Clinical course and progression of severe and critically ill patients with corona virus disease 2019

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Research

Keywords: COVID-19, SARS-CoV-2, Severe pneumonia, Arbidol

Posted Date: March 12th, 2020

DOI: https://doi.org/10.21203/rs.3.rs-17043/v1

Abstract

Background The emergence of Corona Virus Disease 2019 (COVID-19) in Wuhan, China at the end of 2019 is a major public health issue, causing to a large global outbreak. However, the information regarding the clinical characteristic and progression of severe and critically ill patients with COVID-19 is scarce.

Methods: We conducted a single-center, retrospective, observational study and enrolled 126 severe and critically ill adult patients who were admitted to the intensive care unit (ICU) of Tongji hospital, between Feb 1 and Feb 20, 2020.

Results: Of 126 patients, 85 patients with the positive of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) were included. The mean age of 85 patients was 68.3 (SD 10.5) years. More than half were men, 55 (62.4%) had chronic illness. 57 (66.3%) patients had died before Feb 28, 2020. the median duration from onset of illness to death, hospitalization to death and ICU admission to death were 22 (17.0-26.0) days, 9.0 (6.0-13.0) days and 5.0 (2.0-6.0) days, respectively. Compared with survivors, non-survivors were more likely old (69.6 [SD 10.22] vs 65.6 [10.9]). Furthermore, the non-survivors had higher white blood cell (WBC) and neutrophil count, neutrophil percentage, high-sensitive C-reactive protein (hs-CRP) and lower lymphocyte and platelet count, lymphocyte percentage and albumin. Notably, arbidol may improve the survival of severe and critically ill patients.

Conclusions: Our study reveals the non-survivors had worse blood routine and other clinical monitors. Additionally, arbidol may play useful role in the survival of severe and critically ill patients, which needs further validation.

Introduction

Since Dec 8, 2019, cases of unidentified pneumonia emerged in Wuhan, Hubei province, China[1]. A novel coronavirus, SARS-CoV-2, was identified to be accountable for this disease[1, 2]. Evidence pointing to human-to-human transmission in hospital and family settings has been accumulating[3, 4]. As of 28 February 2020, a total of 83,310 patients were confirmed to be affected with SARS-CoV-2 in 50 countries/regions, according to the World Health Organization (WHO) report, which declared coronavirus outbreak a global health emergency. Significantly, it is estimated that about 32% of patients have developed severe pneumonia, 15% patients worsened in a short period of time and died of multiple organ failure[1].

At present, the information regarding the characteristics of severe and critically ill patients with COVID-19 is scarce. In this study, we did a comprehensive exploration of the clinical characteristics and progression of severe and critically ill patients with confirmed SARS-CoV-2 pneumonia admitted to ICU of Tongji hospital, Tongji Medical College, Huazhong University of Science and Technology.

Methods

Study design and participants

This single-center, retrospective, observational study was done at Tongji Hospital of Huazhong University of Science and Technology, which was a designated hospital for severe and critically ill patients with COVID-19 by the government. According to the World Health Organization interim guidance[5], the diagnostic criteria of COVID-19 was based on the virus RNA detection, the clinical characteristics, the chest imaging, and the ruling out common pathogen. We retrospectively analysed 126 patients admitted to ICU from Feb 1, 2020, to Feb 20, 2020. Patients with negative results or without SARS-COV-2 nucleic acid detection were excluded. The clinical outcomes of patients were followed up to February 28, 2020.

Data Collection

Epidemiological, clinical and laboratory characteristics were recorded. The patients' medical history as well as treatment and outcome data, were also obtained through data collection tables in electronic medical records. Any missing or uncertain records were collected and clarified through direct communication with involved health-care providers and their families. Data were reviewed by a team of specialists. We collected data on age, sex, chronic medical histories, symptoms from onset to hospital admission (fever, cough, dyspnea, fatigue, diarrhea, myalgia, headache, confusion, vomiting, abdominal pain, chest pain, dizziness, hemoptysis and sore throat), laboratory results, treatment (antiviral agents, corticosteroid, and respiratory support) and living status. The time of disease onset was defined as the day of symptom onset. The time from the first symptom to the fever clinics, hospital admission, and clinical outcomes were recorded.

