients, competing risk analysis using the Fine and Gray model was also performed [12]. All subjects were followed until the occurrence of events of interest, death or the end of the study (31 December 2011).

2.4. Statistical Analysis

Data analysis was performed using the SAS statistical package, version 9.4 (SAS Institute, Inc., Cary, NC, USA). The baseline characteristics are presented as descriptive statistics (means, standard deviations, counts, and percentages). Categorical baseline variables were compared using Pearson’s chi-square test or Fisher exact test. For continuous variable, the Kolmogorov-Smirnov test was applied to test for a normal distribution. When the continuous variable was normally distributed, an independent t-test was used. If the normality assumption was violated, a nonparametric Wilcoxon rank sum test was used. To minimize the imbalance in baseline characteristic covariates between the sepsis and non-sepsis groups, we performed 1:1 propensity score matching. Covariates that may have caused interference or biased the association between exposure and outcome of interest including demographic characteristics, comorbidities and severe exacerbations of COPD in the one year prior to the index date (never, 1, or ≥2 times/year) were included in the propensity matching.

The cumulative incidence rates of severe exacerbations were compared between the sepsis and non-sepsis groups before and after propensity score matching. Crude and adjusted hazard ratios (HRs) were calculated using Poisson regression with the non-sepsis cohort selected as the reference group. The crude incidence rates of other outcomes (mortality, pneumonia and serious pneumonia) were obtained as the total number of events during the follow-up period divided by person-days. The Schoenfeld Residuals test was used to test the proportional hazards assumption. Cox proportional regression models were used with the non-sepsis cohort as the reference group. Crude HRs and adjusted HRs of individual outcomes were also evaluated after adjusting for the propensity score. We also used the Fine-Gray model in our incidence rate and time-to-event model to account for competing risks in the mortality model to derive subdistribution HRs (sub-HR) of secondary outcomes. A two-sided p-value < 0.05 was considered to indicate statistical significance in all analyses.
3. Results

3.1. Baseline Demographic Characteristics

The medical records of 91,197 patients with COPD from 2000 to 2010 were reviewed, of whom 14,238 were enrolled as the sepsis cohort and 76,959 as the non-sepsis cohort. The demographic characteristics of both groups are summarized and shown in Table 1. The sepsis group tended to be older than the non-sepsis group. In addition, there were significant differences in sex, COPD index year, monthly income, medications for hypertension (beta-blockers, angiotensin-converting-enzyme inhibitors (ACEis) and angiotensin receptor blockers (ARBs), medications for COPD and statins between the two groups. In terms of baseline comorbidities, except for diabetes mellitus, the sepsis cohort had higher rates of myocardial infarction, congestive heart failure, peripheral vascular disease, cerebrovascular disease, dementia, rheumatologic disease, peptic ulcer disease, hemiplegia or paraplegia, renal disease, moderate or severe liver disease, and tumors. After 1:1 propensity score matching, 8774 patients with COPD were identified in each group to have similar characteristics including age, sex, income, baseline comorbidities and medications (Figure 1).

Table 1. Baseline characteristics of study population stratified by sepsis before and after propensity score matching.

