Decreased CO₂ Levels as Indicators of Possible Mechanical Ventilation-Induced Hyperventilation in COVID-19 Patients: A Retrospective Analysis

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Background: Six months since the outbreak of coronavirus disease (COVID-19), the pandemic continues to grow worldwide, although the outbreak in Wuhan, the worst-hit area, has been controlled. Thus, based on the clinical experience in Wuhan, we hypothesized that there is a relationship between the patient’s CO₂ levels and prognosis.

Methods: COVID-19 patients’ information was retrospectively collected from medical records at the Leishenshan Hospital, Wuhan. Logistic and Cox regression analyses were conducted to determine the correlation between decreased CO₂ levels and disease severity or mortality risk. The Kaplan-Meier curve analysis was coupled with the log-rank test to understand COVID-19 progression in patients with decreased CO₂ levels. Curve fitting was used to confirm the correlation between computed tomography scores and CO₂ levels.

Results: Cox regression analysis showed that the mortality risk of COVID-19 patients correlated with decreased CO₂ levels. The adjusted hazard ratios for decreased CO₂ levels in COVID-19 patients were 8.710 [95% confidence interval (CI): 2.773–27.365, \( P < 0.001 \)], and 4.754 (95% CI: 1.380–16.370, \( P = 0.013 \)). The adjusted odds ratio was 0.950 (95% CI: 0.431–2.094, \( P = 0.900 \)). The Kaplan-Meier survival curves demonstrated that patients with decreased CO₂ levels had a higher risk of mortality.

Conclusions: Decreased CO₂ levels increased the mortality risk of COVID-19 patients, which might be caused by hyperventilation during mechanical ventilation. This finding provides important insights for clinical treatment recommendations.

Keywords: infectious disease, pneumonia, COVID-19, CO₂, mechanical ventilation
BACKGROUND

In December 2019, an outbreak of pneumonia of unknown etiology was reported in Wuhan, China, which then rapidly evolved into a pandemic (1). By January 7, 2020, Chinese scientists had rapidly isolated the novel coronavirus, the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), with an incubation period of 2–14 days, and a potential asymptomatic human-to-human transmission; it is known to cause the coronavirus disease (COVID-19) (2–4). COVID-19 has been controlled in China, although the global number of infections continues to grow rapidly and has led to more than five million infections and 630,000 deaths (5).

In COVID-19 patients, fever and cough are the most common symptoms. There may also be uncommon symptoms, such as diarrhea (6). Thus, researchers have found that SARS-CoV-2 affects multiple organs in addition to the patients’ lungs, based on the understanding garnered from COVID-19 studies. This explains the pathological changes identified from the minimal autopsies of three patients who died of COVID-19 in Chongqin, China (7–9). Studies have shown that the main targeted organs of SARS-CoV-2 are the lungs and airways. Furthermore, damage to other organs significantly increases the mortality rate of COVID-19 patients (10).

The measurement of carbon dioxide (CO₂) level in blood is vital not only for the early detection of respiratory depression and airway disorders but also for airway management (11). Hypoxemia and hypercapnia predicted poor prognosis for COVID-19 patients in a previous study (4). Hence, this study aimed to investigate whether decreased CO₂ levels would influence the prognosis of COVID-19 patients.

METHODS

Study Design and Participants

In this retrospective study, we collected data from 1,880 patients, who were clinically diagnosed with COVID-19 between February 8, 2020, and March 19, 2020, at Wuhan Leishenshan Hospital. Exclusion criteria included missing data on mortality and CO₂ level, pregnancy, death on admission, embolization, and transfer to any other hospital; thus, 1,776 patients were included finally. Data about demographics, medical history, treatment, laboratory findings, and imaging data were collected from the patients’ original medical records. Two physicians independently reviewed these data.

This study was approved by the Research Ethics Commission of the Zhongnan Hospital of Wuhan University (approval number: 20200074). The need for patient consent was waived by the ethics committee because of the urgent need for insights into this rapidly evolving infectious disease.

