Interaction of Acute Respiratory Failure and Acute Kidney Injury on in-Hospital Mortality of Patients with Acute Exacerbation COPD

Dawei Chen 1
Linglin Jiang 1
Jing Li 2
Yan Tan 3
Mengqing Ma 4
Changchun Cao 4
Jing Zhao 1
Xin Wan 1

1Department of Nephrology, Nanjing First Hospital, Nanjing Medical University, Nanjing, Jiangsu, People’s Republic of China; 2Department of Nephrology, Affiliated Hospital of Jiangsu University, Zhenjiang, Jiangsu, People’s Republic of China; 3Department of Respiratory Medicine, Nanjing First Hospital, Nanjing Medical University, Nanjing, Jiangsu, People’s Republic of China; 4Department of Nephrology, Sir Run Run Hospital, Nanjing Medical University, Nanjing, Jiangsu, People’s Republic of China

Purpose: Both acute respiratory failure (ARF) and acute kidney injury (AKI) are two common complications in patients with acute exacerbation of chronic obstructive pulmonary disease (AECOPD). Moreover, both ARF and AKI are reported as increasing the risk of mortality of patients with AECOPD. However, the interaction of ARF and AKI on the mortality of patients with AECOPD remains unknown. Therefore, the aim of this study is to investigate the joint effect of ARF and AKI on in-hospital mortality in AECOPD patients.

Patients and Methods: We performed a retrospective, observational cohort study of data from Nanjing First Hospital. The effect of AKI and ARF on in-hospital mortality was assessed using a multivariate logistic regression model. Additive interaction was assessed with the relative excess risk due to interaction.

Results: A total of 1647 participants were enrolled. ARF and AKI occurred in 515 (31.3%) and 357 (21.7%) patients, respectively. Overall, in-hospital mortality was 5.7%. The in-hospital mortality of the neither ARF nor AKI group, the ARF only group, the AKI only group, and both the ARF and AKI group were 0.8%, 7.0%, 7.5%, and 29.9%, respectively. After multivariate logistic regression analysis, the independent factors for in-hospital death included: albumin (OR 0.88, 95% CI 0.83–0.93, P < 0.001), ARF only (OR 8.53, 95% CI 3.64–19.99, P < 0.001), AKI only (OR 8.99, 95% CI 3.58–22.55, P < 0.001), and both ARF and AKI (OR 39.13, 95% CI 17.02–89.97, P < 0.001). The relative excess risk due to interaction was 22.62 (95% CI, 0.31 to 44.93), the attributable proportion due to interaction was 0.59 (95% CI, 0.36 to 0.79), and the synergy index was 2.46 (95% CI, 1.44 to 4.20), indicating ARF and AKI had a significant synergic effect on in-hospital mortality.

Conclusion: ARF and AKI had a synergistic effect on in-hospital mortality in AECOPD patients.

Keywords: acute respiratory failure, acute kidney injury, in-hospital mortality, acute exacerbation chronic obstructive pulmonary disease

Introduction
Chronic obstructive pulmonary disease (COPD) affects approximately 400 million people and is already the third leading cause of death in the world, which the World Health Organization predicted would not occur until 2030.1 In China, the prevalence of COPD in people aged 20 years or older is 8.6% (nearly 100 million Chinese adults), and more than 1 million people die and more than 5 million people be disabled due to COPD each year.2 Acute exacerbation of COPD (AECOPD) is an important factor of the death in patients with COPD,3 and is also the main expenditure portion of medical expenses for patients with COPD.4
Both acute respiratory failure (ARF) and acute kidney injury (AKI) are two common complications in patients with AECOPD. AECOPD is the third most common etiology in medical patients hospitalized because of ARF, and AKI occurs in patients with AECOPD ranging from 1.9% to 21.3%. Moreover, both ARF and AKI are reported as increasing the risk of mortality of patients with AECOPD. However, the interaction of ARF and AKI on the mortality of patients with AECOPD remains unknown. Therefore, the aim of this study is to investigate the joint effect of ARF and AKI on mortality in AECOPD patients.

