Different Pattern of Viral Infections and Clinical Outcomes in Patient With Acute Exacerbation of Chronic Obstructive Pulmonary Disease and Chronic Obstructive Pulmonary Disease With Pneumonia

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Respiratory viruses are well-known causes of acute exacerbation of chronic obstructive pulmonary disease (AE-COPD) and also important pathogens for concomitant pneumonia in COPD (CP-COPD). However, the differences in a viral infection pattern and clinical impacts of respiratory viruses between the two groups have not been well investigated. The clinical and microbiological data from COPD patients admitted with AE-COPD (n = 281) or CP-COPD (n = 284) between January 2010 and December 2012 were reviewed. After excluding 88 patients (40 with AE-COPD and 48 with CP-COPD) who did not undergo a multiplex RT-PCR test for respiratory viruses, the demographic characteristics, identified viruses, and clinical outcomes of the AE-COPD and CP-COPD groups were compared. Respiratory viruses were identified in 41.9% of AE-COPD group and 33.5% of the CP-COPD groups. The most common virus was influenza virus in the AE-COPD group (33.7%) versus human coronavirus (24.1%) in the CP-COPD group. Influenza virus was significantly more common in the AE-ACOPD group and 33.5% of the CP-COPD groups. The most common virus was influenza virus in the AE-COPD group (33.7%) versus human coronavirus (24.1%) in the CP-COPD group. Influenza virus was significantly more common in the AE-ACOPD group than in the CP-COPD group (P < 0.01). In-hospital mortality of AE-COPD and CP-COPD were 1.2% and 12.3%, respectively (P < 0.01). Among CP-COPD patients, in-hospital mortality of patients with only viral infection group, only bacterial infection group, and viral-bacterial co-infection were 2.6%, 25.8%, and 17.5%, respectively (P = 0.01). Respiratory viruses were commonly identified in both AE-COPD and CP-COPD, influenza virus and human coronavirus were the most common viruses identified in AE-COPD and CP-COPD patients, respectively. The mortality rates of only viral infection group was significantly lower than only bacterial infection or viral-bacterial co-infection group in CP-COPD patients. J. Med. Virol. 88:2092–2099, 2016.

KEY WORDS: acute exacerbation; COPD; outcome; pneumonia; respiratory virus

INTRODUCTION

Chronic obstructive pulmonary disease (COPD) is one of the leading global causes of mortality and morbidity [Pingleton et al., 1992; Pena et al., 2000]. According to a recent study, the overall prevalence of COPD has been estimated as high as 10% of the population.

Abbreviations: AE, acute exacerbation; BAL, bronchoalveolar lavage; COPD, chronic obstructive pulmonary disease; CP, concomitant pneumonia; FEV1, forced expiratory volume in 1 sec; FVC, forced vital capacity; GOLD, global initiative for chronic obstructive lung disease; SD, standard deviation

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world’s population [Soriano et al., 2010]. Acute exacerbation of COPD (AE-COPD) and concomitant pneumonia in COPD (CP-COPD) are two serious conditions that often complicate COPD [Wedzicha and Seemungal, 2007; Mullerova et al., 2012]. Respiratory viruses are a well-known cause of AE-COPD, which are responsible for 39–56% of AE-COPD [Seemungal et al., 2001; Rohde et al., 2003]. Recently, newly discovered respiratory viruses such as human metapneumovirus, human coronavirus NL63 and HKU1, and bocavirus have been added as important causes of AE-COPD [Ringshausen et al., 2009; Kherad et al., 2010]. Also, with the development and application of technology to detect viral nucleic acid, the detection of respiratory viruses in AE-COPD has markedly improved [Mohan et al., 2010].

