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"Ventilator-free days" composite outcome in patients with SARS-CoV-2 infection treated with tocilizumab: A retrospective competing risk analysis

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ABSTRACT

Background: SARS-CoV-2 infection demonstrates a wide range of severity, with more severe cases presenting with a cytokine storm with elevated serum interleukin-6; hence, the interleukin-6 receptor antibody tocilizumab was used for the management of severe cases.
Objective: To explore the effect of tocilizumab on ventilator-free day composite outcomes among critically ill patients with SARS-CoV-2 infection.
Methods: This retrospective propensity score-matching study compared mechanically ventilated patients who received tocilizumab to a control group.
Results: Twenty-nine patients in the intervention group were compared to 29 controls. The matched groups were similar. The ventilator-free days composite outcome was higher in the intervention group (sub-distribution hazard ratio 2.7, 95% confidence interval [CI]: 1.2–6.3; $p = 0.02$), the mortality rate in the intensive care unit was not different (37.9% vs 62%, $p = 0.1$), and actual ventilator-free days were significantly longer in the tocilizumab group (mean difference 4.7 days; $p = 0.02$). Sensitivity analysis showed a significantly lower hazard ratio for death in the tocilizumab group (HR 0.49, 95% CI: 0.25–0.97; $p = 0.04$). Positive cultures were not significantly different among the groups (55.2% vs 34.5% in the tocilizumab and control groups, respectively; $p = 0.1$).
Conclusions: Tocilizumab may improve the composite outcome of ventilator-free days at day 28 among mechanically ventilated patients with SARS-CoV-2 infection. It is associated with significantly longer actual ventilator-free days, insignificantly lower mortality, and higher superinfection.

Introduction

An international pandemic was declared by the World Health Organization on March 11, 2020, as a result of a rapidly spreading viral infection causing pneumonia and respiratory symptoms,[1] which was identified as a novel positive-sense-single strand RNA virus of the family Coronaviridae, capable of infecting a range of hosts including humans, that soon came to be recognized as SARS-CoV-2.[2] Despite all measures of containment, the pandemic has spread globally, and by March 12, 2022, more than 450 million cases and 6 million fatalities had been confirmed worldwide.[1] It is well known, however, that not all positive cases demonstrate similar signs, symptoms, or severity. SARS-CoV-2 infection demonstrates a fairly wide spectrum of symptoms, ranging from asymptomatic cases to mild respiratory complaints, severe pneumonia, and severe acute respiratory distress syndrome (ARDS).[3] Furthermore, up to 10% of cases are on the severe end of the spectrum, experiencing multi-organ failure in addition to ARDS and requiring mechanical ventilation and/or admission to intensive care units (ICU).[4]

Critically ill patients with SARS-CoV-2 infection show elevated levels of pro-inflammatory cytokines, particularly interleukin 2 and 6 (IL2, IL6),[5] and serum levels of such cytokines—particularly IL6—are

Abbreviations: WHO, World Health Organization; RNA, Ribonucleic Acid; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; ARDS, Acute Respiratory Distress Syndrome.; ICU, Intensive Care Unit.; IL, Interleukin; TCZ, Tocilizumab; FDA, Food and Drug Administration; VFD, Ventilator Free Days; aVFD, actual Ventilator Free Days; RT-PCR, reverse transcription – polymerase chain reaction; HIV, human immunodeficiency virus; IRB, institutional review board; BMI, body mass index; SHR, sub-distribution hazard ratio; IQR, interquartile range; CI, confidence interval; SOFA, sequential organ failure assessment; HR, Hazard ratio

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higher than in patients with milder presentation[6] and have been associated with poor outcomes.[6,7] These findings, coupled with post-mortem evidence of severe alveolar edema, patches of inflammatory infiltrates, and proteinaceous exudates,[8] suggest that a cytokine storm secondary to the host's dysregulated immune response may be associated with SARS-CoV-2 infection.[4,9]

Tocilizumab (TCZ) is a humanized anti-interleukin 6 receptor monoclonal antibody[5] that targets both forms of receptors, namely soluble and membrane bound receptors.[10] It has been postulated that TCZ treatment may be able to attenuate the so-called cytokine storm associated with SARS-CoV-2 infection and prevent the progress of the infection into ARDS.[4,5] Moreover, TCZ was licensed by the United States Food and Drug Administration for the management of cytokine release syndrome.[11] Hence, this study was performed to assess the impact of treatment with TCZ on critically ill patients with SARS-CoV-2, utilizing a composite outcome measure commonly used in critical care studies. Ventilator-free days (VFD) at 28 days is used to quantify the efficacy of therapies and interventions on morbidity in the presence of a competing event of death.[12,13] We hypothesized that treatment with TCZ would increase the chance of patients being alive and extubated on day 28, compared to being mechanically ventilated or deceased.