Materials and Methods

Study Design

The study was approved by the Ethics Committee of Nanjing First Hospital. Because of the retrospective study, this study was performed with an approved waiver of informed consent. We conducted a retrospective review of consecutive patients with AECOPD admitted to Nanjing First Hospital from January 2014 to January 2017. The diagnostic criteria for AECOPD were as follows: (i) history of COPD (forced expiratory volume in one second (FEV1)/forced vital capacity (FVC) <0.70 at the clinical stable state) and (ii) an acute worsening of respiratory symptoms (such as dyspnea, cough, or sputum purulence) and warrant hospital admission. Inclusion criterion: patients with COPD exacerbation required hospitalization. Exclusion criteria: patients without full medical records, patients with a urinary-tract infection, patients with a history of stage 5 chronic kidney disease (CKD), and those undergoing dialysis prior to hospital admission.

Definitions of ARF and AKI

ARF defined as an arterial oxygen tension (PaO₂) <60 mmHg in acute state. AKI was defined as a serum creatinine (SCr) change that met the 2012 Kidney Disease Improving Global Outcomes criteria: an increase in the SCr level by ≥0.3 mg/dL within 48 h or ≥1.5-fold from the baseline within 7 days. Urine output data were not obtained and were not used for AKI. The baseline level of SCr was defined as the lowest one during hospitalization.

Data Collection

Data were collected from the medical records: gender, age, comorbid conditions (hypertension, anemia, diabetes mellitus, coronary artery disease, chronic cor pulmonale, atrial fibrillation, and cerebrovascular diseases), laboratory tests (albumin, neutrophil ratio, platelet count, triglyceride, total cholesterol, high-density lipoprotein, and low-density lipoprotein), and complications (ARF and AKI).

Statistical Analysis

The statistical analysis was performed using statistical software SPSS 22.0 (IBM Corporation, Armonk, NY, USA). Categorical variables were expressed as percentages and were analyzed by the chi-squared test or Fisher’s exact test where appropriate. Continuous variables were shown to be the mean and standard deviation (SD) for normally distributed data, or the median and interquartile range (IQR) for non-normally distributed data. Continuous variables with normal distribution were compared using a Student’s t-test, while continuous variables with non-normal distribution were assessed by Mann–Whitney U-tests. All subjects were categorized into four subgroups according to the complications of ARF and AKI. All variables were initially estimated through univariate logistic regression analysis, and only statistically significant variables were incorporated into the multivariable logistic regression model. P < 0.05 was considered as statistically significant. To examine the interaction between ARF and AKI on in-hospital death in AECOPD patients, multivariable logistic regression analysis was used to obtain the covariance matrix and regression coefficients. Microsoft Excel sheet was used to calculate three measures: the relative excess risk due to interaction (RERI); the attributable proportion due to interaction (AP); and the synergy index (SI).

Results

Study Population

A total of 1823 patients were hospitalized with AECOPD, and 176 (9.6%) patients were excluded due to exclusion criteria. Finally, 1647 participants were enrolled for analysis. For the study population, most (77%) patients were male, and the median age of the overall cohort was 78 years (IQR: 71–84). ARF occurred in 515 (31.3%) patients, and 357 (21.7%) patients developed AKI. In particular, 157 (9.5%) had ARF and AKI, 358 (21.7%) had ARF without AKI, 200 (12.2%) did not have ARF but developed AKI, and 932 (56.6%) had neither ARF nor AKI. Overall, in-hospital mortality was 5.7% (94/1647). Table 1 shows the demographic, comorbid conditions, laboratory tests and in-hospital mortality of participants categorized by ARF and AKI. The in-hospital mortality of the neither ARF nor AKI group, the ARF only
group, the AKI only group, and both the ARF and AKI group were 0.8%, 7.0%, 7.5%, and 29.9%, respectively.

