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Subcutaneous tocilizumab in adults with severe and critical COVID-19: A prospective open-label uncontrolled multicenter trial

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ABSTRACT

Potential therapeutic approaches in coronavirus disease 2019 (COVID-19) comprise antiviral and immunomodulatory agents; however, no immunomodulator drug has been approved. This multicenter, prospective, open-label, uncontrolled study aimed to assess the use of subcutaneous tocilizumab in adult patients with severe and critical COVID-19. Tocilizumab was added to the standard care of therapy at a dose of 324 mg (< 100 kg bodyweight) or 486 mg (≥ 100 kg bodyweight). The study endpoints were all-cause mortality rate, changes in oxygen-support level, oxygen saturation, body temperature, respiratory rate, and laboratory variables during the study, and drug safety. Of 126 patients enrolled, 86 had severe and 40 had critical disease. Most patients were male (63.49%) and aged below 65 (78.57%). By day 14 of the study, 4.65% (4/86) of severe patients and 50.00% (20/40) of critical patients died. By the end, 6.98% (6/86) of severe patients and 60.00% (24/40) of critical patients died. Outcomes concerning three additional endpoints (oral temperature, oxygen saturation, and respiratory rate) were significantly improved as early as three days after tocilizumab administration in both groups of subjects, more considerably in severe patients. Significant improvement in the required level of oxygenation was reported in severe patients seven days after tocilizumab administration. No tocilizumab-related serious adverse event occurred in this study. Subcutaneous tocilizumab might improve some clinical parameters and reduce the risk of death in COVID-19 patients, particularly if used in the early stages of respiratory failure.

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1. Introduction

The coronavirus disease 2019 (COVID-19) pandemic, caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), is

causing significant morbidity and mortality around the world. Similar to SARS-CoV and Middle East respiratory syndrome coronavirus (MERS-CoV), SARS-CoV-2 belongs to the genus betacoronavirus and is an enveloped, positive-strand RNA virus [1]. Respiratory droplet

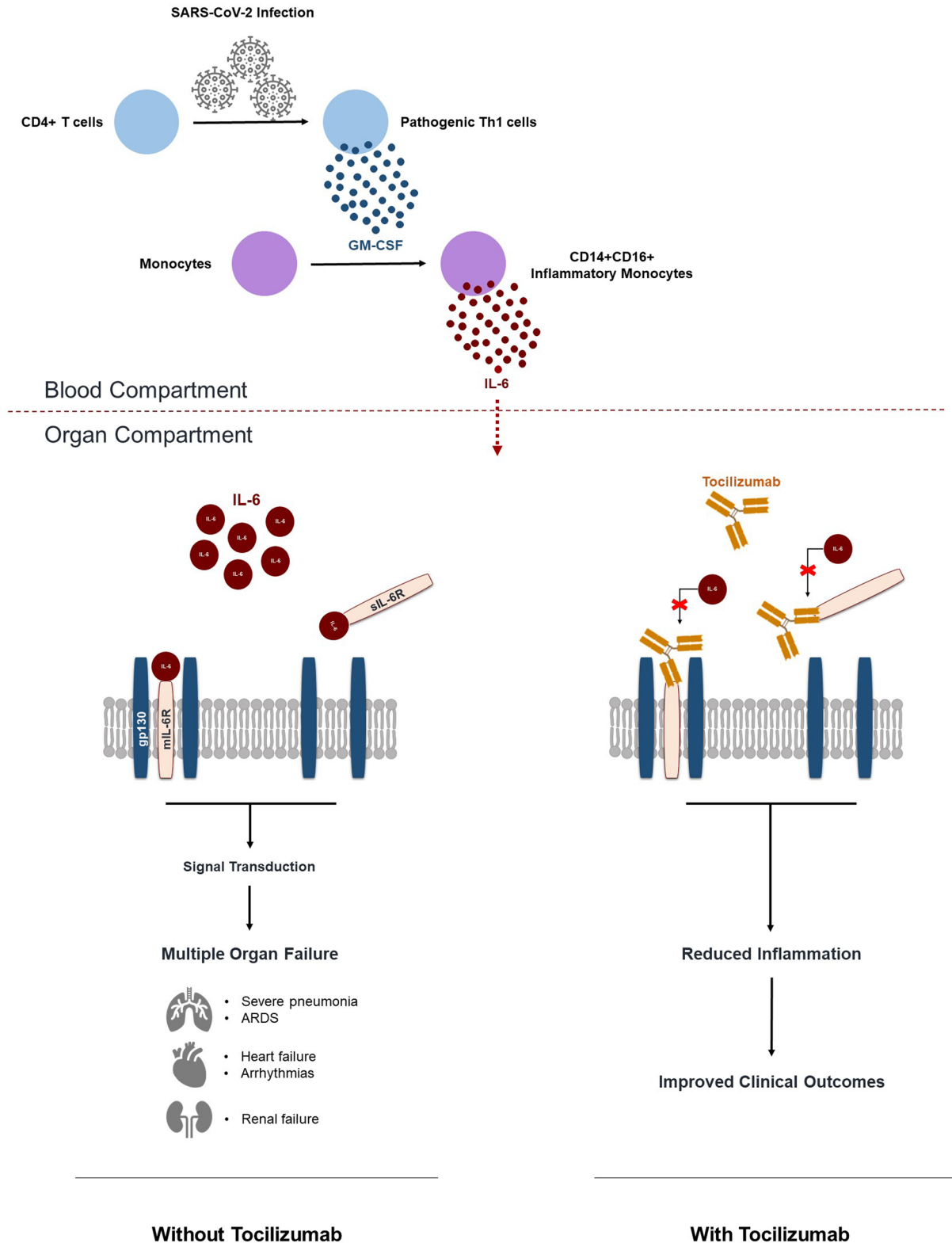


Fig. 1. Activation of pathogenic T cells and inflammatory monocytes following SARS-CoV-2 infection and the mechanism of action of tocilizumab. Tocilizumab inhibits sIL-6R and mIL-6R-mediated signaling and can potentially improve the clinical outcomes in severe COVID-19. ARDS, acute respiratory distress syndrome; GM-CSF, granulocyte-macrophage colony-stimulating factor; gp130, glycoprotein 130; IL-6, interleukin 6; mIL-6R, membrane-bound IL-6 receptor; sIL-6R, soluble IL-6 receptor; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.