On the other hand, the role of respiratory viruses in CP-COPD has not been well investigated. Until recently, there have been only a few reports on the role of respiratory viruses in CP-COPD patients [Mallia and Johnston, 2007; Ko et al., 2008; Molinos et al., 2009; Vanspauwen et al., 2012]. Moreover, these previous studies have several limitations. Some were focused on a specific virus such as influenza virus [Mallia and Johnston, 2007] or an RT-PCR test was performed in only small portion of the studies patients [Ko et al., 2008; Molinos et al., 2009]. Furthermore, to the best our knowledge, none of the prior studies compared the viral etiologies and their clinical outcomes between AE-COPD and CP-COPD. We aimed to investigate the distributions and clinical impact of respiratory viruses in AE-COPD and CP-COPD patients.

**METHODS**

**Study Setting, Patients, and Data Collection**

This retrospective cohort study was performed at Asan Medical Center, a 2,700-bed tertiary referral hospital in Seoul, Republic of Korea. The current study focused on COPD patients admitted from January 2010 to December 2012. All patients admitted to hospital due to COPD during study period were screened, and all those diagnosed with AE-COPD or CP-COPD were included in the study (see below for definitions). Data regarding clinical outcomes and microbiologic results were collected according to a standardized protocol. If a patient was admitted to the hospital more than once during study period, only the first admission was included in the AE-COPD or CP-COPD groups. Also, all clinical samples obtained from patients within first 72 hr after admission were included in the study. The study protocol was approved by the Institutional Review Board of Asan Medical Center. Informed consent was waived due to the retrospective nature of this study.

**Definitions**

Diagnosis and severity of COPD were defined by the Global Initiative for Chronic Obstructive Lung Disease (GOLD) guidelines [Vestbo et al., 2013]. AE-COPD was defined clinically by presentation of at least two of the following symptoms; increased shortness of breath, increased sputum volume and purulence with no definite pneumatic infiltration on chest X-ray [Anthonisen et al., 1987]. CP-COPD is defined as a pneumonia in COPD patients. Pneumonia was defined as the presence of a new radiographic pulmonary infiltration plus two or more of the following; (i) fever (38.5°C or higher) or hypothermia (<36.5°C); (ii) leukocytosis or leukopenia (white blood cells >10,000/mm³ or <4,000/mm³); or (iii) purulent tracheal aspirate or sputum [Pingleton et al., 1992; Mandell et al., 2007].

**Microbiologic Evaluation**

Microbiological examination included a gram stain and culture of sputum, endotracheal aspirates, or bronchoalveolar lavage (BAL) fluid, blood cultures, and a Binax Now urinary antigen test for *Streptococcus pneumoniae* and *Legionella pneumophila* serogroup 1 (Binax Inc., Portland, ME). A PCR assay using BD ProbeTec ET Atypical Pneumonia Assay (Becton Dickinson Diagnostic Systems, Sparks, MD) was used to detect atypical pathogens including *Mycoplasma pneumoniae*, *Chlamydia pneumoniae*, and *L. pneumophila*. For viral detection, a multiplex RT-PCR kit (Seeplex 15RV ACE Detection kit, Seegene Inc., Seoul, Korea) for influenza virus A and B, respiratory syncytial virus A and B, adenovirus, human metapneumovirus, parainfluenza virus types 1 to 4, enterovirus, rhinovirus, human coronavirus 229E/ NL63, OC43, HKU1 were used. The RT-PCR kit used in this study has been validated in published studies [Bibby et al., 2011; Gharabaghi et al., 2011].

**Statistical Analysis**

Data from the AE-COPD and CP-COPD groups were compared using the Student’s t-test or Mann–Whitney U test (continuous variables) and the χ² test or Fisher’s exact test (categorical data). Also, multivariate logistic regression analysis was performed to identify independent risk factors for mortality, particularly in CP-COPD patients. Variables showing a reasonable relationship with mortality or with P-values less than 0.2 in the univariate analysis were included in the multivariate analysis. The results were expressed as adjusted odds ratios (aORs) with 95% confidence intervals (CIs). Furthermore, we performed a separate χ² test for in-hospital mortality in CP-COPD patients with different etiologies. All P-values were two-tailed and statistical significance was set at P < 0.05. All statistical analyses were performed using SPSS version 18.0 for Windows (IBM SPSS, Inc., Chicago, IL).
RESULTS

