Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

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The safety and effectiveness of tocilizumab in older adult critically ill patients with COVID-19: a multicenter, cohort study

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ABSTRACT

Objectives: Evidence supports tocilizumab (TCZ) benefit and safety in adult patients with severe COVID-19. However, its effectiveness in critically ill older adult patients remains questionable. Thus, the study aimed to evaluate the safety and effectiveness of TCZ in older critically ill patients with COVID-19.
Methods: A multicenter, retrospective study for all critically ill older adults (aged ≥65 years) with confirmed COVID-19 infection and admitted to the intensive care units (ICUs). Eligible patients were categorized into two groups based on TCZ use during ICU stay (control vs TCZ). Propensity score (PS) matching was used (1:1 ratio) based on the selected criteria. The primary outcome was the in-hospital mortality.
Results: A total of 368 critically ill older adult patients were included in the study. Fifty one patients (13.8%) received TCZ. The in-hospital mortality was lower in the TCZ group (HR 0.41; 95% CI 0.22–0.76, *P*-value = 0.005). Patients who received TCZ had lower odds of respiratory failure requiring mechanical ventilation (OR [95% CI]: 0.32 [0.10–0.98], *P*-value = 0.04). No statistically significant differences were found between the two groups for 30-days mortality, ventilator-free days, length of stay, and complications during ICU stay.
Conclusion: Tocilizumab use in critically ill older adult patients with COVID-19 is associated with lower in-hospital mortality and a similar safety profile.

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Introduction

Since the novel severe acute respiratory sydnrome coronavirus 2 (SARS-CoV-2) emergence in 2019 (Huang et al., 2020), coronavirus disease 2019 (COVID-19) has caused more than four million deaths globally (World Health Organization, 2021). COVID-19 pneumonia can progress to acute respiratory distress syndrome, multiorgan dysfunction, or death (Que et al., 2022). This progression may be attributed to the body's inflammatory response exacerbating inflammatory mediators such as cytokines and chemokines, leading to cytokine storm (Que et al., 2022). Therefore, many treatment modalities such as antiviral therapy, antibiotic therapy, immunomodulating agents, and corticosteroids have been investigated to mitigate COVID-19 symptoms, reduce disease progression, and ultimately prevent mortality (RECOVERY Collaborative Group, 2021; REMAP-CAP Investigators et al., 2021; Shaffer, 2020).

Critically ill patients with severe COVID-19 exhibit elevated inflammatory markers, including interleukin-6 (IL-6) (Rizvi and Gallo De Moraes, 2021). Therefore, many studies have investigated using IL-6 targeting immunomodulators to treat COVID-19 (REMAP-CAP Investigators et al., 2021; Rizvi and Gallo De Moraes, 2021; Stone et al., 2020; Al Sulaiman et al., 2021a; RECOVERY Collaborative Group, 2021). A randomized controlled trial by the RECOVERY Collaborative Group demonstrated tocilizumab's (TCZ) effectiveness in reducing mortality and improving clinical outcomes in hospitalized patients with COVID-19 (RECOVERY Collaborative Group, 2021). A systematic review and meta-analysis including 17 observational studies that compared TCZ with systemic steroid versus standard of care in patients with severe COVID-19 reported a lower mortality rate in patients receiving TCZ (Alkofide et al., 2021). Moreover, a recent systematic review and meta-analysis including 52 studies confirmed TCZ mortality benefits in the intensive care unit (ICU) and non-ICU patients regardless of the use of systemic corticosteroids, but TCZ did not significantly reduce mortality in the included observational studies (Kyriakopoulos et al., 2021).

Even though most evidence supports the efficacy of TCZ use in patients with severe COVID-19 (Van den Eynde et al., 2021; REMAP-CAP Investigators et al., 2021; Kimmig et al., 2020; Kyriakopoulos et al., 2021; Mahale et al., 2020; RECOVERY Collaborative Group, 2021), its effectiveness, specifically in patients with COVID-19 aged 65 years or older who are at higher risk of mortality, remains questionable (Bhatraju et al., 2020; Grasselli et al., 2020). Older adult patients admitted to the ICU with COVID-19 have a higher number of comorbidities and a higher risk of death in the ICU (Grasselli et al., 2020). A retrospective study conducted by our group has found that the overall ICU mortality within 30 days was 42.3%, and up to 40% of included patients were aged 65 years old or older, but we did not assess the use of TCZ in the previous study (Al Sulaiman et al., 2021b). Although the RECOVERY trial that included both ICU and non-ICU patients reported mortality benefits with TCZ use in older adult patients (≥70–<80 years) and a respiratory rate (95% confidence interval [CI]) of 0.83 (0.72–0.94), this group only represented 24% of the included patients at baseline (RECOVERY Collaborative Group, 2021). Another two-center study conducted by our group that included critically ill patients with COVID-19 compared the effectiveness and safety of two TCZ dosing regimens in adults older than 18 years with a mean age of 59.0 (standard deviation [SD] ± 12.8) (Al Sulaiman et al., 2021a). However, most of the previously conducted studies investigated TCZ efficacy and safety, focusing on adults aged 18 years or above with none of these studies addressing TCZ's benefit and risk in high-risk populations such as older adults (Alkofide et al., 2021; Van den Eynde et al., 2021; Kimmig et al., 2020; Mahale et al., 2020; Shaffer, 2020; Stone et al., 2020). Therefore, this study aims to compare the safety and effectiveness of TCZ versus control in critically ill older adult patients (aged ≥65 years) with COVID-19.