| Patient characteristics | Before Propensity Score Matching | After Propensity Score Matching |
|-------------------------|---------------------------------|---------------------------------|
|                         | Non-Sepsis Cohort | Sepsis Cohort | p-Value | Non-Sepsis Cohort | Sepsis Cohort | p-Value |
|                         | n = 76,959 | n = 14,238 | | n = 8774 | n = 8774 | |
| Age (year)              | 63.45 ± 11.56 | 70.7 ± 10.23 | <0.0001 | 69.15 ± 10.88 | 68.93 ± 10.77 | 0.1994 |
| Years from COPD diagnosis to index date | 3.24 ± 2.83 | 4.13 ± 3.1 | <0.0001 | 3.04 ± 3.04 | 3.2 ± 2.78 | <0.0001 |
| Male sex                |                   |                   |         |                   |                   |         |
|                         |                  |                  |         |                  |                  |         |
| Index year (COPD)       |                   |                   |         |                  |                  |         |
| 2000                    | 12,013 (15.61%)  | 3547 (24.91%)   |         | 1746 (19.90%)   | 1708 (19.47%)   |         |
| 2001                    | 10,156 (13.20%)  | 2456 (17.25%)   |         | 1285 (14.65%)   | 1314 (14.98%)   |         |
| 2002                    | 8437 (10.96%)    | 1811 (12.72%)   |         | 1030 (11.74%)   | 1056 (12.04%)   |         |
| 2003                    | 6567 (8.53%)     | 1281 (9.00%)    |         | 777 (8.86%)     | 794 (9.05%)     |         |
| 2004                    | 6392 (8.99%)     | 1224 (9.60%)    |         | 768 (8.77%)     | 784 (9.94%)     |         |
| 2005                    | 5256 (7.67%)     | 1010 (7.09%)    |         | 682 (7.77%)     | 679 (7.74%)     |         |
| 2006                    | 5373 (6.98%)     | 811 (5.70%)     | <0.0001 | 591 (6.74%)     | 582 (6.63%)     |         |
| 2007                    | 5512 (7.16%)     | 721 (5.06%)     | <0.0001 | 594 (6.77%)     | 577 (6.98%)     | <0.0001 |
| 2008                    | 5031 (6.54%)     | 560 (3.93%)     | <0.0001 | 504 (5.74%)     | 492 (5.61%)     |         |
| 2009                    | 5485 (7.13%)     | 468 (3.29%)     | <0.0001 | 435 (4.96%)     | 441 (5.03%)     |         |
| 2010                    | 5563 (7.25%)     | 349 (2.45%)     | <0.0001 | 362 (4.13%)     | 347 (3.95%)     |         |
| Monthly income, n (%)   |                   |                   |         |                  |                  |         |
| <19,100                 | 26,149 (33.98%)  | 5764 (40.48%)   | <0.0001 | 3458 (39.41%)   | 3524 (40.16%)   | <0.0001 |
| 19,100–41,999           | 39,338 (51.12%)  | 7014 (49.26%)   | <0.0001 | 4352 (46.60%)   | 4297 (48.97%)   | <0.0001 |
| ≥42,000                 | 11,472 (14.91%)  | 1460 (10.25%)   |         | 964 (10.99%)    | 953 (10.86%)    |         |
| Hospital level, n (%)   |                   |                   |         |                  |                  |         |
| Level 1                 | 15,271 (19.84%)  | 4986 (35.02%)   | <0.0001 | 3097 (35.30%)   | 3137 (35.75%)   | <0.0001 |
| Level 2                 | 16,246 (21.11%)  | 6191 (43.48%)   |         | 3599 (41.02%)   | 3599 (40.98%)   |         |
| Level 3                 | 9098 (11.82%)    | 2835 (19.91%)   |         | 1537 (18.25%)   | 1537 (18.25%)   |         |
| Level 4                 | 36,344 (47.23%)  | 226 (1.59%)     | <0.0001 | 265 (3.25%)     | 226 (2.58%)     | <0.0001 |
| COPD severe AE          |                   |                   |         |                  |                  |         |
| 0                       | 61,315 (79.67%)  | 1466 (10.30%)   | <0.0001 | 1381 (15.74%)   | 1466 (16.71%)   | <0.0001 |
| 1                       | 7064 (9.18%)     | 3076 (21.60%)   |         | 2402 (27.38%)   | 2501 (28.50%)   |         |
| ≥2                      | 8590 (11.13%)    | 9696 (68.10%)   | <0.0001 | 4991 (56.88%)   | 4607 (54.79%)   | <0.0001 |
| Medication for hypertension |                  |                   |         |                  |                  |         |
| Beta-blocker or ARB     |                   |                   |         |                  |                  |         |
| Aspirin                 | 9837 (12.99%)    | 2474 (17.38%)   | <0.0001 | 1433 (16.33%)   | 1436 (16.37%)   | <0.0001 |
| Statin                  | 10,515 (13.66%)  | 1625 (11.47%)   | <0.0001 | 1069 (12.18%)   | 1059 (12.07%)   | 0.8171  |
| NSAID                   | 60,636 (78.79%)  | 11,275 (79.19%) | 0.2856  | 7070 (80.58%)   | 7013 (79.93%)   | 0.2797  |
| COPD drug               |                   |                   |         |                  |                  |         |
| Oral Steroid            | 29,962 (38.93%)  | 7966 (56.09%)   | <0.0001 | 4795 (54.65%)   | 4765 (53.14%)   | 0.6493  |
| LABA                    | 865 (1.12%)      | 303 (2.13%)     | <0.0001 | 213 (2.43%)     | 211 (2.40%)     | 0.9217  |
| SABA                    | 8354 (10.66%)    | 3149 (22.12%)   | <0.0001 | 1817 (20.71%)   | 1868 (20.61%)   | 0.8667  |
| LAMA                    | 3716 (4.83%)     | 1273 (9.48%)    | <0.0001 | 713 (8.15%)     | 691 (7.88%)     | 0.5404  |
| ICS                     | 12,567 (16.33%)  | 3749 (26.33%)   | <0.0001 | 2218 (25.28%)   | 2225 (25.36%)   | 0.9033  |
Table 1. Cont.