Abbreviations: COVID-19, coronavirus disease; CO₂, carbon dioxide; CI, confidence interval; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; CT, computed tomography; GGO, ground-glass opacities; SD, standard deviation; IQR, median and interquartile range; WBC, white blood cell; PLT, platelet; MV, mechanical ventilation; ARDS, acute respiratory distress syndrome.

Primary Outcomes in This Study

In this study, the survival and illness severity of COVID-19 patients during hospitalization and images obtained from computed tomography (CT) scan were used to evaluate the patients’ primary outcomes. However, survival was the most significant indicator. According to the Seventh Interim Guidance of Diagnosis and Treatment of COVID-19 published by the Chinese National Health Commission, one patient was staged into mild COVID-19 in this study. Thus, the severity of COVID-19 was categorized into three degrees: mild/common, severe, and critical.

Furthermore, after fulfilling the common standard criteria, all chest CT images were inspected and independently categorized by two experienced radiologists using the following scoring system according to previous studies and the characteristics of COVID-19. Score 1 included ground-glass opacities (GGO) characteristics, reticulation or cord change, consolidation, and pleural effusion, in which each feature was assigned one point, and Score 1 was the sum of these features. Score 2 (from 0 to 4 points) was generated depending on the area of involvement of the lung lobes as follows: no involvement, 0; < 25% involvement, 1; 26–50% involvement, 2; 51–75% involvement, 3; 76–100% involvement, 4; the total score was the sum of scores 1 and 2.

Statistical Analyses

Continuous variables with normal distribution are presented as mean ± standard deviation (SD) or median and interquartile range (IQR). A CO₂ level ≤ 23 mmol/L was considered a decreased level (normal CO₂ range: 23–31 mmol/L). Furthermore, differences in continuous variables between the groups (decreased and non-decreased levels of CO₂), were determined using independent group t-test or the Mann-Whitney U-test. Categorical variables are presented as frequencies and percentages. For the proportions of categorical variables, the chi-square test was used to compare participants with decreased and non-decreased CO₂ levels. When parameters were expected to have a count ≤ 5, the Fisher exact test was used.

To determine whether the decreased CO₂ levels would influence the prognosis of COVID-19 patients, we used Cox regression analysis, after adjusting for age, history of cardiovascular disease, erythrocyte count, hemoglobin, leucocyte count, platelet count, lymphocyte count, and oxygen support. Furthermore, Kaplan-Meier analyses with log-rank tests were used to analyze the survival trends of patients.

All statistical analyses were performed using SPSS (version 23.0 for Windows) and EmpowerStats (version 2.0). A two-sided P ≤ 0.05 was considered statistically significant.

RESULTS

Demographics, Clinical Information, and Laboratory Findings

The demographic characteristics and symptoms of this study cohort of 1,776 patients are presented in Table 1. The ratio of female to male patients was approximately one. The IQR value of age in this study population was 59 (48–68) years,
with no apparent differences in the groups with decreased and non-decreased CO₂ levels.

In patients with cardiovascular comorbidity, a significant difference was observed between decreased and non-decreased CO₂ levels. However, there were no significant differences in other comorbidities, including pulmonary disease, endocrine disease, malignancy, and neurological disorders. Furthermore, among COVID-19 patients with decreased or non-decreased CO₂ levels, those with gastrointestinal disorders showed a significant difference. However, concerning fever, fatigue, or respiratory and neurological symptoms, there were no significant intergroup differences (Table 1).

We analyzed the laboratory results and the blood coagulation tests of patients in two groups (Table 2), and most of the laboratory indicators showed significant differences. The results of the blood coagulation test, except fibrinogen and thrombin time, showed significant intergroup differences among COVID-19 patients. The clinical treatment and outcomes are presented in Table 2. Anticoagulants and types of oxygen support significantly differed among patients in the two groups. However, the use of antiviral drugs, corticosteroids, and traditional Chinese medicine showed no significant differences between the groups. Concerning outcomes, disease progression showed a significant difference, with no significant difference in other outcome parameters.

