Analysis of 92 deceased patients with COVID-19

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Abstract
This retrospective study aimed to analyze the clinical characteristics and complications in death cases with novel coronavirus disease-19 (COVID-19). We collected the medical records of 92 patients with COVID-19, who died in the time period ranging from 6 January 2020 to 25 February 2020, in Renmin Hospital of Wuhan University and summarized the clinical characteristics of complications. There were 91 death cases in which different complications were developed, including acute respiratory distress syndrome (ARDS) (73/91), myocardial injury (31/91), liver injury (15/91), renal insufficiency (14/91), multiple organ dysfunction syndrome (MODS) (14/91), and pneumothorax (1/91). Among these patients, 83 patients had at least one complication. However, one patient who died of recurrent gastrointestinal bleeding was not directly linked to COVID-19. The main complications of deceased patients with COVID-19 were ARDS, myocardial injury, liver injury, renal insufficiency, and MODS.

KEYWORDS
ARDS, complications, COVID-19, inflammatory, SARS-CoV-2

1 | INTRODUCTION
Since December 2019, there has been an outbreak of a novel coronavirus disease-9 (COVID-19) in Wuhan, China. The coronavirus has been named as severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) currently, which has a phylogenetic similarity to SARS-CoV.1 Patients with COVID-19 have been documented both in hospitals and in community. In total, 81865 cases of COVID-19, including 3335 death cases till 8 April, have been confirmed. The average mortality rate was about 4.07%.2 The common clinical manifestations were fever, dry cough, fatigue, myalgia, dyspnea, normal or decreased leukocyte counts, and radiographic evidence of pneumonia. In severe cases, patients were prone to various complications, especially death cases.3-6 To illustrate the clinical characteristics of complications, we collected medical records of 92 deceased patients with COVID-19.

2 | METHODS
2.1 | Patients
In this study, medical records of 92 patients with COVID-19, enrolled in Renmin Hospital of Wuhan University, who died during the time period ranging from 6 January 2020 to 25 February 2020 were collected. All patients were laboratory-confirmed positives of SARS-CoV-2, as determined by quantitative RT-PCR on nasopharynx swab samples. Diagnosis of COVID-19 was based on the New Coronavirus Pneumonia Prevention and Control Program (3rd edition), published by the National Health Commission of China.7 The study was approved by the Institutional Ethics Committee of Renmin Hospital of Wuhan University.
2.2 | Data collection and definitions

The information of patients who died of COVID-19 was collected, including medical records, laboratory results, and computed tomography. The entire information was obtained and curated with a customized data collection form. Two investigators independently reviewed the data collection forms to verify data accuracy. Complication was defined as a dangerous disease or condition arising from COVID-19. Acute respiratory distress syndrome (ARDS) was diagnosed according to the Berlin definition. The cause of death generally means condition or diseases leading to death directly.

2.3 | Statistical analysis

A statistical analysis was done with SPSS, version 20.0. The results were expressed as means ± SD or median (interquartile range). The Student t test was performed to examine the differences between groups. P value less than .05 was considered as statistically significant.

3 | RESULTS

3.1 | Clinical characteristics of deceased patients with COVID-19

As shown in Table 1, the average age of 92 patients was 69.8 ± 14.5 years, ranging from 30 to 97 years, including 49 males and 43 females. The mean survival time from the onset of symptoms to death was 14.3 ± 6.0 days. In total, 91 patients presented with at least one complication, including ARDS (73/91), myocardial injury (31/91), liver injury (15/91), renal injury (14/91), multiple organ dysfunction syndrome (MODS) (14/91), and pneumothorax (1/91). In addition, there was one patient who died of recurrent esophageal varices from cirrhosis, indirectly related to COVID-19.

3.2 | Underlying disease

In total, 65 patients had underlying diseases, which were hypertension (51/92), heart disease (16/92), diabetes (13/92), cerebrovascular disease (10/92), malignancy (4/92), chronic liver diseases (3/92), chronic renal insufficiency (2/92), hematological system disease (2/92), and chronic obstructive pulmonary disease (1/92) (Table 1).

