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Single versus multiple doses of Tocilizumab in critically ill patients with coronavirus disease 2019 (COVID-19): A two-center, retrospective cohort study

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ABSTRACT

Purpose: To evaluate the effectiveness and safety of the optimal tocilizumab dosing regimen.
Methods: A two-center, retrospective cohort study, for COVID19 critically ill patients admitted to the intensive care units (ICUs). We included critically ill patients aged 18 years or older who received tocilizumab during ICU stay. Patients were divided into two groups based on the number of the received tocilizumab doses. The primary outcome was the in-hospital and 30-day mortality. Propensity score (PS) matching was used (1:1 ratio) based on the selected criteria.
Results: A total of 298 patients were included in the study; 70.4% (210 patients) received a single dose of tocilizumab. After adjusting for possible confounders, the 30-day mortality (HR 0.79 95% CI 0.43–1.45 $P = 0.44$) and in-hospital mortality (HR 0.81; 95% CI 0.46–1.49; $P = 0.53$) were not significantly different between the two groups. On the flip side, patients who received multiple doses had higher pneumonia odds than a single dose (OR 3.81; 95% CI 1.79–8.12 $P = 0.0005$).
Conclusion: Repeating tocilizumab doses were not associated with a mortality benefit in COVID-19 critically ill patients, but it was associated with higher odds of pneumonia compared to a single dose.

1. Background

Coronavirus disease 2019 (COVID-2019) is a global pandemic that rapidly spread worldwide [1]. Since the novel severe acute respiratory syndrome coronavirus (SARS-CoV-2) emergence, it has affected more than a hundred million individuals and caused more than three million deaths globally [2]. Patients affected with COVID-19 usually manifest

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with respiratory symptoms ranging from mild to severe pneumonia and acute respiratory distress syndrome (ARDS) [3,4]. Around 10–15% of patients with moderate to severe symptoms require hospitalization, and up to 5% require intensive care unit (ICU) [5-9]. The mortality rate of patients with COVID-19 admitted to the ICU ranging from 26% to 48.3% [7,10,11].

The clear pathophysiology of the SARS-CoV-2 remains undetermined [9]. However, several reports have shown an elevation in proinflammatory cytokines in response to SARS-COV-2 [3,9]. Critically ill patients with COVID-19 usually experience a state called "cytokine release syndrome" (CRS). During this state, the body produces inflammatory cytokines and chemokines that have been associated with the occurrence of ARDS and secondary hemophagocytic lymphohistiocytosis [9,12]. These reactions may contribute to multiple organ failure and increased mortality [9,12]. In COVID-19 patients, increased interleukin-6 (IL-6) levels are linked with poor disease prognosis [13]. Thus, several studies have assessed the use of therapeutic agents targeting IL-6 in critically ill patients [6,14-18].

Tocilizumab is a recombinant humanized anti-IL-6 receptor monoclonal antibody approved to treat rheumatoid arthritis and other rheumatologic diseases. Since the CRS may induce ARDS, many studies have investigated the off-label use of tocilizumab in patients with COVID-19 pneumonia [6,15,19,20]. A systemic review and meta-analysis including 45 studies reported that tocilizumab use in critically ill patients with COVID-19 has shown mortality benefit and is associated with clinical improvement [3,20]. A recent randomized controlled trial (RCT) by the RECOVERY collaborative group demonstrated mortality benefits and clinical improvement with tocilizumab use in hospitalized patients with COVID-19 experiencing progressive symptoms [20].

In most published studies, patients initially received one dose of tocilizumab; if they do not clinically improve, a second dose was given in 8 to 72 h [6,15,17,19,20,21]. However, none of the previous studies investigated the benefit of a single to multiple doses of tocilizumab; instead, they compared tocilizumab to standard care or placebo [6,15,17,19,20,21]. Therefore, this study aims to compare the effectiveness of a single dose tocilizumab to multiple doses regimen in critically ill patients with COVID-19.

2. Patients and methods

2.1. Study design

This is a two-center retrospective cohortstudy that included adult critically ill patients with confirmed COVID-19 who were admitted to the ICUs at two tertiary hospitals in Saudi Arabia between March 01, 2020, to March 31, 2021. The COVID-19 diagnosis was confirmed according to reverse transcriptase-polymerase chain reaction (RT-PCR) obtained from nasopharyngeal or throat swabs. All patients were followed until they were discharged from the hospital or died during in-hospital stay whichever occurred first. The study was approved by King Abdullah International Medical Research Center (KAIMRC) in June 2021 (Ref.# NRC21R/191/05).

2.2. Participants

Critically ill patients who were admitted to ICU with confirmed COVID-19 were eligible for inclusion. Patients were excluded if they were aged <18 years of age, ICU length of stay (LOS) was less than a day, death within 24 h of ICU admission, did not receive tocilizumab during ICU stay, received tocilizumab prior to ICU admission or labeled as "Do-Not-Resuscitate" within 24 h of ICU admission (Fig. 1). Eligible patients were classified into two groups based on the number of doses for tocilizumab administered during ICU stay; patients who received one dose of tocilizumab, categorized under the "single dose," and patients who received two or more doses of tocilizumab were categorized under the "Multiple-dose" group. Tocilizumab use was based on the Saudi Ministry of Health (MOH) protocol for COVID-19 patients according to the eligibility criteria in patients with confirmed or suspected CRS [22,23] The recommended dose of tocilizumab was single 4–8 mg/kg using actual body weight (maximum 800 mg) by IV infusion; a repeated dose may be given based on the clinical judgment [22,23].