### Analysis of Patient Prognosis

Table 3 shows the mortality risk of COVID-19 patients with decreased and non-decreased CO₂ levels. Both unadjusted and adjusted Cox regression analyses showed that decreased CO₂ levels were associated, with poor prognosis compared to non-decreased CO₂ levels. After adjustment for age, history of cardiovascular disease, WBC, PLT, oxygen support, and lymphocyte count, the odds ratio for decreased CO₂ levels in COVID-19 patients were 4.754 [95% confidence interval (CI): 1.380–16.370, \( P = 0.013 \)]. The hazard ratio for decreased CO₂ levels in COVID-19 patients was 8.710 (95% CI: 2.773–27.365, \( P < 0.001 \)), and 4.754 (95% CI: 1.380–16.370, \( P = 0.013 \)) after adjustment. Furthermore, the Kaplan-Meier curves illustrated that patients with decreased CO₂ levels faced higher mortality risks (Figure 1). With the fitted curves, though, in Figure 2A, the curves of patients with non-decreased CO₂ levels showed a slight downward trend, the CO₂ levels of most patients were increased (Figures 2B–F).

### DISCUSSION

In this latest outbreak of pneumonia due to COVID-19, patients initially presented with fever with or without respiratory symptoms, although various degrees of pulmonary abnormalities developed later in all patients (1, 12). Furthermore, Tian et al. reported the early phase of the lung pathology of COVID-19 pneumonia in a lung cancer excision, which exhibited edema, proteinaceous exudate, focal reactive hyperplasia of pneumocytes with patchy inflammatory cellular infiltration, and multinucleated giant cells. However, hyaline membranes were not prominent (13). A report demonstrated that the rate of critical illnesses among COVID-19 patients was ~26%, and critically ill patients had 61.5% mortality (12, 14). In another study from Wuhan, the 28-day mortality of COVID-19 patients who received...
### TABLE 2 | Laboratory and blood coagulation test results, clinical treatment, and outcomes of 1,776 patients with COVID-19.

| Covariate | All patients (n = 1,776), Median (IQR)/n (%) | Non-declined CO₂ (n = 1,343), Median (IQR)/n (%) | Declined CO₂ (n = 433), Median (IQR)/n (%) | P-value |
|-----------|---------------------------------------------|------------------------------------------------|-------------------------------------------|-------|
| Laboratory test | | | | |
| Leucocyte count, ×10^9/L | | | | |
| 3.5–9.5 | 1,585 (89.35) | 1,211 (76.40) | 374 (23.60) | 0.035 |
| <3.5 | 104 (5.86) | 75 (72.12) | 29 (27.88) | |
| >9.5 | 85 (4.79) | 55 (64.71) | 30 (35.29) | |
| Neutrophil count, ×10^9/L | | | | |
| 1.8–6.3 | 1,553 (87.54) | 1,185 (76.30) | 388 (23.70) | 0.029 |
| <1.8 | 116 (6.54) | 88 (75.86) | 28 (24.14) | |
| >6.3 | 105 (5.92) | 68 (64.76) | 37 (35.24) | |
| Lymphocyte count, ×10^9/L | | | | |
| 1.1–3.2 | 1,457 (82.13) | 1,103 (75.70) | 354 (24.30) | 0.848 |
| <1.1 | 291 (16.40) | 216 (74.23) | 75 (25.77) | |
| >3.2 | 26 (1.47) | 22 (84.62) | 4 (15.38) | |
| Erythrocyte count, ×10^12/L | | | | |
| 4.3–5.8 | 638 (35.85) | 477 (75.00) | 159 (25.00) | 0.820 |
| <4.3 | 1,127 (63.53) | 855 (75.87) | 272 (24.13) | |
| >5.8 | 11 (0.63) | 9 (81.82) | 2 (18.18) | |
| Monocyte count, ×10^9/L | | | | |
| 0.1–0.6 | 1,251 (70.52) | 968 (77.38) | 283 (22.62) | 0.012 |
| <0.1 | 6 (0.34) | 3 (50.00) | 3 (50.00) | |
| >0.6 | 517 (29.14) | 370 (71.57) | 147 (28.43) | |
| Hemoglobin, g/L | | | | |
| 130.0–175.0 | 712 (40.14) | 535 (75.14) | 177 (24.86) | 0.664 |
| <130.0 | 1,057 (59.58) | 803 (75.97) | 254 (24.03) | |
| >175.0 | 5 (0.28) | 3 (60.00) | 2 (40.00) | |
| Platelet count, ×10^9/L | | | | |
| 125.0–350.0 | 1,546 (87.15) | 1,185 (76.65) | 361 (23.35) | 0.011 |
| <125.0 | 76 (4.28) | 48 (63.16) | 28 (36.84) | |
| >350.0 | 152 (8.57) | 108 (71.05) | 44 (28.95) | |
| Albumin, g/L | | | | |
| 40–55 | 449 (25.35) | 340 (75.72) | 109 (24.28) | 0.921 |
| <40 | 1,322 (74.65) | 998 (75.49) | 324 (24.51) | |
| Alanine aminotransferase, U/L | | | | |
| 9–50 | 1,421 (80.24) | 1,076 (75.72) | 345 (24.28) | 0.918 |
| <9 | 96 (5.42) | 71 (73.96) | 25 (26.04) | |
| >50 | 254 (14.34) | 191 (75.20) | 63 (24.80) | |
| Aspartate aminotransferase, U/L | | | | |
| 15–40 | 1,304 (73.63) | 991 (76.00) | 313 (24.00) | 0.175 |
| <15 | 317 (17.90) | 243 (76.66) | 74 (23.34) | |
| >40 | 150 (8.47) | 104 (69.33) | 46 (30.67) | |
| Total bilirubin, µmol/L | | | | |
| 5.0–21.0 | 1,582 (89.33) | 1,207 (76.30) | 375 (23.70) | 0.099 |
| <5.0 | 120 (6.78) | 82 (68.33) | 38 (31.67) | |
| >21.0 | 69 (3.90) | 49 (71.01) | 20 (28.99) | |

