Clinical characteristics and risk factors for mortality in patients with coronavirus disease 2019 in intensive care unit: a single-center, retrospective, observational study in China

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Research

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Abstract

Background: Coronavirus disease 2019 (COVID-19) is a potentially life-threatening contagious disease which has spread all over the world. Risk factors for the clinical outcomes of COVID-19 pneumonia in intensive care unit (ICU) have not yet been well determined.

Methods: In this retrospective, single-centered, observational study, we consecutively included 47 patients with confirmed COVID-19 who were admitted to the ICU of Leishenshan Hospital in Wuhan, China, from February 24 to April 5, 2020. Clinical characteristics and outcomes were collected and compared between survivors and non-survivors. Multivariable logistic regression was used to explore the risk factors associated with death in patients of COVID-19.

Results: The study cohort included 47 adult patients with a median age of 70.55 ± 12.52 years, and 30 (63.8%) patients were men. Totally 15 (31.9%) patients died. Compared with survivors, non-survivors were more likely to develop septic shock (6 [40%] patients *vs* 3 [9.4%] patients), disseminated intravascular coagulation (3 [21.4%] *vs* 0), and had higher score of APACHE II (25.07 ± 8.03 *vs* 15.56 ± 5.95), CURB-65 (3[2-4] *vs* 2[1-3]), Sequential Organ Failure Assessment (SOFA) (7[5-9] *vs* 3[1-6]), higher level of D-dimer (5.74 [2.32-18] *vs* 2.05 [1.09-4.00]) and neutrophil count (9.4 [7.68-14.54] *vs* 5.32 [3.85-9.34]). SOFA score (OR 1.47, 1.01–2.13; $p=0.0042$) and lymphocyte count (OR 0.02, 0.00–0.86; $p=0.042$) on admission were independently risk factors for mortality. Patients with higher lymphocyte count ($>0.63 \times 10^9/L$) and lower SOFA score ≤ 4 on admission had a significantly well prognosis than those with lower lymphocyte count ($\leq 0.63 \times 10^9/L$) and higher SOFA score >4 in overall survival.

Conclusions: Higher SOFA score and lower lymphocyte count on admission were associated with poor prognosis of patients with COVID-19 in ICU. Lymphocyte count may serve as a promising prognostic biomarker.

Introduction

A novel coronavirus, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) was firstly isolated from a cluster of patients with pneumonia of unknown cause in Wuhan, China^[1]. In February 2020, the virus and its associated disease were designated coronavirus disease 2019 (COVID-19), which has been declared a public health emergency of international concern by World Health Organization (WHO)^[2]. It has been reported that the number of patients infected with SARS-Cov-2 has reached 5,137,100 globally, and 330,578 patients have died of COVID-19 till 22 May, 2020.

According to the WHO–China Joint Mission on COVID-19 report, 13.8% of the patients with laboratory-confirmed COVID-19 developed severe disease and 6.1% required intensive care^[3]. In a previous study of 1099 patients with laboratory-confirmed COVID-19 from 552 hospitals in 30 provinces, 5.0% were admitted into the ICU, 2.3% underwent invasive mechanical ventilation, and 1.4% died^[4]. Two subsequent studies reported that 23%–26% of COVID-19 cases required ICU admission and the mortality rate varied

from 4.3–11%, while most patients in these studies were still hospitalized at the time of manuscript submission^[5–6]. Increasing evidences revealed that the mortality of critically ill patients with SARS-CoV-2 pneumonia is considerable^[7–8].

Certain epidemiological features and clinical characteristics of COVID-19 have been previously reported to be associated with the outcome. Older age with comorbidities was at high-risk of developing ARDS and death^[7, 9]. A recent study from two designated hospitals in Wuhan demonstrated increasing odds of in-hospital death for patients with older age, higher Sequential Organ Failure Assessment (SOFA) score, and d-dimer greater than 1 µg/L on admission^[10]. However, limited studies evaluated the risk factors for COVID-19 related death in ICU. Thus, in this retrospective study, we aimed to explore the risk factors for mortality by investigating the clinical and laboratory features and short-term outcomes of severe cases of COVID-19 from a designated hospital in Wuhan.