2.3. Setting

This study was conducted in two tertiary governmental hospitals; King Abdulaziz Medical City, Riyadh, and King Abdulaziz University Hospital, Jeddah. The primary site for this study is King Abdulaziz Medical City (Riyadh).

2.4. Data collection

Study data were collected from the patients' electronic medical records and managed using Research Electronic Data Capture (REDCap®) 9.1.2 software hosted by King Abdullah International Medical Research Center (KAIMRC). We collected patients' demographic data, comorbidities, vital signs, and severity scores (i.e., Acute Physiology and Chronic Health Evaluation II (APACHE II), Sequential Organ Failure Assessment (SOFA) scores), Glasgow Coma Score (GCS). In addition, acute kidney injury (AKI), the need for mechanical ventilation (MV), and MV parameters (e.g., PaO2/FiO2 ratio, FiO2 requirement) within 24 h of ICU admission were also collected. Furthermore, laboratory tests such as renal profile, liver function tests (LFTs), coagulation profile (i.e., INR, aPTT, fibrinogen, D-dimer), and inflammatory markers baseline (e.g., CRP, procalcitonin, serum iron) within 24 h of ICU admission and during stay were collected. Moreover, microbial isolates (i.e., bacteria and fungus) were identified in the blood, urine, wound, drainage, cerebrospinal fluid (CSF), and respiratory specimens.

2.5. Study outcomes

The study aims to compare the effectiveness and the safety of two tocilizumab dosing regimens. The primary outcome was the in-hospital and 30-day mortality compared between the single versus multiple tocilizumab doses administered to critically ill patients with COVID 19. The secondary outcomes were the hospital LOS, ICU LOS, MV duration, and ICU-related complication (s) during ICU stay (i.e., bacteremia, pneumonia (hospital andventilator acquired), secondary fungal infection, AKI, acute liver injury, respiratory failure required MV, and thrombosis/infarction).

2.6. Definition (s)

- Secondary fungal infection was identified through the blood, urine, wound, drainage, cerebrospinal fluid (CSF), and/or respiratory cultures. The fungal growth is considered significant if the growth is ≥ of 100,000 CFU/mL in sputum or endotracheal aspiration shows; bronchoalveolar lavage (BAL) shows a growth ≥ of 10,000 CFU of single organism/mL for protected specimen brushes (PSBs), and ≥ 100,000 CFU of single organism/ml=L for BAL fluid [24]. Additionally, urinary cultures were considered significant if showing a growth of ≥100,000 CFU/mL of no more than two species of microorganisms. Cultures were excluded if the laboratory reported them as a "contaminant sample"[25-27]
- Hospital-acquired pneumonia (HAP) was defined as bacterial or fungal pneumonia (other than COVID-19) that occurs ≥48 h after admission and did not appear to be incubating at the time of admission [28].
- Ventilator-acquired pneumonia (VAP) was defined as bacterial or fungal pneumonia (other than COVID-19) that develops 48 h or longer after mechanical ventilation [28].
- Arterial/venous thrombosis (i.e., myocardial infarction (MI), ischemic stroke, pulmonary embolism, deep vein thrombosis) was defined during ICU stay using The International Classification of Diseases, Tenth Revision, Clinical Modification (ICD10-CM) [29].

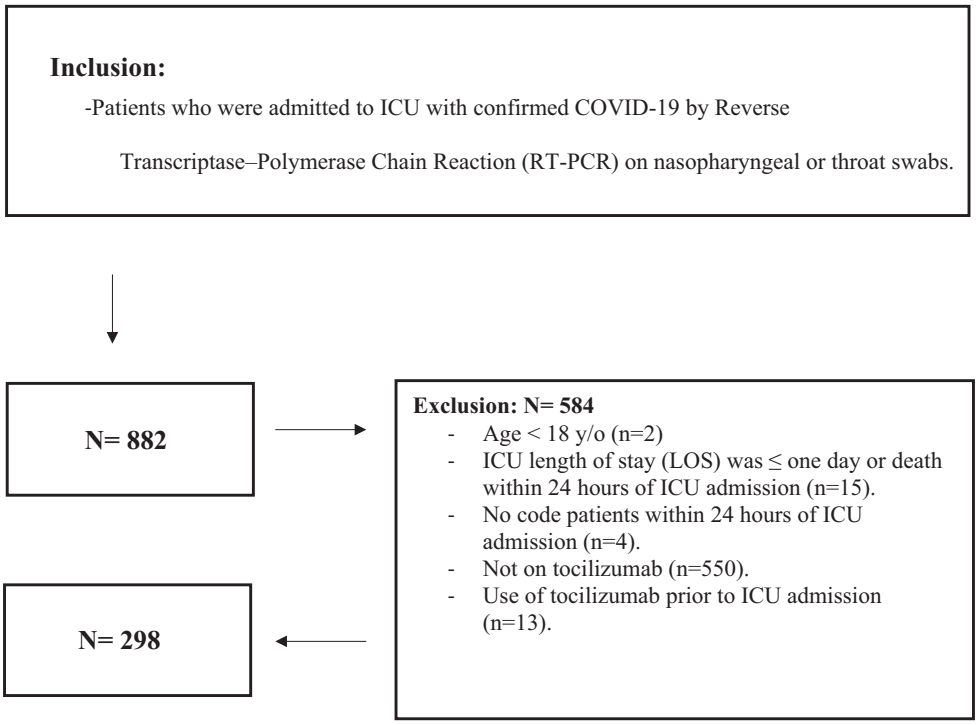

Fig. 1. Patients flowchart.

