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Research Article

Adding Baricitinib to the Standard Treatment in Severe COVID-19 Patients: A Retrospective Cohort Study

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Abstract

Background: The severe form of coronavirus disease 2019 (COVID-19) is mainly marked by hyper inflammation and the associated multi-organ damage it causes. Baricitinib has been shown to have dual anti-inflammatory and antiviral effects. Our study aims to evaluate the effect of adding Baricitinib to the standard treatment on clinical and laboratory outcomes in patients with COVID-19 pneumonia.

Methods: In this retrospective cohort study conducted at three tertiary hospitals affiliated with Babol University of Medical Sciences, the medical records of 129 adult patients with severe COVID-19 pneumonia were reviewed. Patients were divided into two groups: one received standard treatment with remdesivir and corticosteroids, and the other received Baricitinib (4 mg daily for up to 14 days) in addition to the standard treatment. Outcomes included duration of hospital stay, 14- and 28-day mortality, arterial oxygen saturation, disease severity, invasive ventilation need, and ICU admission.

Results: Among the 129 patients (mean age 55.33 ± 14.88 years; 34.1% men), the Baricitinib group showed significantly lower disease severity at 14 days (p=0.02), reduced 14-day (0/66 vs 8/63, p=0.003) and 28-day mortality (1/66 vs 9/63, p=0.008), and greater arterial oxygen saturation improvement (p<0.001). The ICU and invasive ventilation duration did not differ between the two groups (p = 0.58 and p = 0.99, respectively).

Conclusion: This study found that adding Baricitinib to the standard treatment in severe COVID-19 pneumonia could reduce mortality and disease severity and improve arterial blood oxygen saturation compared to standard treatment only

Keywords: COVID-19, SARS-CoV-2, Baricitinib, Inflammation Mediators, Pneumonia

Introduction

The coronavirus disease 2019 (COVID-19) pandemic was started by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) in December 2019 in China (1, 2). As of September 2024, the World Health Organization (WHO) reported over 770 million cases, with over 7 million deaths worldwide due to COVID-19 since the beginning of the pandemic. Even after the emergence of new treatment options and the availability of vaccines, roughly a thousand daily cases are still being reported to WHO worldwide (3). COVID-19 presents with a spectrum of clinical manifestations, ranging from asymptomatic cases to severe respiratory failure. About 15% of the patients progress to severe disease, which usually results in hospitalization in the intensive care unit (ICU) for respiratory assistance or may even lead to death (4, 5). The leading cause of severe illness is overwhelming inflammation rather than the infection itself, which results in multi-organ damage. This exaggerated immune response is often regarded as a "cytokine storm" since many types of cytokines play a role in this process (6, 7). The cytokine storm is characterized by elevated levels of IL-6, TNF-α, and IFN-γ, which cause endothelial damage and multi-organ failure (8).

One of the cell's immune regulatory pathways is the Janus kinase/signal transducer and activator of transcription (JAK/STAT) signaling pathway, which involves transducing extracellular stimuli, including cytokines and hormones, to the cell nucleus (9). Drugs that inhibit this pathway can exhibit anti-inflammatory effects. One such drug is Baricitinib, which was first approved in the European Union in 2017 for the treatment of moderate to severe rheumatoid arthritis (RA) in adults (10). Unlike many other biological immune modulators that inhibit only one cytokine, Baricitinib can inhibit multiple cytokines, including interleukin-6 (IL-6) and interferon (IFN) (11). Baricitinib can also have antiviral activity by interfering with ACE-II (angiotensin-converting enzyme 2) binding and stopping the virus from entering the cell (12). Some studies highlighted that Baricitinib can moderate the inflammation in COVID-19 and improve patients' clinical status, especially in those receiving noninvasive ventilation (13, 14).

Despite current evidence of Baricitinib effectiveness in clinical trials (15, 16), real-world data can further investigate its effectiveness in combination with standard treatments for severe COVID-19 pneumonia. This study provides information about the applications of Baricitinib in clinical settings by analyzing the results in a retrospective cohort and aims to evaluate the effect of adding Baricitinib to the standard treatment on clinical and laboratory outcomes in patients with COVID-19 pneumonia.