Methods

Study Design

All procedures described here have been approved by the ethics committee of Leishenshan Hospital. This single-center, retrospective study was conducted at Leishenshan Hospital (Wuhan, China), which is a designated hospital with 1600 beds, including two ICUs (A and B). All critically ill patients with confirmed COVID-19 admitted to B-ICU from February 24 to April 5 2020 were consecutively enrolled. Critically ill COVID-19 was defined as those admitted to ICU who required mechanical ventilation or had a fraction of inspired oxygen (FiO₂) of at least 60% or complicated with septic shock and other organ failure^[11]. All patients were diagnosed with COVID-19 pneumonia according to WHO interim guidance^[12]. The primary outcome was 60-day mortality after ICU admission.

Data collection

All the patients' electronic medical records, nursing records, laboratory findings, and radiological examinations were reviewed. We collected data including demographics, underlying chronic diseases (chronic heart disease, chronic pulmonary disease, diabetes, malignancy, malnutrition, chronic liver disease and chronic kidney disease), laboratory findings, chest computed tomographic scans, treatment (including antiviral therapy, antibiotics, corticosteroid therapy, oxygen support, renal replacement therapy and extracorporeal membrane oxygenation), clinical complications (septic shock, acute respiratory distress syndrome [ARDS], secondary infection, acute kidney injury and acute cardiac injury) and outcome data during the hospital admission. The CURB-65, Sequential Organ Failure Assessment (SOFA), and Acute Physiology and Chronic Health Evaluation II scores (APACHE II) scores were evaluated on the day of ICU admission. Septic shock was defined according to the 2016 Third International Consensus Definition for Sepsis and Septic Shock^[13]. Acute kidney injury was identified according to the Kidney Disease: Improving Global Outcomes definition^[14]. Acute cardiac injury was diagnosed if serum levels of

cardiac biomarkers (eg, high-sensitive cardiac troponin I) were above the 99th percentile upper reference limit ^[15]. Acute respiratory distress syndrome (ARDS) was diagnosed according to the Berlin Definition ^[16]. Secondary infection was diagnosed if the patients had clinical symptoms or signs of nosocomial pneumonia or bacteraemia, and was combined with a positive culture of a new pathogen from a lower respiratory tract specimen (including the sputum, transtracheal aspirates, or bronchoalveolar lavage fluid, or from blood samples taken ≥ 48 h after admission) ^[17].

Statistical analysis

Continuous variables and categorical variables were presented as median (IQR), mean $\pm$ standard deviation and number (%), respectively. Continuous variables were compared using the Mann-Whitney *U* test. The chi-square test or Fisher's exact test was used to compare categorical variables. All significant variables with $p < 0.10$ in univariate analysis were considered to be candidates for entry into a forward stepwise multivariate logistic regression model. Forward stepwise selection was performed to develop the final model. The predictive performance of the lymphocyte count and SOFA at admission for outcome was assessed with the receiver operating characteristics (ROC) curves with Area Under Curve (AUC). Patient survival according to appropriated cutoff value of the lymphocyte count and SOFA score at admission were determined using the log-rank test and displayed using Kaplan–Meier curves. A *P* value less than 0.05 were considered statistically significant. All data were analyzed using the IBM SPSS Statistics for Windows (version 19.0). Odds ratio (OR) and 95% confidence interval (CI) was calculated to evaluate the strength of any association.

Results

Baseline characteristics

By April 5, 2020, 52 patients were admitted to B-ICU of Wuhan Leishenshan hospital. After excluding 5 patients without confirmed SARS-CoV-2 RNA or without complete information, we finally included 47 inpatients in this study (Table 1). The mean age was 70.55 ± 12.52 years (range 38 ~ 93 years). Among all included patients, 30 (63.8%) patients were male. Comorbidities were present in 40 (68.1%) patients, with hypertension being the most common comorbidity ($n = 25$ [53.2%]), followed by diabetes ($n = 18$ [38.3%]), and chronic kidney disease ($n = 15$ [31.9%]). The median APACHE II score of all patients was 18.6 ± 7.79 . A total of 34 (72.3%) patients had findings of bilateral infiltrates on radiographic imaging.

Differences Of Clinical Characteristics Between Survivors And Non-survivors

The median SOFA score of non-survivors (7, IQR 5–9) was much higher than that of survivors (3, IQR 1–6). The median lymphocyte count of ICU patients was $0.77 \times 10^9/L$ (IQR 0.54–1.29), which was $0.54 \times 10^9/L$ (IQR 0.26–0.63) in non-survivors. Concentrations of C-reactive protein, procalcitonin, interleukin-6 (IL-6) and interleukin-1B (IL-1B) were significantly higher in non-survivors than those in survivors.