(Continued)
| Covariate                                      | All patients (n = 1,776), Median (IQR)/n (%) | Non-declined CO₂ (n = 1,343), Median (IQR)/n (%) | Declined CO₂ (n = 433), Median (IQR)/n (%) | P-value |
|------------------------------------------------|---------------------------------------------|--------------------------------------------------|---------------------------------------------|---------|
| Creatinine, µmol/L                             |                                             |                                                  |                                             | <0.001  |
| 64.0–104.0                                     | 812 (45.72)                                 | 627 (77.22)                                      | 185 (22.78)                                 |         |
| <64.0                                          | 877 (49.38)                                 | 674 (76.85)                                      | 203 (23.15)                                 |         |
| >104.0                                         | 87 (4.90)                                   | 42 (48.82)                                       | 45 (51.72)                                  |         |
| Procalcitonin, ng/mL                           |                                             |                                                  |                                             | 0.002   |
| <0.05                                          | 999 (66.42)                                 | 770 (77.08)                                      | 229 (22.92)                                 |         |
| > =0.05                                        | 505 (33.58)                                 | 352 (69.70)                                      | 153 (30.30)                                 |         |
| Interleukin-6, pg/mL                           |                                             |                                                  |                                             | 0.247   |
| 0–7.0                                          | 602 (83.96)                                 | 445 (73.92)                                      | 157 (26.08)                                 |         |
| >7.0                                           | 115 (16.04)                                 | 79 (68.70)                                       | 36 (31.30)                                  |         |
| SARS-CoV-19 IgM                                |                                             |                                                  |                                             | 0.598   |
| No                                             | 387 (64.61)                                 | 303 (78.29)                                      | 84 (21.71)                                  |         |
| Yes                                            | 212 (35.39)                                 | 162 (76.42)                                      | 50 (23.58)                                  |         |
| SARS-CoV-19 IgG                                |                                             |                                                  |                                             | 0.772   |
| No                                             | 49 (8.67)                                   | 37 (75.51)                                       | 12 (24.49)                                  |         |
| Yes                                            | 516 (91.33)                                 | 399 (77.33)                                      | 117 (22.67)                                 |         |
| Blood coagulation test                         |                                             |                                                  |                                             |         |
| Prothrombin time, s                            |                                             |                                                  |                                             | <0.001  |
| 9.4–12.5                                       | 1,461 (92.41)                               | 1,126 (77.07)                                    | 335 (22.93)                                 |         |
| <9.4                                           | 1 (0.06)                                    | 1 (100.00)                                       | 0 (0)                                       |         |
| >12.5                                          | 119 (7.53)                                  | 64 (53.76)                                       | 55 (46.22)                                  |         |
| International Normalized Ratio                 |                                             |                                                  |                                             | 0.004   |
| 0.8–1.3                                        | 1,504 (85.13)                               | 1,144 (76.06)                                    | 360 (23.94)                                 |         |
| <0.8                                           | 19 (1.20)                                   | 14 (73.88)                                       | 5 (26.32)                                   |         |
| >1.3                                           | 58 (3.67)                                   | 33 (56.90)                                       | 25 (43.10)                                  |         |
| Activated partial thromboplastin time, s       |                                             |                                                  |                                             | 0.012   |
| 25.1–36.5                                      | 1,038 (65.65)                               | 785 (75.63)                                      | 253 (24.37)                                 |         |
| <25.1                                          | 462 (29.22)                                 | 356 (77.06)                                      | 106 (22.94)                                 |         |
| >36.5                                          | 81 (5.12)                                   | 50 (61.73)                                       | 31 (38.27)                                  |         |
| Fibrinogen, (g/L)                              |                                             |                                                  |                                             | 0.291   |
| 2.38–4.98                                      | 1,178 (74.51)                               | 883 (74.96)                                      | 296 (25.04)                                 |         |
| <2.38                                          | 307 (19.42)                                 | 240 (78.18)                                      | 67 (21.82)                                  |         |
| >4.98                                          | 96 (6.07)                                   | 68 (70.83)                                       | 28 (29.17)                                  |         |
| Thrombin time, s                               |                                             |                                                  |                                             | 0.930   |
| <=16.6                                         | 237 (14.99)                                 | 178 (75.11)                                      | 59 (24.89)                                  |         |
| >16.6                                          | 1,344 (85.01)                               | 1,013 (75.37)                                    | 331 (24.63)                                 |         |
| D-dimer, g/L                                   |                                             |                                                  |                                             | 0.41    |
| Clinical treatment                              |                                             |                                                  |                                             |         |
| Drugs                                          |                                             |                                                  |                                             | <0.001  |
| Antibiotic                                     | 515 (29.00)                                 | 377 (73.20)                                      | 138 (26.80)                                 | 0.130   |
| Antiviral drugs                                 | 858 (48.31)                                 | 665 (76.34)                                      | 203 (23.66)                                 | 0.494   |
| Antimalarial drugs                              | 139 (7.83)                                  | 108 (77.70)                                      | 31 (22.30)                                  | 0.552   |
| Anticoagulants                                  | 119 (6.70)                                  | 79 (66.39)                                       | 40 (33.61)                                  | 0.015   |
| Corticosteroid                                 | 104 (5.86)                                  | 72 (69.23)                                       | 32 (30.77)                                  | 0.118   |
| Vitamin C                                      | 246 (13.85)                                 | 187 (76.02)                                      | 59 (23.98)                                  | 0.876   |
| Traditional Chinese medicine                   | 1,523 (85.75)                               | 1,159 (76.10)                                    | 364 (23.90)                                 | 0.247   |
TABLE 2 | Continued