Characteristics of in-Hospital Death in AECOPD Patients

Table 2 shows the differences between the survival group and the death group. Compared with the survival group, patients in the death group were of advanced age (81 years versus 78 years, \( P < 0.001 \)). Patients in the death group were more likely to have the comorbidities of anemia (43.6% versus 29.8%, \( P = 0.005 \)), coronary artery disease (41.5% versus 27.9%, \( P = 0.005 \)), and chronic cor pulmonale (54.3 versus 39.9, \( P = 0.006 \)). Patients in the death group had a higher neutrophil ratio (86.0% versus 77.9%, \( P < 0.001 \)), and triglyceride (0.95 versus 0.82, \( P = 0.030 \)), while they had lower platelet counts (161 versus 184, \( P = 0.007 \)), high-density lipoprotein (1.06 versus 1.16, \( P = 0.014 \)), low-density lipoprotein (2.10 versus 2.35, \( P = 0.012 \)), and albumin (31.7 versus 35.2, \( P < 0.001 \)). In addition, comparison with the neither ARF nor AKI group, the ARF only group (OR 9.92, 95% CI 4.25–23.15, \( P < 0.001 \)), the AKI only group (OR 10.71, 95% CI 4.31–26.64, \( P < 0.001 \)), and both the ARF and AKI group (OR 56.46, 95% CI 24.91–127.98, \( P < 0.001 \)) had significantly increased in-hospital death risk.

Independent Factors for in-Hospital Death in AECOPD Patients

After multivariate logistic regression analysis, the independent factors for in-hospital death included: albumin (OR 0.88, 95% CI 0.83–0.93, \( P < 0.001 \)), ARF only (OR 8.53, 95% CI 3.64–19.99, \( P < 0.001 \)), AKI only (OR 8.99, 95% CI 3.58–22.55, \( P < 0.001 \)), and both ARF and AKI (OR 39.13, 95% CI 17.02–89.97, \( P < 0.001 \)) (Table 3).

Biological Interaction of ARF and AKI on in-Hospital Death in AECOPD Patients

Figure 1 shows the excess risks due to ARF, AKI, and their interaction in an analysis of in-hospital mortality adjusted for all risk factors. As shown in Table 4, we found a statistically significant synergistic interaction between ARF and AKI on in-hospital death. The estimated RERI was 22.62 (95% CI 0.31–44.93), indicating that there would be 22.62 relative excess risks due to the

Table 1 Characteristics of Participants Categorized by ARF and AKI

| Variables                              | Neither ARF nor AKI (n = 932) | ARF Only (n = 358) | AKI Only (n = 200) | Both ARF and AKI (n = 157) | P value |
|----------------------------------------|------------------------------|-------------------|-------------------|--------------------------|---------|
| Demographics                           |                              |                   |                   |                          |         |
| Gender (male), n (%)                    | 722 (77.5)                   | 265 (74.0)        | 157 (78.5)        | 117 (74.5)               | 0.476   |
| Age (years)                            | 77 (70–83)                   | 78 (69–83)        | 82 (76–85)        | 80 (76–86)               | <0.001  |
| Comorbid conditions, n (%)             |                              |                   |                   |                          |         |
| Hypertension                           | 480 (51.5)                   | 176 (49.2)        | 126 (63.0)        | 90 (57.3)                | 0.007   |
| Anemia                                 | 237 (25.4)                   | 115 (32.1)        | 85 (42.5)         | 67 (42.7)                | <0.001  |
| Diabetes mellitus                      | 138 (14.8)                   | 60 (16.8)         | 38 (19.0)         | 28 (17.8)                | 0.412   |
| Coronary artery disease                | 244 (26.2)                   | 78 (21.8)         | 85 (42.5)         | 65 (41.4)                | <0.001  |
| Chronic cor pulmonale                  | 288 (30.9)                   | 214 (59.8)        | 85 (42.5)         | 84 (53.5)                | <0.001  |
| Atrial fibrillation                    | 92 (9.9)                     | 25 (7.0)          | 35 (17.5)         | 22 (14.0)                | 0.001   |
| Cerebrovascular diseases               | 187 (20.1)                   | 63 (17.6)         | 84 (27.0)         | 40 (25.5)                | 0.026   |
| Laboratory tests                       |                              |                   |                   |                          |         |
| Albumin (g/L)                          | 35.7 (33.1–38.3)             | 34.4 (32.1–37.2)  | 34.9 (32.1–37.7)  | 32.5 (29.0–35.4)         | <0.001  |
| Neutrophil ratio (%)                   | 74.8 (66.6–82.8)             | 81.2 (72.8–88.2)  | 80.1 (73.0–88.4)  | 86.8 (80.1–91.0)         | <0.001  |
| Platelet count (\(10^9/L\))           | 188 (147–228)                | 177 (135–222)     | 181 (146–216)     | 155 (121–203)            | 0.125   |
| Triglyceride (mmol/L)                  | 0.80 (0.62–1.11)             | 0.82 (0.66–1.07)  | 0.88 (0.67–1.18)  | 0.91 (0.70–1.16)         | <0.001  |
| Total cholesterol (mmol/L)             | 3.96 (3.35–4.65)             | 3.94 (3.39–4.65)  | 3.94 (3.30–4.77)  | 3.54 (2.97–4.49)         | 0.005   |
| High density lipoprotein (mmol/L)      | 1.18 (0.97–1.39)             | 1.16 (0.94–1.40)  | 1.11 (0.90–1.36)  | 1.03 (0.80–1.25)         | <0.001  |
| Low density lipoprotein (mmol/L)       | 2.35 (1.82–2.94)             | 2.34 (1.92–2.95)  | 2.42 (1.84–2.96)  | 2.05 (1.49–2.77)         | 0.124   |
| Outcome                                |                              |                   |                   |                          |         |
| In-hospital mortality, n (%)           | 7 (0.8)                      | 25 (7.0)          | 15 (7.5)          | 47 (29.9)                | <0.001  |