Methods

Study design

This study was a multicenter, retrospective cohort including critically ill older adult patients (aged ≥65 years) with confirmed COVID-19 and admitted to the ICUs at four hospitals in Saudi Arabia from March 1, 2020, until March 31, 2021. All patients were observed until they were discharged from the hospital or died during their stay. Because of the study's retrospective observational nature, informed consent from study participants was waived. This project was approved by the King Abdullah International Medical Research Center (KAIMRC) (IRB number NRC21R.434.10) as the primary site.

Study participants

We included all older adult patients (age ≥65 years) admitted to the ICUs with confirmed COVID-19. Patients were diagnosed with COVID-19 using reverse transcriptase-polymerase chain reaction (RT-PCR) nasopharyngeal or throat swabs. Patients were excluded if the ICU length of stay (LOS) ≤ 1 day, died within the first 24 hours of ICU admission, were labeled as "do-not-resuscitate," received TCZ before ICU admission or after 24 hours of ICU admission (Figure 1). Eligible patients were then categorized based on TCZ use during ICU stay into two groups (control vs TCZ). TCZ has been approved for the treatment in patients with severe COVID-19 in Saudi Arabia, according to the Saudi Ministry of Health guidelines for COVID-19 management in critically ill patients (Saudi Ministry of Health, 2021). TCZ was administered as a single dose of 4–8 mg/kg based on the actual body weight (maximum 800 mg) through IV infusion; a repeated dose was given based on clinical assessment (Saudi Ministry of Health, 2021).

Study settings

The study was conducted at four hospitals representing three regions in Saudi Arabia: King Abdulaziz Medical City (Riyadh), King Abdulaziz University Hospital (Jeddah), King Abdullah bin Abdulaziz University Hospital (Riyadh), and King Salman Specialist Hospital (Hail). The primary center was King Abdulaziz Medical City - National Guard Health Affairs (NGHA) (Riyadh).

Data collection

Each patient's data were collected and handled using KAIMRC Research Electronic Data Capture (REDCap®) version 9.1.2 software. The following demographic and laboratory data were collected within 24 hours of ICU admission: comorbidities, vital signs, renal profile (i.e., estimated glomerular filtration rate [eGFR]), liver function tests (i.e., total bilirubin, alanine aminotransferase, aspartate aminotransferase), coagulation profile (i.e., international normalized ratio, activated partial thromboplastin time, platelets count), and inflammatory and surrogate markers (ferritin, D-dimer, and C-reactive protein [CRP]). Moreover, severity score baseline (i.e., Acute Physiology and Chronic Health Evaluation II (APACHE II), Sequential Organ Failure Assessment (SOFA)), Glasgow Coma Score (GCS), acute kidney injury (AKI), prone positioning, the needs for mechanical ventilation (MV) and MV parameters (e.g., lowest arterial oxygen tension [PaO_2]/fraction of inspired oxygen [FiO_2] ratio, highest FiO_2 requirement) within 24 hours of ICU admission were documented. In addition, early use of corticosteroids and pharmacological venous thromboembolism prophylaxis were recorded for the eligible patients.