transmission from infected patients is known to be the main route of COVID-19 transmission to the community [2]. According to the latest world health organization (WHO) COVID-19 epidemiological update, over 34.8 million cases were confirmed by national authorities by 10:00 central European summer time (CEST), 05 October 2020, and this number is fast increasing. Since the beginning of the pandemic in December 2019, the global mortality rate of COVID-19 was 2.96% (over 1,030,000 deaths). The Americas is the most affected region accounting for 49% of global cases and 55% of cumulative deaths [3]. Although most patients experience either asymptomatic infection or non-severe disease, a large number of patients die due to complications such as multiple organ failure, severe pneumonia, acute respiratory distress syndrome (ARDS), heart failure, arrhythmias, renal failure, and septic shock [4,5]. Studies in China [6–8] and Italy [9,10] found that older age, male sex, smoking, and comorbidities such as respiratory diseases, diabetes, hypertension, and cardiovascular diseases are risk factors associated with severe disease and death in patients with COVID-19.

In asymptomatic and paucisymptomatic patients, controlled and effective host immune response suppresses viral load. However, in medically complicated patients, immune evasion and rapid replication of SARS-CoV-2 can be followed by a dysregulated immune response and extensive release of inflammatory mediators [11]. In these patients, the combination of direct destruction of virus-infected cells and indirect destruction via hyperinflammatory response leads to lung epithelium damage and unfavorable clinical outcomes [12]. Accordingly, potential therapeutic approaches comprise antiviral agents to eradicate SARS-CoV-2 (such as remdesivir, lopinavir/ritonavir, and favipiravir) and immunomodulator agents (such as tocilizumab, dexamethasone, and interferon beta) to dampen inflammation by modulating proinflammatory cytokines [13]. Many treatments are being investigated in COVID-19 clinical trials, yet only a few are approved by regional authorities. By 05 October 2020, remdesivir was the only approved treatment by the Therapeutic Goods Administration (TGA) in Australia [14], the European Medicines Agency (EMA) [15], and the Pharmaceuticals and Medical Devices Agency (PMDA) in Japan [16]. The United States Food and Drug Administration (U.S. FDA) also has issued an emergency use authorization (EUA) to permit the emergency use of this unapproved antiviral product [17]. Moreover, the National Institutes of Health (NIH) and EMA's human medicines committee (CHMP) recommend the use of dexamethasone in COVID-19 patients who require oxygen support [18,19].

Several studies have documented increased serum levels of a wide range of cytokines such as tumor necrosis factor- α (TNF- α), interferon-gamma (IFN- γ), granulocyte-macrophage colony-stimulating factor (GM-CSF), interleukin (IL)-2, IL-4, IL-6, and IL-10 in COVID-19 patients, with significantly higher levels in severe to critical cases [7,20–23]. Infection with SARS-CoV-2 results in the activation of CD4 + T cells to become GM-CSF-expressing pathogenic T helper (Th) 1 cells [24]. Abnormally high levels of activated Th17 cells are also observed in severe- to critically-ill COVID-19 patients, which can take part in the extensive release of inflammatory mediators such as IL17, GM-CSF, IL21, and IL22 [23,25]. This cytokine environment results in the generation of inflammatory CD14 + CD16 + monocytes with high expression of IL-6 [24]. IL-6 has the capability to induce the development of Th17 cells and plays a major role in the COVID-19-associated hyperinflammation [26,27]. A meta-analysis comparing IL-6 levels between patients with noncomplicated and complicated COVID-19 (six studies; 1302 patients) found 2.9-fold higher levels in the latter group [28]. Moreover, a clinical investigation found substantially higher levels of IL-6 in the endotracheal aspirates of COVID-19 patients, compared to their blood samples [29]. This indicates a compartmental inflammation in COVID-19 patients, with a distinctly higher presence of inflammatory mediators in the lung compartment (Fig. 1).

In order to restrain the overactivity of the immune system and excessive inflammation, different classes of immune-based therapies are being explored in COVID-19 clinical trials, including IL-6 inhibitors, IL-

1 inhibitors, corticosteroids, Janus kinase inhibitors, and COVID-19 convalescent plasma [30,31]. Tocilizumab is a recombinant humanized IL-6 receptor antagonist. This monoclonal antibody is approved by the U.S. FDA in severe or life-threatening cytokine release syndrome (induced by chimeric antigen receptor (CAR) T-cell therapy) [32], rheumatoid arthritis [33], giant cell arteritis [34], polyarticular juvenile idiopathic arthritis [35], and systemic juvenile idiopathic arthritis [36]. In COVID-19 patients, the blockage of the IL-6 receptor by tocilizumab could potentially reduce the cytokine release and acute phase reactant production, hence, alleviating the symptoms and improving the clinical outcomes. Besides several case reports, a number of published studies including four retrospective cohort studies [22,37–39], two prospective open-label studies [40,41], and a case series [42], the preliminary results of a randomized controlled trial (#NCT04331808) [43], and the results of two meta-analysis studies [44,45] (risk ratios [RRs] of 0.45 and 0.73, 95% confidence intervals [CIs] of 0.38–0.55 and 0.57–0.93, respectively) support the use of tocilizumab for severe COVID-19. By contrast, in one other meta-analysis [46], the beneficial impact of tocilizumab on COVID-19 mortality did not reach statistical significance (RR of 0.62, 95% CI of 0.31–1.22), and data from these studies are conflicting.