Nucleic Acid Detection Of Sars-cov-2

All COVID-19 patients enrolled in this study were laboratory-confirmed cases, which were identified with nucleic acid detection of SARS-CoV-2 from a throat swab samples using RT-PCR. Two target genes were used, including open reading frame lab (ORF1ab) and nucleocapsid protein (N), and the sequences were as follows: ORF1ab: forward primer: 5’-CCC TGT GGG TTT TAC ACT TAA – 3’; reverse primer: 5’-ACG ATT GTG CAT CAG CTG A -3’; N: forward primer: 5’-GGG GAA CTT CTC CTG CTA GAA T -3’; reverse primer: 5’-CAG ACA TTT TGC TCT CAA GCT G -3’. The RT-PCR assay was performed using a SARS-CoV-2 nucleic acid detection kit, according to the manufacturer’s protocol (Beijing Genomics Institution and Geneodx biotechnology Co. Ltd). Positive test results for two target genes were considered as laboratory-confirmed infection.

Statistical analysis

Differences on clinical data between survivors and non-survivors were compared using independent t-test or Mann–Whitney test for continuous data and chi-square test or the Fisher’s exact test for categorical variables

All statistical analysis was performed by the statistical software packages R (http://www.R-project.org, The R Foundation) and the EmpowerStats (http://www.empowerstats.com, X&Y Solutions, Inc., Boston, MA) with a two-sided significance threshold of $p < 0.05$.

Result

Demographic characteristic

As is shown in the flow chart (Fig. 1), a total of 126 patients were admitted to the ICU during Feb 1 to Feb 20, 2020. Among them, 41 cases were excluded, including 19 patients with negative results of SARS-CoV-2 nucleic acid detection which have been confirmed at least twice and 22 patients without SARS-CoV-2 detection which were admitted by clinical diagnosis for COVID-19. Finally, 85 patients with laboratory confirmed were included in this study. The mean age was 68.3 years (SD 10.5) and patients older than 60 years account for 74.7% (65), while 41 (48.2%) were older than 70 years (Table 1). More than half of this cohort were men (62.4%). 55 (62.4%) patients had at least one underlying diseases including cardiovascular and cerebrovascular diseases (41 [48.2%]), endocrine system disease (19 [22.4%]), respiratory system disease (6 [7.1%]), chronic kidney disease (4 [4.7%]), digestive system disease (3 [3.5%]), malignancy (3 [3.5%]) and autoimmune disease (1 [1.2%]).

On admission, 12(14.1%) patients were classified as common pneumonia, 55 (64.7%) were severe pneumonia and the remaining (18 [21.2%]) were critically ill patients, according to the clinical classification of severity by the National Health Committee of the People's Republic of China (http://www.nhc.gov.cn/). For common pneumonia, the median duration from admission to deterioration to severe pneumonia was 2.0 (1.8–4.2) days. By the end of Feb 28, 1 patient was discharged after recovery, 4 patients were transferred to general ward. 57 (67.1%) patients had died. And the median duration from onset of illness to death, hospitalization to death and ICU admission to death were 22 (17.0–26.0) days, 9.0 (6.0–13.0) days and 5.0 (2.0–6.0) days, respectively. Compared with survivors, non-survivors were more likely male (39 [68.4%] vs 18 [31.6%]) and old (69.6 [SD 10.22] vs 65.6 [10.9]). Surprisingly, no chronic medical illness differences were observed between survivors and non-survivors.