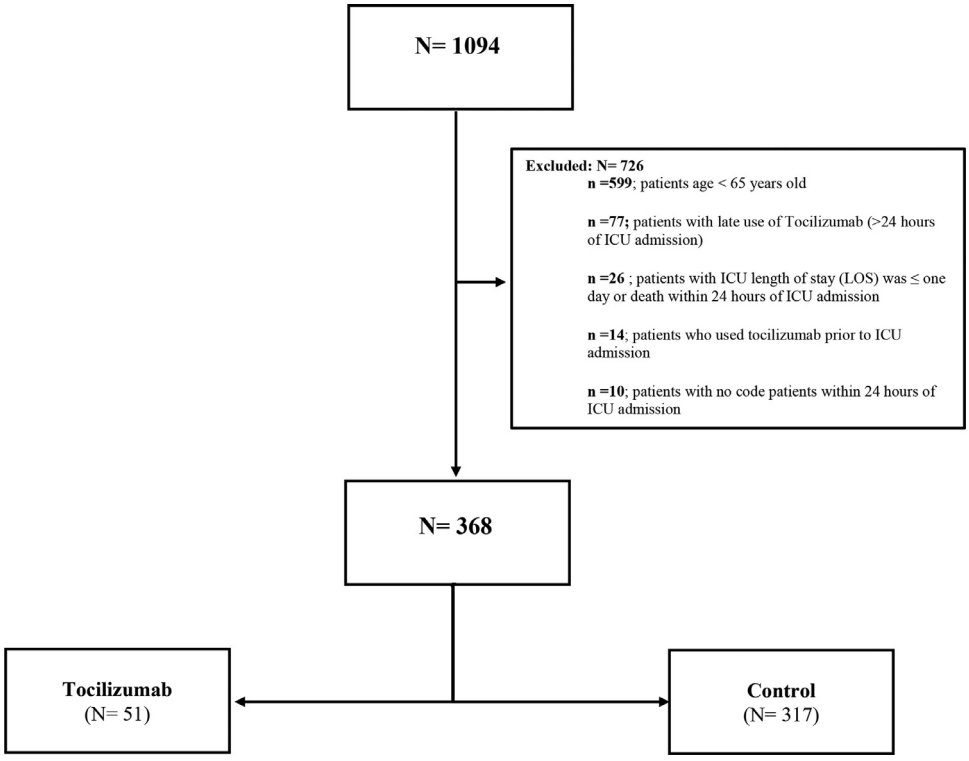

Figure 1. Flowchart of patients admitted to the ICU (before propensity score match). ICU, intensive care unit.

Study outcomes

The study aims to assess the effectiveness and safety of TCZ use in critically ill older adult patients (aged ≥65 years) with COVID-19. The primary outcome was the in-hospital mortality compared between patients who received TCZ versus the control group during the ICU stay. The secondary outcomes were the 30-day mortality, hospital LOS, ICU LOS, ventilator-free days (VFDs), and ICU-related complication(s) during the ICU stay (i.e., acute kidney injury, acute liver injury, secondary fungal infection, respiratory failure requiring MV, and the use of inotropes/vasopressors as supportive measures).

The in-hospital mortality (primary outcome) was defined as death occurring for any cause during hospital stay; patients who were discharged from the hospital alive were presumed to survive. The remaining secondary outcome definitions are provided in the Supplementary file (Table S1**).**

Statistical analysis

We presented continuous variables as mean and SD, or median with lower and upperquartile (Q1, Q3) , as appropriate. Whilecategorical variables as number (percentage). The normality assumptions were assessed for all numerical variables using the Shapiro-Wilk test and graphical representations using histograms and Q-Q plots. Model fit was assessed using the Hosmer-Lemeshow goodness-of-fit test.

Baseline characteristics and outcome variables were compared between the two study groups for statistical differences. For categorical variables, we used the chi-square or Fisher's exact test. While, for normally distributed continuous variables we used Student *t*-test and, Mann-Whitney *U* testfor other non-normally distributed continuous variables . Multivariable Cox proportional hazards regression analysis were performed for the 30-day and in-hospital mortality. Multivariable logistic and negative binomial regression analysis were used for the other outcomes considered in this study. The odds ratios (OR), hazard ratio (HR), or estimates with the 95% CIs were reported as appropriate. Regression analysis was done by considering the PS as one of the covariates in the model. No imputation was made for missing data because 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.

PS matching procedure (Proc PS match) (SAS, Cary, North Carolina) was used to match patients who received TCZ (active group) to patients who did not (control group) based on patient's age, APACHE II score, use of systemic corticosteroids, and AKI status within 24 hours of ICU admission. A greedy nearest neighbor matching method was used in which one patient who received TCZ matched with one patient who did not, 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 SD.

Results

A total of 1094 patients admitted to the ICU were screened; 368 older adult patients (aged ≥65 years) were eligible based on the eligibility criteria as shown in Figure 1. Of those, 51 patients (13.8%) received TCZ during their ICU stay. After PS matching (1:1 ratio), 94 patients were included based on predefined criteria. All included patients received TCZ within 24 hours of ICU admission. A total of twenty four patients (47%) received a single dose of TCZ.

Demographic and clinical characteristics

Before PS matching, most patients were male (65.8%), with a mean age of 75.6 years (SD 7.88). The most common underlying comorbidities in our patients were hypertension (70.7%), diabetes mellitus (68.2%), and dyslipidemia (26.5%) (Table 1). There were

Table 1
Baseline characteristics.