Compared with survivors, non-survivors were more likely to develop septic shock (6 [40%] vs 3 [9.4%]), and disseminated intravascular coagulation (3 [21.4%] vs 0).

Clinical Outcomes

For the primary outcome, 15 (31.9%) of 47 patients died in our study. ARDS (12; 25.5%), acute cardiac injury (12; 25.5%), acute kidney injury (10; 21.3%), were frequently observed in ICU patients. Three patients developed bloodstream infections during hospitalization, of which *Klebsiella pneumoniae*, *Staphylococcus aureus* and *Enterococcus faecalis* were identified. Invasive mechanical ventilation was performed to 13 (27.7%) patients, 9 of whom died. The median duration from admission to invasive mechanical ventilation and invasive mechanical ventilation to death were 6.0 (2.00–11.00) days, and 5.54 ± 5.98 days respectively. Two patients received extracorporeal membrane pulmonary oxygenation (ECMO) as rescue therapy, one of whom survived. Forty-five (95.7%) patients received intravenous antibiotics and 11 (23.4%) received systematic corticosteroid. Three patients (6.4%) received COVID recovery patient plasma treatment who all survive (Table 1).

Risk Factors Of Mortality

Univariate analysis revealed that variables of APACHE II, CURB-65, SOFA, ARDS, chronic heart disease, septic shock, lymphocyte count, neutrophil count were associated with death (table 2). In the multivariable logistic regression model, we found that SOFA score (OR = 1.47, 95% CI = 1.01–2.13, P = 0.04) and lymphocyte count at admission (OR = 0.02, 95% CI = 0.00–0.86, P = 0.04) were independent factors related to mortality (Table 2)

Predictive value of lymphocyte count and SOFA for survival

Baseline lymphocyte count was significantly higher in survivors than non-survivors. In survivors, lymphocyte count was lowest on admission and improved during hospitalization, whereas decreased continuously until death in non-survivors (Fig. 1).

AUC of lymphocyte count statistically significant in the group of survivors or non-survivors (AUC 0.865; 95% CI, 0.375–0.781; P < 0.0001). Optimal cutoff value of lymphocyte count was $0.63 \times 10^9/L$. Patients with higher lymphocyte count ($> 0.63 \times 10^9/L$) on admission had a significantly well prognosis than those with lower lymphocyte count ($\leq 0.63 \times 10^9/L$) in overall survival (P = 0.001) (Fig. 2).

AUC of SOFA score statistically significant in the group of survivors or non-survivors (AUC 0.860; 95% CI, 0.728–0.944; P < 0.0001). Optimal cutoff value of SOFA score was 4. Patients with lower SOFA score ≤ 4 on admission had a significantly well prognosis than those with higher SOFA score > 4 in overall survival (P = 0.001) (Fig. 3).

Discussion

In this retrospective study, we found that survivors and non-survivors differed in clinical characteristics and inflammatory indicators. Our findings demonstrated that survivors and non-survivors differed in clinical characteristics and inflammatory indicators. Higher SOFA score and lower lymphocyte count on admission were associated with higher odds of in-hospital death. More importantly, lymphocyte count at admission may serve as a predictive biomarker for survival in severe COVID-19 cases.

Age and comorbidity have previously been reported to be factors indicating poor outcome of COVID-19. The patients admitted to ICU were found to be older and have more comorbidities than those not admitted to ICU^[5]. In addition, older age was confirmed to be associated with death in patients with COVID-19 in Zhou's study^[10]. The median age of patients in this study was older than that of the above two studies and comorbidities were present in 68.1% of patients in our ICU. However, the mortality rate of COVID-19 patients in our cohort is 31.9%, which was numerically lower than that reported in other ICUs in Wuhan^[7-8,10,18]. Moreover, age and complications seemed not to be independent risk factors for death in our cohort. There are several explanations for the varied mortality among studies. First, with the epidemic development, more medical resources were invested in Wuhan, more provisional ICUs were established, and the clinical capacity to treat patients has been greatly improved. Second, the median time from illness onset to admission was reduced. Third, the proportion of patients who required mechanical ventilation was lower in our ICU than that of above studies.