We conducted a multicenter prospective study in patients with severe or critical COVID-19 to assess the outcomes following subcutaneous tocilizumab treatment. This relatively large study would improve the data available on the use of subcutaneous tocilizumab in COVID-19 patients. Moreover, this study's results could help determine the proper timing for the administration of tocilizumab, based on the severity of the disease.

2. Patients and methods

2.1. Study design

This multicenter, prospective, open-label, uncontrolled study was performed in eight tertiary care centers in Iran, between 15 March and 22 June 2020. The study was approved by the research ethics committee at the National Institution for Medical Research Development, #IR.NIMAD.REC.1398.414. The trial was registered at the Iranian Registry of Clinical Trials (IRCT.ir), #IRCT20150303021315N17.

2.2. Study population

We assessed all adult COVID-19 patients' eligibility with a confirmed diagnosis of SARS-CoV-2 infection either by polymerase chain reaction (PCR) or by computed tomography (CT) of the chest. We included patients with fever defined as an oral temperature of 37.8 °C (100°F) or higher, cough, shortness of breath, or respiratory rate of more than 30 breaths per minute that had a peripheral blood oxygen saturation (SpO₂) of 93% or less in room air and a serum IL-6 level of three times upper limit of normal or higher. We excluded patients with a known hypersensitivity to tocilizumab or any other component of the formulation, history of infection with hepatitis B virus (HBV), hepatitis C virus (HCV), human immunodeficiency virus (HIV), history of immunodeficiency, hepatic disorders, bone marrow suppression defined as absolute neutrophil count (ANC) below 2000/mm³ or platelet count below 100,000/mm³, active peptic ulcer, active diverticulitis, or any other gastrointestinal disorders that increase the risk of gastrointestinal perforation, pregnancy, breast-feeding, any concurrent active infection other than COVID-19, and severe renal impairment defined as a glomerular filtration rate (GFR) of below 30 mL/min/1.73 m². All subjects enrolled met the criteria for severe disease defined by the Report of the WHO-China Joint Mission on Coronavirus Disease 2019 (COVID-19) [47], published on 28 February 2020, as tachypnoea (30 breaths/minute or more), resting oxygen saturation of 93% or less, or a ratio of arterial oxygen partial pressure to fractional inspired oxygen (PaO₂/FIO₂) of below 300 mmHg. Patients with respiratory failure requiring

mechanical ventilation, shock, or other organ failure requiring transfer to the intensive care unit (ICU) were considered critical. All patients or their legal guardians provided written informed consent prior to the administration of tocilizumab.

2.3. Study interventions

Patients received subcutaneous injections of tocilizumab (AryoGen Co., Iran) at a dose of 324 mg (as two simultaneous 162 mg injections) for patients weighing < 100 kg and at a dose of 486 mg (as three simultaneous 162 mg injections) for patients weighing 100 kg or more along with the standard-of-care (SOC) treatment in each study center. SOC treatment included supportive care, antiviral agents, hydroxychloroquine, subcutaneous interferon beta-1a, and antibiotic agents.

2.4. Study outcomes

We followed up patients until hospital discharge or death. Our primary outcome was all-cause mortality rate during the hospital stay. As secondary outcomes, we evaluated changes in SpO₂, body temperature, respiratory rate, and laboratory values, including serum levels of C-reactive protein (CRP) and white blood cell (WBC) count from baseline through the last day of hospital stay. In addition, we assessed the change in patients' required oxygen-support class based on a six-point ordinal scale. The scale consists of the following steps: 1, no supplemental oxygen; 2, nasal catheter oxygen inhalation; 3, mask oxygen inhalation; 4, noninvasive positive pressure ventilation; 5, invasive mechanical ventilation; and 6, death. Adverse events were monitored and reported throughout the study.

2.5. Statistical analysis

Demographic data were presented with descriptive statistics, and categorical variables were compared using the chi-square test. Continuous variables were expressed as median (IQR). Between-group differences were analyzed using the Mann-Whitney *U* test, and within-group changes during the study were analyzed using the Wilcoxon signed-rank test. Mortality rates were expressed as numbers (%), and Kaplan-Meier curves were used to plot the survival data. Log-rank test was used to analyze the statistical significance of survival differences between severe and critical patients. Statistical analyses were

performed using STATA version 14.0 (Stata Corporation, Texas, USA) and R version 3.6.3 (R Foundation for Statistical Computing, Vienna, Austria). P-values < 0.05 were considered as statistically significant.

