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Disclosing COVID-19's Global Impact: From Causes to Direct Reactions

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RESEARCH ARTICLE

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Abstract: Importance Following its initial report in Wuhan, China, the coronavirus disease 2019 (COVID-19) is a new infectious disease that has since spread throughout the world. The clinical consequences of COVID-19 pneumonia are not well defined in terms of risk factors at this time.

Objective to provide an account of the clinical features and results in COVID-19 pneumonia patients who either died or experienced acute respiratory distress syndrome (ARDS).

Participants, Design, and Environment A retrospective cohort analysis was conducted on 201 patients who were admitted to Wuhan Jinyintan Hospital in China between December 25, 2019, and January 26, 2020, and had confirmed cases of COVID-19 pneumonia. The follow-up period ended on February 13, 2020.

Exposures: Pneumonia with COVID-19 confirmed.

Principal Results and Measures the progression of ARDS and demise. Additionally gathered and examined were data related to epidemiology, demographics, clinical, laboratory, management, treatment, and outcome.

Results The interquartile range for the 201 patients was 43–60 years, with a median age of 51 years. Of these, 128 patients (63.7%) were male. Eighty-four (41.8%) of the patients experienced ARDS, and 44 (52.4%) of them passed away. More patients with dyspnea (50 of 84 [59.5 percent] patients and 30 of 117 [25.6 percent] patients, respectively [difference, 33.9 percent; 95 percent CI, 19.7 percent -48.1 percent]) and comorbidities like hypertension (23 of 84 [27.4 percent] patients and 16 of 117 [13.7 percent] patients, respectively [difference, 13.7 percent ; 95 percent CI, 1.3 percent -26.1 percent]) and diabetes were present in those who developed ARDS compared to those who did not (16 of 84 [19.0 percent] patients and 6 of 117 [5.1 percent] patients, respectively [difference, 13.9 percent ; 95 percent CI, 3.6 percent -24.2 percent]). Risk factors connected to the onset of ARDS and its progression were found in bivariate Cox regression analysis.

Conclusions and Pertinence Due to a less robust immune response, older age was linked to a higher risk of developing ARDS and death. While having a high fever was linked to the development of ARDS, it was also linked to better outcomes for ARDS patients. Furthermore, patients who develop ARDS may benefit from methylprednisolone treatment.

Keywords: *Coronavirus, SARS-CoV-2, Mortality, Risk Factors, Retrospective Cohort Analysis*

Introduction:

Following its initial discovery in Wuhan, Hubei Province, China, the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has now spread to 37 other countries, including the US, Japan, Australia, and France. In January 2020, SARS-CoV-2—a distinct clade within the sarbecovirus subgenus of the Orthocoronavirinae subfamily—was discovered as the causative agent of COVID-19, or coronavirus illness. The most common symptoms that COVID-19 patients

experience are fever, myalgia or exhaustion, and dry cough. While most patients are believed to have a good prognosis, outcomes can be worse for older people and those with long-term underlying medical issues. Within a week of the disease's inception, patients with severe illnesses may have dyspnea and hypoxemia, which could swiftly lead to end-organ

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failure or acute respiratory distress syndrome (ARDS). 4 A number of COVID-19's clinical traits and epidemiological traits have been previously documented. However, the risk variables associated with poor clinical outcomes have not been well defined, and most investigations were based on relatively small sample numbers. Here, we describe the clinical features and risk factors for ARDS development following hospital admission as well as the course of ARDS to death in COVID-19 pneumonia patients from a single Wuhan, China hospital.

Techniques: Population Study

This study is a retrospective cohort of 201 hospitalised patients, aged 21–83, receiving treatment at Jinyintan Hospital in Wuhan, China, for confirmed cases of COVID-19 pneumonia. Every patient had COVID-19 pneumonia, according to the World Health Organization's interim standards. According to hospital data, six patients were admitted between December 25, 2019, and January 26, 2020. Huang et al. and Chen et al. have previously published reports on ten of the 201 cases. 3 The study was approved by the ethical council of Jinyintan Hospital, and participants were permitted to withhold their informed consent.