	Before propensity score				After propensity score			
	Overall (N = 368)	Control (N = 317)	Tocilizumab (N = 51)	*P*-value	Overall (N = 94)	Control (N = 47)	Tocilizumab (N = 47)	*P*-value
Age (years), mean (SD)	75.6 (7.88)	76.0 (7.98)	73.4 (6.95)	**0.012**[b]	73.1 (6.71)	73.0 (6.45)	73.2 (7.02)	0.994[b]
Gender – male, n (%)	237 (65.8)	201 (65)	36 (70.6)	0.44[c]	65 (69.9)	32 (69.6)	33 (70.2)	0.945[c]
Weight (kg), mean (SD)	77.9 (15.66)	77.9 (15.71)	77.5 (15.49)	0.934[b]	77.6 (14.44)	77.8 (13.21)	77.3 (15.69)	0.872[a]
APACHE II score, median (Q1, Q3)	15.0 (11, 25)	16.0 (11, 25)	14.0 (12, 26)	0.457[b]	13.0 (11, 21)	13.0 (10, 20)	14.0 (12, 26)	0.327[b]
SOFA score, median (Q1, Q3)	5.0 (3.00, 8.00)	5.0 (3.00, 8.00)	4.0 (3.00, 9.00)	0.504[b]	4.0 (3.00, 8.00)	5.0 (3.00, 8.00)	4.0 (3.00, 9.00)	0.689[b]
Early use of systemic corticosteroids within 24 hours of admission, n (%)	259 (71.5)	216 (69.5)	43 (84.3)	**0.03**[c]	77 (82.8)	37 (80.4)	40 (85.1)	0.550[c]
Prone status, n (%)	81 (23.3)	66 (22.1)	15 (30.0)	0.224[c]	24 (26.7)	9 (20.5)	15 (32.6)	0.192[c]
Estimated Glomerular Filtration Rate (**eGFR) baseline, median (Q1, Q3)**	63.00 (32.00, 87.00)	62.00 (31.00, 86.00)	68.50 (34.00, 96.00)	0.179[b]	68.00 (38.00, 95.00)	70.00 (40.50, 91.00)	68.00 (34.00, 96.00)	0.930[b]
AKI within 24 hours of ICU admission, n (%)	114 (32.5)	102 (33.9)	12 (24.0)	0.166[c]	23 (24.7)	11 (23.9)	12 (25.5)	0.856[c]
Mechanical ventilation within 24 hours of ICU admission, n (%)	266 (73.9)	232 (75.1)	34 (66.7)	0.205[c]	66 (71.0)	35 (76.1)	31 (66.0)	0.282[c]
Inotropes/vasopressors use within 24 hours of admission), n (%)	89 (25.1)	77 (25.4)	12 (23.5)	0.774[c]	23 (24.7)	11 (23.9)	12 (25.5)	0.856[c]
Lactic acid baseline (mmol/L), median (Q1, Q3)	1.7 (1.30, 2.30)	1.8 (1.31, 2.33)	1.6 (1.20, 2)	0.165[b]	1.7 (1.27, 2.2)	1.7 (1.31, 2.23)	1.5 (1.2, 2)	0.353[b]
Platelet count baseline (10^9/L), median **(Q1, Q3)**	236.0 (178, 302)	234.5 (176.5, 300.5)	243.0 (198, 331)	0.390[b]	251.5 (186, 307.5)	262.0 (188, 321)	240.0 (183, 304)	0.761[a]
Total WBC baseline (10^9/L), median (Q1, Q3)	9.5 (6.87, 12.90)	9.6 (6.86, 12.95)	9.2 (6.99, 12.60)	0.519[b]	9.5 (6.53, 12.71)	10.6 (6.53, 13.00)	9.1 (6.47, 11.90)	0.216[b]
International normalized ratio (INR), median (Q1, Q3)	1.1 (1.04, 1.25)	1.1 (1.04, 1.25)	1.1 (1.05, 1.20)	0.523[b]	1.1 (1.04, 1.25)	1.1 (1.04, 1.32)	1.1 (1.05, 1.17)	0.472[b]
Activated partial thromboplastin time (aPTT) baseline (Seconds), median (Q1, Q3)	30.7 (27.4, 34.9)	30.9 (27.40, 35.40)	30.1 (27.90, 33.30)	0.334[b]	30.3 (26.95, 34.00)	29.9 (26.80, 34.00)	30.5 (28.10, 33.90)	0.8[b]
Total bilirubin (μmol/L), median (Q1, Q3)	9.0 (6.6, 12.95)	9.0 (6.6, 12.5)	9.7 (6.3, 14.3)	0.511[b]	9.6 (7.1, 14.0)	9.5 (7.5, 11.60)	9.7 (6.50, 14.80)	0.768[b]
Albumin baseline (gm/L), median (Q1, Q3)	31.0 (28.00, 35.00)	32.0 (28, 35)	30.0 (27, 34)	0.157[b]	31.0 (28, 35.5)	33.0 (29, 36)	30.0 (27, 34)	0.063[b]
Alanine aminotransferase (ALT) Baseline (U\L), median (Q1, Q3)	34.0 (23, 56)	33.5 (23, 55.5)	38.0 (24.00, 64.00)	0.576[b]	37.0 (22.00, 66.00)	35.0 (20.00, 72.00)	38.0 (24, 64)	0.931[b]