3. Results

3.1. Baseline characteristics

A total of 126 COVID-19 patients including 86 patients with severe disease and 40 patients with critical disease were included in this study. Most patients were male (63.49%, 80/126) and non-elderly, aged below 65 years (78.57%, 99/126). The mean (SD) and median (range) age was 53.49 (13.26) and 55 (20–85) years. Demographic characteristics of patients were similar in severe and critical patients (table 1). On admission, median (IQR) oral temperature (37.10 °C (36.80–38.00) vs. 37.70 °C (37.00–39.00), p-value = 0.08), respiratory rate (20.00 breaths/min (19.00–24.00) vs. 24.00 breaths/min (20.00–26.00), p-value = 0.07), heart rate (89.00 beats/min (82.00–100.00) vs. 97.50 beats/min (80.00–110.00), p-value = 0.23), and mean arterial pressure (87.50 mmHg (83.33–96) vs. 97.50 mmHg (90–108.33), p-value < 0.001) were higher in critical patients. Baseline values of laboratory measurements are provided in table 1. Most notably, the initial levels of WBC counts (6.90 k/mm³ (5.15–9.08) vs. 10.30 k/mm³ (8.30–13.60), p-value < 0.001) and CRP (22.00 mg/L (6.00–39.00) vs. 48.00 mg/L (6.00–85.20), p-value = 0.097) were higher in critical patients.

3.2. Mortality

The median (IQR) length of hospital stay, from tocilizumab administration until discharge home or death, was 8 days (5–12) (7 days (5–11) in severe patients and 10 days (5.5–14) in critical patients). Individual patient's length of hospital stay and final status (death or discharge) are provided in Fig. A1. By day 14, 68.25% (86/126) of patients were discharged alive from hospital (87.21% (75/86) of severe patients and 27.5% (11/40) of critical patients), 19.05% (24/126) died (4.65% (4/86) of severe patients and 50.00% (20/40) of critical patients), and 12.70% (16/126) were still hospitalized (8.14% (7/86) of severe patients and 22.5% (9/40) of critical patients). By the end, 76.19% (96/126) of patients were discharged alive from the hospital. Of the 86 severe patients, 6 (6.98%) died, while, of the 40 critical patients, 24 (60.00%) died in the hospital. The risk of death was

Table 1

Baseline patient characteristics. Data are median (IQR) or n (%). ALT, alanine aminotransferase; AST, aspartate aminotransferase; CRP, C-reactive protein; INR, international normalized ratio; MAP, mean arterial pressure; sCr, serum creatinine; PTT, partial thromboplastin time; WBC, white blood cell.

	Severe (N = 86)	Critical (N = 40)	Total (N = 126)
Age (year)	53.50 (45.50–62.00)	57.50 (50.00–63.50)	55.00 (46.00–63.00)
< 65	67 (77.91)	32 (80.00)	99 (78.57)
Weight (kg)	75.00 (70.00–80.00)	80.00 (68.50–94.00)	77.00 (70.00–85.00)
> 100	3 (3.49)	3 (7.50)	6 (4.76)
Sex: Female	32 (37.21)	14 (35.00)	46 (36.51)
WBC (k/mm ³)	6.90 (5.15–9.08)	10.30 (8.30–13.60)	7.92 (5.79–11.07)
CRP (mg/L)	22.00 (6.00–39.00)	48.00 (6.00–85.20)	24.00 (6.00–46.00)
ALT (IU/L)	36.50 (24.50–62.00)	46.00 (28.00–61.00)	37.50 (26.00–61.00)
AST (IU/L)	35.00 (25.00–49.00)	49.00 (36.00–82.00)	38.50 (27.50–62.00)
sCr (mg/dL)	1.00 (0.90–1.10)	1.10 (0.90–1.20)	1.00 (0.90–1.20)
PTT (s)	38.00 (30.00–43.00)	36.00 (34.00–39.00)	36.00 (31.00–43.00)
INR	1.14 (1.07–1.23)	1.29 (1.19–1.40)	1.19 (1.08–1.30)
MAP (mmHg)	87.50 (83.33–96.00)	97.50 (90.00–108.33)	93.33 (83.33–98.33)
Respiratory Rate (breaths/min)	20.00 (19.00–24.00)	24.00 (20.00–26.00)	20.00 (19.00–26.00)
Oral temperature (°C)	37.10 (36.80–38.00)	37.70 (37.00–39.00)	37.10 (36.90–38.00)
Heart Rate (beats/min)	89.00 (82.00–100.00)	97.50 (80.00–110.00)	90.00 (82.00–100.00)
Prior or concomitant treatments			
Lopinavir–ritonavir	86 (100)	40 (100)	126 (100)
Antibiotics	86 (100)	40 (100)	126 (100)
Interferon beta-1a	27 (31.40)	14 (35.00)	41 (32.54)
Hydroxychloroquine	26 (30.23)	13 (32.50)	39 (30.95)
Favipiravir	13 (15.12)	3 (7.50)	16 (12.70)