Methods

Study design and participants

This retrospective cohort and multi-center study was conducted in three tertiary hospitals, all of which had ICU units and access to infectious disease and intensive care specialists. Medical records of 129 adult patients admitted with severe COVID-19 pneumonia between February 19 and September 22, 2021, were reviewed. Eligible participants were aged 18 years or older, diagnosed with COVID-19 via positive RT-PCR on nasal/oral swabs or characteristic findings on lung CT scans, and admitted with or progressed to severe COVID-19 pneumonia during hospitalization. Exclusion criteria were active cancer, kindey or hepatic dysfunction at admission (5-fold increase in hepatic enzymes or 3-fold increase plus coagulation test abnormalities), mild or moderate COVID-19 cases, as well as pregnancy and missing/incomplete medical records.

Definitions of COVID-19 pneumonia severity

We used the World Health Organization (WHO) and national classifications of COVID-19 severity (17) :

A) mild: patients with symptomatic COVID-19 but without evidence of viral pneumonia or hypoxemia

B) moderate: clinical signs of pneumonia (febrile, cough, dyspnea, tachypnea) and peripheral oxygen saturation (SpO2) ≥ 90% in room air

C) severe: signs of pneumonia and respiratory rate > 30 breaths/min or severe respiratory distress or SpO2 < 90% in room air

D) critical: acute respiratory distress syndrome (ARDS), sepsis, septic shock, or requiring life-sustaining treatment

Study Groups and Treatment

The patients were classified based on the type of treatment they recived during hospitilization into two groups. The first group has received standard treatment per national guidelines, including remdesivir and corticosteroids (18). The national guidelines recommended intravenous infusion of 200 mg Remdisivir in the first day and 100 mg in the following days in a 5-day course of treatment. As for corticosteroids, daily intravenous 8 mg Dexamethasone or daily oral 0.5 mg/kg Prednisolone for a maximum of 10 days were recommended. The second group has received standard treatment plus 4 mg of Baricitinib tablets daily for up to 14 days. The decision to administer baricitinib was made by the consulting physician based on clinical judgment. No randomization was applied in the allocation of treatment groups.

Data Collection

Assuming a significance level of 0.05 and a power of 80%, the minimum required sample size was calculated to be 63 individuals in the standard treatment group and 63 individuals in the baricitinib treatment group. Baseline characteristics, including demographic data, comorbidities, prior corticosteroid

use, and vital signs (blood pressure, heart rate, respiratory rate, SpO2, and temperature), were extracted from patient records. Laboratory tests at admission and discharge included white blood cell count (WBC), C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), lactate dehydrogenase (LDH), aspartate aminotransferase (AST), alanine aminotransferase (ALT), blood urea nitrogen (BUN), creatinine, prothrombin time (PT), partial thromboplastin time (PTT), and international normalized ratio (INR).

Statistical Analysis

The collected data were entered into SPSS version 23 (IBM Corporation, Armonk, NY, USA) software. The mean and standard deviation for continuous variables and frequency and percentage for categorical variables were calculated. For the comparison of categorical variables, the chi-square test and Fisher's exact test were employed. Depending on the normality of the data, independent t-tests or Mann-Whitney U tests were used to analyze the relationship between continuous and categorical variables. Analysis of covariance (ANCOVA) was used to adjust for potential confounding factors and compare the mean differences in laboratory measurements and clinical outcomes between the two groups. Also, A P-value of ≤ 0.05 was considered significant.

Results

This study included 129 patients with severe COVID-19 pneumonia in this study. The mean age of the patients was 55.33 ± 14.88 years, with 44 (34.1%) being men. The standard treatment group consisted of 63 patients, while 66 patients were in the standard treatment plus Baricitinib group. Baseline characteristics revealed no significant differences between the two groups (Table 1).

Patients were followed throughout their hospitalization, and the measured variables are presented in Table 2. There were no significant differences in ICU admission, invasive ventilation use, or laboratory measures between groups. However, disease severity after 14 days and 14-day and 28-day mortality were significantly lower in the Baricitinib group (p=0.02, p=0.003, and p=0.008, respectively) (Table 2).

Table 3 summarizes the laboratory measurements in the standard treatment group for patients with both admission and discharge data (N=54). In this group, WBC count was higher at discharge, while creatinine, AST, ESR, and CRP were lower. Similarly, Table 4 presents the Baricitinib group data (N=60), showing significantly higher WBC and lymphocyte counts at discharge, along with lower levels of creatinine, AST, ESR, CRP, and LDH.