Abbreviations: ARF, acute respiratory failure; AKI, acute kidney injury.
additive interaction between ARF and AKI. AP revealed that 59% of the total odds of in-hospital death were attributed to the interaction between ARF and AKI. In addition, SI was 2.46 (95% CI, 1.44–4.20), suggesting that the risk of in-hospital death in both ARF and AKI patients was 2.46 times as high as the sum of risks in patients presenting only one single complication.

### Discussion

Both ARF and AKI were two common complications in AECOPD patients.⁵,⁶ Although previous studies had reported that development of a single complication (ARF or AKI) was associated with an increased risk of mortality in patients with AECOPD,¹⁰ the effect of the addition of two complications (ARF and AKI) on in-hospital mortality

### Table 2 Univariate Logistic Analysis of Risk Factors for in-Hospital Death in Patients with AECOPD

| Variables                       | All Patients (n=1647) | Survival Group (n=1553) | Death Group (n=94) | P value |
|---------------------------------|-----------------------|-------------------------|-------------------|---------|
| Demographics                    |                       |                         |                   |         |
| Gender (male)                   | 1261 (76.6)           | 1192 (76.8)             | 69 (73.4)         | 0.456   |
| Age (years)                     | 78 (71–84)            | 78 (70–83)              | 81 (78–86)        | <0.001  |
| Comorbid conditions, n (%)      |                       |                         |                   |         |
| Hypertension                    | 872 (52.9)            | 824 (53.1)              | 48 (51.1)         | 0.707   |
| Anemia                          | 504 (30.6)            | 463 (29.8)              | 41 (43.6)         | 0.005   |
| Diabetes mellitus               | 264 (16.0)            | 246 (15.8)              | 18 (19.1)         | 0.396   |
| Coronary artery disease         | 472 (28.7)            | 433 (27.9)              | 39 (41.5)         | 0.005   |
| Chronic cor pulmonale           | 671 (40.7)            | 620 (39.9)              | 51 (54.3)         | 0.006   |
| Atrial fibrillation             | 174 (10.6)            | 160 (10.3)              | 14 (14.9)         | 0.160   |
| Cerebrovascular diseases        | 344 (20.9)            | 321 (20.7)              | 23 (24.5)         | 0.379   |
| Laboratory tests                |                       |                         |                   |         |
| Albumin (g/L)                   | 35.0 (32.4–37.8)      | 35.2 (32.6–37.9)        | 31.7 (27.8–35.1)  | <0.001  |
| Neutrophil ratio (%)            | 78.4 (69.6–86.0)      | 77.9 (69.0–85.5)        | 86.0 (79.6–90.8)  | <0.001  |
| Platelet count (10⁹/L)          | 182 (141–224)         | 184 (142–225)           | 161 (124–209)     | 0.007   |
| Triglyceride (mmol/L)           | 0.82 (0.64–1.12)      | 0.82 (0.64–1.11)        | 0.95 (0.68–1.21)  | 0.030   |
| Total cholesterol (mmol/L)      | 3.93 (3.31–4.63)      | 3.94 (3.32–4.63)        | 3.75 (3.08–4.59)  | 0.110   |
| High density lipoprotein (mmol/L)| 1.15 (0.94–1.38)      | 1.16 (0.94–1.38)        | 1.06 (0.83–1.32)  | 0.014   |
| Low density lipoprotein (mmol/L)| 2.32 (1.81–2.93)      | 2.35 (1.82–2.93)        | 2.10 (1.64–2.65)  | 0.012   |
| Complications of ARF and AKI, n (%)|                       |                         |                   |         |
| Neither ARF nor AKI             | 932 (56.6)            | 925 (59.6)              | 7 (7.4)           | <0.001  |
| ARF only                        | 358 (21.7)            | 333 (21.4)              | 25 (26.6)         | <0.001  |
| AKI only                        | 200 (12.1)            | 185 (11.9)              | 15 (16.0)         | <0.001  |
| Both ARF and AKI                | 157 (9.5)             | 110 (7.1)               | 47 (50.0)         | <0.001  |