Methods

Study design

This was a retrospective observational study that used analytical statistical methods to compare the outcomes of mechanically ventilated patients who received TCZ to those who did not during the SARS-CoV-2 pandemic, as a composite outcome of both mortality and duration of mechanical ventilation.

Setting and timeframe

This study was conducted in the ICU of a large government hospital in Saudi Arabia. The ICU originally harbors 127 beds and was expanded during the SARS-CoV-2 pandemic to include 300 beds, half of which were isolation single rooms, and the rest were open cohorting areas. It is a closed ICU operated 24/7 by dedicated intensivists with a nursing ratio of 1:1. During the SARS-CoV-2 pandemic, it was a COVID referral center, and we generally followed the management protocols recommended by the Ministry of Health, adapted from international guidelines. This study included patients admitted to the ICU between March 1, 2020, and June 30, 2020. Some patients in this analysis may have been included in a previously published article.[14]

We included patients who were admitted to the ICU during the study period, adults (age $\geq$ 18 years), mechanically ventilated upon ICU admission, confirmed COVID-19-positive (by reverse transcription polymerase chain reaction nasopharyngeal swab), and received at least one dose of TCZ during the course of their treatment. TCZ was administered in our ICU at a dose of 4–8 mg/kg, as an intravenous infusion reconstituted in 100 ml of 0.9% sodium chloride solution over 60 min, and could be followed by a second similar dose 12–24 h later if the patient clinically deteriorated or failed to improve. No other immunomodulatory medications were used in our ICU.

We excluded patients younger than 18 years of age, pregnant women, and those with known pulmonary tuberculosis and human immunodeficiency virus (HIV)-positive cases. Data from all other patients with the same criteria (apart from receiving TCZ) were used to identify a control group (further details follow).

The original study (from which the subset of patients in the current analysis was taken) was approved by the local institutional review board with waiver of consent in view of its retrospective design, and both the original study and this analysis observed the general principles outlined by the Declaration of Helsinki.

Data management

We retrieved the demographic data of all patients who fulfilled the inclusion criteria (age, sex, comorbidities, smoking status, severity score, and body mass index) and serum C-reactive protein levels at ICU admission. All included patients were mechanically ventilated upon ICU admission, and we recorded the date of extubation (if at all) within 28 days and the ICU outcome as a binary variable of death or survival. Furthermore, we also recorded other treatment modalities, including antiviral therapy and steroids. Notably, the recommended dose of steroids according to our protocol is 6–12 mg intravenously for up to 10 days, or until the patient becomes asymptomatic or is discharged from the ICU. Finally, we noted reports of positive cultures during ICU stay.

Outcomes

The primary outcome was a composite outcome of VFD, a common outcome frequently utilized in clinical trials in ICU to quantitatively explore the effect of an intervention or treatment on morbidity in the presence of the competing risk of death.[12,13] Details of VFD are given elsewhere[15] briefly. If the patient dies or remains intubated within 28 days, the outcome is considered a failure, and the patient is awarded zero actual VFD (aVFD). The outcome is considered a success only if the patient was extubated before 28 days and remained alive at day 28; in such cases, the aVFD was the day between extubation and day 28. The outcome does not indicate aVFD if the patient was re-intubated or died within 28 days after being extubated. Secondary outcomes included ICU mortality, aVFD, and grown cultures (of any source or organism) as an adverse event that may arise owing to the use of TCZ, and ICU mortality in patients who received steroids as a subgroup analysis.