- Acute kidney injury (AKI) was defined as a sudden decrease of renal function within 48 h, defined by an increase in absolute SCr of at least 26.5 μmol/L (0.3 mg/dL) or by a percentage increase in SCr ≥ 50% (1.5× baseline value) during ICU stay based on the Acute Kidney Injury Network (AKIN) definition [30].
- Acute liver injury was defined as alanine aminotransferase (ALT) exceeding three times the upper limit of normal or double in patients with elevated ALT baseline.
- Respiratory failure was identified either as hypoxemic respiratory failure (PaO2 < 60 mmHg with a normal or low arterial carbon dioxide tension (PaCO2) or hypercapnic respiratory failure (PaCO2 > 50 mmHg) that requires mechanical ventilation.

2.7. Statistical analysis

We presented numerical variables (continuous variables) as mean and standard deviation (SD), or median and lower quartile (Q1) and upper quartile (Q3), as appropriate and categorical variables as number (percentage). The normality assumptions were assessed for all numerical variables using a statistical test (i.e., Shapiro–Wilk test) and graphical representation (i.e., histograms and Q-Q plots). Model fit assessed using the Hosmer-Lemeshow goodness-of-fit test.

Baseline characteristics and outcome variables were compared between the two groups. We compared categorical variables using the Chi-square or Fisher exact test and the normally distributed continuous variables using the Mann-Whitney *U* test. Multivariable Cox proportional hazards regression analyses were performed for the 30-day and in-hospital mortality. Additionally, Kaplan-Meier (KM) plots were generated for these outcomes. Multivariable regression analysis and negative binomial regression were used for the other outcomes considered in this study. The odds ratios (OR), hazard ratio (HR), or estimates with the 95% confidence intervals (CI) were reported as appropriate. No imputation was made for missing data as the cohort of patients in our study was not derived from random selection. We considered a *P* value of <0.05 statistically significant and used SAS version 9.4 for all statistical analyses.

Propensity score matching procedure (Proc PS match) (SAS, Cary, NC) was used to match patients who received multiple doses of tocilizumab (active group) to patients who received a single dose (control group) based on baseline severity score (i.e., APACHE II), Best GCS, INR, albumin, MV status within 24 h of ICU admission and the use of pharmacological DVT prophylaxis. A greedy nearest neighbor matching method was used. One patient who received multiple doses (active) group was matched with one who received a single dose of tocilizumab (control), which eventually produced the smallest within-pair difference among all available pairs with treated patients. Patients were matched only if the difference in the logits of the propensity scores for pairs of patients from the two groups was less than or equal to 0.5 times the pooled estimate of the standard deviation.

3. Results

A total of 882 patients were screened; only 298 patients were included in this study. Of those included, 210 patients (70.4%) received a single dose, and 88 patients (29.5%) received multiple doses of tocilizumab. After propensity score matching, 128 patients were included (1:1 ratio) according to the selected criteria. Among patients who received multiple doses of tocilizumab, 59 patients (92.2%) received two doses, and five patients (7.8%) received three doses or more, respectively. The median dose in both groups was 400.0 mg (400.00, 600.00). The median time interval between the doses in patients who received multiple doses was 12.0 h (12.00, 24.00).

The majority of patients included in both groups were male (75.7%), with a mean age of 59.0 (SD ± 12.8). The predominant underlying comorbidities were hypertension (55.9%), followed by diabetes mellitus (55.2%) and dyslipidemia (20.8%). There were notable differences between the two groups before propensity score matching; patients who received a single dose have a lower NUTRIC score, APACHE II score, best GCS, albumin level, and INR level baseline. Conversely, patients who received multiple doses of tocilizumab have a lower body mass

index (BMI), MV needs within 24 h of admission, use of pharmacological VTE prophylaxis, and nephrotoxic drugs/material during ICU stay (Table 1). Following the propensity score matching based on the selected criteria, these baseline and demographic characteristics became similar between the two groups.

3.1. Primary outcomes

The 30-day mortality occurred in 22 patients (34.4%) who received multiple doses of tocilizumab (active group) compared to 24 patients (37.5%) who received a single dose (control group) ($P = 0.71$).

Table 1
Baseline characteristics of patients with COVID-19 admitted to the ICU and received tocilizumab before and after propensity score matching:[a, b]