| Patient characteristics     | Non-Sepsis Cohort (n = 76,959) | Sepsis Cohort (n = 14,238) | p-Value | Non-Sepsis Cohort (n = 8774) | Sepsis Cohort (n = 8774) | p-Value |
|-----------------------------|---------------------------------|-----------------------------|---------|-----------------------------|--------------------------|---------|
| Baseline comorbidities      |                                 |                             |         |                             |                          |         |
| Charlson score              | 1.69 ± 1.13                     | 2.35 ± 1.61                 | <0.0001 * | 2.22 ± 1.58                 | 2.21 ± 1.57              | 0.6532 * |
| Myocardial infarction       | 957 (1.24%)                     | 432 (3.03%)                 | <0.0001 | 220 (2.51%)                 | 223 (2.54%)              | 0.8852  |
| Congestive heart failure    | 5133 (6.67%)                    | 2660 (18.68%)               | <0.0001 | 1370 (15.61%)               | 1347 (15.35%)            | 0.6313  |
| Peripheral vascular disease | 614 (0.80%)                     | 228 (1.60%)                 | <0.0001 | 141 (1.61%)                 | 129 (1.47%)              | 0.4617  |
| Cerebrovascular disease     | 3895 (5.06%)                    | 1550 (10.89%)               | <0.0001 | 810 (9.23%)                 | 805 (9.17%)              | 0.8961  |
| Dementia                    | 1075 (1.40%)                    | 956 (6.71%)                 | <0.0001 | 325 (3.70%)                 | 329 (3.75%)              | 0.8733  |
| Renal disease               | 688 (0.89%)                     | 176 (1.24%)                 | 0.0001  | 116 (1.32%)                 | 112 (1.28%)              | 0.7897  |
| Peptic ulcer disease        | 10,577 (13.74%)                 | 2794 (19.62%)               | <0.0001 | 1647 (18.77%)               | 1659 (18.91%)            | 0.8168  |
| Hemiplegia or paraplegia    | 57 (0.07%)                      | 29 (0.20%)                  | <0.0001 | 7 (0.08%)                   | 7 (0.08%)                | 1       |
| Renal disease               | 1966 (2.55%)                    | 916 (6.43%)                 | <0.0001 | 426 (4.86%)                 | 428 (4.88%)              | 0.9441  |
| Diabetes                    | 3407 (4.43%)                    | 661 (4.44%)                 | 0.2526  | 431 (4.91%)                 | 421 (4.88%)              | 0.7254  |
| Moderate or severe liver disease | 3456 (4.49%)                  | 1335 (9.50%)                | <0.0001 | 824 (9.39%)                 | 827 (9.43%)              | 0.9382  |
| Tumor                       | 9634 (12.52%)                   | 2389 (16.78%)               | <0.0001 | 1374 (15.66%)               | 1377 (15.69%)            | 0.9503  |

* Wilcoxon rank sum test. COPD: chronic obstructive pulmonary disease; ACEI: angiotensin-converting enzyme inhibitor; ARB: angiotensin II receptor blocker; NSAID: nonsteroidal anti-inflammatory drugs; LABA: long acting beta agonist; SABA: short acting beta agonist; LAMA: long acting antimuscarinics; ICS: inhaled corticosteroid; AE: acute exacerbation.

Figure 1. Flow chart of study cohort population selection. COPD: chronic obstructive pulmonary disease.
3.2. Outcomes Analysis

Following matching, the post-index overall cumulative incidence rates of total acute exacerbations were 11.19/person-years in the sepsis group and 6.21/person-years in the non-sepsis group (adjusted HR = 1.38, 95% CI, 1.38–1.40). With regards to overall acute exacerbation events, the sepsis group also had higher risks of severe exacerbations (adjusted HR = 2.05, 95% CI, 2.02–2.08), severe exacerbations requiring hospitalization (adjusted HR = 2.30, 95% CI, 2.24–2.36), and severe exacerbations leading to an emergency room visit (adjusted HR = 1.91, 95% CI, 1.87–1.94). The results before matching were similar to those after matching (Table 2).

Table 2. Cumulative incidence rates and hazard ratios of COPD patients with acute exacerbation, severe acute exacerbation, severe acute exacerbation requiring hospitalization and ED visit before and after propensity score matching in sepsis and non-sepsis cohort.

| Outcomes                                | Sepsis Cohort IR (person-years) | Non-Sepsis Cohort IR (person-years) | Crude HR (95% CI) | Adjusted HR * (95% CI) |
|-----------------------------------------|---------------------------------|-------------------------------------|--------------------|------------------------|
| Before propensity score matching        |                                 |                                     |                    |                        |
| Total AE                                | 11.93                           | 4.67                                | 1.51 (1.50–1.52)   | 1.48 (1.48–1.49)       |
| Severe AE                               | 2.87                            | 0.36                                | 2.46 (2.42–2.50)   | 4.62 (4.58–4.67)       |
| Severe AE requiring hospitalization     | 1.17                            | 0.13                                | 2.76 (2.69–2.82)   | 5.44 (5.36–5.53)       |
| Severe AE requiring ED visit            | 1.70                            | 0.24                                | 2.30 (2.25–2.34)   | 4.19 (4.14–4.24)       |
| After propensity score matching         |                                 |                                     |                    |                        |
| Total AE                                | 11.20                           | 6.21                                | 1.39 (1.38–1.40)   | 1.39 (1.38–1.40)       |
| Severe AE                               | 2.44                            | 0.92                                | 2.05 (2.02–2.08)   | 2.05 (2.02–2.08)       |
| Severe AE requiring hospitalization     | 0.99                            | 0.33                                | 2.30 (2.24–2.36)   | 2.30 (2.25–2.36)       |
| Severe AE requiring ED visit            | 1.45                            | 0.59                                | 1.91 (1.87–1.94)   | 1.91 (1.87–1.95)       |

*: adjusted for propensity score. AE: acute exacerbation; ED: emergent department; IR: incidence rate; HR: hazard ratio; CI: confidence interval.