Clinical Characteristics

Cough (82.1%), dyspnea (77.4%) and fever (75.3%) were the most common symptoms of illness, followed by fatigue (50.0%), diarrhea (28.6%) and myalgia (22.6%), whereas hemoptysis (3.5%) and sore throat (1.2%) were rare. During hospitalization, 57 (67.1%) patients received antiviral treatment. Arbidol was given to 48 (56.5%), interferon nebulization to 22 (25.9%), lopinavir/ritonavir to 10 (11.8%), oseltamivir to 7 (8.2%) and ribavirin to 2 (2.4%). 78 (91.8%) patients were treated with systemic glucocorticoid. Surprisingly, arbidol may increase the survival of severe and critically ill patients (log-rank test, $p = 0.0081$, Fig. 2A) at data cutoff. Whereas, such therapeutic effect was not observed in other antiviral drugs or glucocorticoid administration (Fig. 2B-F).

23 (27.7%) patients were treated with high-flow nasal cannula, 52 (61.2%) with non-invasive ventilator to assist ventilation, 54 (63.5%) with mechanical ventilation, 2 (2.4%) with extracorporeal membrane oxygenation (ECMO). 19 patients were still using ventilators at data cutoff. Compared with survivors, non-survivors were more likely to receive invasive mechanical ventilation.

Laboratory Findings In Severe And Critically Ill Patients

The laboratory parameters of severe and critically ill patients with COVID-19 on admission were shown in Fig. 3. Compared with survivors, non-survivors were more likely accompanied by higher WBC (Fig. 3A) and neutrophil count (Fig. 3B), neutrophil percentage (Fig. 3F). Furthermore, the non-survivors were also characterized by severe lymphopenia (Fig. 3C and G) during hospitalization, so were albumin and platelet count. Moreover, the liver and renal function were more likely worse in non-survivors, as manifested by higher levels of alanine aminotransferase (ALT, Fig. 3H), aspartate aminotransferase (AST, Fig. 3I), blood urea nitrogen (BUN, Fig. 3M) and creatinine (Fig. 3N) in the serum originated from non-survivors cohort. However, the ratio for AST and ALT was no detected perceptible differences between non-survivors and survivors (Fig. 3J), so was the ratio for BUN and creatinine (Fig. 3O).

It was noted that the levels of brain natriuretic peptide (BNP) underwent a steady decrease during hospitalization in both survivors and non-survivors, indicating that cardiac failure of the patients was improved after treatment (Fig. 3S). According to previous data, sepsis was one of important reasons for the death of patients with COVID-19[6, 7]. Indeed, compared with survivors, an increasing trend was existed for hs-CRP (Fig. 3Q) and Procalcitonin (PCT, Fig. 3R), indicators for infection. However, “cytokine storm” was not observed, as manifested by similar levels of cytokines (IL-1β, IL-2R, IL-6, IL-8 IL-10 and TNF-α) between survivors and non-survivors (Table 3).

Discussion

In the last two decades, coronavirus has caused two large-scale pandemics, severe acute respiratory syndrome (SARS) in 2002[8, 9] and the Middle East respiratory syndrome (MERS) in 2012[10, 11]. Recently, a novel coronavirus, SARS-CoV-2, induced an outbreak of pneumonia in Wuhan, China and spread rapidly around the world[12–14]. Furthermore, the mortality of the patients with COVID-19 was unacceptable high[1, 6]. Until now, almost 3,000 patients lost their life due to the SARS-COV-2 infection. Since the serious of plague epidemic, it is emergent to learn the information regarding the characteristic of severe and critically ill patients with COVID-19. In this study, we did a comprehensive exploration of the clinical characteristics and progression of severe and critically ill patients with confirmed COVID-19 admitted to ICU of Tongji hospital.

In this study, we identified the differences the demographic and clinical manifestations between the survivors and non-survivors. Indeed, high mortality rates were observed in patients with severe or critically ill patients, consistent with previous report[15]. Furthermore, the variation tendency of laboratory examination for severe and critically ill patients was described during hospitalization. The non-survivors

had higher WBC and neutrophil count, neutrophil percentage, hs-CRP and lower lymphocyte and platelet count, lymphocyte percentage and albumin. Surprisingly, treatment with abidol may be useful for the survival of these patients. Collectively, our data might highlight the clinical significance in the enhanced attention towards severe and critically ill patients with COVID-19.