Table 5 compares laboratory measurements across all patients in both groups, as well as ICU and invasive ventilation durations. Arterial blood oxygen saturation was significantly higher in the Baricitinib group

(p<0.001). However, ICU stay and invasive ventilation duration were similar between groups (p=0.58 and p=0.99, respectively).

Table 1. Baseline Characteristics of all patients in both groups

Variable	Standard treatment (n = 63)	Baricitinib + standard treatment (n = 66)	P value*
Age (Mean ± SD)	57.95 ± 13.05	52.83 ± 16.14	0.05
Time from Symptom Onset to Admission (Days)	7.21 ± 4.01	7.17 ± 2.96	0.95
Duration of Hospital Stay (Days)	8.21 ± 5.40	8.83 ± 6.05	0.54
Systolic Blood Pressure (mmHg)	112.14 ± 18.98	111.82 ± 17.44	0.92
Diastolic Blood Pressure (mmHg)	71.49 ± 10.71	70.38 ± 8.74	0.52
Heart Rate (BPM)	89.16 ± 13.80	90.11 ± 16.34	0.72
Respiratory Rate (breaths/min)	20.05 ± 2.65	19.89 ± 2.69	0.74
Arterial Oxygen Saturation (%)	86.81 ± 6.23	87.88 ± 8.01	0.40
Body Temperature (°C)	37.07 ± 0.73	36.99 ± 0.63	0.54
Gender, n (%)			1.00
Male	21 (33.3%)	23 (34.8%)	
Female	42 (66.7%)	43 (65.2%)	
Corticosteroid Use Before Admission, n (%)			0.61
No	61 (96.8%)	65 (98.5%)	
Yes	2 (3.2%)	1 (1.5%)	
Diabetes, n (%)			0.98
No	44 (69.8%)	45 (68.2%)	
Yes	19 (30.2%)	21 (31.8%)	
Hypertension, n (%)			1.00
No	44 (69.8%)	47 (71.2%)	
Yes	19 (30.2%)	19 (28.8%)	
Ischemic Heart Disease, n (%)			0.42
No	54 (85.7%)	52 (78.8%)	
Yes	9 (14.3%)	14 (21.2%)	
Heart Failure, n (%)			1.00
No	62 (98.4%)	65 (98.5%)	
Yes	1 (1.6%)	1 (1.5%)	
Kidney Disease, n (%)			0.49
No	62 (98.4%)	66 (100%)	
Yes	1 (1.6%)	0 (0%)	
Stroke, n (%)			0.61
No	61 (96.8%)	65 (98.5%)	
Yes	2 (3.2%)	1 (1.5%)	
Hyperlipidemia, n (%)			0.68
No	56 (88.9%)	56 (84.8%)	
Yes	7 (11.1%)	10 (15.2%)	

SD, standard deviation; mmHg, milimeters mercury; BPM, beats per minute; n, Number; %, Percentage; °C, Grade Celsius

*** A p-value of < 0.05 was considered statistically significant.**

Table 2. Clinical outcomes comparison between the standard treatment and the Baricitinib plus standard treatment groups

Variable	Standard treatment (n = 63)	Baricitinib + standard treatment (n = 66)	P value*
ICU admission, n (%)			1.00
No	51 (81%)	53 (80.3%)	
Yes	12 (19%)	13 (19.7%)	
Invasive ventilation required, n (%)			0.32
No	55 (87.3%)	62 (93.9%)	
Yes	8 (12.7%)	4 (6.1%)	
Neutropenia during stay, n (%)			0.61
No	61 (96.8%)	65 (98.5%)	
Yes	2 (3.2%)	1 (1.5%)	
Lymphopenia during stay, n (%)			0.31
No	24 (38.1%)	32 (48.5%)	
Yes	39 (61.9%)	34 (51.5%)	
Elevated hepatic enzymes during admission, n (%)			0.59
No	42 (66.7%)	40 (60.6%)	
Yes	21 (33.3%)	26 (39.4%)	
Elevated creatinine during admission, n (%)			1.00
No	51 (81%)	53 (80.3%)	
Yes	12 (19%)	13 (19.7%)	
COVID-19 severity after 14 days, n (%)			0.02
Mild	36 (57.1%)	44 (66.7%)	
Moderate	18 (28.6%)	21 (31.8%)	
Severe	9 (14.3%)	1 (1.5%)	
14-day mortality, n (%)			0.003
No	55 (87.3%)	66 (100%)	
Yes	8 (12.7%)	0 (0%)	
28-day mortality, n (%)			0.008
No	54 (85.7%)	65 (98.5%)	
Yes	9 (14.3%)	1 (1.5%)	