The SOFA and qSOFA assessments are useful diagnostic tools for predicting hospital mortality among adults with community-acquired pneumonia (CAP) and sepsis in the ICU^[19-20]. Asai's study suggested that the combination of a qSOFA score ≥ 2 and a SOFA score ≥ 4 was an independent unfavorable prognostic factor for 30-day mortality among CAP patients^[21]. SOFA criteria predicting infection-related in-hospital mortality in ICU patients performed better than SIRS criteria and qSOFA score^[22]. For adult patients with COVID-19, higher SOFA score at admission was also reported to be one of the risk factors for death, which was confirmed in our study^[10]. Non-survivors in our study had a mean SOFA of 7, which was higher than previously reported^[10]. SOFA scores may accurately evaluate the severity of patients with COVID-19 in ICU, but further prospective studies are warranted to evaluate the role of SOFA in predicting outcome of patients outside the ICU.

Our findings suggested that lymphocytes may be a promising biomarker reflecting the treatment efficacy and prognosis. The respiratory and immune systems are the main targets of SARS-CoV attack, and extensive consolidation of the lung, diffuse alveolar damage and decreased immune function are the main causes of death. In the autopsy of patients with SARS, there was massive necrosis of splenic lymphoid tissue and localized necrosis in lymph nodes^[23]. In patients with COVID-19, the novel coronavirus might also mainly act on lymphocytes, especially T lymphocytes^[24]. Helper T cells, suppressor T cells and regulatory T cells in COVID-19 cases were all below normal level, and more obviously damaged in severe cases, which suggested a role for dysregulated immune responses in COVID-19 pathogenesis^[24]. Zhou et al. reported that baseline lymphocyte count was significantly higher in survivors than non-survivors, and lymphocyte count improved during hospitalisation while severe

lymphopenia was observed until death in non-survivors^[10], which was consistent with phenomenon found in our study. In the current study, lower lymphocyte count on admission was associated with mortality, and patients with higher lymphocyte count ($>0.63 \times 10^9/L$) on admission had a significantly well prognosis than those with lower lymphocyte count ($\leq 0.63 \times 10^9/L$) in overall survival. The concept that lymphocytes may serve as a potential therapeutic target deserves further investigation.

Our study has several limitations. First, it was a retrospective, single center study with relatively small sample size. Laboratory tests for example serum ferritin and lymphocyte subsets percentage were not performed in all patients. Second, the proportion of patients with comorbidities was higher than that reported in previous studies. In addition, some patients and their guardians gave up endotracheal intubation and mechanical ventilation. The abovementioned factors might affect the prognosis. Third, limited medical resources may delay hospitalization or admission for some patients in the early stage and several patients were transferred to other hospitals for comorbidities, which influenced the follow-up.

Conclusions

Old age and comorbidities are commonly seen in COVID-19 patients admitted to ICU. Higher SOFA score, and lower lymphocyte count on admission were risk factors for death of adult patients with COVID-19 in ICU. Lymphocyte count on admission may serve as a potential prognostic marker.

Declarations

Ethics approval

All procedures described here have been approved by the ethics committee of School of Medicine, Shanghai Jiaotong University.

Consent to participate

Not applicable.

Consent for publication

Not applicable.

Availability of data and materials

The datasets during and/or analyzed during the current study available from the corresponding author on reasonable request.

Conflicts of Interest

The authors have declared that no conflicts of interest exist.

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None.

Authors' contributions

All authors have seen the manuscript and approved to submit to your journal. Contributions: (I) Conception and design: H Huang, X Xu; (II) Administrative support: C Zhu; (III) Provision of study materials or patients: H Huang, L Tian, Y Hang, CH Huang; (IV) Collection and assembly of data: X Liu, F Sai; (V) Data analysis and interpretation: X Liu, L Li, Y Ye; (VI) Manuscript writing: All authors; (VII) Final approval of manuscript: All authors.

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Tables

Due to technical limitations the Tables are available as download in the Supplementary Files.

Figures

Figure 1

Temporal changes in lymphocyte count from illness onset in patients hospitalized with COVID-19

Survival proportions1

Figure 2

There was a significant difference in overall survival between the group with lymphocyte $> 0.63 \times 10^9/L$ and the group with lymphocyte $\leq 0.63 \times 10^9/L$

Survival proportions2

Figure 3

There was a significant difference in overall survival between the group with SOFA score ≤ 4 and the group with SOFA score >4

Supplementary Files

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