Abbreviations: ARF, acute respiratory failure; AKI, acute kidney injury; AECOPD, acute exacerbation of chronic obstructive pulmonary disease.

### Table 3 Multivariate Logistic Analysis of Risk Factors for in-Hospital Death in Patients with AECOPD

| Variables                       | Mortality (%) | OR   | 95% CI       | P value |
|---------------------------------|---------------|------|--------------|---------|
| Albumin                         | –             | 0.88 | 0.83–0.93    | <0.001  |
| Complications of ARF and AKI    |               |      |              |         |
| Neither ARF nor AKI             | 0.8% (7/932)  | Reference | Reference | <0.001  |
| ARF only                        | 7.0% (25/358) | 8.53 | 3.64–19.99   | <0.001  |
| AKI only                        | 7.5% (15/200) | 8.99 | 3.58–22.55   | <0.001  |
| Both ARF and AKI                | 29.9% (47/157)| 39.13 | 17.02–89.97 | <0.001  |

Abbreviations: ARF, acute respiratory failure; AKI, acute kidney injury; AECOPD, acute exacerbation of chronic obstructive pulmonary disease; OR, odds ratio; CI, confidence interval.
was still unknown. In this study, we explored the interactive effect of ARF and AKI on the in-hospital death of patients with AECOPD.

After multivariate logistic regression analysis, we found that albumin, ARF only, AKI only, and both ARF and AKI were independently associated with in-hospital death in AECOPD patients. Serum albumin level was part of the acute-phase protein response, and low level of serum albumin may reflect a persistent inflammation or worsening clinical status during AECOPD.\(^{17,18}\) Previous studies had also reported that low level of serum albumin was not only related to prolong hospital stay, but also increase mortality in AECOPD patients.\(^{19,20}\) Our results also indicated that low level of serum albumin could increase in-hospital mortality in AECOPD patients. We found that patients with ARF and AKI had increased 8.53-fold and 8.99-fold in-hospital death risk, respectively. However, once patients coexisted with ARF and AKI, the in-hospital death risk was increased to 39.13-fold. Furthermore, after interaction analysis, we found a statistically significant synergistic interaction between ARF and AKI on in-hospital death of patients with AECOPD. Similarly, compared to patients without ARF and AKI, Kim et al reported that patients undergoing high-risk intraabdominal general surgery procedures with ARF and AKI had 14.2 times and 10.8 times risk for postoperative mortality, respectively.\(^{21}\) Moreover, patients undergoing high-risk intraabdominal general surgery procedures coexisted with ARF and AKI, and the postoperative death risk was increased to 65.2 times.\(^{21}\) In addition, the development of ARF and AKI also showed significant positive additive interactions to further increase the risk of mortality.\(^{21}\)

The estimated RERI was 22.62, indicating that there would be 22.62 relative excess risk due to the additive interaction between ARF and AKI. AP revealed that 59% of the total odds of in-hospital death were attributed to the interaction between ARF and AKI. In addition, SI was 2.46, suggesting that the risk of in-hospital death in both ARF and AKI patients