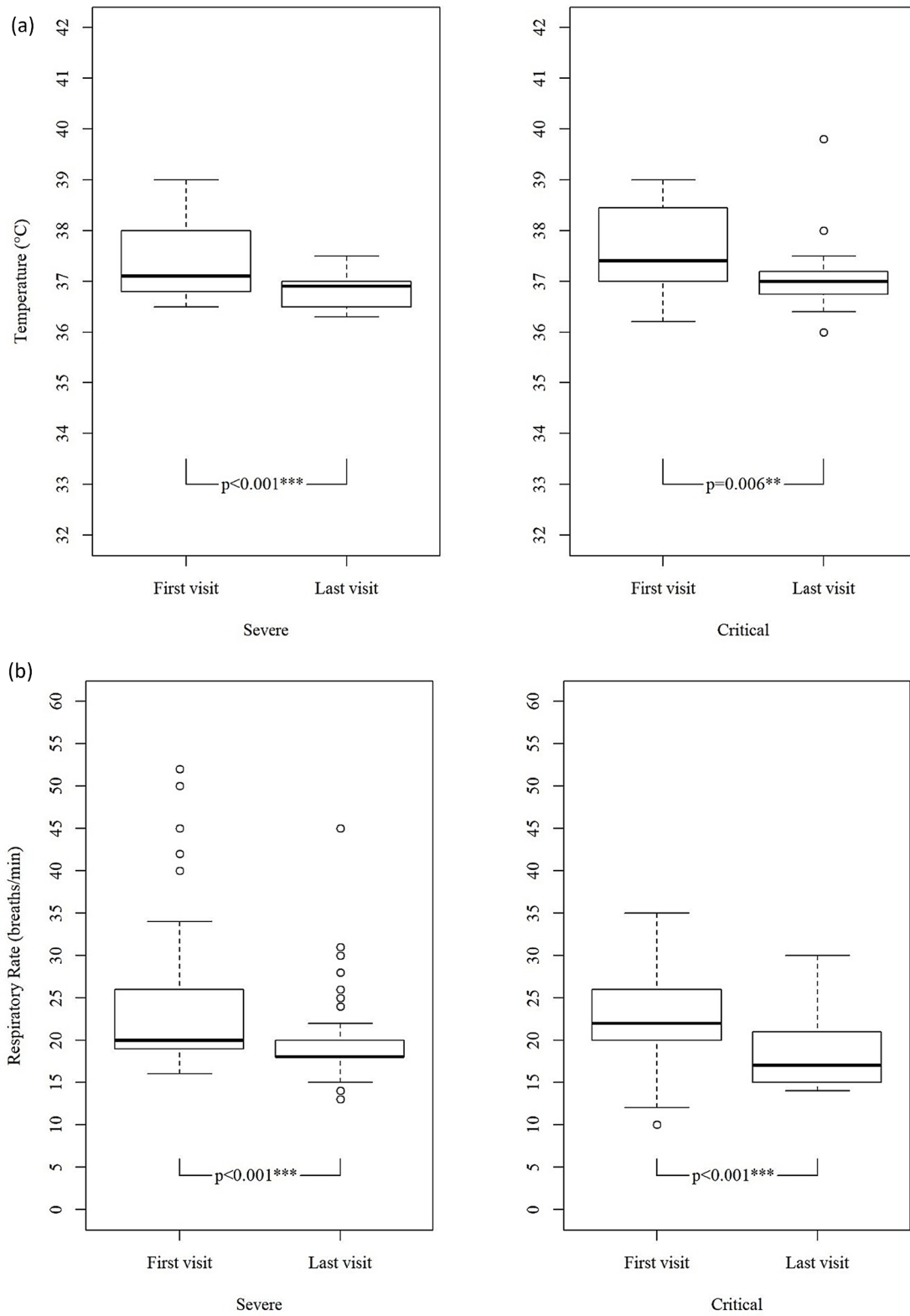


Fig. 3. Changes in body temperature (A), respiratory rate (B), and oxygen saturation (C) in the two groups of patients from baseline through the last day of hospital stay. *p-value < 0.05; **p-value < 0.01; ***p-value < 0.001.

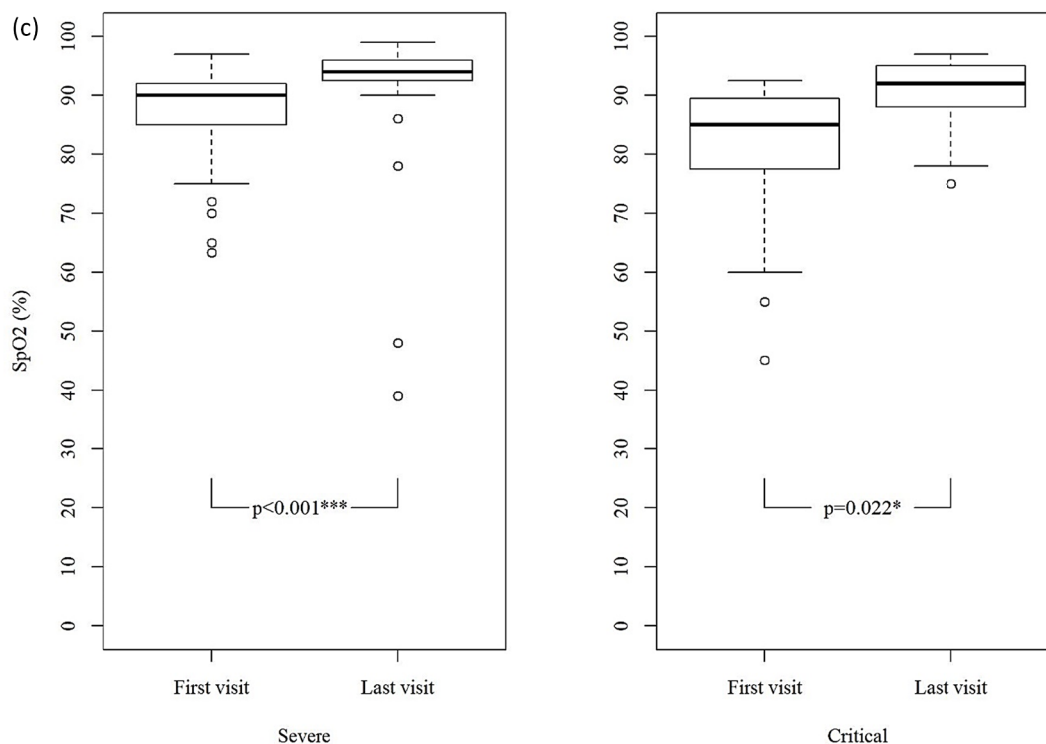


Fig. 3. (continued)