Aspartate aminotransferase (AST) Baseline (U\L), median (Q1, Q3)	51.0 (35, 80)	51.0 (35, 80)	54.0 (38.00, 88.00)	0.573[b]	48.5 (36.00, 77.00)	48.0 (34.00, 77.00)	50.0 (38, 85)	0.812[b]
Creatine phosphokinase (CPK) baseline (U/l), median (Q1, Q3)	139.0 (68, 378)	136.5 (71, 361)	174.0 (58, 483)	0.834[b]	164.0 (69.00, 459.50)	144.0 (72, 361)	174.0 (58, 563)	0.926[b]
C-reactive protein (CRP) baseline (mg/l), median (Q1, Q3)	119.0 (48, 189)	105.0 (37.25, 182)	161.0 (71, 199)	**0.049**[b]	137.0 (71, 182)	128.5 (63, 182)	159.5 (74.00, 186.45)	0.506[b]
Procalcitonin (ng/ml), median (Q1, Q3)	0.4 (0.14, 1.26)	0.4 (0.16, 1.20)	0.4 (0.12, 1.50)	0.714[b]	0.4 (0.13, 1.50)	0.4 (0.20, 1.77)	0.4 (0.13, 0.99)	0.397[b]
Fibrinogen level baseline (gm/l), median (Q1, Q3)	5.2 (3.96, 7.02)	5.2 (4, 7.01)	5.4 (2.53, 7.27)	0.438[a]	4.9 (2.53, 7.02)	4.9 (2.58, 7.02)	5.0 (2.47, 7.10)	0.788[a]
D-dimer level baseline (mg/l), median (Q1, Q3)	1.7 (0.88, 3.90)	1.7 (0.88, 3.90)	1.9 (0.85, 3.66)	0.868[b]	1.7 (0.91, 3.07)	1.5 (0.95, 3.07)	1.7 (0.85, 2.72)	0.798[b]
Ferritin level baseline (ug/l), median (Q1, Q3)	636.6 (314, 1388)	565.6 (293.80, 1295.00)	1052.5 (648.85, 1887.00)	**0.007**[b]	805.2 (433.40, 1487)	555.2 (383.6, 1295)	992.9 (648.85, 1689)	0.065[b]
Blood glucose level baseline (mmol/L) , median (Q1, Q3)	11.8 (8.3, 15.3)	12.0 (8.4, 15.40)	11.1 (8.1, 14.85)	0.451[b]	11.1 (8.1, 15.7)	11.1 (8.6, 17.1)	11.0 (7.8, 14.85)	0.517[b]
Lowest PaO_2/FiO_2 ratio within 24 hours of admission, median (Q1, Q3)	83.9 (59.9, 130.6)	82.5 (59.78, 136.1)	89.2 (61.12, 124)	0.920[b]	84.6 (59.33, 116.5)	79.2 (59.25, 109.8)	87.0 (61.12, 119.8)	0.622[b]
Respiratory rate (RR) baseline (Breath per minute)baseline, median (Q1, Q3)	26.0 (22, 32)	26.0 (22, 32)	28.0 (21.00, 32.00)	0.757[b]	25.0 (20.50, 30.00)	24.0 (20.00, 29.00)	28.0 (21, 32)	0.102[b]
Maximum temprature baseline (C°), median (Q1, Q3)	37.2 (37.00, 37.80)	37.2 (37, 37.9)	37.1 (36.90, 37.50)	0.127[b]	37.2 (37, 37.60)	37.2 (37, 37.7)	37.1 (37, 37.5)	0.147[b]
Patient received nephrotoxic drugs/material during ICU stay, n (%)	294 (82.4)	251 (82.0)	43 (84.3)	0.69[c]	80 (87)	41 (91.1)	39 (83.0)	0.247[c]
Comorbidity, n (%)								
Atrial fibrillation	16 (4.4)	12 (3.9)	4 (7.8)	0.2[d]	6 (6.5)	2 (4.3)	4 (8.5)	0.414[d]
Heart failure	54 (14.9)	46 (14.8)	8 (15.7)	0.868[c]	11 (11.8)	4 (8.7)	7 (14.9)	0.354[c]
Hypertension (HTN)	256 (70.7)	222 (71.4)	34 (66.7)	0.492[c]	65 (69.9)	35 (76.1)	30 (63.8)	0.2[c]
Diabetes mellitus (DM)	247 (68.2)	218 (70.1)	29 (56.9)	0.06[c]	59 (63.4)	34 (73.9)	25 (53.2)	**0.038**[c]
Dyslipidemia (DLP)	96 (26.5)	83 (26.7)	13 (25.5)	0.857[c]	31 (33.3)	19 (41.3)	12 (25.5)	0.106[c]
Chronic kidney disease (CKD)	65 (18)	59 (19)	6 (11.8)	0.214[c]	14 (15.1)	9 (19.6)	5 (10.6)	0.228[c]
Ischemic heart disease (IHD)	45 (12.4)	42 (13.5)	3 (5.9)	0.126[c]	8 (8.6)	6 (13.0)	2 (4.3)	0.13[d]
Chronic obstructive pulmonary disease (COPD)	10 (2.8)	9 (2.9)	1 (2.0)	0.706[d]	3 (3.2)	2 (4.3)	1 (2.1)	0.544[d]
Asthma	17 (4.7)	16 (5.1)	1 (2.0)	0.319[d]	3 (3.2)	2 (4.3)	1 (2.1)	0.544[d]
Cancer (any type)	10 (2.8)	8 (2.6)	2 (3.9)	0.585[d]	3 (3.2)	1 (2.2)	2 (4.3)	0.57[d]
Deep vein thrombosis (DVT)	4 (1.1)	4 (1.3)	0 (0.0)	0.415[d]	1 (1.1)	1 (2.2)	0 (0)	0.31[d]