| Covariate                      | All patients \((n = 1,776)\), Median (IQR)/n (%) | Non-declined CO\(_2\) \((n = 1,343)\), Median (IQR)/n (%) | Declined CO\(_2\) \((n = 433)\), Median (IQR)/n (%) | \(P\)-value |
|--------------------------------|---------------------------------------------------|----------------------------------------------------------|---------------------------------------------------|-------------|
| Oxygen support                 |                                                   |                                                          |                                                   |             |
| Low–flow nasal cannula         | 269 (15.15)                                      | 226 (84.01)                                              | 43 (15.99)                                        | <0.001      |
| Positive pressure nasal cannula| 34 (1.91)                                        | 27 (79.41)                                               | 7 (20.59)                                         | 0.603       |
| High–flow nasal cannula        | 16 (0.90)                                        | 13 (81.25)                                               | 3 (18.75)                                         | 0.598       |
| Invasive mechanical ventilation| 5 (0.30)                                         | 1 (20.00)                                                | 4 (80.00)                                         | 0.004       |
| ECMO                           | 1 (0.06)                                         | 0 (0)                                                    | 1 (100.00)                                       | 0.078       |
| Outcomes                       |                                                   |                                                          |                                                   |             |
| CT scores                      |                                                   |                                                          |                                                   | 0.416       |
| 1–4                            | 74 (39.57)                                       | 57 (77.03)                                               | 17 (22.97)                                        |             |
| 5–7                            | 113 (60.43)                                      | 81 (71.68)                                               | 32 (28.32)                                        |             |
| Disease progression            |                                                   |                                                          |                                                   | <0.001      |
| Stableness/hospitalization     | 1 (0.06)                                         | 1 (100.00)                                               | 0 (0)                                             |             |
| Improvement/recover            | 1,738 (99.09)                                    | 1,323 (76.12)                                            | 415 (23.88)                                       |             |
| Death                          | 15 (0.86)                                        | 4 (26.67)                                                | 11 (73.33)                                        |             |
| Days in hospital, median (IQR) | 18 (13–24)                                       | 18 (13–24)                                               | 18 (12–23)                                        | <0.001      |
| ICU care                       | 29 (90.63)                                       | 18 (62.07)                                               | 11 (37.93)                                        |             |
| Severity on admission          |                                                   |                                                          |                                                   | 0.359       |
| Mild/common                    | 1,473 (82.94)                                    | 1,123 (76.24)                                            | 350 (23.76)                                       |             |
| Severe                         | 281 (15.82)                                      | 205 (72.95)                                              | 76 (27.05)                                        |             |
| Critical                       | 22 (1.24)                                        | 15 (68.18)                                               | 7 (31.82)                                         |             |
| Severity at worst              |                                                   |                                                          |                                                   | 0.226       |
| Mild/common                    | 928 (52.40)                                      | 718 (77.40)                                              | 210 (22.60)                                       |             |
| Severe                         | 800 (45.20)                                      | 592 (74.00)                                              | 208 (26.00)                                       |             |
| Critical                       | 43 (2.40)                                        | 31 (72.10)                                               | 12 (27.90)                                        |             |