	Before propensity score (PS) adjustment				After propensity score (PS) adjustment			
	Overall (298)	Single ($N = 210$)	Multiple ($N = 88$)	P-value	Overall (128)	Single ($N = 64$)	Multiple ($N = 64$)	P-value
Age (Years), Mean (SD)	59.0 (12.8)	59.6 (12.9)	57.3 (12.4)	0.18[a]	57.3 (12.1)	57.6 (12.6)	57.0 (11.7)	0.62[a]
Gender – Male, n (%)	215 (75.7)	155 (76.4)	60 (74.1)	0.69[b]	97 (77.0)	52 (82.5)	45 (71.4)	0.14[b]
Weight (kg), Mean (SD)	83.7 (2.8)	84.7 (21.3)	81.3 (19.7)	0.11[a]	81.3 (19.3)	83.5 (21.5)	79.0 (16.6)	0.13[a]
BMI, Mean (SD)	31.2 (7.9)	31.6 (8.2)	29.9 (7.1)	0.03[a]	30.4 (7.3)	31.4 (7.5)	29.5 (6.9)	0.06[a]
APACHE II score, Median (Q1,Q3)	13.0 (9.0, 21.5)	12.5 (9.5, 20.0)	15.0 (8.5, 25.0)	0.11[a]	15.0 (9.0, 25.0)	14.0 (9.0, 25.0)	15.0 (8.0, 25.0)	0.56[a]
SOFA score, Median (Q1,Q3)	4.0 (3.0, 8.0)	4.0 (3.0, 80.0)	5.0 (3.5, 7.0)	0.51[a]	4.5 (3.0, 7.0)	5.0 (3.0, 7.0)	4.0 (3.0, 7.0)	0.71[a]
NUTRIC Score, Median (Q1,Q3)	3.0 (2.0, 5.0)	3.0 (2.0, 5.0)	4.0 (2.0, 5.5)	0.05[a]	4.0 (2.0, 5.0)	3.0 (2.0, 5.0)	4.0 (3.0, 5.0)	0.32[a]
Best GCS, Median (Q1,Q3)	15.0 (15.0, 15.0)	15.0 (14.0, 15.0)	15.0 (15.0, 15.0)	0.03[a]	15.0 (15.0, 15.0)	15.0 (15.0, 15.0)	15.0 (15.0, 15.0)	0.99[a]
Systemic corticosteroids, n (%)	266 (93.0)	186 (91.6)	80 (96.4)	0.15[b]	120 (95.2)	59 (93.7)	61 (96.8)	0.40[b]
Proning status, n (%)	98 (35.3)	68 (34.2)	30 (38.0)	0.55[b]	53 (44.2)	27 (45.0)	26 (43.3)	0.85[b]
Serum creatinine Baseline (mmol/l), Median (Q1,Q3)	85.5 (67.0, 120.0)	84.0 (66.0, 121.0)	87.0 (72.0, 120.0)	0.24[a]	87.5 (72.0, 120.0)	88.0 (68.0, 130.0)	87.0 (73.0, 112.0)	0.82[a]
Acute Kidney Injury (AKI) Within 24 h of ICU admission, n (%)	53 (18.9)	34 (16.8)	19 (24.1)	0.16[b]	30 (24.0)	14 (22.2)	16 (25.8)	0.64[b]
Mechanical Ventilation within 24 h of ICU admission, n (%)	217 (75.3)	162 (79.0)	55 (66.3)	0.02[b]	89 (70.6)	45 (71.4)	44 (69.8)	0.84[b]
A-a Gradient, Median (Q1,Q3)	422.4 (281.4, 578.5)	415.4 (292.7, 572.3)	477.7 (230.7, 596.7)	0.83[a]	447.6 (247.9, 595.3)	430.3 (247.9, 576.8)	461.1 (252.4, 600.2)	0.88[a]
Oxygenation Index (OI), Mean (SD)	24.4 (16.4)	25.2 (17.1)	20.0 (11.9)	0.42[a]	20.6 (16.2)	21.0 (16.2)	20.2 (12.9)	0.87[a]
Vasoactive Inotropic Score, Mean (SD)	5.6 (40.6)	1.8 (8.9)	14.8 (73.3)	0.52[a]	6.6 (47.2)	0.7 (2.76)	12.3 (65.6)	0.80[a]
Lactic acid Baseline (mmol/L), Mean (SD)	2.6 (9.3)	2.8 (10.9)	2.2 (1.9)	0.81[a]	2.2 (1.8)	2.0 (1.4)	2.3 (2.2)	0.81[a]
Platelets count Baseline (10^9/L), Median (Q1,Q3)	251.0 (190.0, 323.0)	254.0 (189.0, 324.0)	250.0 (194.0, 307.0)	0.53[a]	243.0 (189.0, 310.0)	242.0 (180.0, 316.0)	250.0 (192.0, 300.0)	0.91[a]
Total WBC Baseline (10^9/L), Median (Q1,Q3)	9.6 (6.7, 13.3)	9.4 (6.7, 12.6)	9.9 (6.7, 14.0)	0.53[a]	9.0 (6.4, 13.2)	8.9 (6.1, 12.7)	9.1 (6.6, 14.0)	0.79[a]
Total bilirubin level (umol/L), Median (Q1,Q3)	9.8 (6.8, 13.7)	10.0 (7.0, 14.3)	9.0 (6.4, 12.8)	0.13[a]	9.0 (6.5, 13.0)	10.0 (7.0, 13.7)	9.0 (6.0, 12.0)	0.18[a]
Albumin level (gm/L), Median (Q1,Q3)	34.0 (30.0, 37.0)	33.0 (30.0, 36.0)	36.0 (31.0, 40.5)	0.01[a]	36.0 (33.0, 40.0)	36.0 (33.0, 38.8)	36.7 (33.0, 40.5)	0.52[a]