(*continued on next page*)

Table 1 (*continued*)

	Before propensity score				After propensity score			
	Overall (N = 368)	Control (N = 317)	Tocilizumab (N = 51)	*P*-value	Overall (N = 94)	Control (N = 47)	Tocilizumab (N = 47)	*P*-value
Pulmonary embolism (PE)	3 (0.8)	2 (0.6)	1 (2.0)	0.336[d]	1 (1.1)	0 (0)	1 (2.1)	0.32[d]
Liver disease (any type)	9 (2.5)	8 (2.6)	1 (2.0)	0.8[d]	3 (3.2)	2 (4.3)	1 (2.1)	0.544[d]
Stroke	35 (9.7)	31 (10.0)	4 (7.8)	0.634[d]	9 (9.7)	5 (10.9)	4 (8.5)	0.7[d]

AKI, acute kidney injury; APACHE II, Acute Physiology and Chronic Health Evaluation II; ICU, intensive care unit;PaO_2/FiO_2, arterial oxygen tension/fraction of inspired oxygen; Q1, first interquartile; Q3, third interquartile; SOFA, Sequential Organ Failure Assessment; SD, standard deviation; WBC, white blood cell count.

[a] *t*-test is used to calculate the *P*-value.

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

[c] Chi-square test is used to calculate the *P*-value.

[d] Fisher's exact test is used to calculate *P*-value.

Table 2
Regression analysis for the outcomes after propensity score matching.

Outcomes	Crude analysis		*P*-value[c]	HR (95% CI)	*P*-value[e]
	Control	Tocilizumab			
In-hospital mortality, n (%)[a]	31 (67.4)	17 (37.8)	0.005	0.41 (0.22–0.76)	0.005
30-day mortality, n (%)[a]	26 (56.5)	16 (34.8)	0.04	0.66 (0.35–1.24)	0.19
			***P*-value**[d]	**Beta coefficient (estimates) (95% CI)**	***P*-value**[f]
Ventilator-free days, mean (SD)[a]	8.8 (12.5)	12.3 (13.3)	0.17	0.32 (−0.70 to 1.34)	0.54
ICU length of stay (days), median (Q1, Q3)[b]	10.0 (3.00, 15.00)	12.5 (8.00, 18.00)	0.37	0.36 (−0.17 to 0.89)	0.18
Hospital length of stay (days), median (Q1, Q3)[b]	25.0 (10.00, 40.00)	22.0 (14.50, 36.00)	0.84	0.20 (−0.30 to 0.71)	0.43

CI, confidence interval; HR, hazard ratio; ICU, intensive care unit; Q1, first interquartile; Q3, third interquartile; SD, standard deviation.

[a] Denominator of the percentage is the total number of patients.

[b] Denominator is patients who survived.

[c] Chi-square test is used to calculate the *P*-value.

[d] Wilcoxon rank-sum test is used to calculate the *P*-value.

[e] Cox proportional hazards regression analysis is used to calculate HR and *P*-value.

[f] Generalized linear model is used to calculate beta coefficient (estimates) and *P*-value.

some notable differences in the baseline characteristics between the two groups before PS matching. Patients who received TCZ were younger, received more systemic corticosteroids within 24 hours of ICU admission, had higher CRP and ferritin levels at baseline. After adjusting PS matching based on the selected criteria, all baseline and demographic characteristics were similar between the two groups except for diabetes mellitus, which was more prevalent in the control group, as listed in Table 1.

Outcomes

In-hospital and 30-day mortality

In a crude analysis, there was a significant difference in the in-hospital (37.8% vs 67.4%, *P*-value = 0.005) and 30-day (34.8% vs 56.5%, *P*-value = 0.04) mortality in patients who received TCZ compared with the control, respectively. In addition, after the Cox proportional hazards regression analysis, the in-hospital mortality was significantly lower in patients who received TCZ than in those who did not (HR 0.41; 95% CI 0.22–0.76, *P*-value = 0.005). Moreover, in patients who received TCZ, fewer deaths occurred within 30 days of admission than in patients who did not receive TCZ; however, this finding did not reach the statistical significance in regression analysis (HR 0.66; 95% CI 0.35–1.24, *P*-value = 0.19) as listed in Table 2**.** In a Kaplan-Meier curve, the administration of TCZ was associated with better survival outcomes in older adult patients with COVID-19 as shown in Figure 2.

Ventilator-free days and LOS

The mean ventilator-free days was longer in crude analysis toward patients who received TCZ with a mean of 12.3 (±13.3) days compared with 8.8 (±12.5) days in the control group. However, it failed to reach the statistically significant difference after regression analysis with a beta coefficient (95% CI): 0.32 (−0.70 to 1.34), *P*-value = 0.54 (Table 2).

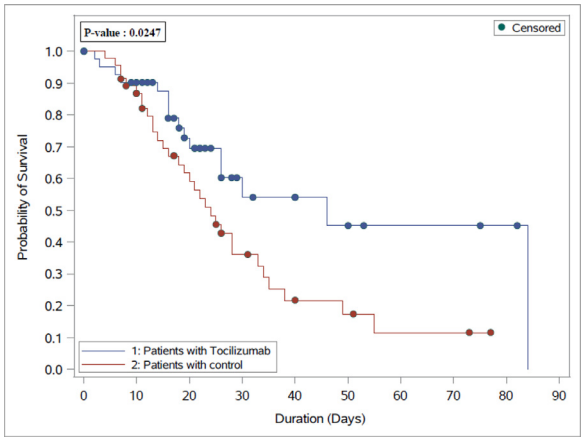

Figure 2. Overall survival plot during the hospital stay comparing patients who received tocilizumab versus the control group.