TABLE 3 | The hazards ratio and odds ratio associated with decreased CO\(_2\) of patients with COVID-19 mortality/severity.

| Group                        | COX regression analysis | Logistic regression analysis |
|------------------------------|-------------------------|-----------------------------|
|                              | HRs                     | 95 % CI                     | \(P\)-value | ORs                      | 95 % CI                     | \(P\)-value |
| Univariate analysis          |                         |                             |             |                         |                             |             |
| Non-declined                 | Ref                     |                             |             | Ref                     |                             |             |
| Declined                     | 8.710                   | 2.773–27.365               | <0.001      | 1.213                   | 0.617–2.384                | 0.575       |
| Multivariate Analysis*       |                         |                             |             |                         |                             |             |
| Non-declined                 | Ref                     |                             |             | Ref                     |                             |             |
| Declined                     | 4.754                   | 1.380–16.370               | 0.013       | 0.960                   | 0.431–2.094                | 0.900       |

*Adjust for Age, History of cardiovascular disease, Erythrocyte count, Hemoglobin, Leucocyte count, Platelet count, Lymphocyte count, Oxygen support.

mechanical ventilation (MV) was 81%, and patients with the acute respiratory distress syndrome (ARDS) had a mortality rate of nearly 50% \((14, 15)\). Thus, it is undisputed that the lungs and airways are the target organs of this coronavirus infection.