Regarding the effect on secondary outcomes, the sepsis group had higher risks of mortality (incidence rate: 23.75 per 100 person-days vs. 11.34 per 100 person-days, adjusted HR = 2.27, 95% confidence interval (CI), 2.14–2.41), pneumonia (incidence rate: 26.41 per 100 person-days vs. 10.34 per 100 person-days, adjusted HR = 2.70, 95% CI, 2.5–2.91), and serious pneumonia (incidence rate: 5.84 per 100 person-days vs. 1.98 per 100 person-days, adjusted HR = 2.89, 95% CI, 2.5–3.33) after propensity score matching compared with the non-sepsis group. These results were consistent to those before propensity score matching. In competing risk analysis performed by adjusting for mortality due to causes other than the outcomes of interest, sepsis was still significantly associated with pneumonia (sub-HR = 1.86, 95% CI, 1.75–1.98) and serious pneumonia (sub-HR = 2.09, 95% CI, 1.86–2.35) after matching (Table 3). Kaplan-Meier analysis for the cumulative incidence also yielded significant differences and higher risks of mortality (p < 0.001), pneumonia (p < 0.001), and serious pneumonia (p < 0.001) in the sepsis group (Figure 2).
Table 3. Incidence rates and risks of pneumonia, serious pneumonia of COPD patients comparing between sepsis and non-sepsis cohort before and after propensity score matching.

| Outcomes            | Event | Non-Sepsis Cohort Person-Days | Incidence Rate (Event/Person Days) | Event | Sepsis Cohort Person-Days | Incidence Rate (Event/Person Days) | Crude HR (95%CI) | Sub-HR *(95%CI) | Adjusted HR * (95%CI) |
|---------------------|-------|-------------------------------|-----------------------------------|-------|---------------------------|-----------------------------------|----------------|----------------|----------------------|
| **Before propensity score matching** Mortality | 11,229 | 260,716.08                    | 4.31%                             | 8479  | 27,981.77                 | 30.30%                            | 6.16 (5.99–6.34) | 2.21 (2.12–2.3) |
| Serious pneumonia   | 1779  | 258,983.85                    | 0.69%                             | 1750  | 25,806.44                 | 6.78%                             | 8.87 (8.3–9.48)  | 2.18 (1.96–2.42) |
| Pneumonia           | 10,245| 240,762.13                    | 4.26%                             | 5805  | 17,961.49                 | 32.32%                            | 6.37 (6.16–6.58) | 1.74 (1.65–1.83) |
| **After propensity score matching** Mortality | 2972  | 26,215.48                     | 11.34%                            | 4811  | 20,256.42                 | 23.75%                            | 2.28 (2.15–2.42) | 2.27 (2.14–2.41) |
| Serious pneumonia   | 509   | 25,758.90                     | 1.98%                             | 1098  | 18,700.63                 | 5.84%                             | 2.88 (2.5–3.33)  | 2.09 (1.86–2.35) |
| Pneumonia           | 2280  | 22,044.38                     | 10.34%                            | 3554  | 13,455.45                 | 26.41%                            | 2.69 (2.49–2.9)  | 2.7 (2.5–2.91)   |

*: Adjusting for mortality as competing risk; *: Adjusted for propensity score. HR, hazard ratio; sub-HR, subdistribution hazard ratio.
4. Discussion

This study compared two matched cohorts each with 8774 patients with COPD with or without sepsis, and found that the sepsis group had poorer outcomes due to higher risks of severe exacerbations, mortality, pneumonia, and serious pneumonia. After adjusting for mortality from causes other than the outcomes of interest as a competing risk and propensity score, the results still showed consistent findings. In addition, in subgroup analysis, the negative effect of sepsis on the outcomes of the patients with COPD remained significant.

This study has several strengths. Spirometry is crucial and the most objective diagnostic tool used to diagnose COPD [13]. In order to ensure the accuracy of the diagnosis of COPD, we only enrolled patients who received a pulmonary function test within one year before and after the COPD diagnosis was made. Patients were also excluded if the COPD diagnosis was altered after the pulmonary test. The 2016 Surviving Sepsis Campaign (SSC) guidelines and the published 3rd International Consensus Definitions for sepsis and septic shock (Sepsis-3) revised definitions of sepsis...
emphasize organ dysfunction related to a dysregulated host response to infection [5,14]. Although the Sequential Organ Failure Assessment (SOFA) or quick SOFA (qSOFA) score is currently the most commonly used scoring system, the most appropriate scoring system to assess organ dysfunction is controversial [14–16]. In this study, we defined sepsis according to ICD-9-CM codes including all infections with related acute organ dysfunction as validated in a previous study [17]. These selection criteria were more comprehensive and similar to a modern definition of sepsis. We also performed propensity score matching to minimize the effects of possible confounding variables, and therefore we believe our findings are more representative and generalized.

Sepsis is associated with a high rate of mortality, however the reported rate varies widely from 10–52% depending on the how the data are collected [18–20]. Sepsis is also associated with poor long-term outcomes and increased risks of death following discharge, recurrent infections, readmission and worse quality of life. An increased incidence of bacterial infection of both respiratory tract and non-respiratory tract (i.e., urinary tract) origin has been reported in patients with COPD [6]. This increased incidence may be due to the following factors: 1. impaired barrier function of the respiratory tract in COPD resulting in bacterial colonization in the airway; 2. systemic inflammatory characteristic of COPD associated with multiple comorbidities [21]; 3. the usage of corticosteroids and anticholinergic agents [10,22–24]; and 4. possible adverse behavior, especially smoking [25]. However, to the best of our knowledge, the effect of sepsis on COPD subgroups has not been investigated in detail in previous studies.