3.3 | The causes of death

The causes of death in patients with COVID-19 were ARDS (73/92), septic shock (7/92), myocardial infarction (6/92), heart failure (2/92), MODS (2/92), esophageal varices (1/92), and pneumothorax (1/92) (Table 1).

| TABLE 1 | Clinical features of deceased patients with COVID-19 |
| --- | --- |
| **Clinical features** | **Average age (range) (N = 92)** 69.8 ± 14.5 (30.0-97.0) |
| Age group, y | 20-40 4/92 (4.3%) |
| | 41-60 19/92 (20.6%) |
| | 61-80 47/92 (51.1%) |
| | >80 22/92 (23.9%) |
| **Sex** | Male 49/92 (53.3%) |
| | Female 43/92 (46.7%) |
| **Chronic underlying disease (N = 92)** | All 65/92 (70.7%) |
| | Hypertension 51/92 (56.1%) |
| | Heart disease 16/92 (20.7%) |
| | Diabetes 13/92 (18.3%) |
| | Cerebrovascular disease 10/92 (10.9%) |
| | Malignancy 4/92 (4.3%) |
| | Chronic liver disease 3/92 (3.3%) |
| | Chronic renal insufficiency 2/92 (2.2%) |
| | Hematological system disease 2/92 (2.2%) |
| | Chronic obstructive pulmonary disease 1/92 (1.1%) |
| **Number of comorbidity diseases** | 0 27/92 (29.3%) |
| | 1 30/92 (32.6%) |
| | 2 23/92 (25.0%) |
| | ≥3 12/92 (13.0%) |
| **Survival time from the onset of symptoms to death (N = 92)** | Median survival time (range), d 14.3 ± 6.0 (3-31) |
| | 3-7 9/92 (9.8%) |
| | 8-14 44/92 (47.8%) |
| | 15-21 28/92 (30.4%) |
| | 22-28 8/92 (8.7%) |
| | >28 3/92 (3.3%) |
| **Complications (N = 91)** | ARDS 73/91 (80.2%) |
| | Myocardial injury 31/91 (34.1%) |
| | Liver injury 15/91 (16.5%) |
| | Renal injury 14/91 (15.4%) |
| | MODS 14/91 (15.4%) |
| | Pneumothorax 1/91 (1.1%) |
| **The causes of death (N = 92)** | ARDS 73/92 (79.3%) |
| | Septic shock 7/92 (7.6%) |
| | Myocardial infarction 6/92 (6.5%) |
| | Heart failure 2/92 (2.2%) |
| | MODS 2/92 (2.2%) |
| | Pneumothorax 1/92 (1.1%) |
| | Esophageal varices 1/92 (1.1%) |

Note: Data are presented as mean ± SD, n/N (%), and N represents the number of patients included in the study. Complications were counted except one patient who died of recurrent gastrointestinal bleeding. Abbreviations: ARDS, acute respiratory distress syndrome; COVID-19, coronavirus disease 2019; MODS, multiple organ dysfunction syndrome.
3.4 | Acute respiratory distress syndrome

The main death cause of COVID-19 in this study was ARDS (73/92).

3.5 | Pneumothorax

There was one patient who had fever for 3 days and he/she died of pneumothorax on day 5 of hospitalization.

3.6 | Inflammatory markers

The inflammatory markers, including procalcitonin (PCT), C-reactive protein (CRP), and serum amyloid A (SAA), were investigated in this study. During hospitalization, 39 patients had a high level of inflammatory markers. Also, 28 patients showed a high level of PCT (>10-fold), 34 patients had a high level of CRP (>5-fold), and 30 patients had a high level of SAA (above 300 mg/L). Median levels of PCT, CRP, and SAA in patients with inflammation state were 1.80 ng/mL (P < .05), 148.0 (P < .01), and 300.0 mg/L (P < .01), respectively, compared with patients without inflammation state (shown in Table 2).

3.7 | Myocardial injury

There were 31 patients who had increased myocardial enzymes during hospitalization. Also, 31 patients had abnormal cardiac troponin I (cTnI) (upper limited unit [ULN] < 0.04 ng/mL), and in 24 patients, it was much higher than 0.78 ng/mL, which means an obvious myocardial injury. In addition to cTnI, there was also an increase in creatine kinase-MB (CK-MB) and myoglobin (Mb). In patients with myocardial injury, the median levels of cTnI (P < .05), CK-MB (P < .05), and Mb (P < .05) were 2.47 ng/mL, 6.8 ng/mL, and 629.0 μg/L, respectively, compared with patients without myocardial injury (shown in Table 2).