Procedures

Reviewing and gathering clinical, epidemiological, and outcome data from electronic medical records was done by a team of medical professionals and medical students with training. Individuals were monitored through February 13, 2020. Each component of each definition of clinical outcomes was recorded independently and examined by two writers (C.W. and X.C.). The deidentified patient identification was assigned to safeguard patient confidentiality, and the computer containing the electronic data was password-protected and secured.

Using the same previously described technique, throat swab samples were taken from each patient upon admission in order to detect SARS-CoV-2 infection. Real-time reverse transcriptase–polymerase chain reaction assays were then employed to examine the samples. 3 As previously mentioned, the pathogenic detection was established in four institutions: the Chinese Academy of Medical Sciences, the Chinese Center for Disease Control and Prevention, the Academy of Military Medical Sciences, and the Wuhan Institute of Virology of the Chinese Academy of Sciences.

Real-time reverse transcriptase–polymerase chain reaction tests were also used to detect other respiratory infections in 173 individuals, such as respiratory syncytial virus, adenovirus, parainfluenza virus, influenza A virus, and influenza B virus. Through sputum culture, potential bacterial or fungal pathogens were identified. Patients also had computed tomography or chest x-rays, as well as regular blood testing, coagulation, biochemical tests, and blood gas analysis.

Nasal cannula, noninvasive mechanical ventilation (NMV), invasive mechanical ventilation (IMV), or IMV plus extracorporeal membrane oxygenation (ECMO)—the highest degree of oxygen assistance provided during hospitalization—was documented. Unless otherwise noted, the majority of the clinical data included in this investigation was obtained on the first day of hospital admission. The highest patient temperature was determined using the self-reported highest temperature before to hospital admission in order to reduce therapeutic interference during hospitalisation. 65 years of age or older was considered elder. 37.3 °C or higher was the threshold for fever, while 39 °C or above was the threshold for high fever.

Outcomes

The onset of ARDS and the mortality of ARDS patients were the two outcomes that were assessed. To define ARDS, the World Health Organization's interim guidelines were employed. Sixth Statistical Extraction

In descriptive analyses, the variables were reported as number or median (interquartile range [IQR]) (percent). Variations in the patient characteristic distributions across outcome subgroups are presented with 95% confidence intervals. The $\chi 2$ test or the Fisher exact test were used to compare categorical data. The Mann-Whitney-Wilcoxon test was utilised to examine continuous data that was distributed nonnormally.

To calculate the HRs and 95% confidence intervals (CIs) between individual factors on the onset of ARDS or the progression of ARDS to death, bivariate Cox proportional hazard ratio (HR) models were employed. Different sample sizes were caused by missing data. Using the log-rank test and the Kaplan-Meier method, survival curves were created. The interval between hospital admission and events (ARDS or death) was called the "time to events."

Nonmissing data served as the foundation for the analyses pertaining to the various components; missing data was not imputed. Every test was two-sided, and statistical significance was defined as a P value of less than.05. IBM SPSS version 23.0 or R software version 3.6.0 were used for all analyses (R Foundation for Statistical Computing).

Results

Demographics and Characteristics

This study had 201 patients in total. 128 people (63.7%), with a median age of 51 years (IQR, 43-60 years), were male. Fever (n = 188 [93.5 percent]), cough (n = 163 [81.1 percent]), productive cough (n = 83 [41.3 percent]), dyspnea (n = 80 [39.8 percent]), and weariness or myalgia (n = 65 [32.3 percent]) were the most often self-reported symptoms at the beginning of the illness. The majority of patients (n = 154, or 76.6 percent) had fever and cough; 74 patients (34.8 percent) had fever and dyspnea; 66 patients (32.8 percent) had fever and headache, myalgia, or exhaustion; and 13 patients (6.5 percent) had fever alone. Radiographic imaging revealed bilateral infiltrates in 191 individuals (95.0%), while unilateral infiltrates were found in 10 patients (5.0%). There were sixty-six (32.8%) patients with comorbidities.