Patients

During the 3-year-study period, a total of 1,628 COPD patients were admitted to Asan Medical Center. Of these patients, 281 patients were classified to the AE-COPD group and 284 patients were classified to the CP-COPD group. After excluding 88 patients (40 with AE-COPD and 48 with CP-COPD) who did not undergo a multiplex RT-PCR test for respiratory viruses, 241 AE-COPD patients and 236 CP-COPD patients were finally included for analysis.

Baseline Characteristics and Initial Laboratory Data

Table I shows the baseline characteristics of patients and laboratory data. The mean age (±SD) was 71.9 (±9.3) and 412 patients (86.4%) were male. Diabetes mellitus was the most common comorbidity, followed by congestive heart failure, and malignancy. Congestive heart failure tended to be more common in the AE-COPD group (14.5% vs. 8.9%, P = 0.06). Recent FEV$_1$ was significantly lower in the AE-COPD than that in the CP-COPD group (47.6% predicted value vs. 53.1%, P = 0.01). The AE-COPD patients were also more likely to receive systemic steroid treatment (12.8% vs. 5.1%, P < 0.01) and to be on home oxygen therapy at the time of admission (13.3% vs. 7.2%, P = 0.02). Median values of white blood cells counts, C-reactive protein (CRP) level, and procalcitonin level were significantly higher in the CP-COPD patients. Other baseline characteristics are shown in Table SI.

Distribution of Pathogens Identified

We analyzed with all respiratory samples. Respiratory samples comprised nasal swabs or sputum samples (n = 384), BAL only (n = 33), or both (n = 60). Table II includes the distributions of the pathogens identified. One or more respiratory pathogens were identified in 112 AE-COPD patients (46.5%) and 145 CP-COPD patients (61.4%) (P < 0.01). Among the AE-COPD patients, 101 patients had viral infections (41.9%, 101/241), 53 had bacterial infections (22.0%, 53/241), and 42 had

| TABLE I. Baseline Characteristics and Initial Laboratory Data of 477 COPD Patients |
|-----------------------------------|----------------|----------------|----------------|----------|
| Total   | AE-COPD (n = 241) | CP-COPD (n = 236) | P-value |
| Age     | 71.9 ± 9.3        | 71.1 ± 9.5       | 72.8 ± 9.1 | 0.66     |
| Male sex | 412 (86.4)%       | 201 (83.4)       | 211 (89.4) | 0.06     |
| Smoking | 35.9 ± 25.9       | 35.4 ± 26.0      | 36.5 ± 26.0 | 0.64     |

Comorbidity

| Diabetes mellitus | 66 (13.8) | 29 (12.0) | 37 (15.7) | 0.25     |
| Congestive heart failure | 56 (11.7) | 35 (14.5) | 21 (8.9) | 0.06     |
| Malignancy | 39 (8.2) | 17 (7.1) | 22 (9.3) | 0.56     |
| Cerebrovascular attack | 18 (3.8) | 10 (4.1) | 8 (3.4) | 0.68     |
| Liver cirrhosis | 9 (1.9) | 7 (2.9) | 2 (0.9) | 0.10     |
| Chronic renal failure | 6 (1.3) | 2 (0.8) | 4 (1.7) | 0.39     |
| Immunosuppressed hosts | 60 (12.6) | 36 (14.9) | 24 (10.2) | 0.12     |

Pulmonary function test (within 6 months, % predicted)

| FEV$_1$ | 50.6 ± 19.8 | 47.6 ± 20.3 | 53.1 ± 19.1 | 0.01     |

GOLD stage

| Mild | 27 (8.6) | 9 (6.2) | 18 (10.7) | 0.09     |
| Moderate | 127 (40.4) | 53 (36.6) | 74 (43.8) | 0.09     |
| Severe | 113 (36.0) | 55 (37.9) | 58 (34.3) | 0.09     |
| Very severe | 47 (15.0) | 28 (19.3) | 19 (11.2) | 0.11     |
| Admission to ICU | 65 (13.2) | 26 (10.8) | 37 (15.7) | 0.11     |