### Table 4 Measures for Estimation of Biological Interaction Between ARF and AKI for the Risk of in-Hospital Death in Patients with AECOPD

| Measures of Biological Interaction | Estimate | 95% CI       |
|-----------------------------------|----------|--------------|
| RERI                              | 22.62    | 0.31–44.93   |
| AP                                | 0.59     | 0.36–0.79    |
| SI                                | 2.46     | 1.44–4.20    |

**Abbreviations:** ARF, acute respiratory failure; AKI, acute kidney injury; AECOPD, acute exacerbation of chronic obstructive pulmonary disease; RERI, relative excess risk due to interaction; AP, attributable proportion; SI, synergy index; CI, confidence interval.
was 2.46 times higher than the sum of risks in patients presenting only one single complication. Hence, it is important to improve the prognosis of AECOPD to avoid the development of AKI and ARF.

However, our study was epidemiologic in nature and did not provide direct evidence for the exact mechanisms underlying this synergism. Recent years, the lungs-kidneys crosstalk had been focused on the critically ill patients. ARF may induce renal damage via the following mechanisms: (1) hypoxia was known to be able to reduce the renal blood flow and contribute to decrease the glomerular filtration; correspondingly, hypercapnia reduced renal blood flow directly by activating renal vasoconstriction and indirectly by systemic vasodilation secondary to high PaCO₂. (2) Systemic pro-inflammatory mediators were released from the injured lungs, and were associated with AKI. More specifically, increased levels of interleukin-6, plasminogen activator inhibitor-1, and soluble tumor necrosis factor receptors I and II in ARF were associated with the development of AKI. COPD could increase intra-abdominal pressure, and then caused renal edema because of diminished venous drainage, which led to a vicious cycle that further increased intra-abdominal pressure. (3) Mechanical ventilation that had improved lung function in ARF had undesirable effects on decreased renal function, which could be induced by hemodynamic and blood gas disturbances, neurohumoral negative effects, and bio-trauma. On the other hand, AKI may induce lung injury via the following mechanisms: (1) AKI may lead to lung injury by increasing production of inflammatory mediators. (2) AKI caused a significantly decreased expression in the pulmonary predominant water channel, aquaporin 5, possibly contributing to lung injury. Therefore, it was important to determine the exact mechanisms between ARF and AKI, which could improve the prognosis of AECOPD patients.

There are several limitations in our study. First, it is a single-centered retrospective study. A prospective multicenter study is needed to confirm our conclusions. Second, the data set lacks of data on other organ systems (such as the heart, liver or gut), which might have affected in-hospital mortality of AECOPD patients. Third, as urine output is not monitored in most of the patients, this study does not use the urine output standard to diagnose AKI.

**Conclusion**

We present epidemiologic evidence that ARF and AKI independently increase the risk of in-hospital death in patients with AECOPD. More importantly, we find that the simultaneous development of ARF and AKI demonstrate positive additive interactions, which imply that the two complications interact synergistically to further increase the risk of in-hospital mortality above and beyond what would be expected with one complication alone. Our observations underline the importance of understanding the clinical implications of altered organ system function and the recognition that these two complications may have far-reaching effects when ARF combines with AKI simultaneously. Further studies will be required to determine the complex mechanism behind the synergistic effect and to explore the best therapeutic targets for the prevention of the interactive injury between lungs and kidneys.

**Abbreviations**

COPD, chronic obstructive pulmonary disease; AECOPD, acute exacerbation of chronic obstructive pulmonary disease; ARF, acute respiratory failure; AKI, acute kidney injury; FEV₁, forced expiratory volume in one second; FVC, forced vital capacity; CKD, chronic kidney disease; PaO₂, arterial oxygen tension; SCr, serum creatinine; SD, standard deviation; IQR, interquartile range; RERI, relative excess risk due to interaction; AP, attributable proportion due to interaction; SI, synergy index; OR, odds ratio; CI, confidence interval; PaCO₂, arterial carbon dioxide pressure.

**Data Sharing Statement**

Datasets are available from the corresponding author upon reasonable request.

**Ethics Approval and Consent to Participate**

This study protocol was approved by the Nanjing First Hospital Institutional Review Board. Individual patient consent was waived on condition that all patient data were de-identified before evaluation because this study was a retrospective analysis. Confidentiality and the protection of data will be respected at all times. This study was conducted in accordance with the Declaration of Helsinki.