Although the most common cause of acute exacerbations in patients with COPD appears to be from the respiratory tract infection (viral or bacterial) [13,26], exacerbations do not always coexist with an acute infection. The ecological features of infection, including increased bacterial burden with low community diversity associated with multiple indices of host inflammation such as alveolar neutrophilia and increased alveolar concentration of catecholamines, are consistently lacking in patients with exacerbations of COPD. However, critical illnesses such as sepsis will alter the ecosystem of the body’s microbiota due to various pathophysiological (i.e., glucose and electrolyte disturbances, impairment in IgA production, loss of secreted antimicrobial peptides in the mucosal barrier or endogenous opioid production) and therapeutic (sedatives, opiates, and catecholamines) factors, and is clearly involved in the pathogenesis of subsequent frequent exacerbations [27]. Furthermore, sepsis-induced organ dysfunction, such as renal function impairment, central nervous system dysfunction, and muscle wasting, may also contribute to long-term disabilities and increase the risk of mortality in patients with COPD [7,28,29].

Currently, the most commonly used tool to assess COPD is based on the “ABCD” grouping re-defined by the 2017 Global Initiative for Chronic Obstructive Pulmonary Disease (GOLD) guidelines, which also recommends the choice of therapy [13]. The COPD assessment tool takes account of the presence and severity of abnormalities in spirometry, clinical symptoms, exacerbation history and comorbidities, but not the influence of previous sepsis. In light of the fact that the impact of sepsis on patients with COPD is significant, sepsis should not be neglected when making treatment decisions for patients with COPD. Several therapies and approaches have been shown to have beneficial impacts on sepsis, including statins, theophylline, macrolides, and vaccinations, and they may play a role in treatment for COPD [30–35]. On the other hand, the agents commonly used to control COPD which may increase the risk of infection including corticosteroids and anticholinergics, should be used more cautiously in select patients [10,22,23]. Additional large and well-designed studies with more in-depth research on the control and prevention of sepsis in patients with COPD are essential and may lead to a more comprehensive COPD treatment strategy.

There are several limitations to this study. First, the diagnosis of COPD was made according to ICD-9 codes, which were mainly registered by clinical physicians. Although the accuracy was confirmed by strict screening criteria in our study, and the reliability of ICD-9 codes has been validated in previous studies [17,36,37], this issue remains a concern. Secondly, COPD is now considered to be a disease with single or combined “phenotypes” that describe the differences between individuals [38,39].
However, the impact of sepsis on different phenotypes of COPD was not available in this study. Third, the risk of mortality from sepsis varies depending on the severity of sepsis and comorbidities, however the association between the severity of sepsis and different groups of COPD (i.e., “ABCD” groups) could not be determined in the present study. Fourth, the exact results of spirometry were not be available in NHIRD. Thus, we could not classify the severity of COPD in this study. However, we used the number of COPD exacerbation episodes as an indicator and matched this data between sepsis and non-sepsis cohort. Fifth, our study revealed a relatively high proportion of patients received oral steroid therapy. Even though it was a real-world condition in Taiwan, this could limit the generalizability of our findings. Finally, similar to other database studies, some possible confounding factors such as smoking, environmental factors, appropriateness of antimicrobial use for pneumonia, Medical Research Council (MRC) Dyspnea scale, radiologic findings of pneumonia, and compliance of orders which may also have affected the outcomes were lacking.

5. Conclusion

Under Taiwan’s NHI program, our investigation showed that sepsis survivors among patients with COPD had a higher risk of severe exacerbations, pneumonia, serious pneumonia, and mortality compared to patients with COPD without sepsis. In light of these important findings, the negative effects of sepsis on patients with COPD should be considered in clinical practice. Furthermore, more efforts should be put into the early detection and prevention of sepsis to improve the prognosis and quality of life in patients with COPD.

Author Contributions: C.-H.C. and C.-Y.W. are the guarantors of this paper. H.-C.W., C.-J.Y. and L.C. contributed to the study design and supervision of the work. C.-H.C. and C.-C. L. contributed to interpretation of the results of the study and wrote the manuscript. Y.-H.W. contributed to manuscript preparation and statistical analysis. C.-Y.W. contributed to the study design, manuscript preparation and editing.

Funding: This work was supported from National Science Council (NSC104-2314-B-002-185-MY2, 101-2325-B-002-064, 102-2325-B-002-087, 103-2325-B-002-027, 104-2325-B-002-035, 105-2325-B-002-030, 104-2314-B-567-002, 105-2314-B-567-001), Cardinal Tien Hospital (CTH107A-2A23) and from National Health Research Institutes (intramural funding).