Laboratory data on admission

| Oxygen saturation (%) on ABGA or pulse oxymetry | 94 (89–96) | 93 (88–96) | 94 (90–97) | 0.06     |
| White blood cells, mm$^3$ | 10100 (7500–13450) | 9300 (7500–12700) | 10500 (7525–14250) | 0.02     |
| C-reactive protein, mg/dl | 4.53 (0.99–12.52) | 2.52 (0.44–7.20) | 7.21 (2.31–17.30) | <0.01     |
| Procalcitonin, ng/ml | 0.20 (0.05–0.87) | 0.11 (0.05–0.39) | 0.36 (0.08–2.23) | <0.01     |

AE-COPD, acute exacerbation of COPD; CP-COPD, concomitant pneumonia in COPD; FEV$_1$, forced expiratory volume in 1 sec; GOLD, global initiative for chronic obstructive lung disease.

P-values are extracted by comparing between AE-COPD versus CP-COPD group.

Values are reported as mean ± SD, median (25th–75th Percentiles) or as frequency (%).

Pack years was evaluated in ever-smoker only.

Immunosuppressed hosts as follows: (i) daily administration of corticosteroids (at least 5 mg per day of prednisolone or an equivalent drug); (ii) solid organ or hematopoietic stem cell transplant recipients; (iii) patients that received chemotherapy for an underlying malignancy during the last 6 months; and (iv) patients with an underlying acquired immune deficiency disorder.

Pulmonary function test was done in 314 patients (AECOPD; 145 patients, COPD pneumonia; 169 patients).

Oxygen saturation was recorded on room air.
viral-bacterial co-infections (17.4%, 42/241). Among the CP-COPD patients, 79 patients had viral infections (33.5%, 79/236), 106 had bacterial infections (44.0%, 106/236), and 40 had viral-bacterial co-infections (16.9%, 40/236). Also, viral co-infections were identified in 7.5% (18/241) of patients in the AE-COPD group and in 4.7% (11/236) of patients in the CP-COPD group. Bacterial co-infections were identified in 3.3% (8/241) of patients in the AE-COPD group and in 7.6% (18/236) of patients in the CP-COPD group.

Table II indicates the distributions of viral pathogens identified in both groups. Viral infections tended to be more common in the AE-COPD group ($P = 0.06$). Influenza virus (n = 34) was the most commonly identified virus in the AE-COPD group, followed by rhinovirus (n = 25), parainfluenza virus (n = 23), and human coronavirus (n = 15). In contrast, human coronavirus was the most common virus in the CP-COPD group (n = 19), followed by rhinovirus (n = 18), parainfluenza virus (n = 17), and influenza virus (n = 15). Influenza virus was significantly more common in the AE-COPD group than in the CP-COPD group (14.1% [34/241] vs. 6.4% [15/236], $P < 0.01$). Almost all of the influenza virus types identified in the two groups were type A (33/34 in AE-COPD and 13/15 in CP-COPD).

Table II also lists the distributions of bacterial pathogens in both groups. Bacterial infections were significantly more common in the CP-COPD group ($P < 0.01$). *S. pneumoniae* (n = 16) was the most commonly identified in the AE-COPD group, followed by *Pseudomonas aeruginosa* (n = 11),
Klebsiella pneumoniae (n = 9), and Staphylococcus aureus (n = 8). By contrast, S. aureus was the most common bacteria in the CP-COPD group (n = 24), followed by Acinetobacter baumannii (n = 21), P. aeruginosa (n = 21), and K. pneumonia (n = 17). S. aureus and A. baumannii were significantly more common in the CP-COPD group than in the AE-COPD group (P < 0.01).