INR, Median (Q1,Q3)	1.1 (1.0, 1.2)	1.1 (1.0, 1.2)	1.1 (1.1, 1.2)	0.002[a]	1.1 (1.0, 1.2)	1.1 (1.0, 1.2)	1.1 (1.0, 1.2)	0.05[a]
Creatine phosphokinase (CPK) (U/L), Median (Q1,Q3)	231.5 (84.0, 550.0)	233.0 (97.0, 510.0)	223.0 (69.0, 554.0)	0.59[a]	190.0 (72.0, 427.0)	177.5 (101.5, 366.5)	193.0 (69.0, 572.0)	0.95[a]
C-reactive protein (CRP) (mg/L),Median (Q1,Q3)	160.5 (101.0, 238.0)	158.5 (100.0, 256.0)	170.5 (109.5, 214.0)	0.98[a]	168.0 (83.4, 221.5)	159.0 (76.0, 220.0)	171.0 (111.0, 223.0)	0.54[a]
Fibrinogen level (gm/l), Median (Q1,Q3)	5.9 (4.3, 7.4)	5.8 (4.5, 7.4)	6.2 (4.1, 7.4)	0.80[a]	6.3 (4.4, 7.5)	5.8 (4.4, 7.5)	6.4 (4.4, 8.1)	0.87[a]
D-dimer level (mg/L), Median (Q1,Q3)	1.2 (0.7, 3.2)	1.1 (0.7, 2.8)	1.3 (0.7, 5.6)	0.17[a]	1.0 (0.6, 3.1)	0.8 (0.6, 1.7)	1.1 (0.6, 4.9)	0.16[a]
Ferritin level (ug/L), Median (Q1,Q3)	1034.5 (558.1, 2092.0)	1105.0 (559.9, 2114.0)	901.7 (556.3, 1998.0)	0.40[a]	1034.5 (547.7, 1972.5)	1114.0 (712.7, 2018.0)	856.1 (442.4, 1768.0)	0.13[a]
Blood glucose level Baseline (mmol/L), Median (Q1,Q3)	10.6 (7.50, 15.4)	10.6 (7.5, 15.6)	10.3 (6.9, 14.2)	0.79[a]	10.4 (6.9, 15.8)	10.4 (6.8, 15.8)	11.2 (8.0, 15.3)	0.49[a]
PaO2/FiO2 ratio within 24 h of admission, Median (Q1,Q3)	80.0 (57.4, 122.4)	82.4 (61.7, 117.8)	68.2 (51.8, 124.0)	0.07[a]	79.6 (54.5, 124.0)	90.9 (63.2, 136.0)	67.5 (51.3, 114.4)	0.05[a]
Respiratory Rate (RR) Baseline, Median (Q1,Q3)	30.0 (25.0, 35.0)	30.0 (26.0, 35.0)	30 (22.0, 35)	0.18[a]	30.0 (24.0, 35.0)	30.0 (25.0, 35.0)	30.0 (22.5, 35.0)	0.67[a]
Pharmacological DVT prophylaxis use during ICU stay,n (%)	261 (90.6)	197 (96.1)	64 (77.1)	<0.0001[b]	104 (82.5)	55 (87.3)	49 (77.8)	0.16[b]
Patient received nephrotoxic drugs/material during ICU stay, n (%)	251 (87.2)	185 (90.2)	66 (79.5)	0.01[b]	99 (79.2)	53 (85.5)	46 (73.0)	0.09[b]
Comorbidity								
Atrial fibrillation, n (%)	8 (2.8)	6 (2.9)	2 (2.4)	0.81[b]	4 (3.2)	2 (3.2)	2 (3.2)	>0.99[b]
Heart Failure, n (%)	17 (5.9)	13 (6.3)	4 (4.8)	0.62[b]	8 (6.3)	5 (7.9)	3(4.8)	0.47[b]
Hypertension, n (%)	161 (55.9)	116 (56.6)	45 (54.2)	0.71[b]	73 (57.9)	38 (60.3)	35 (55.6)	0.59[b]
Diabetes Mellitus (DM), n (%)	159 (55.2)	111 (54.1)	48 (57.8)	0.57[b]	73 (57.9)	37 (58.7)	36 (57.1)	0.86[b]
Dyslipidemia (DLP), n (%)	60 (20.8)	48 (23.4)	12 (14.5)	0.09[b]	25 (19.8)	15 (23.8)	10 (15.9)	0.26[b]
Ischemic heart disease (IHD), n (%)	13 (4.5)	10 (4.9)	3 (3.6)	0.64[b]	6 (4.8)	3 (4.8)	3 (4.8)	>0.99[b]
Chronic kidney disease (CKD), n (%)	22 (7.6)	17 (8.3)	5 (6.0)	0.51[b]	8 (6.3)	5 (7.9)	3 (4.8)	0.46[b]
Cancer, n (%)	10 (3.5)	7 (3.4)	3 (3.6)	0.93[b]	8 (6.3)	5 (7.9)	3 (4.8)	0.47[b]
Asthma, n (%)	19 (6.6)	14 (6.8)	5 (6.0)	0.80[b]	8 (6.3)	5 (7.9)	3 (4.8)	0.47[b]
Chronic obstructive pulmonary disease (COPD), n (%)	4 (1.4)	4 (2.0)	0 (0.0)	0.20[b]	1 (0.8)	1 (1.6)	0 (0.0)	0.32[b]
Liver disease (any type), n (%)	3 (1.0)	2 (1.0)	1 (1.2)	0.86[b]	1 (0.8)	0 (0.0)	1 (1.6)	0.32[b]
Stroke, n (%)	10 (3.5)	8 (3.9)	2 (2.4)	0.53[b]	1 (0.8)	0 (0.0)	1 (1.6)	0.32[b]
Pulmonary Embolism, n (%)	3 (1.0)	2 (1.0)	1 (1.2)	0.86[b]	0 (0.0)	0 (0.0)	0 (0.0)	NA