n, Number; %, Percentage, Neutropenia = Neutrophils < 1500 cell/microliters; Lymphopenia = Lymphocytes , 1500 cells/microliters

*** A p-value of < 0.05 was considered statistically significant.**

Table 3. **Comparison of laboratory measurements at admission and discharge in the standard treatment group**

Variable	**Admission (N=54) Mean ± SD**	**Discharge (N=54) Mean ± SD**	**P value***
WBC, count/µL	7329.63 ± 3884.69	9744.44 ± 4133.6	<0.001
Lymphocytes, count/µL	1122.72 ± 503.08	1218.59 ± 691.32	0.16
PT, seconds	15.76 ± 18.94	16.13 ± 18.90	0.94
PTT, seconds	39.14 ± 23.85	37.69 ± 22.96	0.78
INR	1.09 ± 0.19	1.13 ± 0.23	0.28
BUN, mg/dL	23.96 ± 22.59	27.69 ± 22.53	0.09
Creatinine, mg/dL	1.38 ± 1.75	1.07 ± 0.81	0.11
AST, U/L	52.01 ± 40.07	39.33 ± 26.70	0.01
ALT, U/L	48.37 ± 68.61	44.29 ± 33.81	0.65
LDH, U/L	829.44 ± 349.64	869.01 ± 706.01	0.81
ESR, mm/hr	37.40 ± 23.09	22.00 ± 20.17	0.047
CRP, mg/L	71.74 ± 65.82	36.64 ± 58.73	0.01

SD, standard deviation; n, Number; WBC, white blood cell counts; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; LDH, lactate dehydrogenase; AST, aspartate aminotransferase; ALT, alanine aminotransferase; BUN, blood urea nitrogen; PT, prothrombin time; PTT, partial thromboplastin time; INR, international normalized ratio (INR), µL, microliter; mg/dL, miligram per deciliter; U/L, unit per liter; mm/hr, milimeter per hour
* A p-value of < 0.05 was considered statistically significant.

Table 4**. Comparison of laboratory measurements at admission and discharge in the Baricitinib plus standard treatment group**

Variable	**Admission (N=60) Mean ± SD**	**Discharge (N=60) Mean ± SD**	**P value***
WBC, count/µL	7096.67 ± 3269.74	9881.46 ± 4116.46	<0.001
Lymphocytes, count/µL	1133.19 ± 598.24	1312.27 ± 717.37	0.047
PT, seconds	12.69 ± 1.12	12.82 ± 1.17	0.57
PTT, seconds	37.57 ± 21.12	34.08 ± 15.52	0.45
INR	1.10 ± 0.18	1.11 ± 0.17	0.66
BUN, mg/dL	21.93 ± 14.18	22.54 ± 8.04	0.70
Creatinine, mg/dL	1.01 ± 0.35	0.90 ± 0.21	<0.001
AST, U/L	47.48 ± 20.81	31.48 ± 18.42	<0.001
ALT, U/L	36.83 ± 18.27	41.23 ± 24.88	0.24
LDH, U/L	827.22 ± 271.87	593.67 ± 167.75	0.03
ESR, mm/hr	38.27 ± 21.20	23.86 ± 10.87	0.002
CRP, mg/L	65.28 ± 51.71	22.80 ± 23.72	<0.001

SD, standard deviation; n, Number; WBC, white blood cell counts; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; LDH, lactate dehydrogenase; AST, aspartate aminotransferase; ALT, alanine aminotransferase; BUN, blood urea nitrogen; PT, prothrombin time; PTT, partial thromboplastin time; INR, international normalized ratio (INR), µL, microliter; mg/dL, miligram per deciliter; U/L, unit per liter; mm/hr, milimeter per hour
* A p-value of < 0.05 was considered statistically significant.