Seasonal Distribution

Figure 1 shows the seasonal distribution of admitted patients during the study period. The number of admitted patients was largest during the winter season (December to February) in both groups. Figure S1 shows the seasonal distribution of each viral pathogen in AE-COPD and CP-COPD. Influenza virus predominated from December to February. Parainfluenza virus and human coronavirus were mainly present from May to November and from January to June, respectively. Human metapneumovirus peaked in the spring season (April and May). Rhinovirus and respiratory syncytial virus were present throughout the year with a little winter season dominancy.

Clinical Outcomes

Table III compares the clinical outcomes between the AE-COPD and CP-COPD groups. Despite an initial ICU admission rate that was not significantly different between the groups (10.8% vs. 15.7%, P = 0.12), CP-COPD patients initially admitted to the general ward were more likely to need ICU care than AE-COPD patients during a hospital stay (1.7% vs. 8.5%, P < 0.01). Among patients who needed ICU care, the median length of an ICU stay (4 vs. 11 days, P < 0.01) and total mechanical ventilation time (100 hr vs. 300 hr, P < 0.01) were significantly longer in the CP-COPD group. Median hospital stay was significantly longer in the CP-COPD group (7 vs. 9 days, P < 0.01) and in-hospital mortality was significantly higher in the CP-COPD group (1.2% vs. 12.3%, P < 0.01). Among CP-COPD patients, in-hospital mortalities of patients with only viral infection group, only bacterial infection group, and a viral-bacterial co-infection were 2.6%, 25.8%, and 17.5%, respectively (P < 0.01) (Table SII). However, there was no difference in in-hospital mortality between these same groups among AE-COPD patients (P = 0.45) (Table SIII). The results of a separate \( \chi^2 \) test conducted using data about in-hospital mortality among CP-COPD patients revealed that the only viral infection group had a significantly better outcome than the only bacterial infection (P < 0.01) or viral bacterial co-infection (P < 0.03) groups. However, in-hospital mortality rates of patients with bacterial infection alone and those with viral-bacterial co-infections were not significantly different (P = 0.35). Univariate logistic regression analysis identified single viral infection as a significant independent predictor of 28 day mortality in CP-COPD patients (hazard ratio, 0.090; 95% CI, 0.012–0.689; P = 0.02). Single viral infection remained a significant predicting factor in multivariate logistic regression analysis (hazard ratio, 0.095; 95% CI, 0.012–0.740; P = 0.03) (Table SIV).

DISCUSSION

Our current study investigated the distributions of respiratory viruses and the clinical impacts of respiratory viral infections in AE-COPD versus CP-COPD. While respiratory viruses were frequently identified in both AE-COPD (41.9%) and CP-COPD (33.5%), the distribution of identified viruses between two groups showed different patterns. Influenza virus was the most common pathogen in AE-COPD versus human coronavirus in CP-COPD. Rhinovirus has been reported as the most common cause of AE-COPD in the majority of prior investigations [Seemungal et al., 2001; Rohde et al., 2003; Hutchinson et al., 2007; McManus et al., 2008; Hershenson, 2013], although human metapneumovirus [Martinello et al., 2006] or respiratory syncytial virus [Dimopoulos et al., 2012] occasionally have been reported as the most common cause. Here, we found that influenza virus (14.1%) was the most commonly identified virus in the AE-COPD group, followed by rhinovirus (10.4%). The Hong Kong group also showed that influenza virus was most commonly identified in AE-COPD patients [Ko et al., 2008]. However, these findings should be interpreted with caution as both studies included AE-COPD patients who were admitted to general hospitals. Therefore, a bias might have been introduced if less severely affected patients did not come to our tertiary care hospital.