[a] Wilcoxon rank sum test is used to calculate the P-value.
[b] Chi square is used to calculate P-value.

Additionally, the in-hospital mortality in the active group occurred in 24 (38.3%) patients compared to 26 (40.6%) patients in the control group ($P = 0.79$). At multivariable cox proportional hazards regression analyses after adjusting for the possible confounders, the 30-day mortality (HR 0.79; 95% CI 0.43–1.45 $P = 0.44$) and in-hospital mortality (HR 0.81; 95% CI 0.46–1.49 $P = 0.53$) were not significantly different between the two groups (Table 2). Moreover, the overall survival probabilities were similar during hospital stay between the two groups before and after PS matching (Figs. 2 and 3).

3.2. Secondary outcomes

In crude analysis, the ICU complications during ICU stay, including respiratory failure required MV, acute kidney injury, liver injury, and thrombosis, were all similar in both groups. Conversely, patients who received multiple doses of tocilizumab had significantly more pneumonia (60.9% vs. 28.1%, $p = 0.0002$). Based on the multivariable logistic regression analysis, there was a higher odds of pneumonia by four-fold in patients who received multiple doses of tocilizumab (OR 3.81; 95% CI, 1.79–8.12 $p = 0.02$) (Table 3). Among patients who have hospital/ventilator-acquired pneumonia, the most common pathogens detected were *P. aeruginosa* (29.3%) and *A. baumannii* (29.3%), followed by Yeast (19.5%) and Klebsiella pneumonia (9.8%).

This study showed no difference in patients who received a single dose compared to multiple doses of tocilizumab in terms of MV duration during ICU stay (8.5 days vs. 12.0 days, $p = 0.14$), ICU LOS (9.5 days vs. 10.0 days, $p = 0.87$), or hospital length of stay (19.5 days vs. 19.0 days, $p = 0.96$) respectively (Table 3). Moreover, as shown in Table 4, no differences in the follow-up inflammatory markers such as serum iron, ferritin, and CRP levels during ICU stay when patients were given single or multiple doses of tocilizumab. On the other hand, D-dimer and procalcitonin levels were significantly higher in patients who received multiple doses of tocilizumab ((beta coefficient 0.79 (95% CI 0.29, 1.23), $P = 0.002$), and (beta coefficient 3.06 (95% CI 2.05, 4.06), $P < 0.0001$) respectively) (Table 4).

4. Discussion

In this retrospective study, including critically ill patients with COVID-19, there were no significant differences in the mortality rate, AKI, liver injury, and thrombosis during ICU stay between patients who received a single dose versus multiple-dose tocilizumab after propensity score matching. However, the multiple-dose tocilizumab group had significantly higher hospital/ventilation-acquired pneumonia odds than the single-dose group (OR 3.81 (95% 1.79–8.12) $P = 0.0005$). Although patients usually receive more than one dose of tocilizumab if they clinically did not improve, which may indicate that these patients were sicker. In this study, we used propensity score matching to adjust based on baseline severity score (i.e., APACHE II), best GCS, INR, albumin, MV status, leaving no significantly apparent differences at baseline among the two groups.

Our findings were similar to a previous retrospective study showing that multiple-dose tocilizumab did not significantly reduce all-cause mortality, thrombosis, AKI, and hospital LOS [18]. Furthermore, an RCT evaluated single-dose tocilizumab versus usual care in ICU patients with COVID-19 found no significant difference in 15-day, in-hospital, and 28-days mortality between the two groups [21]. Additional RCTs reported no mortality benefits in patients who received multiple doses of tocilizumab than standard therapy [6,16]. In contrast, a systemic review and meta-analysis found that tocilizumab use in critically ill patients

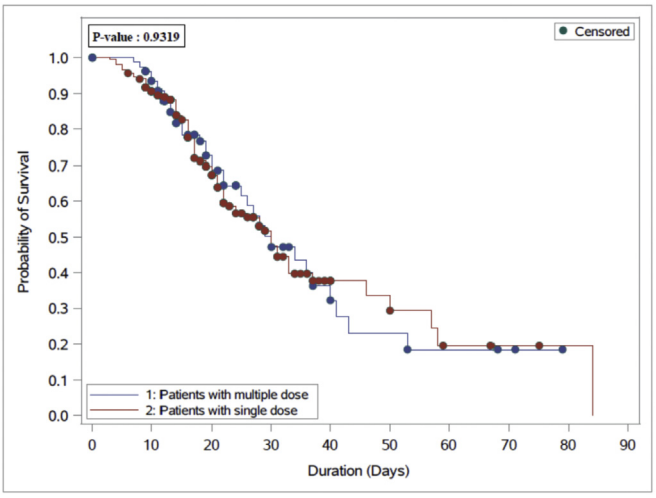

Fig. 2. Overall survival plot during the hospital stay comparing patients who received multiple doses of tocilizumab (88 patients) versus the control group (210 patients) - Before PS matching.

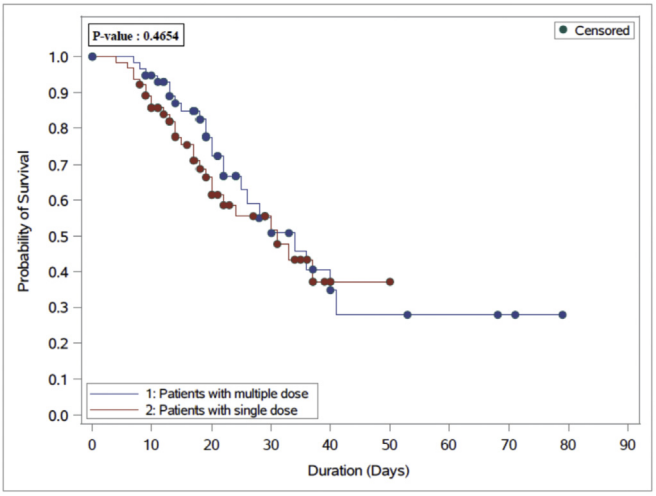

Fig. 3. Overall survival plot during the hospital stay comparing patients who received multiple doses of tocilizumab (64 patients) versus the control group (64 patients) - After PS matching.

Table 2
Regression analysis for the primary outcomes.