3.8 | Liver injury

There were 15 patients who experienced liver injury in our study. In total, 10 patients had elevated alanine aminotransferase (ALT) and aspartate aminotransferase (AST), more than three times of ULN, and four patients had increased total bilirubin (TBIL) (more than three times of ULN). The highest TBIL of 92 patients was 439 μmol/L. The median levels of ALT, AST, and TBIL in patients with liver injury were 117 U/L (P > .05), 157 U/L (P > .05), and 47.0 μmol/L (P < .05) (Table 2), respectively, compared with patients without liver injury. We also collected the level of albumin; the average albumin of 92 patients with COVID-19 was 31.1 ± 4.4 g/L (data not showed), lower than ULN (>35 g/L).

3.9 | Renal insufficiency

There were 14 patients who suffered renal injury after infection of SARS-CoV-2. None of them had chronic renal insufficiency.

### TABLE 2 | Characters of laboratory findings in deceased patients with COVID-19

|                      | All patients (N = 92) | With complication | Without complication | P value |
|----------------------|-----------------------|-------------------|----------------------|---------|
| **Inflammatory markers** |                       |                   |                      |         |
| PCT (<0.10 ng/mL)    | 0.08 (0.01-95.7)       | 1.80 (0.10-95.7)  | 0.04 (0.01-0.09)     | .02     |
| CRP (0-10.0 mg/L)    | 40.0 (3.2-200.0)       | 148.0 (12.0-200.0)| 21.8 (3.2-199.3)     | <.01    |
| SAA (<10.0 mg/L)     | 175.0 (21.0-300.0)     | 300.0 (38.5-300.0)| 123.0 (21.0-300.0)   | <.01    |
| **Myocardial injury** |                       |                   |                      |         |
| cTnI (0-0.04 ng/mL)  | 0.97 (0.006-92.40)     | 2.47 (0.13-92.40) | 0.02 (0.006-0.03)    | .016    |
| CK-MB (0.5-5.0 ng/mL)| 3.2 (1.0-300.0)        | 6.8 (2.1-300.0)   | 2.9 (1.0-32.0)       | .227    |
| Mb (0-110.0 μg/L)    | 619.5 (25.2-1000.0)    | 629.0 (45.8-1000.0)| 26.3 (25.2-125.4)   | <.01    |
| **Liver injury**     |                       |                   |                      |         |
| ALT (9-50 U/L)       | 27 (3-1693)            | 117 (55-1693)     | 26 (3-50)            | .058    |
| AST (15-40 U/L)      | 31 (11-6000)           | 157 (70-6000)     | 31 (11-40)           | .144    |
| TBIL(0-23.0μmol/L)   | 13.6 (4.2-439.0)       | 47.0 (24.0-439.0) | 12.0 (4.2-22.7)      | .016    |
| **Renal insufficiency** |                     |                   |                      |         |
| Scr (44-133 μmol/L)  | 86 (34-428)            | 262 (139-428)     | 79 (34-124)          | <.01    |
| BUN (3.6-9.5 mmol/L) | 8.9 (3.4-48.0)         | 30.0 (21.0-48.0)  | 8.6 (3.4-25.8)       | <.01    |
| GFR (>90.0 mL/min)   | 89.6 (9.0-135.0)       | 18.0 (9.0-38.0)   | 91.5 (49.5-135.0)    | <.01    |

Note: Data are presented as median (interquartile range) and P values comparing abnormal and normal are derived from Student’s t-test. Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; BUN, blood urea nitrogen; CK-MB, creatine kinase-MB; COVID-19, novel coronavirus disease-19; CRP, C-reactive protein; cTnI, cardiac troponin I; GFR, glomerular filtration rate; Mb, myoglobin; PCT, procalcitonin; SAA, serum amyloid A; Scr, serum creatinine; TBIL, total bilirubin.
Also, seven patients were found with elevated serum creatinine (SCr) at admission. However, there were other seven patients who had normal SCr at admission and an increased level of SCr in the second test, accompanied by a decrease in glomerular filtration rate (GFR). The median levels of SCr, blood urea nitrogen, and GFR in patients with renal insufficiency were 262 μmol/L (P < .01), 30.0 mmol/L (P < .01), 18.0 mL/min (P < .01), respectively, compared with the patients without renal injury (shown in Table 2).