Unexpectedly, human coronavirus was the most commonly identified virus in our CP-COPD group, which has not been reported before. Excluding outbreaks of severe acute respiratory syndrome (SARS)-coronavirus [Peiris et al., 2003] or Middle East respiratory syndrome (MERS)-coronavirus [Assiri et al., 2013],
human coronavirus have never been regarded as a common cause of pneumonia. The presence of viruses in pneumonia patients does not necessarily mean that these viruses are the true pathogen of pneumonia. In our current study, of the 19 CP-COPD patients with human coronavirus infection, 12 (63.2%) had bacterial co-infection, including six with *S. aureus* and two with *S. pneumoniae*. A prior report showed that there was an increase in *S. aureus* acquisition during the SARS period [Yap et al., 2004]. Recently, a Polish group reported that human coronavirus NL63 increases the streptococcal adherence to respiratory epithelial cells [Golda et al., 2011], and that human coronavirus NL63 infection is associated with an increase in platelet-activating factor receptor (PAF-R) expression, which promotes adherence of *S. pneumoniae*. Our study supports the work by Golda et al. who saw the same events but in an in vitro assay. These findings suggest that human coronavirus infection might be associated with a risk of pneumonia development through bacterial co-infection in COPD patients. Further studies will be needed to confirm this result.

Regarding the bacterial pathogens identified in our present investigation, *S. aureus* and *A. baumannii* were significantly more commonly identified in the CP-COPD group than the AE-COPD group. These bacteria are a well-known cause of health-care associated pneumonia (HCAP) or hospital acquired pneumonia (HAP) [Yoo et al., 2013]. However, *A. baumannii* has not been listed as the cause of AE-COPD and *S. aureus* is an uncommon cause of AE-COPD (approximately 0–6%) [Domenech et al., 2013; Reissig et al., 2013]. Exposure to recent antibiotics during hospital stay might have influenced the type of pathogen, and more than 20% of CP-COPD patients were hospital-acquired infections or health care associated pneumonia. The patients in the CP-COPD with *S. aureus* group received antibiotics more frequently than those in the other pathogen group (62.5% [15/24] vs. 11.0% [9/82], \( P < 0.01 \)). In addition, previous studies performed in Korea showed that *S. aureus* and *A. baumannii* are important pathogens, particularly in HCAP and HAP patients (with ranges of 6.1–19.8% and 2.0–16.0%, respectively) [Choi et al., 2012; Hong et al., 2014].

Although AE-COPD patients have a greater severity of disease than CP-COPD patients in baseline pulmonary function test, CP-COPD patients were associated with poorer clinical outcomes than AE-COPD patients, in terms of length of hospital stay and in hospital mortality. We found that few investigators to date have compared the outcomes between AE-COPD and CP-COPD. Recently, a Spanish group compared the clinical outcomes between 133 AE-COPD patients and 116 CP-COPD patients [Huerta et al., 2013]. Similar to the results of our study, AE-COPD patients had a greater severity of disease than CP-COPD patients. However, in their results, in-hospital mortalities of AE-COPD group and CP-COPD group were 3.0% and 3.4%, respectively, which are quite different from those of our patients especially in the CP-COPD group (1.2% in the AE-COPD group and 12.3% in the CP-COPD group). We thought that these differences might reflect a different severities of illness in the two patient populations. The ICU admission rate of patients between two groups were different (in the Spanish study 3.8% in the AE-COPD group, 2.6% in the CP-COPD group versus 10.8% and 15.7% of the our studied patients in each). This difference might explain the outcome difference between the two groups.

Among patients with a viral infection, with regard to bacterial co-infection, 41.6% of our AE-COPD patients and 50.6% of our CP-COPD patients had a bacterial co-infection, respectively. Notably, among our CP-COPD patients, only viral infection group had significantly better outcomes than the only bacterial infection group or the viral bacterial co-infection group. This finding suggests that when bacterial co-infection complicates viral infection, it can lead to poorer outcomes. However, according to a separate \( \chi^2 \) test, the mortality rates of patients with bacterial infection alone and virus–bacteria co-infection were not significantly different. Thus, it seems that the impact of viral infection on the mortality of CP-COPD patients with bacterial infection may not