Treatments in Hospital

Out of the 201 patients, 165 (82.1%) required oxygen support during their hospital stay. The most intensive levels among these that were reported were nasal cannula (n = 98, NMV (n = 61 [30.3 percent]), IMV (n = 5 [2.5 percent]), and IMV with ECMO (n = 1 [0.5 percent]). Antiviral therapy (n = 170 [84.6 percent]) and empirical antibiotic treatment (n = 134 [66.7 percent]) were administered to the majority of the 201 patients (n = 196 [97.5 percent]). These comprised oseltamivir (n = 134 [66.7 percent]), ganciclovir (n = 81 [40.3 percent]), lopinavir/ritonavir (n = 30 [14.9 percent]), and interferon alfa (n = 22 [10.9 percent]). N-acetyl-L-cysteine and glutathione were part of the antioxidant therapy that was administered to the majority of patients (n = 106; 52.7 percent). Methylprednisolone was administered to sixty-two (30.8%) and seventy-eight (34.8%) of the patients.

Laboratory Indices

The laboratory results upon hospital admission. 166 (85.6%) of the 194 individuals had elevated high-sensitivity C-reactive protein. 126 out of 197 individuals, or 64.0%, in this group had lymphocytopenia. Neutropenia affected 68 out of 197 patients, or 34.5 percent. Leukocytosis affected 46 out of 197 patients, or almost 25% of the total. Elevated levels of alanine aminotransferase (ALT; 59 of 198 [29.8%]) and aspartate aminotransferase (AST) were seen in some individuals who had liver damage (ALT; 43 of 198 [21.7 percent]). The majority of patients exhibited increased myocardial indices when they first arrived: lactate dehydrogenase (LDH) was elevated in 135 of 198 patients (68.2%), and creatine kinase muscle-brain isoform was elevated in 9 of 198 patients (4.5%). Elevated serum creatinine and plasma urea (9 of

198, or 4.5 percent) were indicative of renal damage in a small number of individuals (9 of 198. Of Seventy-four (144) out of the twenty-one patients were released from the hospital as of February 13, 2020. Thirteen patients, or 6.5 percent, remained in the hospital after the median hospital stay of thirteen days (IQR: 10–16 days). 84 (41.8%) of the patients in the group experienced ARDS, 53 (26.4%) were hospitalised to the intensive care unit, 67 (33.3%) required mechanical ventilation, and 44 (21.9%) passed away. Of the 67 patients who were put on mechanical ventilation, 44 (65.7%) passed away, 14 (20.9%) were released from the hospital, and 9 (13.4%) stayed there. Two days was the median interval between admission and the onset of ARDS (IQR, 1-4 days). Every patient who passed away had ARDS and was on mechanical breathing.

ARDS had higher pre-admission temperatures (difference, 0.30 °C; 95 percent confidence interval, 0.00-0.50 °C; P =.004) and were older (difference, 12.0 years; 95 percent confidence interval, 8.0-16.0 years; P <.001). Compared to patients without ARDS, a higher proportion of ARDS patients (difference, 33.9 percent; 95 percent confidence interval, 19.7 percent–48.1%; P <.001) had dyspnea as their primary symptom. Patients with ARDS had a higher percentage of comorbidities than patients without ARDS, such as diabetes (difference, 13.9 percent; 95 percent CI, 3.6 percent -24.2 percent; P =.002) and hypertension (difference, 13.7 percent; 95 percent CI, 1.3 percent -26.1 percent). Furthermore, individuals with ARDS had a lower likelihood of receiving antiviral medication compared to those without the condition (difference, −14.4 percent; 95 percent confidence interval, −26.0 percent to −2.9).The value of the following indices was significantly higher in ARDS patients than in non-ARDS patients: total bilirubin [difference, 1.90 μM; 95 percent CI, 0.60-3.30 μM; P =.004]; renal dysfunction indices (urea [difference, 1.69 mM; 95 percent CI, 1.10-2.29 mM; P =.001]); inflammation-related indices (interleukin-6 [IL-6] [difference, 0.93 pg/mL; 95 percent CI, 0.07-1.98 pg/mL; P =.03]); and coagulation function indices (D-dimer [difference, 0.52 μg/mL; 95 percent CI, 0.21-0.94 μg/mL; P =.001]). On the other hand, there was a substantial drop in the counts of lymphocytes (difference, −0.34 ×109/L; 95 percent CI, −0.47 to −0.22 ×109/L; P <.001) and CD8 T cells (difference, −66.00 cells/μL; 95 percent CI, −129.00 to −7.00 cells/μL; P =.03).