**Acknowledgments**

We are grateful for the support of the Information Department of Nanjing First Hospital.

**Author Contributions**

All authors made substantial contributions to conception and design, acquisition of data, or analysis and interpretation of data; took part in drafting the article or revising it critically for
References

1. Labaki WW, Rosenberg SR. Chronic Obstructive Pulmonary Disease. *Ann Intern Med.* 2020;173(3):ITC17–ITC32. doi:10.7326/AITC202008040

2. Wang C, Xu J, Yang L, et al. Prevalence and risk factors of chronic obstructive pulmonary disease in China (the China Pulmonary Health [CPH] study): a national cross-sectional study. *Lancet.* 2018;391(10131):1706–1717. doi:10.1016/S0140-6736(18)30841-9

3. Pavord ID, Jones PW, Burgen PR, Rabe KF. Exacerbations of COPD. *Int J Chron Obstruct Pulmon Dis.* 2016;11 Spec Iss:21–30. doi:10.2147/COPD.S85978

4. Perera PN, Armstrong EP, Sherrill DL, Skrepnek GH. Acute exacerbations of COPD in the United States: inpatient burden and predictors of costs and mortality. *COPD.* 2012;9(2):131–141. doi:10.3109/15412255.2011.650239

5. Ocal S, Ortac EE, Ozturk O, Hayran M, Topeli A, Coplu L. Long-term outcome of chronic obstructive pulmonary disease patients with acute respiratory failure following intensive care unit discharge in Turkey. *Clin Respir J.* 2017;11(6):975–982. doi:10.1111/crj.12540

6. Barakat MF, McDonald HI, Collier TJ, Smeeth L, Nitsch D, Quint JK. Acute kidney injury in stable COPD and at exacerbation. *Int J Chron Obstruct Pulmon Dis.* 2015;10:2067–2077. doi:10.2147/COPD.S88759

7. Ozsancak UA, Habesgolu MA. Epidemiology of NIV for acute respiratory failure in COPD patients: results from the international surveys vs. the “Real World.” *COPD.* 2017;14(4):429–438. doi:10.1080/15412255.2017.1336527

8. Wan X, Chen D, Tan Y, et al. Incidence, risk factors, and prognostic implications of acute kidney injury in patients with acute exacerbation of COPD. *Int J Chron Obstruct Pulmon Dis.* 2020;15:1085–1092. doi:10.2147/COPD.S238343

9. Fabbian F, De Giorgi A, Manfredini F, et al. Impact of renal dysfunction on in-hospital mortality of patients with severe chronic obstructive pulmonary disease: a single-center Italian study. *Int Urol Nephrol.* 2016;48(7):1121–1127. doi:10.1007/s11255-016-1272-5

10. Connors AF, Dawson NV, Thomas C, et al. Outcomes following acute exacerbation of severe chronic obstructive lung disease. The SUPPORT investigators (Study to Understand Prognoses and Preferences for Outcomes and Risks of Treatments). *Am J Respir Crit Care Med.* 1996;154(4 Pt 1):959–967. doi:10.1164/ajrccm.154.4.8887592

11. Vestbo J, Hurd SS, Agusti AG, et al. Global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease: GOLD executive summary. *Am J Respir Crit Care Med.* 2013;187(4):347–365. doi:10.1164/ajrccm.2012-0596PP

12. Roussos C, Koutsoukou A. Respiratory failure. *Eur Respir J Suppl.* 2003;22(47):3s–14s. doi:10.1183/09031936.03.00038503

13. Kellum JA, Lameire N. Diagnosis, evaluation, and management of acute kidney injury: a KDIGO summary (Part 1). *Crit Care.* 2013;17(1):204. doi:10.1186/cc11454

14. Hosmer DW, Lemeshow S. Confidence interval estimation of interaction. *Epidemiology.* 1992;3(5):452–456. doi:10.1097/00001648-199209000-00012

15. Andersson T, Alfredsson L, Källberg H, Zdravkovic S, Ahlborn A. Calculating measures of biological interaction. *Eur J Epidemiol.* 2005;20(7):575–579. doi:10.1007/s10654-005-7835-x