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**TABLE III.** Comparison of Clinical Outcome Between AE-COPD and CP-COPD

| Outcome                        | Total (n = 477) | AE-COPD (n = 241) | CP-COPD (n = 236) | P-value |
|-------------------------------|----------------|------------------|------------------|---------|
| Admission to ICU              | 63 (13.2)*     | 26 (10.8)        | 37 (15.7)        | 0.12    |
| ICU transfer during hospital stay | 24 (5.0)    | 4 (1.7)          | 20 (8.5)         | <0.01   |
| Mechanical ventilation        | 58 (12.1)      | 17 (7.0)         | 41 (17.4)        | <0.01   |
| Length of ICU stay (days)     | 6 (3–15)       | 4 (2–6)          | 11 (4–24)        | <0.01   |
| Total MV time* (hours)        | 210 (100–480)  | 100 (25–145)     | 300 (190–720)    | <0.01   |
| Length of hospital stay (days)| 8 (4–14)       | 7 (4–11)         | 9 (4–19)         | <0.01   |
| 28 days mortality             | 17 (3.6)       | 2 (0.8)          | 15 (6.4)         | <0.01   |
| In hospital mortality         | 32 (6.7)       | 3 (1.2)          | 29 (12.3)        | <0.01   |

*Values are extracted by comparing between AE-COPD versus CP-COPD group.
*Values are reported as mean ± SD or as frequency (%) or median (25th–75th Percentiles).
*Mechanical ventilation was applied in 58 patients (AE-COPD; 17 patients, COPD pneumonia; 41 patients).
be additive. Our study has several limitations to note. First, because the study was of retrospective design, respiratory virus PCR was not performed for some patients. This may have introduced selection bias to the study sample. However, most of admitted patients (85.8% of AE-COPD patients and 83.1% of CP-COPD patients, respectively) were evaluated by RT-PCR in our hospital. Second, our study was performed at a single center in Korea, and our results may not be fully applicable to other settings. Because nearly all patients were tertiary referrals from other hospitals, the study population might not be representative of the general population. Third, the viruses identified by a sensitive RT-PCR could not be bystanders, rather than causative pathogens. If other admitted patients who had neither AE-COPD nor CP-COPD were included as controls, we might indirectly be able to estimate the proportion of non-significant colonizers. However, this is not possible due to the retrospective design of the study. It was also difficult to establish a cause–effect relationship and it is not clear whether people developed AE-COPD or CP-COPD following infection. Fourth, our study did not include control patients with viral infection alone (without AE-COPD or CP-COPD) and it was, thus, difficult to determine the precise role of the virus in mortality due to AE-COPD or CP-COPD. Also, due to the retrospective nature of the study, some data were missing. For example, it was very difficult to obtain an accurate time of transfer from other hospitals and data of prior antibiotics use. Since we often did not know how long a patient was resident in the transferring hospital, we could not take this into account. Finally, since the number of each virus was relatively small, the characteristics of each viral infection could not be compared between the groups.

In conclusion, respiratory viral infection is common to both AE-COPD and CP-COPD. However, the distribution of respiratory viruses involved was different between these two groups of patients. The clinical outcomes of CP-COPD patients with only viral infection were better than those with only bacterial infection or viral-bacterial co-infection. The factors associated with the clinical outcomes of CP-COPD patients included age and presence of bacterial infection. These findings warrant future studies of larger scale with appropriate control patients.

**AUTHORS’ CONTRIBUTION**

YK contributed to study conception and design. HCK, SHC, JWH, HSS, SBH, CML contributed to acquisition of data. HCK, SHC, YK contributed to analysis and interpretation of data. HCK, SHC contributed to statistical analysis. HCK, SHC, YK contributed to writing a manuscript. HCK, SHC, JWH, SBH, CML, YK contributed to review and accepting the manuscript. YK has been identified as the guarantor of the paper, taking responsibility for the integrity of the work as a whole, from inception to published article.

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