These factors included higher age (≥65 years), high fever (≥39 °C), comorbidities (e.g., hypertension, diabetes), neutrophilia, lymphocytopenia (as well as lower counts of CD3 and CD4 T-cells), elevated end-organ related indices (e.g., AST, urea, LDH), elevated inflammation-related indices (e.g., serum ferritin and high-sensitivity C-reactive protein) and elevated coagulation function-related indicators (PT and D-dimer). Methylprednisolone treatment seems to have made patients sicker than it did those who did not receive it. In particular, compared to patients who did not receive methylprednisolone, a greater percentage of patients who received the medication were graded higher on the Pneumonia Severity Index7 (P =.01;.

Within the subset of patients with ARDS, the patients who passed away had a lower percentage of high fever (difference, −31.8 percent; 95 percent CI, −56.5 percent to −7.1 percent; P = .007) and were older (difference, 18.0 years; 95 percent CI, 13.0-23.0 years; P < .001) than the patients who lived. Additionally, their percentages of hypertension were higher (difference, 18.9 percent; 95 percent confidence interval, -2.0 percent to 39.7 percent; P =.05). Antiviral medication was administered to fewer patients who died (difference, −40.7 percent; 95 percent CI, −58.5 percent to −22.9 percent; P < .001). Of the 44 ARDS patients that passed away, 38 (86.4%) received the highest level of oxygen support: IMV; 5 (11.4%) received IMV; and 1 (2.3%) received IMV plus ECMO.

The value of indices related to liver damage (total bilirubin [difference, 2.60 μM; 95 percent CI, 0.30-5.20 μM; P =.03]), renal dysfunction (urea [difference, 1.50 mM; 95 percent CI, 0.50-2.70 mM; P =.004]), inflammation (IL-6 [difference, 3.88 pg/mL; 95 percent CI, 2.20-6.13 pg/mL; P <.001]), and coagulation function (D-dimer [difference, 2.10 μg/mL; 95 percent CI, 0.89-5.27 μg/mL; P =.001]) were significantly higher in patients with ARDS who died. Nonetheless, there was a substantial drop in the counts of lymphocytes (difference, -0.23 ×109/L; 95 percent CI, -0.41 to -0.07 ×109/L; P =.004) and CD8 T cells (difference, -134 cells/μL; 95 percent CI, - 221 to -10 cells/μL; P =.05.

Bivariate Cox models revealed that a number of variables linked to the ARDS development—such as lymphocyte counts, CD3 and CD4 T-cell counts, AST, prealbumin, creatinine, hyperglycemia, low-density lipoprotein, serum ferritin, and PT—were not linked to death. On the other hand, IL-6 was statistically significantly linked to mortality. High temperature was adversely correlated with death, even though it was linked to a higher risk of developing ARDS (HR, 1.77; 95 percent CI, 1.11-2.84). (HR, 0.41; 95 percent CI, 0.21-0.82).

In summary, of the ARDS patients, 23 out of 50 (46.0%) died after receiving methylprednisolone treatment, while 21 out of 34 (61.8%) died after not receiving methylprednisolone treatment. Methylprednisolone treatment appeared to have lowered the mortality risk in ARDS patients (HR, 0.38; 95% confidence interval, 0.20-0.72; P =.003).

Discussion

We described the clinical features and risk factors linked to clinical outcomes in patients with COVID-19 pneumonia in this cohort research, including patients who advanced from ARDS to death and those who developed ARDS after admission. Due to confounding by indication—that is, sicker patients were more likely to receive methylprednisolone—those who got treatment had a significantly higher risk of developing ARDS. Methylprednisolone treatment, however, seemed to lower the mortality risk in ARDS patients. These results imply that methylprednisolone therapy may be helpful for COVID-19 pneumonia patients, particularly for those who have experienced ARDS as their illness progresses. However, given the possibility of bias and residual confounding in this observational study with a small sample, these results should be considered cautiously.