4. Discussion

An accentuated host immune response to SARS-CoV-2 leads to lung damage and respiratory failure in severe and critical stages of COVID-19. Despite the very poor prognosis of these patients, no immunomodulatory agent is yet approved for routine clinical practice in COVID-19 patients. Different studies report a very wide range of mortality rates in severe and critical patients, from 0% [48] to 84.6% [49]. We observed a mortality rate of 6.98% (6/86) in patients with severe disease, which is close to 7.7% (7/90) reported by De Rossi et al. [39] in tocilizumab-treated patients with respiratory failure following SARS-CoV-2 infection. With a retrospective cohort design, they have included patients with severe pneumonia with a similar definition to that of our study. The authors reported a significantly better survival rate in patients treated with tocilizumab compared to those who received SOC only (multivariate hazard ratio: 0.057; 95% C.I. = 0.017–0.187, p -value < 0.001). They have excluded patients with a critical respiratory condition requiring either invasive or noninvasive mechanical ventilation, while we have evaluated these patients as a distinct group of subjects. The overall mortality rate in our critical patients was 60.0% (24/40), far more than the severe patients (p -value < 0.001). Based on a recently published meta-analysis [50], the combined mortality rates in ICU admitted patients were 59.5% (calculated using the studies to the end of March 2020) and 41.6% (calculated using all eligible studies); however, the criteria for ICU admission were different in the included studies. In an observational controlled trial on 154 mechanically ventilated COVID-19 patients, tocilizumab was associated with an increased incidence of superinfection compared to the control (54% vs. 26%, p -value < 0.001). However, the mortality risk did not differ significantly among tocilizumab-treated patients with and without superinfection (22% vs. 15%, p -value = 0.42), and tocilizumab was associated with a significant reduction in mortality compared to the control (hazard ratio of 0.55 and 95% CI of 0.33–0.90) [51].

Collectively, on the one hand, our encouraging results in severe patients and on the other hand, the poor survival rate in critical patients confirms the rationale of De Rossi et al. for considering tocilizumab at the early stages of respiratory failure, before the development of a critical condition requiring assisted mechanical ventilation, and not when the lung damage has already occurred.

To date, none of the randomized controlled trials of tocilizumab in COVID-19 are published; however, the interim results of the CORIMUNO-TOCI (#NCT04331808) trial were announced through a press release on 27 April 2020, and Roche provided a summary of the findings of the COVACTA (#NCT04320615) trial on 29 July 2020 [43,52]. According to the preliminary results of the CORIMUNO-TOCI trial, 8 mg/kg intravenous administration of tocilizumab significantly reduced the probability of death or need for ventilation compared to the SOC treatment alone. However, in the COVACTA trial, only a positive trend in the time to hospital discharge was observed in the tocilizumab group, and the trial did not meet the main endpoints of significant improvements in clinical status and survival rate. The interim report of CORIMUNO-TOCI only considered patients who did not require ventilator support at the beginning of the trial. In contrast, according to the unpublished manuscript of COVACTA [53], 70.4% (207/294) of tocilizumab-treated patients were ventilator-dependent at the baseline of this study. Altogether, the promising results of CORIMUNO-TOCI, along with our positive results in severe patients and low survival rates in critical patients, highlight the importance of appropriate timing in the administration of tocilizumab in COVID-19.

In our study, rapid and consistent improvements in body temperature, respiratory rate, and blood oxygenation were observed as early as three days post-tocilizumab and sustained thereafter. As IL-6 is an important component of the so-called “cytokine storm” following SARS-CoV-2 infection, rapid amelioration of the clinical measures of disease severity in a significant proportion of patients could be attributed to the inhibition of IL-6-mediated signaling by tocilizumab. These results are

consistent with those of three relatively small studies in China (15 subjects) [54], Qatar (25 subjects) [55], and Italy (63 subjects) [40], in which satisfactory changes in body temperature, respiratory parameters, and inflammatory markers were observed a short time after tocilizumab administration. Similarly, in a prospective study of 100 severe COVID-19 patients in Italy, a rapid improvement of the clinical condition occurred in most (58%) of the patients within 12–72 h after tocilizumab administration. Moreover, the authors reported sustained clinical benefit in all patients with an initial clinical response through the end-of-study follow-up (day 10) [56].

We reported significantly improved levels of required oxygen-support class in severe patients in days seven and 14 post-tocilizumab. Fernández-Ruiz et al. [57], in a retrospective analysis of 88 patients with severe COVID-19 pneumonia, reported a declined level of required oxygen therapy in the majority of patients (73.9%) by day 14. Similarly, Alattar et al. [55], in a retrospective study of 25 severe COVID-19 patients, reported a considerable reduction in the proportion of patients on invasive ventilation from 84% at baseline to 60% and 28% on days seven and 14 post-tocilizumab, respectively. During this pandemic, intensive care units around the world are overrun by the huge number of critically ill patients, and hospitals are struggling with shortages in resources such as mechanical ventilators [58]. This situation highlights the benefits of a treatment that ameliorates the oxygen-support requirements and reduces the need for ICU admission.