Statistical methods

Patients who fulfilled the inclusion criteria constituted the intervention group, and we used the data of all other patients with the same criteria apart from receiving TCZ to identify a control group using propensity score matching. We intuitively chose the matching criteria of age, sex, severity score, comorbidities, smoking status, body mass index, and the receipt of steroids and antiviral medications. Matching was performed using the 1:1 nearest neighbor method with a caliber width of 0.2 without replacement. The reason we did not follow the classical method of propensity score matching, where logistic regression is performed using receiving TCZ as the dependent variable to identify variables to match upon,[16] is that we expected a small number of patients receiving TCZ with numerous matching criteria so that if all were included in a logistic regression model, it would have violated the rule of thumb of 10 events/variable, which would have resulted in over-fitting.[17]

Once the matched control group was identified, the primary outcome was assessed in a competing risk regression analysis, utilizing the patients' status as alive and extubated as the event of interest, whereas dead or still intubated as the competing risk.[15] The primary outcome was reported as the sub-distribution hazard ratio (SHR) according to the Fine and Gray method.[18] In this method, the risk of interest and the competing risk are mutually exclusive; that is, if one event occurred, the other could not.

We summarized the data of the intervention and control groups by median and interquartile range (IQR) for continuous variables and compared them using Student's t-test or Wilcoxon rank sum test as appropriate. Categorical variables were summarized as frequency and percentage and compared them by chi^2 or Fisher's exact tests as appropriate. Comparisons are presented with corresponding 95% confidence intervals (CI) and *p*-values.