Table 5. Comparison of clinical and laboratory measurements at admission and discharge between the standard treatment and the Baricitinib plus standard treatment groups

Variable	Standard treatment (n = 63) Mean ± SD	Baricitinib + standard treatment (n = 66) Mean ± SD	P value*
WBC, count/µL			0.072
Admission	7118.03 ± 3770.30	6848.48 ± 3226.92	
Discharge	9744.44 ± 4133.60	9881.46 ± 4116.46	
Lymphocytes, count/µL			0.44
Admission	1104.06 ± 497.45	1111.87 ± 578.34	
Discharge	1226.69 ± 684.53	1324.02 ± 708.33	
PT, seconds			0.28
Admission	15.04 ± 16.58	12.79 ± 1.25	
Discharge	15.57 ± 17.11	12.78 ± 1.10	
PTT, seconds			0.44
Admission	38.40 ± 23.10	43.89 ± 29.23	
Discharge	38.39 ± 24.46	33.14 ± 13.79	
INR			0.59
Admission	1.09 ± 0.18	1.12 ± 0.19	
Discharge	1.14 ± 0.24	1.11 ± 0.16	
BUN, mg/dL			0.09
Admission	22.87 ± 21.47	21.14 ± 13.65	
Discharge	27.51 ± 22.35	22.29 ± 8.07	
Creatinine, mg/dL			0.51
Admission	1.32 ± 1.64	0.99 ± 0.34	
Discharge	1.07 ± 0.81	0.90 ± 0.21	
AST, U/L			
Admission	50.06 ± 37.83	50.13 ± 27.56	0.12
Discharge	39.25 ± 25.81	32.91 ± 19.83	
ALT, U/L			
Admission	44.82 ± 64.10	37.33 ± 18.18	0.92
Discharge	43.73 ± 32.67	43.20 ± 28.22	
LDH, U/L			
Admission	758.48 ± 283.88	770.51 ± 301.77	0.17
Discharge	765.30 ± 685.03	680.33 ± 316.30	
ESR, mm/hr			
Admission	38.77 ± 27.41	38.39 ± 23.32	0.77
Discharge	35.87 ± 32.60	27.04 ± 17.04	
CRP, mg/L			
Admission	69.27 ± 65.45	60.97 ± 48.61	0.24
Discharge	51.15 ± 96.32	20.16 ± 21.70	
SpO2, %			<0.001
Admission	86.81 ± 6.23	88.33 ± 6.68	
Discharge	94.11 ± 2.05	95.52 ± 2.09	
Duration of ICU stay, days	1.57 ± 4.34	2.01 ± 4.68	0.58
Duration of invasive ventilation, days	0.87 ± 3.63	0.86 ± 3.53	0.99
*** A p-value of < 0.05 was considered statistically significant.**			

Discussion

This study found that compared to the standard treatment, adding 4 mg daily dose of Baricitinib provided better outcomes in reducing the 14-day and 28-day mortality rate due to severe COVID-19, reducing disease severity, and improving SpO2. An observational study by Rodriguez-Garcia et al. compared patients receiving Baricitinib plus corticosteroids with those receiving corticosteroids alone and reported significantly greater SpO2 improvement in the Baricitinib plus corticosteroids group (19). Rosas et al. conducted a study in Spain and reported similar improvements in arterial oxygen pressure for Baricitinib (20). Ely et al. conducted a randomized placebo-controlled trial on critical COVID-19 patients requiring invasive ventilation incorporating 4 mg Baricitinib for up to 14 days in combination with standard treatment and found 28-day and 60-day mortality had significant reductions in the Baricitinib group, but the hospitalization duration and ventilator-free days did not differ significantly (21). The COV-BARRIER trial has also showed that addition of Baricitinib to standard care was associated with reduced mortality in hospitalised adults with COVID-19 (16). Kalil et al. have also conducted a double-blind, randomized, placebo-controlled trial with 4 mg Baricitinib plus remdesivir treatment and found that the addition of Baricitinib significantly reduced recovery time, accelerating clinical improvement while also having even fewer serious adverse events compared with remdesivir alone (14). Moreover, A prospective cohort study done by Hasan et al. compared the higher Baricitinib dose of 8 mg daily to 4 mg daily and found that the 8 mg dose could lower the ICU admission and intubation support rate (13). Therefore, it is likely that the higher dose of Baricitinib can have more desired effects, and the decision to administer the higher dose or the usual dose should be weighed against possible adverse events for severe cases of COVID-19 patients. Baricitinib's reported adverse effects include thromboembolic events, especially in the setting of COVID-19 that induces a hypercoagulopathy state (19, 22). Other reported adverse effects of Baricitinib include elevated liver enzymes and secondary infections (23). Generally, Baricitinib is well tolerated in COVID-19 patients, and the reported complications in previous studies were rare (14, 24, 25).