Our study was performed using the subcutaneous dosage form of tocilizumab (162 mg/ 0.9 mL) with a dose of 324 mg (in patients weighing below 100 kg, $n = 120$) or 486 mg (in patients weighing 100 kg or more, $n = 6$). This dosing schedule is similar to many other studies that used subcutaneous tocilizumab in COVID-19 patients [38–40]. While the intravenous dosage form is generally considered for the cytokine release syndrome [59], the subcutaneous injection was used in our study centers and many others around the world due to the unavailability of the intravenous tocilizumab. A pharmacokinetic/pharmacodynamic study found comparable effects of 162 mg tocilizumab on serum levels of soluble IL-6 receptor (sIL-6R) and CRP either using a subcutaneous or intravenous injection in healthy volunteers and concluded that the 162 mg subcutaneous and intravenous tocilizumab are pharmacodynamically equivalent [60]. Moreover, in the only pharmacokinetic study of 324 mg subcutaneous tocilizumab, the area under the concentration-time curve (AUC) of the 4 mg/kg intravenous tocilizumab (during a 4-week interval) was found to be close to that of a single-dose 324 mg subcutaneous injection ($13,000 \pm 5800$ and $10,800 \pm 3220$ $\mu\text{g}\cdot\text{h}/\text{mL}$, respectively) [61]. These two studies (performed by the same groups) found higher absolute pharmacokinetic bioavailability of tocilizumab with higher subcutaneous doses; 22.7% with 81 mg, 48.8% with 162 mg, 75.9% with 324 mg, and 83.0% with 648 mg injections. Collectively, it could be concluded that 324 mg subcutaneous tocilizumab (and 486 mg in subjects with heavier body-weight) is a reasonable substitute for the 4–8 mg/kg intravenous tocilizumab, which is the recommended dose by the China National Health Commission [62] and is used in clinical studies [22,63]. In the study protocol of several randomized controlled trials of tocilizumab in COVID-19, infusion at a dose of 8 mg/kg is considered for all participants [43,53,64–66]. Hence, as 648 mg subcutaneous tocilizumab is considered equivalent to 8.23 mg/kg by Morcos et al. [61], doses higher than 324/468 mg subcutaneous tocilizumab could also be considered in the future studies. In previous studies on patients with severe COVID-19, no difference was observed between the benefits of subcutaneous and intravenous tocilizumab on mortality rates. Guaraldi et al. [38] reported mortality rates of 7.7% (7/91) and 6.8% (6/88), and Sciascia et al. [40] reported mortality rates of 10.3% (3/29) and 12.9% (4/31) with subcutaneous and intravenous tocilizumab, respectively. These two routes of administration of tocilizumab are generally known to

have similar safety profiles with the only exception of a higher risk of injection site reactions with the subcutaneous form [67,68]; however, no injection site reaction was reported in our study, which could be because of the small number of injections per patient. Accordingly, based on the available information on the pharmacokinetic/pharmacodynamic and safety profiles of subcutaneous and intravenous tocilizumab and the clinical efficacy results of the above-mentioned studies in COVID-19 patients, a similar clinical response would be expected with the two formulations of tocilizumab.

Uncontrolled design is the main limitation of our study. Without a control group, we cannot have certainty on the interpretation of our observations. This limitation would be specifically important in this pandemic situation, as surges in the number of hospitalized COVID-19 patients put major pressure on healthcare systems and may result in the presence of different confounders in different study settings. Despite this limitation, our study furthers the available evidence on the use of tocilizumab in severe and critical COVID-19 patients. Moreover, our data represents the largest published study on subcutaneous use of tocilizumab in COVID-19 and, even more generally, in patients with the cytokine-release syndrome.

In summary, we observed significant improvements in some clinical parameters of our COVID-19 patients following the subcutaneous administration of tocilizumab. Looking at the mortality rates of severe and critical patients, it can be concluded that subcutaneous tocilizumab might be capable of reducing the risk of death, particularly if used in the early stages of respiratory failure. The final results of the ongoing randomized controlled trials of tocilizumab for COVID-19 are needed to complement the available data on the safe and effective use of tocilizumab in COVID-19.

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CRediT authorship contribution statement

Reza Malekzadeh: Investigation, Writing - review & editing. **Atefeh Abedini:** Investigation, Writing - review & editing. **Behzad Mohsenpour:** Investigation, Writing - review & editing. **Ehsan Sharifipour:** Investigation, Writing - review & editing. **Roya Ghasemian:** Investigation, Writing - review & editing. **Seyed Ali Javad-Mousavi:** Investigation, Writing - review & editing. **Rozita Khodashahi:** Investigation, Writing - review & editing. **Mahboobeh Darban:** Investigation, Writing - review & editing. **Saeed Kalantari:** Investigation, Writing - review & editing. **Nafiseh Abdollahi:** Investigation, Writing - review & editing. **Mohammad Reza Salehi:** Investigation, Writing - review & editing. **Abbas Rezaei Hosseinabadi:** Investigation, Writing - review & editing. **Farzin Khorvash:** Investigation, Writing - review & editing. **Melika Valizadeh:** Investigation, Writing - review & editing. **Farzaneh Dastan:** Investigation, Writing - review & editing. **Sahar Yousefian:** Investigation, Writing - review & editing. **Hamed Hosseini:** Investigation, Writing - review & editing. **Nassim Anjidani:** Methodology, Resources, Writing - original draft. **Payam Tabarsi:** Conceptualization, Methodology, Formal analysis, Investigation, Supervision, Writing - review & editing.

Declaration of Competing Interest

N Anjidani is the head of the medical department of Orchid Pharmed company which is in collaboration with AryoGen Pharmed company with respect to conducting clinical trials.

Appendix A

See Fig. A1 and Table A1.