Acknowledgments: This study is based in part on data from the National Health Insurance Research Database provided by the Bureau of National Health Insurance of the Department of Health, Taiwan, and managed by National Health Research Institutes, Taiwan. The sponsor had no role in the design of the study, the collection and analysis of the data, or the preparation of the manuscript. The Taiwan Clinical Trial Consortium for Respiratory Diseases (TCORE) includes Chong-Jen Yu (NTUH, Director of Coordinating Center and Core PI of Committee), Hao-Chien Wang (NTUH, PI of Committee), Diahn-Warng Perng (Taipei Veterans General Hospital, PI of Committee), Shih-Lung Cheng (Far Eastern Memorial Hospital, PI of Committee), Jeng-Yuan Hsu (Taichung Veterans General Hospital, PI of Committee), Wu-Huei Hsu (China Medical University Hospital, PI of Committee), Ying-Huang Tsai (Chang Gung Memorial Hospital, Chia-Yi, PI of Committee), Tzuen-Ren Hsiue (National Cheng Kung University Hospital, PI of Committee), Meng-Chih Lin (Chang Gung Memorial Hospital, Kaohsiung, PI of Committee), Yeun-Chung Chang (National Cheng Kung University Hospital, PI of Committee), Cheng-Yi Wang (Cardinal Tien Hospital, PI of Committee), Yeun-Chung Chang (NTUH, PI of Committee), Huo-Cheng Yang (National Yang-Ming University, PI of Committee), Chung-Ming Chen (NTU, PI of Committee), Cing-Syong Lin (Changhua Christian Hospital, PI of Committee), Likwang Chen (National Health Research Institutes, PI of Committee), Yu-Feng Wei (E-Da Hospital, PI of Committee), Inn-Wen Chong (Kaohsiung Medical University Chung-Ho Memorial Hospital, PI of Committee).

Conflicts of Interest: The authors declare no conflict of interest.
Abbreviations

TCORE  Taiwan Clinical Trial Consortium for Respiratory Diseases  
COPD  Chronic Obstructive Pulmonary Disease  
NHI  National Health Insurance  
NHIRD  National Health Insurance Research Database  
ICD-9-CM  International Classification of Diseases, Ninth Revision, Clinical Modification  
ACCP/SCCM  American College of Chest Physicians/Society of Critical Care Medicine  
CCI  Charlson comorbidity index  
NSAID  Non-Steroidal Anti-inflammatory Drug  
PPI  Proton-Pump Inhibitor  
LABA  Long-Acting Beta Agonist  
SABA  Short-Acting Beta Agonist  
LAMA  Long-Acting Muscarinic Antagonist  
ICS  Inhaled Corticosteroid  
ACEi  Angiotensin-Converting-Enzyme inhibitors  
ARB  Angiotensin Receptor Blocker  
HR  Hazard ratios  
sub-HR  subdistribution HRs  
SSC  Surviving Sepsis Campaign  
SOFA  Sequential Organ Failure Assessment  
GOLD  Global Initiative for Chronic Obstructive Pulmonary Disease  