We reported 85 patients who were admitted to ICU with confirmed SARS-CoV-2 infection. 57 (67.1%) patients have died and 28 patients was survived as of February 28, 2020. In recent studies, the mortality rate of patient with COVID-19 varied from 1.36%-61.5%, according to different reports[15–17]. While the mortality rate of other two coronavirus diseases, SARS and MERS, was 9.6% and 35%, respectively[18]. In our study, the mortality rate of ICU severe and critically ill patients with COVID-19 was 67.1% as of February 28, 2020, due to no effective drugs confirmed by clinical trial against SARS-CoV-2 were available. Disease onset may progress rapidly and worsened in a short period of time and died of multiple organ failure. We observed the median time from admission to death, from onset to death, from ICU admission to death were 9, 22, 5 days. These periods were very short. If the patients did not admission to hospital or ICU in time, they may have no chance to reverse disease. In non-survivors, 52.6% patients are older than 70-year and 68.4% patients are male. It indicated that old, male patients are more likely than others to die.

Most patients in our study had fever, cough, and dyspnea prior to admission, the other symptoms include fatigue, diarrhea, myalgia, headache, confusion, vomiting, abdominal pain, chest pain, dizziness, hemoptysis, sore throat. It was noted that the percent of dyspnea is much higher than previous studies[1, 6], indicating that dyspnea may be the premonitory symptom for severe and critically ill patients and more attention should be paid.

Notably, no perceptible differences were observed for blood routine examination between survivors and non-survivors at admission. However, with the disease progress, we found neutrophil percentage of non-survivors was always more than 90% from 3 days after admission, while that of survivors underwent a steady decrease, and reduce to 81.8% at 18 days after admission, indicating the percentage of neutrophil maybe a key predictor of death. Furthermore, non-survivors were more likely accompanied by lymphopenia than the survivors during hospitalization, which were comparable with other COVID-19 studies[1, 17]. For liver and renal function, the non-survivors seem have more liver and renal injury, evidenced by higher levels of ALT, LDH, BUN, Creatinine and lower levels of albumin, which might be caused by COVID-19 induced multiple organ dysfunction syndrome (MODS) or medication use, while no obvious differences were observed in heart injury between survivors and non-survivors. Collectively, the variation tendency of neutrophil percentage, lymphocyte, albumin and LDH may reveal the prognosis of the disease.

Up to now, there is no effective specific treatment for COVID-19[19]. In our study, antibiotics, antiviral therapy, and systemic corticosteroids were used for most patients. Whereas, it was reported that antivirus, corticosteroids and immunoglobulin treatment had no significant effect to patients[20]. In another study, researchers used remdesivir, an antiviral drug against a wide array of RNA viruses, in the treatment of

COVID-19 and achieved perfect results[21]. In our study, the antiviral treatment included lopinavir/Ritonavir, arbidol, oseltamivir, ribavirin and interferon. Interestingly, we found arbidol might be effective to improve the survival of severe and critically ill patients with COVID-19. Arbidol was an influenza virus fusion inhibitor. Besides its inhibitory effect on HA-mediated fusion, arbidol exhibited a more general membrane perturbing effect, explaining its broad activity against several viruses distinct from influenza virus[22]. So arbidol may provide new ideas for the treatment of patients with COVID-19.

In our study, the patient with hypoxemia used high flow nasal cannula and mechanical ventilation. 2 patients received ECMO, one was dead, the other remained hospitalized as of February 28, 2020. There is no sufficient evidence to certify respiratory support and ECMO could decrease mortality.

Our research has some obvious limitations. First, due to different clinical teams, some laboratory observations are missing for certain day, such as BNP, PCT, fibrinogen, D-dimer and so on. Second, due to the retrospective nature of this study, a systematic selection bias could be introduced. Third, the effect of the current antiviral treatments should be considered with caution. Although arbidol seem likely to improve the survival of those patients, high-quality clinical interventional studies are needed to investigate the effect of arbidol on COVID-19.