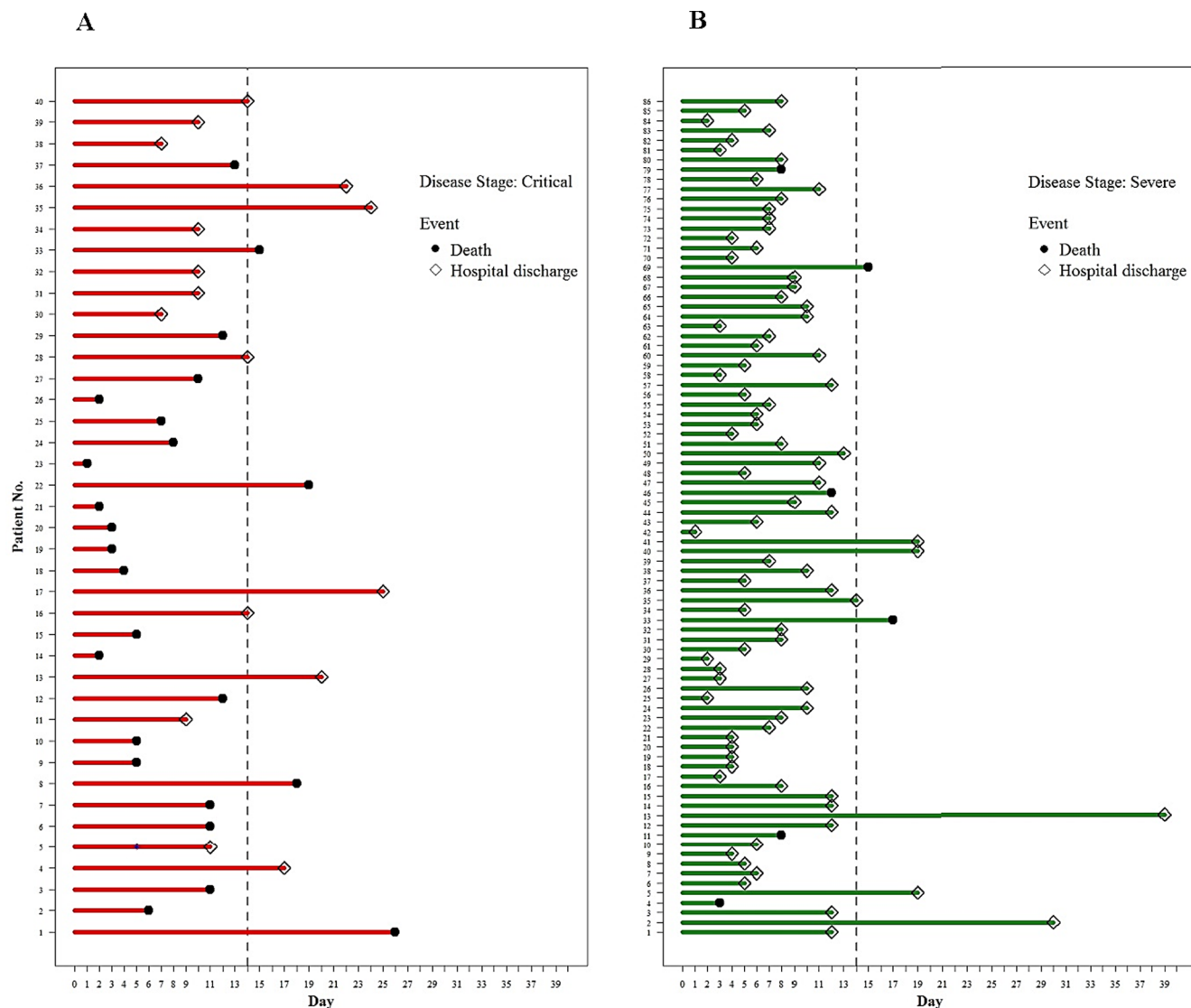


Fig. A1. Individual participant's time-to-event data in critical (A) and severe (B) patients from the day of tocilizumab injection through hospital discharge or death.

Table A1

		Baseline measurement	Last measurement	p-value
WBC (k/mm ³)	Severe	6.90 (5.15–9.08)	7.71 (5.43–12.02)	** 0.008
	Critical	10.30 (8.30–13.60)	10.50 (8.41–19.21)	** 0.009
CRP (mg/L)	Severe	22.00 (6.00–39.00)	3.20 (1.00–13.00)	*** < 0.001
	Critical	48.00 (6.00–85.20)	20.00 (2.50–54.00)	0.689
ALT (IU/L)	Severe	36.50 (24.50–62.00)	57.00 (35.50–115.00)	*** < 0.001
	Critical	46.00 (28.00–61.00)	54.00 (43.00–66.00)	0.232
AST (IU/L)	Severe	35.00 (25.00–49.00)	44.00 (27.00–71.00)	0.171
	Critical	49.00 (36.00–82.00)	50.00 (33.00–78.00)	0.925
sCr (mg/dL)	Severe	1.00 (0.90–1.10)	0.90 (0.80–1.00)	0.061
	Critical	1.10 (0.90–1.20)	1.08 (0.90–1.70)	0.584
PTT (s)	Severe	38.00 (30.00–43.00)	31.00 (27.00–36.00)	*** < 0.001
	Critical	36.00 (34.00–39.00)	33.00 (22.00–40.00)	0.191
INR	Severe	1.14 (1.07–1.23)	1.12 (1.02–1.22)	0.132
	Critical	1.29 (1.19–1.40)	1.20 (1.10–1.35)	0.253

Changes in laboratory values in the two groups of patients from baseline through the last day of hospital stay. Data are median (Q1-Q3). ALT, alanine aminotransferase; AST, aspartate aminotransferase; CRP, C-reactive protein; PTT, partial thromboplastin time; sCr, serum creatinine; WBC, white blood cell. **p-value < 0.01; ***p-value < 0.001.

Appendix B. Supplementary material

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.intimp.2020.107102>.

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