The ICU and hospital LOS were not statistically significant in patients who received TCZ compared with the control group (12.5 [8.0–18.0] vs 10.0 [3.0–15.0], *P*-value = 0.37 and 22 [14.5–36.0] vs 25 [10.0–40.0], *P*-value = 0.84, respectively). Moreover, there was no significant difference in ICU LOS (beta coefficient, 95% CI: 0.36 [−0.17 to 0.89], *P*-value = 0.18) or hospital LOS (beta coefficient, 95% CI: 0.20 [−0.30 to 0.71], *P*-value = 0.43) between the two groups after regression analysis (Table 2).

Complications during ICU stay

Patients who received TCZ had lower odds of respiratory failure requiring MV (OR [95% CI]: 0.32 [0.10–0.98], *P*-value = 0.04). In addition, other complications during ICU such as AKI, liver injury, and

Table 3
Regression analysis for ICU complication(s) and supportive measure(s) after propensity score matching.

Outcomes	Crude analysis		*P*-value[b]	OR (95% CI)	*P*-value[d]
	Control	Tocilizumab			
Acute kidney injury, n (%)[a]	28 (60.9)	24 (51.1)	0.34	0.66 (0.29–1.52)	0.33
Liver injury, n (%)[a]	5 (10.9)	4 (8.5)	0.70[c]	0.76 (0.19–3.04)	0.69
Respiratory failure requiring MV, n (%)	41 (89.1)	34 (72.3)	**0.04**	0.32 (0.10–0.98)	**0.04**
Inotropes/vasopressors use during ICU stay as supportive measures, n (%)[a]	30 (69.8)	27 (57.4)	0.23	0.87 (0.38–1.98)	0.74
Secondary fungal infection, n (%)[a]	8 (24.2)	9 (23.7)	0.96	0.93 (0.30–2.86)	0.89

CI, confidence interval; ICU, intensive care unit; MV, mechanical ventilation; OR, odds ratio.
[a] Denominator of the percentage is the total number of patients.
[b] Chi-square test is used to calculate the *P*-value.
[c] Fisher's exact test is used to calculate the *P*-value.
[d] Multivariate logistic regression analysis is used to calculate OR and *P*-value.

secondary fungal infection were lower than the control; however, these results did not reach statistical significance (Table 3).

Discussion

This multicenter retrospective study found that the in-hospital mortality rate was significantly lower in older adult patients who received TCZ than those who did not. However, the 30-day mortality was numerically lower in the TCZ group but did not reach a statistically significant difference. In contrast, the in-hospital mortality was statistically significantly lower in older adult patients who received TCZ, which might be because of a longer follow-up period that may detect other hospital-related complications. Similarly, the odds of respiratory failure requiring MV were significantly lower in older adult patients with COVID-19 who received TCZ during the ICU stay.

In our study, older adult patients with COVID-19 who received TCZ had a significant reduction in the in-hospital mortality. This result was consistent with previous studies' findings showing survival benefit following TCZ administration among patients with COVID-19 (Hermine et al., 2021; Kimmig et al., 2020; RECOVERY Collaborative Group, 2021; REMAP-CAP Investigators et al., 2021; Salama et al., 2021; Soin et al., 2021; Stone et al., 2020; Van den Eynde et al., 2021). In our previous study, increasing the number of TCZ doses showed no significant difference in mortality, rather it showed higher odds of pneumonia in patients who received multiple TCZ doses (Al Sulaiman et al., 2021a). However, all these reports included adult patients with COVID-19 not specific to older adult patients. Unlike adult patients, older adult patients usually have multiple chronic conditions that complicate COVID-19 disease outcome or progression and management and increase their risk of mortality (Salama et al., 2021; Saudi Ministry of Health, 2021). The mean age of patients included in our study was 73.2 years, which indicated an older population compared with the mean age of patients included in the REMAP-CAP and RECOVERY trials at 61.5 and 63.3 years, respectively (Stone et al., 2020; RECOVERY Collaborative Group, 2021). Even though our patients had a higher CRP level and a lower PaO_2/FiO_2 at baseline than those included in other studies, our mortality benefit is consistent with the previous studies (Grasselli et al., 2020; RECOVERY Collaborative Group, 2021; Stone et al., 2020). All study patients in our cohort received their first dose of TCZ during their first day of ICU admission, which could justify the reduction of in-hospital mortality as early use might target the peak of the cytokine's releases; this agrees with some reported data from previous studies. The time to the first dose of TCZ in RECOVERY and REMAP-CAP trials was relatively consistent to our study with a median of 2 and 1.2 days, respectively (RECOVERY Collaborative Group, 2021; Stone et al., 2020).