### 3.10 Multiple organ dysfunction syndrome

There were 14 patients who had multiple organ dysfunction syndrome (MODS). Among them, PCT increased significantly in 12 patients, suggesting a possible infection, and 4 patients were associated with myocardial injury.

### 4 DISCUSSION

The most common complication was ARDS (73/92) in COVID-19, which was similar to SARS outbreak in 2003. The histological examination of death cases showed bilateral diffuse alveolar damage with cellular fibromyxoid exudates. An evident desquamation of pneumocytes and hyaline membrane formation indicated acute respiratory distress syndrome. Similar to the SARS, after heavy inflammation lesions of lung, some patients progressed to pulmonary fibrosis, which could affect lung function in the long term, especially in old age.

It was reported that cardiovascular complications were common in patients with SARS. In this study, 31 patients had obvious myocardial damage with increased levels of cTn. The median levels of cTnI and Mb in patients with myocardial injury increased significantly, compared with the patients without myocardial injury. There were six patients who were diagnosed with myocardial infarction, which was fatal. The potential mechanism for COVID-19‐caused myocardial injury might be a virus‐induced cytokine storm. Inflammatory cell infiltration and inflammatory cytokines release can directly lead to apoptosis or necrosis of myocardial cells.

The inflammatory markers (PCT, CRP, and SAA) were elevated frequently in patients with COVID‐19. The median levels of PCT, CRP, and SAA increased significantly in patients with inflammation, which suggests that the pathogenesis of COVID‐19 is related to systemic inflammatory response syndrome that may result in MODS.

Studies have shown that cytokine storms are associated with the exacerbation of a variety of infectious diseases, including SARS and avian influenza. Some related clinical data also suggest that cytokine storm could be associated with disease severity. Therefore, controlling the overt inflammatory response induced by COVID‐19 may be essential for reducing mortality among critically ill patients with COVID‐19. According to guidelines, low dose (1–2 mg/kg weight) of corticosteroids had been used for 3–5 days to reduce inflammation. However, corticosteroids may not only inhibit the immune system but also increase the chance of secondary bacterial infection and viral shedding period. Hence, their use is still controversial.

It is observed that more than 60% of SARS patients had liver damage, and patients infected with Middle East respiratory syndrome CoV also experienced liver injury. Some studies have reported liver injury in patients with COVID‐19 was common. There were 15 cases experienced liver damage in this research. Pathology study confirmed the presence of virus in liver tissue of patients with SARS, but no virus inclusion bodies were detected, which was similar to autopsy of COVID‐19. A preliminary study showed that the SARS‐CoV‐2 receptor, angiotensin‐converting enzyme 2 (ACE2), was highly expressed in bile duct cells, suggesting that SARS‐CoV‐2 may directly bind to ACE2‐positive bile duct cells and lead to liver dysfunction. It showed that liver injury associated with COVID‐19 may also be due to drug hepatotoxicity, and immune‐mediated inflammation, such as cytokine storms, may also lead to liver damage. Furthermore, liver injury and malnutrition may lead to hypoalbuminemia.

There were 14 patients who suffered renal insufficiency in this study. The median levels of SCR, BUN, and GFR in patients with renal injury showed a statistical significance, compared with the patients without renal injury. Researchers reported that ACE2 receptor of SARS‐CoV was highly expressed in renal tubules, and a recent study indicated that SARS‐CoV‐2 virus can directly infect human renal tubules and consequently lead to an acute renal tubular injury, which means that the infection of SARS‐CoV may damage human renal tubules through the ACE2 receptor. However, more clinical data are needed for interpretation.

In summary, as an emerging infectious disease, SARS‐CoV‐2 caused multiple organ infection. ARDS had the highest incidence, and it was the most common cause of death. In addition, myocardial cell damage and liver and renal damages had been observed in patients with COVID‐19. Among critical patients, aged more than 60 years, underlying diseases and multiple organ failure were common characteristics. Oxygen therapy should be considered during the occurrence of hypoxemia. Early diagnosis and treatment will be helpful to prevent complications and reduce mortality.

### CONFLICT OF INTERESTS

The authors declare that there are no conflict of interests.

### AUTHOR CONTRIBUTIONS

FY prepared and drafted the manuscript, and SS, JZ, JS, and KD helped to collect data. XC revised the paper. All authors approved the final version of the manuscript before submission.

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