16. Knol MJ, VanderWeele TJ, Groenwold RH, Klangel OH, Rovers MM, Grobbee DE. Estimating measures of interaction on an additive scale for preventive exposures. *Eur J Epidemiol.* 2011;26(6):433–438. doi:10.1007/s10654-011-9554-9

17. Gunen H, Hacievliyigil SS, Kosar F, et al. Factors affecting survival of hospitalised patients with COPD. *Eur Respir J.* 2005;26(2):234–241. doi:10.1183/09031936.05.0024804

18. Wang Y, Stavem K, Dahl FA, Humerfelt S, Haugen T. Factors associated with a prolonged length of stay after acute exacerbation of chronic obstructive pulmonary disease (AECOPD). *Int J Chron Obstruct Pulmon Dis.* 2014;9:99–105. doi:10.2147/COPD.S31467

19. Haja MH, Murphy S, Clague H, Sridharan K, Taylor P. Anemia and performance status as prognostic markers in acute hypercapnic respiratory failure due to chronic obstructive pulmonary disease. *Int J Chron Obstruct Pulmon Dis.* 2013;8:151–157. doi:10.2147/COPD.S39403

20. Hasagawa W, Yamauchi Y, Yasunaga H, et al. Factors affecting mortality following emergency admission for chronic obstructive pulmonary disease. *BMC Pulm Med.* 2014;14(1):151. doi:10.1186/1471-2466-14-151

21. Kim M, Brady JE, Li G. Interaction effects of acute kidney injury, acute respiratory failure, and sepsis on 30-day postoperative mortality in patients undergoing high-risk intraabdominal general surgical procedures. *Anesth Analg.* 2015;121(6):1536–1546. doi:10.1213/ANE.0000000000000915

22. Joannidis M, Forni LG, Klein SJ, et al. Lung-kidney interactions in critically ill patients: consensus report of the Acute Disease Quality Initiative (ADQI) 21 Workgroup. *Intensive Care Med.* 2020;46(4):654–672. doi:10.1007/s00134-019-05869-7

23. Husain-Syed F, Slutsky AS, Ronco C. Lung-kidney cross-talk in the critically ill patient. *Am J Respir Crit Care Med.* 2017;194(4):402–414. doi:10.1164/rrc.201602-0420CP

24. Doi K, Ishizu T, Fujita T, Noiri E. Lung injury following acute kidney injury: kidney-lung crosstalk. *Clin Exp Nephrol.* 2011;15(4):464–470. doi:10.1007/s10157-011-0459-4

25. Basa RK, Wheeler DS. Kidney-lung cross-talk and acute kidney injury. *Pediatr Nephrol.* 2013;28(12):2239–2248. doi:10.1007/s00467-012-2386-3

26. Murugan R, Karajala-Subramanyam V, Lee M, et al. Acute kidney injury in non-severe pneumonia is associated with an increased immune response and lower survival. *Kidney Int.* 2010;77(6):527–535. doi:10.1038/ki.2009.502

27. Liu KD, Glidden DV, Eisner MD, et al. Predictive and pathogenetic value of plasma biomarkers for acute kidney injury in patients with acute lung injury. *Crit Care Med.* 2007;35(12):2755–2761.

28. Hepsokomi M, Englert JA, Baron RM, et al. Ventilator-induced lung injury increases expression of endothelial inflammatory mediators in the kidney. *Am J Physiol Renal Physiol.* 2017;312(4):F654–F660. doi:10.1152/ajprenal.00523.2016

29. Andres-Hernando A, Dursun B, Altmann C, et al. Cytokine production increases and cytokine clearance decreases in mice with bilateral nephrectomy. *Nephrol Dial Transplant.* 2012;27(12):4339–4347. doi:10.1093/ndt/gfs256

30. Kelly KJ. Distant effects of experimental renal ischemia/reperfusion injury. *J Am Soc Nephrol.* 2003;14(6):1549–1558. doi:10.1097/01.ASN.0000064946.94590.46

31. Yabuuchi N, Sagata M, Saigo C, et al. Indoxyl sulfate as a mediator involved in dysregulation of pulmonary aquaporin-5 in acute lung injury caused by acute kidney injury. *Int J Mol Sci.* 2016;18(1):11. doi:10.3390/ijms18010011