Patients with COVID-19 reported having high levels of IL-6 and other inflammatory biomarkers, such as cytokines, macrophage inflammatory protein 1 alpha, and tumor necrosis factor-α (Aldhaeefi et al., 2021; Bhatraju et al., 2020; Grasselli et al., 2020; Soin et al., 2021) The mortality benefit of TCZ in patients with severe COVID-19 remains debatable (Aldhaeefi et al., 2021; Alkofide et al., 2021; Bhatraju et al., 2020; Kyriakopoulos et al., 2021; Soin et al., 2021). This mortality reduction uncertainty could be explained by a theory suggesting this hyperinflammatory immune response represents a natural and possibly beneficial host response against infection and suggestive of macrophage activation (Aldhaeefi et al., 2021; Bhatraju et al., 2020; Grasselli et al., 2020; Soin et al., 2021). In support of this theory, Hermine et al. (2021) failed to show a mortality reduction among patients with COVID-19 receiving TCZ despite including patients with moderate disease (WHO-CPS score of 5), with a lower CRP than our patients, and early administration of TCZ.

Moreover, our patients had higher rates of MV and comorbidities than those included in the COVINTOC trial, which also failed to show a mortality benefit of the TCZ (Soin et al., 2021). Similarly, Salama et al. (2021) and Stones et al. (2020) failed to demonstrate a mortality benefit of the TCZ despite 83% and 64.7% of the study's population being non–critically ill patients, respectively (Alkofide et al., 2021; Kyriakopoulos et al., 2021). Our findings suggest that TCZ could reduce respiratory failure requiring MV and disease progression in high-risk patients such as older adult patients with COVID-19. This finding is contrary to the findings of the RECOVERY trial in which TCZ use did not result in a reduction of respiratory failure requiring MV among patients older than 80 years (RECOVERY Collaborative Group, 2021). However, several studies concurred with our findings and reported that TCZ use is effective in preventing clinical worsening, disease progression, and the need for MV for patients at a higher risk of clinical worsening despite including patients with mild, moderate, and severe COVID-19. However, these results were uncertain about the effectiveness of TCZ in preventing disease progression among older adult patients with COVID-19, given the heterogeneity of the patient population included in these studies (Hermine et al., 2021; Salama et al., 2021; Sciascia et al., 2020; Stone et al., 2020; Toniati et al., 2020; Xu et al., 2020).

In addition, patients treated with TCZ in this study had a trend of prolonged ICU and hospital LOS. This finding was consistent with the RECOVERY trial among patients older than 80 years (RECOVERY Collaborative Group, 2021). Both mortality benefit and the improvement in the respiratory failure among our patients might explain the prolonged ICU and hospital LOS. In addition, having patients in a strictly controlled and isolated environment was one of the precautionary steps to avoid spreading infections during COVID-19 pandemic outside the hospitals.

Regarding the ICU complications, there were no significant differences in the two study groups. TCZ is a potent immunomodulator that works through competitive inhibition of IL-6 binding

to its receptor (Al Sulaiman et al., 2021a; RECOVERY Collaborative Group, 2021). A major concern with administering such therapy among patients with patients with COVID-19 is the serious secondary infections. Several studies have reported more serious secondary infections following TCZ administration (Alkofide et al., 2021; Bhatraju et al., 2020; Kimmig et al., 2020; Stone et al., 2020). In contrast to these studies, we found a nonsignificant difference in the rate of secondary fungal infections. Several studies reported similar findings regarding secondary infections with TCZ versus standard of care (Aldhaeefi et al., 2021; Kyriakopoulos et al., 2021; RECOVERY Collaborative Group, 2021; Sciascia et al., 2020; Soin et al., 2021).

As far as we know, this is one of the first multicenter studies that investigated the efficacy and safety of TCZ in critically ill older adult patients with COVID-19. In addition, PS matching was used to eliminate a greater portion of bias and create a balanced dataset. However, the study is not free of limitations. First, it was a retrospective study that included a relatively small sample size. Second, short follow-up duration may limit capturing further secondary infections or long-term complications. Finally, our study might be underpowered to detect a difference in long-term outcomes.

Conclusion

This study shows that TCZ administration among critically ill older adults with COVID-19 resulted in reduced in-hospital mortality without a significant increase of secondary infections or other ICU complications. Further robust randomized clinical trials evaluating the safety and efficacy of TCZ among older critically ill patients with COVID-19 are needed to confirm our findings.

Declaration of Competing Interests

The authors have no conflicts of interest to declare.

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Ethics approval and consent to participate

The study was approved by King Abdullah International Medical Research Center (KAIMRC), Riyadh, Saudi Arabia (Ref.#. NRC21R.434.10). Throughout the study, participants' confidentiality was rigorously preserved by using an anonymous unique serial number for each individual and confining data to just the investigators. Informed consent was not required because of the research method, which was following the policies of the governmental and local research institutes.

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Author contributions

All authors contributed to data collections, analysis, drafted, revised, and approved the final version of the manuscript. All authors critically revised the manuscript, agreed to be fully accountable for ensuring the integrity and accuracy of the work, and read and approved the final manuscript.

Availability of data and material

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

Consent for publication

Not applicable.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.ijid.2022.05.038.

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