References

1. Lozano, R.; Naghavi, M.; Foreman, K.; Lim, S.; Shibuya, K.; Aboyans, V.; Abraham, J.; Adair, T.; Aggarwal, R.; Ahn, S.Y.; et al. Global and regional mortality from 235 causes of death for 20 age groups in 1990 and 2010: A systematic analysis for the Global Burden of Disease Study 2010. *Lancet* **2012**, *380*, 2095–2128. [CrossRef]  
2. Seemungal, T.A.; Donaldson, G.C.; Paul, E.A.; Bestall, J.C.; Jeffries, D.J.; Wedzicha, J.A. Effect of exacerbation on quality of life in patients with chronic obstructive pulmonary disease. *Am. J. Respir. Crit. Care Med.* **1998**, *157*, 1418–1422. [CrossRef] [PubMed]  
3. Monso, E.; Ruiz, J.; Rosell, A.; Manterola, J.; Fiz, J.; Morera, J.; Ausina, V. Bacterial infection in chronic obstructive pulmonary disease. A study of stable and exacerbated outpatients using the protected specimen brush. *Am. J. Respir. Crit. Care Med.* **1995**, *152*, 1316–1320. [CrossRef] [PubMed]  
4. Ling, S.H.; van Eeden, S.F. Particulate matter air pollution exposure: role in the development and exacerbation of chronic obstructive pulmonary disease. *Int. J. Chron. Obstruct. Pulmon. Dis.* **2009**, *4*, 233–243. [CrossRef] [PubMed]  
5. Rhodes, A.; Evans, L.E.; Alhazzani, W.; Levy, M.M.; Antonelli, M.; Ferrer, R.; Kumar, A.; Sevransky, J.E.; Sprung, C.L.; Nunnally, M.E.; et al. Surviving sepsis campaign: International guidelines for management of sepsis and septic shock: 2016. *Intens. Care Med.* **2017**, *43*, 304–377. [CrossRef] [PubMed]  
6. Inghammar, M.; Engstrom, G.; Ljungberg, B.; Lofdahl, C.G.; Roth, A.; Egesten, A. Increased incidence of invasive bacterial disease in chronic obstructive pulmonary disease compared to the general population—A population based cohort study. *BMC Infect. Dis.* **2014**, *14*, 163–170. [CrossRef] [PubMed]  
7. Liao, K.M.; Lin, T.C.; Li, C.Y.; Yang, Y.H. Dementia increases severe sepsis and mortality in hospitalized patients with chronic obstructive pulmonary disease. *Medicine* **2015**, *94*. [CrossRef] [PubMed]  
8. Chen, C.H.; Huang, K.Y.; Wang, J.Y.; Huang, H.B.; Chou, P.; Lee, C.C. Combined effect of individual and neighbourhood socioeconomic status on mortality of rheumatoid arthritis patients under universal health care coverage system. *Fam. Pract.* **2015**, *32*, 41–48. [CrossRef] [PubMed]  
9. Yang, H.H.; Lai, C.C.; Wang, Y.H.; Yang, W.C.; Wang, C.Y.; Wang, H.C.; Chen, L.; Yu, C.J. Severe exacerbation and pneumonia in COPD patients treated with fixed combinations of inhaled corticosteroid and long-acting beta2 agonist. *Int. J. Chron. Obstruct. Pulmon. Dis.* **2017**, *12*, 2477–2485. [CrossRef] [PubMed]  
10. Wang, C.Y.; Lai, C.C.; Yang, W.C.; Lin, C.C.; Chen, L.; Wang, H.C.; Yu, C.J. The association between inhaled corticosteroid and pneumonia in COPD patients: the improvement of patients’ life quality with COPD in Taiwan (IMPACT) study. *Int. J. Chron. Obstruct. Pulmon. Dis.* **2016**, *11*, 2775–2783. [CrossRef] [PubMed]
11. Lai, C.C.; Lee, M.G.; Lee, W.C.; Chao, C.C.; Hsu, T.C.; Lee, S.H.; Lee, C.C.; National Taiwan University Hospital Health Data Science Research Group. Susceptible period for cardiovascular complications in patients recovering from sepsis. *CMAJ* **2018**, *190*, 1062–1069. [CrossRef] [PubMed]
12. Huang, B.; Yang, Y. Radiofrequency catheter ablation of atrial fibrillation in patients with chronic obstructive pulmonary disease: Opportunity and challenge: Response to Dr. Kumar’s comment. *J. Am. Med. Dir. Assoc.* **2015**, *16*, 83–84. [CrossRef] [PubMed]
13. Vogelmeier, C.F.; Criner, G.J.; Martinez, F.J.; Anzueto, A.; Barnes, P.J.; Bourbeau, J.; Celli, B.R.; Chen, R.; Decramer, M.; Fabbri, L.M.; et al. Global strategy for the diagnosis, management, and prevention of chronic obstructive lung disease 2017 Report. GOLD executive summary. *Am. J. Respir. Crit. Care Med.* **2017**, *195*, 557–582. [CrossRef] [PubMed]
14. Singer, M.; Deutschman, C.S.; Seymour, C.W.; Shankar-Hari, M.; Annane, D.; Bauer, M.; Bellomo, R.; Bernard, G.R.; Chiche, J.D.; Coopersmith, C.M.; et al. The third international consensus definitions for sepsis and septic shock (sepsis-3). *JAMA* **2016**, *315*, 801–810. [CrossRef] [PubMed]
15. Siddiqui, S.; Chua, M.; Kumares, V.; Choo, R. A comparison of pre ICU admission SIRS, EWS and q SOFA scores for predicting mortality and length of stay in ICU. *J. Crit. Care* **2017**, *41*, 191–193. [CrossRef] [PubMed]
16. Serafim, R.; Gomes, J.A.; Salluh, J.; Povoa, P. A comparison of the Quick-SOFA and systemic inflammatory response syndrome criteria for the diagnosis of sepsis and prediction of mortality: A systematic review and meta-analysis. *Chest* **2018**, *153*, 646–655. [CrossRef] [PubMed]
17. Shen, H.N.; Lu, C.L.; Yang, H.H. Epidemiologic trend of severe sepsis in Taiwan from 1997 through 2006. *Chest* **2010**, *138*, 298–304. [CrossRef] [PubMed]
18. Martin, G.S.; Mannino, D.M.; Eaton, S.; Moss, M. The epidemiology of sepsis in the United States from 1979 through 2000. *N. Engl. J. Med.* **2003**, *348*, 1546–1554. [CrossRef] [PubMed]
19. Kaukonen, K.M.; Bailey, M.; Suzuki, S.; Pilcher, D.; Bellomo, R. Mortality related to severe sepsis and septic shock among critically ill patients in Australia and New Zealand, 2000–2012. *JAMA* **2014**, *311*, 1308–1316. [CrossRef] [PubMed]
20. Dombrovskiy, V.Y.; Martin, A.A.; Sunderram, J.; Paz, H.L. Rapid increase in hospitalization and mortality rates for severe sepsis in the United States: A trend analysis from 1993 to 2003. *Crit. Care Med.* **2007**, *35*, 1244–1250. [CrossRef] [PubMed]
21. Barnes, P.J.; Celli, B.R. Systemic manifestations and comorbidities of COPD. *Eur. Respir. J.* **2009**, *33*, 1165–1185. [CrossRef] [PubMed]
22. Drummond, M.B.; Dassenbrook, E.C.; Pitz, M.W.; Murphy, D.J.; Fan, E. Inhaled corticosteroids in patients with stable chronic obstructive pulmonary disease: A systematic review and meta-analysis. *JAMA* **2008**, *300*, 2407–2416. [CrossRef] [PubMed]
23. Yang, L.A.; Clarke, M.S.; Sim, E.H.; Fong, K.M. Inhaled corticosteroids for stable chronic obstructive pulmonary disease. *Cochrane Database Syst. Rev.* **2012**. [CrossRef] [PubMed]
24. Barr, R.G.; Bourbeau, J.; Camargo, C.A.; Ram, F.S. Tiotropium for stable chronic obstructive pulmonary disease: A meta-analysis. *Thorax* **2006**, *61*, 854–862. [CrossRef] [PubMed]
25. Arcavi, L.; Benowitz, N.L. Cigarette smoking and infection. *Arch. Intern. Med.* **2004**, *164*, 2206–2216. [CrossRef] [PubMed]
26. Sethi, S.; Murphy, T.F. Infection in the pathogenesis and course of chronic obstructive pulmonary disease. *N. Engl. J. Med.* **2008**, *359*, 2355–2365. [CrossRef] [PubMed]
27. Dickson, R.P. The microbiome and critical illness. *Lancet Respir. Med.* **2016**, *4*, 59–72. [CrossRef]
28. Joannidis, M.; Druml, W.; Forni, L.G.; Groeneveld, A.B.J.; Honore, P.M.; Hoste, E.; Ostermann, M.; Oudemans-van Straaten, H.M.; Schetz, M. Prevention of acute kidney injury and protection of renal function in the intensive care unit: Update 2017. *Intensive Care Med.* **2017**, *43*, 730–749. [CrossRef] [PubMed]
29. Kollmar, R. Critical illness polyneuropathy and myopathy as neurological complications of sepsis. *Nervenarzt* **2016**, *87*, 236–245. [CrossRef] [PubMed]
30. Almog, Y.; Shefer, A.; Novack, V.; Maimon, N.; Barski, L.; Eizinger, M.; Friger, M.; Zeller, L.; Danon, A. Prior statin therapy is associated with a decreased rate of severe sepsis. *Circulation* **2004**, *110*, 880–885. [CrossRef] [PubMed]
31. Shih, Y.N.; Chen, Y.T.; Chu, H.; Shih, C.J.; Ou, S.M.; Hsu, Y.T.; Chen, R.C.; Quraishi, S.A.; Aisiku, I.P.; Seethala, R.R.; et al. Association of pre-hospital theophylline use and mortality in chronic obstructive pulmonary disease patients with sepsis. *Respir. Med.* **2017**, *125*, 33–38. [CrossRef] [PubMed]
32. Ni, W.; Shao, X.; Cai, X.; Wei, C.; Cui, J.; Wang, R.; Liu, Y. Prophylactic use of macrolide antibiotics for the prevention of chronic obstructive pulmonary disease exacerbation: A meta-analysis. PLoS ONE 2015, 10. [CrossRef] [PubMed]