Conclusions

The mortality of severe and critically ill patients with COVID-19 is high. Old, male patients with high levels of neutrophil percentage, LDH and lower lymphocyte count, albumin, are at increased risk of death. Arbidol seems likely to improve the survival of severe and critically ill patients.

Abbreviations

COVID-19:Corona Virus Disease 2019; ICU:Intensive care unit; SARS-CoV-2:Severe acute respiratory syndrome coronavirus 2; WBC:white blood cell; hs-CRP:high-sensitive C-reactive protein; WHO:World Health Organization.

Declarations

Acknowledgements

We thank all patients and their families involved in the study.

Authors' contributions

YM and YZ designed the protocol. DD, LZ and MZ collected the data, YC assisted in the statistical analysis. JZ and YX assisted with the protocol implementation and paper design. All authors read and approved the final manuscript.

Funding

The present study was supported by the National Natural Science Foundation of China (81800068 and 81700442).

Availability of data and materials

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

Ethics approval and consent to participate

The Ethics Commission of Tongji Hospital of Huazhong University of Science and Technology approved this study (TJ-C20200102). Written informed consent was waived due to the rapid emergence of this infectious disease.

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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Tables

Due to technical limitations, all tables are only available for download from the Supplementary Files section.

Figures

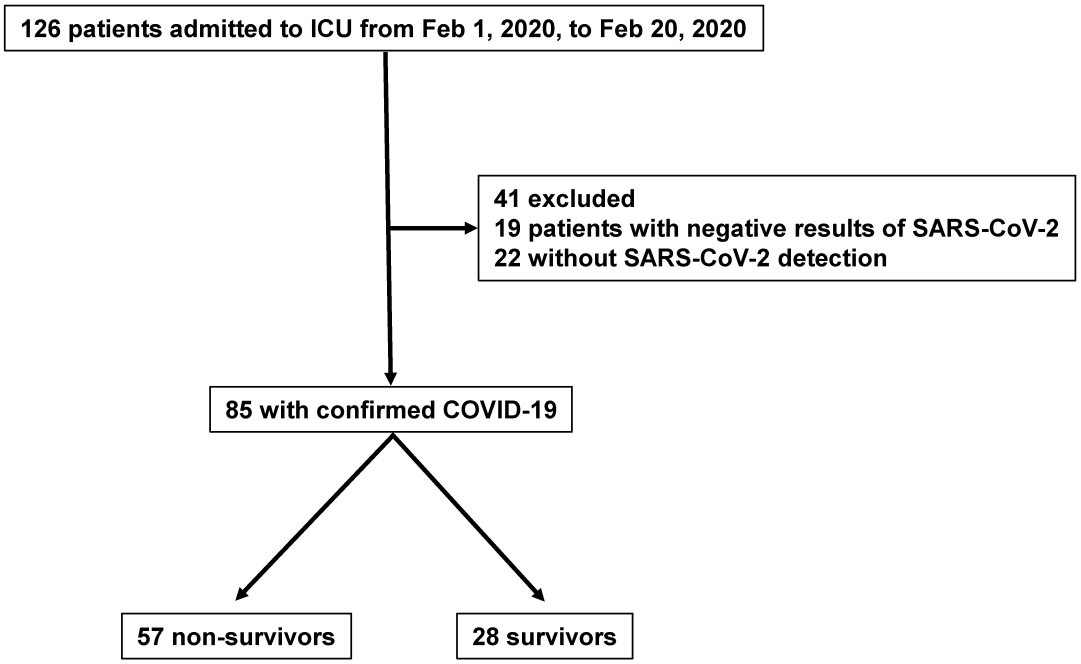

Figure 1

Study flow chart ICU: Intensive care unit; SARS-CoV-2: Severe acute respiratory syndrome coronavirus 2; COVID-19: Corona Virus Disease 2019.