The present study also found that Baricitinib lowered inflammatory marker levels, including ESR, CRP, and LDH. Previous studies showed that Baricitinib can downregulate the inflammatory mediators within two days of treatment (22). Inflammation plays a significant role in the severe state of COVID-19; the count of T cell lymphocytes decreases in most of the patients in the severe state, and in response to lymphopenia, large amounts of proinflammatory cytokines such as, IL-1 (Interleukin-1), IL-6, IL-12, and interferon are released (26, 27). This

inflammatory cascade causes the cytokine storm that ultimately results in acute respiratory distress syndrome (ARDS) and respiratory failure in severe cases of COVID-19. Also, this study found that Baricitinib could increase the lymphocyte count, explaining the favorable results over the standard treatment group. It's been shown that in addition to these anti-inflammatory effects, Baricitinib can also reduce viral load and inhibit endocytosis of SARS-CoV-2 into the cells (28, 29).

In this study, the Baricitinib group had lower serum creatinine at discharge compared to admission, which was not the case for the standard treatment group. It was shown that acute kidney injury (AKI) is one of COVID-19's highly prevalent complications. It is caused in part by the disease's inflammatory state and thereby increases disease severity and mortality (30). As Baricitinib moderates the inflammatory state, kidney function can also be preserved, especially in severe cases of COVID-19.

One limitation of this study was that it was a retrospective observational study, which limits our ability to establish the causality between Baricitinib treatment and the observed outcomes. A larger number of patients could also further generalize our results to the population. Further research is still needed to investigate the optimal dosing of Baricitinib, particularly about minimizing the risk of thromboembolic events, which remains a concern. The role of Baricitinib can also be explored in other existing or upcoming inflammation-based diseases as its anti-inflammatory effects showed promising results.

Conclusions

Inflammation plays a significant role in severe COVID-19 pneumonia, with the associated cytokine storm causing most of the organ damage and morbidity. As an anti-inflammatory agent, Baricitinib was highlighted for its potential effect on COVID-19. This study found that the addition of Baricitinib to the standard treatment in severe COVID-19 pneumonia, could reduce mortality, disease severity and improve arterial blood oxygen saturation compared to the standard treatment only. Despite no significant difference in ICU stay or ventilation duration, improved oxygenation and survival could be due to Baricitinib's modulation of inflammatory pathways, and variability in ICU admission criteria and resource availability may have influenced these results.

Declarations

This research has been approved by the ethics committee of Babol University of Medical Sciences with the reference number IR.MUBABOL.HRI.REC.1401.146

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Author's contribution

Conceptualization: E.J., H.M., M.M.; Methodology: H.S.; Sampling: E.J.; Statistical analysis and investigation: H.S.; Writing - original draft preparation: E.J.; Writing - review and editing: E.J., H.M.

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Consent for publication

Not applicable.

Conflict of interest

The authors declare that they have no competing interests.

Abbreviations

COVID-19 = Coronavirus disease 2019

WHO = World health organization

ICU = Intensive care unit

SpO2 = Peripheral oxygen saturation

ARDS = Acute respiratory distress syndrome

WBC = White blood cell count

CRP = C-reactive protein

ESR = Erythrocyte sedimentation rate

LDH = Lactate dehydrogenase

AST = Aspartate aminotransferase

ALT = Alanine aminotransferase

BUN = Blood urea nitrogen

PT = Prothrombin time

PTT = Partial thromboplastin time

INR = International normalized ratio

AKI = Acute kidney injury

Conflict of interests

The authors declare that they have no competing interests.

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