33. Wedzicha, J.A.; Calverley, P.M.A.; Albert, R.K.; Anzueto, A.; Criner, G.J.; Hurst, J.R.; Miravitlles, M.; Papi, A.; Rabe, K.F.; Rigau, D.; et al. Prevention of COPD exacerbations: A European respiratory society/American thoracic society guideline. Eur. Respir. J. 2017, 50. [CrossRef] [PubMed]

34. Seemungal, T.A.; Wilkinson, T.M.; Hurst, J.R.; Perera, W.R.; Sapsford, R.J.; Wedzicha, J.A. Long-term erythromycin therapy is associated with decreased chronic obstructive pulmonary disease exacerbations. Am. J. Respir. Crit. Care Med. 2008, 178, 1139–1147. [CrossRef] [PubMed]

35. Bekkat-Berkani, R.; Wilkinson, T.; Buchy, P.; Dos Santos, G.; Stefanidis, D.; Devaster, J.M.; Meyer, N. Seasonal influenza vaccination in patients with COPD: A systematic literature review. BMC Pulm. Med. 2017, 17, 79. [CrossRef] [PubMed]

36. Chang, C.H.; Lee, Y.C.; Tsai, C.T.; Chang, S.N.; Chung, Y.H.; Lin, M.S.; Lin, J.W.; Lai, M.S. Continuation of statin therapy and a decreased risk of atrial fibrillation/flutter in patients with and without chronic kidney disease. Atherosclerosis 2014, 232, 224–230. [CrossRef] [PubMed]

37. Lin, L.J.; Cheng, M.H.; Lee, C.H.; Wung, D.C.; Cheng, C.L.; Kao Yang, Y.H. Compliance with antithrombotic prescribing guidelines for patients with atrial fibrillation—a nationwide descriptive study in Taiwan. Clin. Ther. 2008, 30, 1726–1736. [CrossRef] [PubMed]

38. Mirza, S.; Benzo, R. Chronic Obstructive Pulmonary Disease Phenotypes: Implications for Care. Mayo Clin. Proc. 2017, 92, 1104–1112. [CrossRef] [PubMed]

39. Pinto, L.M.; Alghamdi, M.; Benedetti, A.; Zaihra, T.; Landry, T.; Bourbeau, J. Derivation and validation of clinical phenotypes for COPD: A systematic review. Respir. Res. 2015, 16, 50. [CrossRef] [PubMed]

© 2018 by the authors. Licensee MDPI, Basel, Switzerland. This article is an open access article distributed under the terms and conditions of the Creative Commons Attribution (CC BY) license (http://creativecommons.org/licenses/by/4.0/).