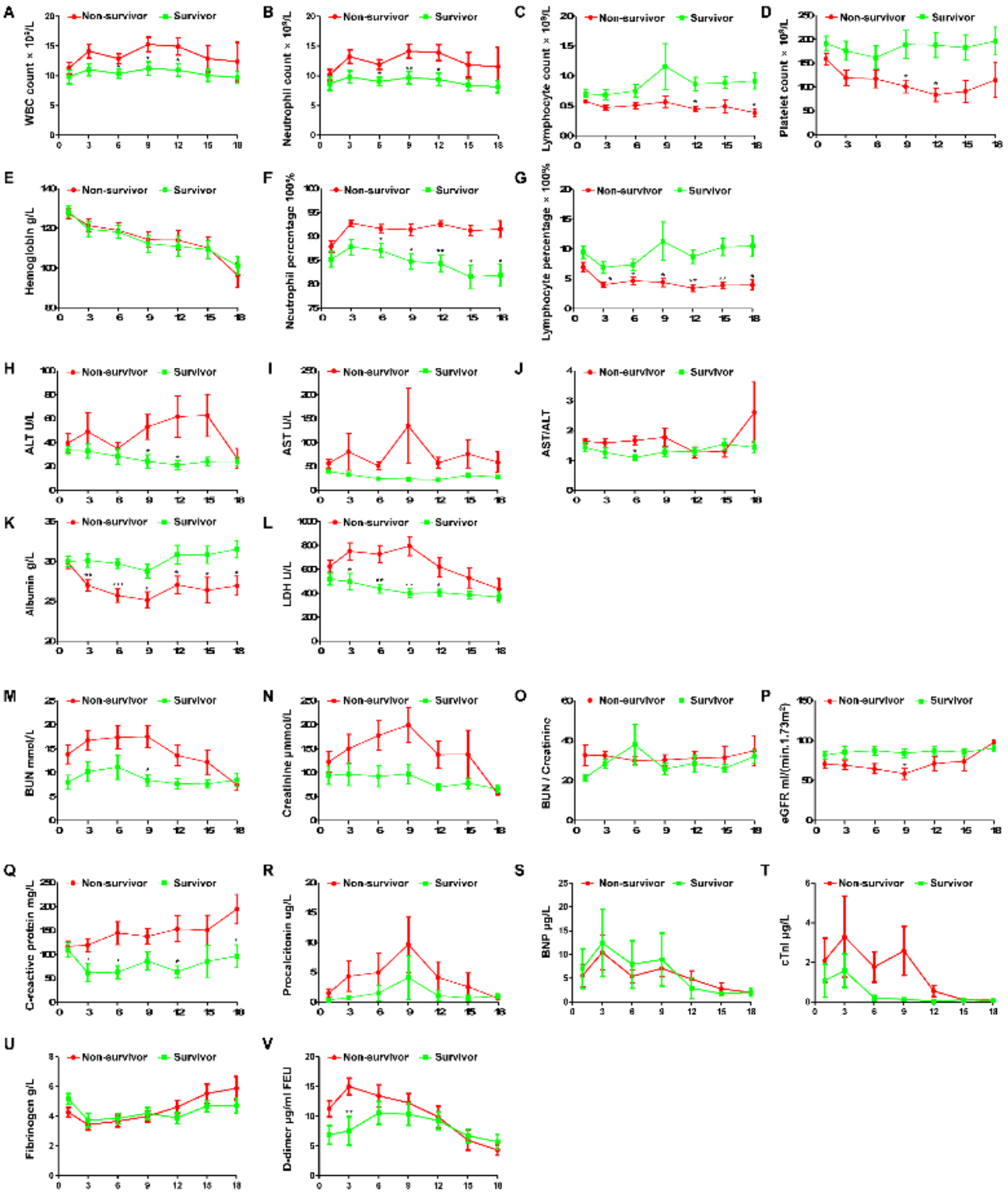

Figure 2

Kaplan-Meier survival curves for severe and critically ill patients with COVID-19. A: Arbidol; B: Lopinavir/ritonavir; C: Oseltamivir; D: Ribavirin; E: Interferon; F: Glucocorticoid.