In this study, we first proposed the correlation of patient prognosis with decreased CO\(_2\) levels. According to the adjusted logistic regression, Cox regression analyses, and Kaplan-Meier curves, decreased CO\(_2\) levels influenced the mortality of patients with COVID-19, but not disease severity. Furthermore, this influence on mortality did not differ by sex. However, decreased CO\(_2\) levels in patients with comorbidity of cardiovascular disease or older age indicated poorer prognosis. Moreover, blood coagulation parameters, such as prothrombin time, international normalized ratio, active partial thromboplastin time, and D-dimer level, showed significant differences between COVID-19 patients with decreased and non-decreased CO\(_2\) levels; however, decreased CO\(_2\) levels showed no significant differences in other laboratory parameters.
The measurement of the CO₂ level is vital in airway management. Capnography is an effective method for the early detection of impaired airway function to identify early respiratory depression and airway disorders (16–18). For example, capnography presented results range 5–240 s earlier than dose pulse oximetry, and in many cases with sedation-induced apnea, doctors at the bedside did not recognize the apnea, whereas capnography could identify it (19, 20). Furthermore, capnography reduces serious complications by early diagnosis (16) and plays a critical role in detecting the CO₂ level of COVID-19 patients, in whom the target organs are the lungs and airways.

Elevated CO₂ levels and hypoxemia were associated with a poor prognosis in COVID-19 patients. For example, in the study conducted by Nuckton et al. (21), elevated CO₂ level likely reflected ARDS severity and an increased dead space fraction. Similarly, Yang et al. reported that most COVID-19 patients usually develop severe pneumonia and are at a high risk factor of ARDS (22). Furthermore, Buchner et al. directly identified that patients with more severe CO₂ retention might have a poor prognosis (23). Thus, most pneumonia patients with high CO₂ levels had poor prognosis.

In our study cohort, we found that decreased CO₂ levels increased mortality but had no significant effect on the disease severity. According to previous studies, the causes of decreased CO₂ levels are as follows: shortness of breath, reduction of pulmonary perfusion and increased alveolar dead space, and MV hyperventilation (11, 24, 25). Because most COVID-19
patients require various forms of oxygen support, among other treatments, we thought that clinicians should focus their attention on MV hyperventilation (26), which is an effective and practical measure to improve patients’ survival. Furthermore, according to the fitted curves, compared with pneumonia patients with non-decreased CO₂ levels, the other study groups’ trend showed an initial decrease and subsequent increase in CO₂ levels. This indicates that the oxygen flow was adjusted to meet the patients’ requirements to treat pneumonia and prevent a decrease in the CO₂ levels due to hyperventilation.

This study has several limitations. Because the Leishenshan hospital was rapidly built as a designated hospital for COVID-19, it was difficult to share laboratory testing data with other hospitals. Thus, the data may be biased. For example, according to our study, there was no correlation between decreased CO₂ levels and illness severity in COVID-19 patients. Furthermore, the mechanism of how oxygen support influences CO₂ levels and thus affects patients’ prognoses requires laboratory verification. However, this study makes a significant scientific contribution by providing evidence indicating that clinicians should pay attention to decreased CO₂ levels in pneumonia patients with COVID-19, and so to prevent hypocapnia and maintain homeostasis.

In this study, we demonstrated that decreased CO₂ levels increased the mortality risk of COVID-19 patients, but showed no significant impact on the severity of pneumonia. Furthermore, our study serves as evidence for clinicians to pay greater attention to the oxygen flow in COVID-19 patients who receive oxygen support to avoid treatment-related injuries. With these changes, the complications of COVID-19 can be further reduced, thereby improving the prognosis of COVID-19 patients with pneumonia.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/supplementary material, further inquiries can be directed to the corresponding authors.

AUTHOR CONTRIBUTIONS

SC, JH, YH, ML, and WL undertook the research. SW and QL performed the analyses and interpretation of data. DH, JL, and RG wrote the main manuscript text and prepared figures. ZL, LG, and XW revised the article critically for important intellectual content and final approval of the version to be submitted. All authors contributed to the design of the study, writing of the manuscript, reviewed, and approved the manuscript.

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Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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