Outcomes	Crude analysis		P-value[b]	Hazard Ratio (HR) (95% CI)	P-value[c]
	Single-dose	Multiple-dose			
30-day mortality, n (%)[a]	24/64 (37.5)	22/64 (34.4)	0.71	0.79 (0.43, 1.45)	0.44
In hospital mortality, n (%)[a]	26/64 (40.6)	23/60 (38.3)	0.79	0.81 (0.46, 1.49)	0.53

[a] Denominator of the percentage is the total number of patients.
[b] Chi-square test is used to calculate the P-value.
[c] Propensity score matching based on patient's baseline severity score (i.e., APACHE II), Best GCS, INR, albumin, MV status within 24 h of ICU admission and the use of pharmacological DVT prophylaxis to calculate hazard ratio and p-value.

Table 3
Regression analysis for secondary outcomes.

Outcomes	Crude analysis		P-value[f]	Odds Ratio (OR) (95% CI)	P-value[g]
	Single-dose	Multiple-dose			
Respiratory Failure Required MV, n (%)[b]	8/18 (44.4)	7/20 (35.0)	0.55	0.78 (0.20, 2.99)	0.71
AKI during ICU stay, n (%)[a]	26/64 (40.6)	22/64 (34.4)	0.46	0.73 (0.35, 1.52)	0.40
Liver Injury during ICU stay, n (%)[a]	4/64 (6.3)	6/64 (9.4)	0.51	1.46 (0.38, 5.62)	0.58
Thrombosis during ICU stay, n (%)[a]	7/64 (10.9)	5/64 (7.81)	0.54	0.62 (0.17, 2.16)	0.45
Secondary infection[a]					
Hospital/Ventilator Acquired Pneumonia, n (%)	18/64 (28.1)	39/64 (60.9)	0.0002	3.81 (1.79, 8.12)	0.0005
Bacteremia, n (%)	5/64 (7.81)	8/64 (12.5)	0.38	1.78 (0.54, 5.86)	0.35
Urinary tract infection, n (%)	3/61 (4.7)	3/61 (4.7)	>0.99	0.97 (0.18, 5.2)	0.97
	Single-dose	Multiple-dose	P-value[e]	beta coefficient (Estimates) (95% CI)	P-value[h]
MV duration during ICU stay (Days), Median (Q1,Q3)[c]	8.5 (4.5, 16.0)	12.0 (7.0, 18.0)	0.14	0.25 (−0.06, 0.55)	0.11
ICU Length of Stay (Days), Median (Q1,Q3)[d]	9.5 (8.0, 23.0)	10.0 (7.0, 17.0)	0.87	0.12 (−0.22, 0.45)	0.49
Hospital Length of Stay (Days), Median (Q1,Q3)[d]	19.5 (11.0, 31.0)	19.0 (13.0, 24.0)	0.96	0.09 (−0.24, 0.42)	0.58

[a] Denominator of the percentage is the total number of patients.
[b] Denominator of the percentage is non-mechanically ventilated patients with 24 h of ICU admission.
[c] Denominator is patients who have respiratory failure required MV.
[d] Denominator is patients who survived.
[e] Wilcoxon rank sum test is used to calculate the P-value.
[f] Chi-square test is used to calculate the P-value.
[g] Multivariate Logistic regression is used to calculate Odds ratio and p-value.
[h] Generalized linear model is to calculate beta coefficient (estimates) and *p*-value.

with COVID-19 reduces mortality and improves outcomes [3]. However, the studies included did not clearly state the exact number of patients who received single versus multiple doses. Besides, The RECOVERY RCT also reported mortality benefit and clinical improvement in patients receiving tocilizumab compared to standard of care. Still, only 29% of the patients in the tocilizumab group received more than one dose of tocilizumab [20]. None of the mentioned studies compared the mortality benefits between various tocilizumab regimens [3,20].

Based on rising evidence on tocilizumab efficacy, the National Institutes of Health (NIH) COVID-19 treatment guidelines recommend using a single dose of IV tocilizumab combined with steroids in hospitalized patients experiencing COVID-19 induced rapid respiratory decompensation [33]. The latest revised Saudi MOH protocol for patients with COVID-19 recommends the same dosing regimen as the NIH within 24 h of ICU admission for patients exhibiting hyperinflammatory symptoms on invasive or non-invasive MV, high flow nasal cannula in combination with dexamethasone [31]. It is noteworthy that practice guidelines previously recommended repeating the dose of tocilizumab within 12 h during the study period [22,23]. However, the recommendation of giving the second dose of tocilizumab was left merely to the providers' clinical judgment if the patients did not improve clinically rather than specified criteria.

In this study, pneumonia odd was almost four times higher in patients who received multiple doses of tocilizumab compared to a single dose. This risk could be related due to tocilizumab immunosuppression properties. [32] Our finding is inconsistent with a study by Kimmig et al. where tocilizumab use was also associated with the presence of a significantly higher incidence of secondary bacterial infections, including hospital-acquired pneumonia and ventilator-associated pneumonia in critically ill COVID-19 (48.1% in tocilizumab group vs. 28.1% in standard care; $P = 0.021$) [34]. Another single-center retrospective study by Quartuccio L et al. found that nearly 42% of the patients who received tocilizumab experienced bacterial infection [32]. However, these studies did not compare the occurrence to multiple doses as in our study [32,34]. Another observational study by Somers et al., including COVID-19 patients on MV, found that patients who received tocilizumab had more superinfections than those who did not, driven mainly by the increase in ventilation-associated pneumonia (45% vs. 20%; $p < 0.001$)[35].On the other hand, a recent meta-analysis of 8 RCTs of hospitalized COVID-19 patients found a lower risk of secondary infections in patients who received tocilizumab [36]. The infection follow-up period was 28 days for the six RCTs and longer in the remaining two RCTs [36]. However, the confidence interval was wide despite the large sample size, and the statistical difference did not persist when limiting the analysis to double-blind RCTs (a total of three, with a sample size of 1058 patients)[36]. The lower risk of secondary infections found in that meta-analysis is surprising as immunomodulators are associated with a higher risk of infections [36]. It is also worth mentioning that the number of tocilizumab doses was not discussed in this meta-analysis or any of the included RCTs [14,15,36]. Thus, health care

Table 4
Follow-up for inflammatory markers.