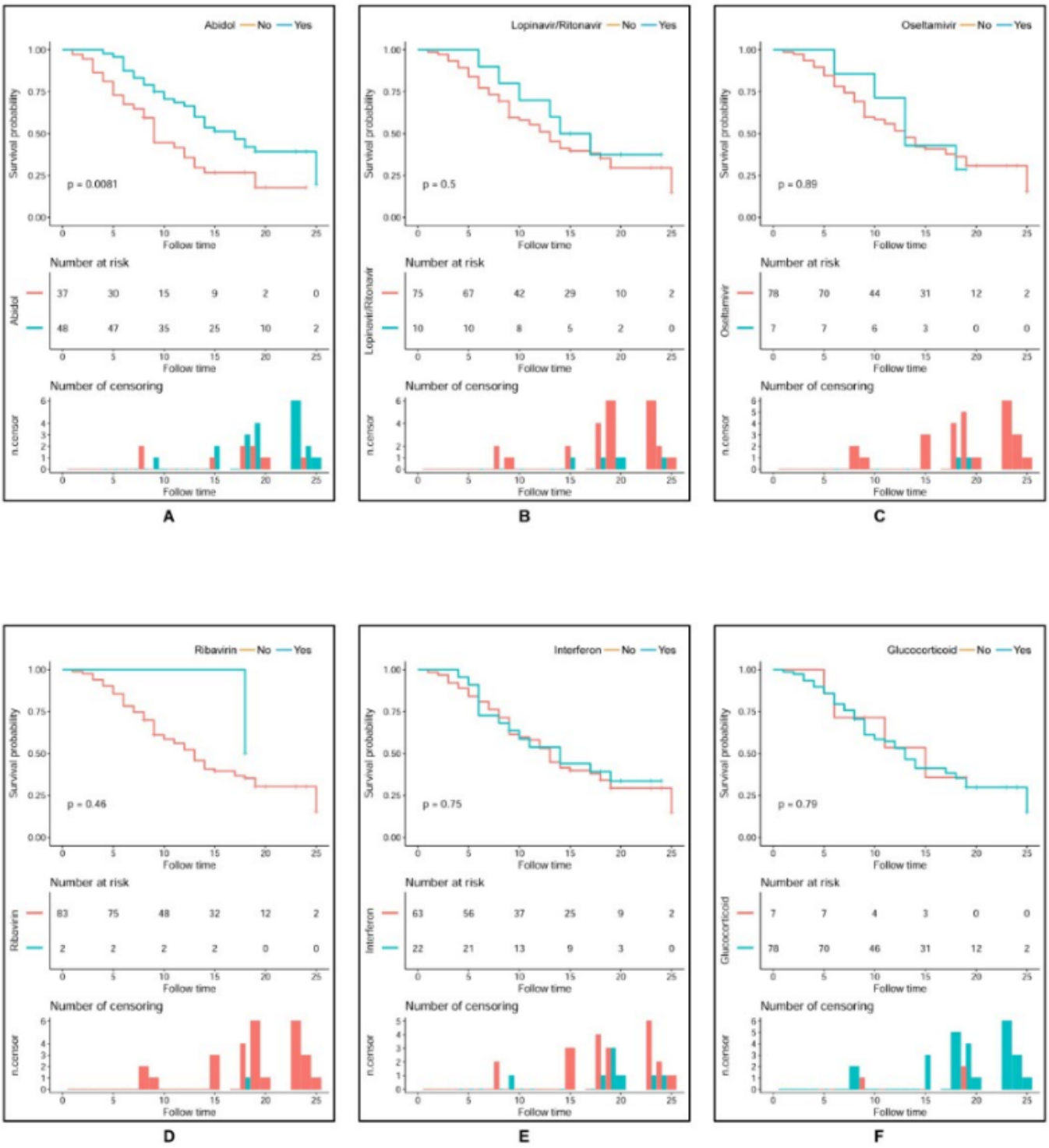

Figure 3

Timeline charts illustrate the laboratory parameters in severe and critically ill patients with COVID-19 on day 1, day 3, day 6, day 9, day 12, day 15 and day 18 after admission. * P <0.05; ** P <0.01. *** P <0.001.

Supplementary Files

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- Table1.docx
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