The following risk variables were associated with the development of ARDS: older age, neutrophilia, organ and coagulation dysfunction, and the progression of ARDS to death (eg, higher LDH and D-dimer). Furthermore, we found that a number of variables linked to the onset of ARDS did not correlate with mortality (eg, comorbidities, lymphocyte counts, CD3 and CD4 T-cell counts, AST, prealbumin, creatinine, glucose, low-density lipoprotein, serum ferritin, PT). Furthermore, the median D-dimer difference between the survival and death groups was greater than the difference between the ARDS and non-ARDS groups, indicating that in certain individuals, disseminated intravascular coagulation was the cause of death. Interestingly, a high fever was negatively correlated with death but positively correlated with the development of ARDS, which is consistent with the findings reported.

It is currently unclear how the extremely dangerous human coronavirus pathogenesis works. It is believed that cytokine storm and viral evasion of cellular immune responses are significant factors in the severity of the disease. 9 Neutrophilia was discovered in the lung11 and peripheral blood10 of SARS-CoV patients. In patients with Middle East respiratory syndrome, there was a correlation between the extent of lung injury and the pulmonary infiltration of neutrophils and macrophages, as well as larger numbers of these cells in the peripheral blood. 12-14 The primary source of cytokines and

chemokines is neutrophils.

ARDS, the primary cause of death for individuals with severe acute respiratory syndrome 15 and Middle East respiratory syndrome, can result from the production of a cytokine storm. 14 This study found that patients with COVID-19 pneumonia who had developed ARDS had much higher neutrophil counts than did patients without ARDS. This finding may have contributed to cytokine storm while also activating neutrophils to carry out an immune response against the virus. This could help to explain the favourable correlation between ARDS and high fever that was observed in the early stages of COVID-19. Furthermore, given that ageing is linked to a reduction in immune function,16 the current study's findings indicated that ageing was associated with both ARDS and death. Older age is therefore associated with death Higher CD3 and CD4 T-cell counts in this study may shield individuals from developing ARDS, but similar findings were not seen when death was examined—possibly due to the small sample size. The CD8 counts of the living were notably higher. These findings highlight the critical functions that CD4 and CD8 T lymphocytes play in COVID-19 pneumonia. Previous investigations have demonstrated that SARS-CoV can infect immune cells such as T lymphocytes, monocytes, and macrophages. It has been discovered that SARS-CoV has the same cell entrance receptors as SARS-CoV-2,17,18. 19 At the beginning of the illness, the numbers of CD3, CD4, and CD8 T-cells declined; this decline lasted until the SARS-CoV pneumonia recovery phase. 19 Additionally, the peripheral blood specimen of the patient had lower CD4 and CD8 T-cell levels. which supported the findings that patients with ARDS and COVID-19 pneumonia had lymphocytopenia (CD3, CD4, and CD8 T cells). Research has shown that T-cell reactions have the ability to prevent innate immunity from being overactivated. It has been revealed that 22 T cells can assist remove SARS-CoV, and that pathological alterations seen in SARS-CoV-infected animals are caused by a poor T-cell response. 23 Our theory was that in order to effectively defend against SARS-CoV-2 infection, lymphocyte responses would need to gradually and persistently rise. To fully understand the involvement of either the CD4 and CD8 T-cell immune response or the neutrophil and lymphocyte response in SARS-CoV-2 infection, more research is required.

Limitations

There are various restrictions on this study. First, during this time only individuals with relatively severe COVID-19 pneumonia were admitted to hospitals due to a lack of medical resources. Secondly, a single-center hospital with a small sample size was used for this investigation. Because of this, there may have been a disproportionately higher number of patients with poor outcomes in this study. Additionally, while determining the factors that affect the clinical outcomes, selection bias may exist. To better identify the clinical features and risk factors of COVID-19 pneumonia, a larger cohort study of patients from Wuhan, China, and other Chinese cities as well as from other countries would be beneficial.

Conclusions

Due to a possibly weakened immune system, older age was linked to an increased risk of ARDS and death. Fever was linked to improved outcomes even though it was also linked to the development of ARDS. There may be distinct pathophysiological changes from hospital admission to ARDS development and from ARDS development to death because a number of factors linked to ARDS development were not linked to mortality. Furthermore, patients who develop ARDS may benefit from methylprednisolone treatment. To find the best COVID-19 medicines, double-blinded randomised clinical trials are still required.

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