Outcomes	Crude analysis		P-value[a]	Beta coefficient (Estimates) (95% CI)	P-value[b]
	Single-dose	Multiple-dose			
Serum iron level (umol/L) follow-up, Mean (SD)	7.55 (±7.40)	7.24 (±6.95)	0.95	−0.02 (−0.59, 0.56)	0.95
D-dimer level (mg/L) follow-up (mg/l), Median (Q1, Q3)	2.80 (1.12, 7.30)	6.23 (1.82, 27.8)	0.01	0.79 (0.29, 1.23)	0.002
Ferritin level (ug/L) follow-up, Median (Q1, Q3)	1192.0 (805.0, 2666.8)	1124.9 (592.6, 2417.6)	0.34	−0.17 (−0.58, 0.23)	0.40
Fibrinogen level (gm/L)follow-up, Median (Q1, Q3)	6.28 (4.3, 7.7)	5.39 (3.4, 7.1)	0.37	−1.30 (−1.95, −0.66)	<0.0001
C-reactive protein(CRP) level (mg/L) follow-up, Median (Q1, Q3)	187.0 (48.3, 289.0)	164.5 (76.9, 265.0)	0.91	0.04 (−0.31, 0.38)	0.83
Creatine phosphokinase(CPK) level (U/L) follow-up, Median (Q1, Q3)	238.0 (124.0, 1013.0)	308 (78.5, 1153.5)	0.69	−0.07 (−0.62, 0.48)	0.81
Procalcitonin level (ng/mL) follow-up, Median (Q1, Q3)	0.43 (0.16, 2.93)	0.48 ((0.11, 4.81)	0.95	3.06 (2.05, 4.06)	<0.0001

[a] Wilcoxon rank sum test is used to calculate the P-value.
[b] Generalized linear model is used to calculate beta coefficient (estimates) and p-value.

providers need to constantly weigh the risk of pneumonia in patients with existing COVID-19 pneumonia to benefit from the repeated doses of tocilizumab in critically ill patients.

In our study, we observed no difference in ICU and hospital LOS of patients who received a single dose compared with patients given multiple doses of tocilizumab (Beta 0.12; 95% CI −0.22, 0.45; $P = 0.49$), (Beta 0.09; 95% CI −0.24–0.42; $P = 0.58$), respectively. However, when tocilizumab was compared to placebo in the COVACTA trial, a lower median time to discharge from the hospital or ready to discharge in the tocilizumab group compared with placebo (20 days vs. 28 days), and the median duration of ICU stay was lower in the tocilizumab group [17]. Also, the RECOVERY trial showed using tocilizumab was associated with a shorter hospital LOS [20]. Moreover, a recent systemic review and meta-analysis including 1583 patients with severe and critical COVID-19 showed no difference in hospital LOS [3]. Even though the meta-analysis findings are comparable to our results, such comparison is still limited because there is no evaluation of the number of tocilizumab doses and its relation with ICU or hospital LOS differences [3].

To our knowledge, this is the only propensity score-matched research that compares two different tocilizumab dose regimens (Single vs. multiple). The use of propensity score matching assisted in reducing bias and adjusting for cofounders. Nonetheless, this study remains to have some limitations. First, this is a small retrospective observational study leaving residual confounders effects despite the use of propensity score matching. Second, the IL-6 levels, which can predict the severity of the disease and guide the tocilizumab, have limited availability at our institution (s). Third, the decision to prescribe tocilizumab to COVID-19 patients was driven by the institutional and the MOH treatment protocols, which continued to change with the emergence of new data [37]. Moreover, the decision of single vs. multiple doses of tocilizumab was subjective based on clinical judgment. The timing between repetitive dosing could affect some of the clinical outcomes, which warrants further studies. Lastly, patient deterioration was not assessed using any scoring system such as the National Early Warning Score 2 (NEWS2) [38]. Due to these limitations, our results need to be confirmed in well-conducted randomized controlled trials.

5. Conclusion

Our study suggests that repeating tocilizumab dose in critically ill patients with COVID-19 carries no additional mortality benefit than single-dose tocilizumab. However, multiple doses of tocilizumab might be linked to higher odds of pneumonia. Further large randomized controlled studies are necessary to identify the optimal dosing regimen of tocilizumab in critically ill patients with COVID-19.

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Availability of data and material

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

Ethics approval and consent to participate

The study was approved in June 2021 by King Abdullah International Medical Research Center Institutional Review Board, Riyadh, Saudi Arabia (Ref.#NRC21R/191/05). All methods were performed in accordance with relevant guidelines and regulations.

Participants' confidentiality was strictly observed throughout the study by using anonymous unique serial number for each subject and restricting data only to the investigators. KAIMRC-IRB committee waived the informed consent due to its retrospective nature.

Consent for publication

Not applicable.

Competing interests

No author has a conflict of interest in this study.

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