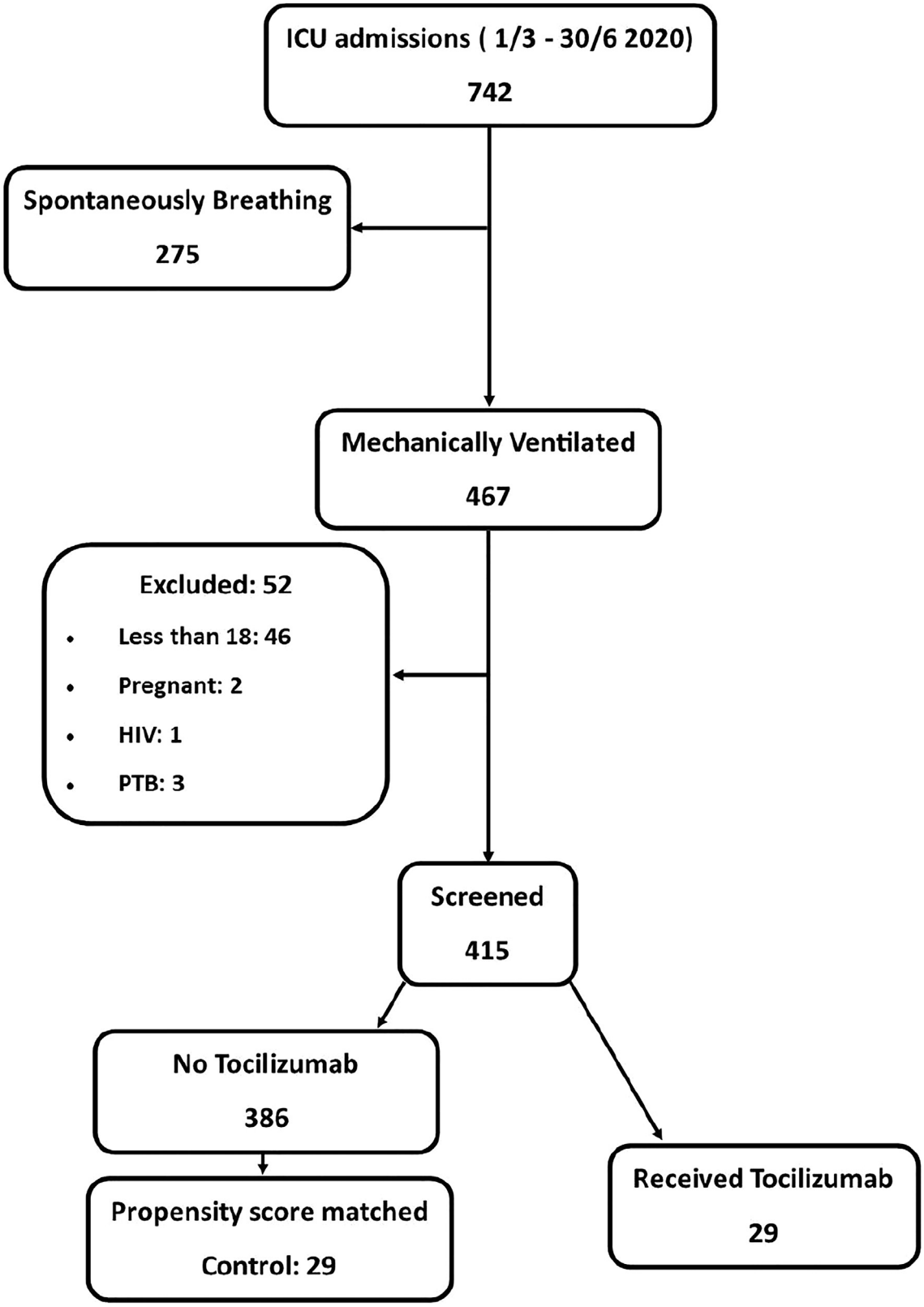

Fig. 1. Patients' and study groups' flow diagram: Flow diagram of included and excluded patients in the study, and matched groups.

Furthermore, we planned a priori to compare 28-day survival among both groups (regardless of the mechanical ventilation status) in a Cox proportional hazard regression model as a sensitivity test for the primary outcome, the result of which is presented as the *p*-value of the log-rank test, along with the corresponding Kaplan–Meier curve.

All statistical tests were two-sided and considered statistically significant with a p-value < 0.05, without correction for multiple

Table 1
Demographic and clinical characteristics of study groups before and after matching.

	Unmatched Groups			Matched Groups		
Variable	TCZ (*n* = 29)	No TCZ (*n* = 386)	*P* value	TCZ (*n* = 29)	No-TCZ (*n* = 29)	*P* value
Age: Median (IQR)	59 (52.5–60.25)	51 (44–57)	0.0001	59 (52.5–60.25)	57 (51.75–63.25)	0.9
Gender: Male (n, %)	21 (72.4%)	262 (67.9%)	0.6	21 (72.4%)	20 (69%)	0.8
SOFA score Median (IQR)	4 (4–5)	4 (4–5)	0.4	4 (4–5)	4 (4–4.25)	0.2
BMI Median (IQR)	27 (23.3–31.2)	25.8 (22.6–29.4)	0.2	27 (23.3–31.2)	25.3 (21.85–28.63)	0.1
Smoking (n, %)	10 (34.5%)	131 (33.9%)	0.9	10 (34.5%)	9 (31%)	0.8
CRP (mg/dl) Median (IQR)	112.1 (106.7–119.4)	115.1 (106.2–124.3)	0.4	112.1 (106.7–119.4)	112.2 (105.8–119.9)	0.8
Anti-viral (n, %)	11 (37.9%)	154 (39.9%)	0.8	11 (37.9%)	12 (41.4%)	0.8
Steroids (n, %)	17 (58.6%)	245 (63.5%)	0.6	17 (58.6%)	16 (55.2%)	0.8

TCZ = Tocilizumab, IQR = interquartile range, SOFA = Sequential organ failure assessment, BMI = body mass index, CRP = C-reactive protein. Unmatched groups had differences in age. No differences between matched groups. All comparisons by Wilcoxon Rank-SUM test for continuous data except for CRP, and Chi^2 test for discrete data.

testing. The commercially available software STATA® was used for analysis (StataCorp. 2017. *Stata Statistical Software: Release 15*. College Station, TX: StataCorp LLC).

Results

During the study period, 742 patients positive of SARS-CoV-2 were admitted to the ICU, of whom 467 were intubated and mechanically ventilated upon ICU admission. We further excluded another 52 patients (46 less than 18 years of age, 2 pregnant women, 3 with known pulmonary tuberculosis, and 1 known HIV case). We screened the remaining 415 patients and identified 29 patients who received at least one dose of TCZ according to our ICU protocol; these 29 patients comprised the intervention group. Of the 386 patients who did not receive TCZ, we matched 29 patients to constitute the control group through the previously described propensity score matching method (Fig. 1), all of whom were diagnosed with SARS-CoV-2 for the first time, and none were admitted to the ICU. Comparison of the demographic and clinical management characteristics of the intervention group to the unmatched group of mechanically ventilated patients showed imbalances only in age, being significantly lower in the unmatched group, which was corrected after propensity score matching, and the intervention and control groups showed no statistically significant differences (Table 1).

The primary outcome of our study was the SHR of being alive and extubated at 28 days as the outcome of interest. In terms of the competing risk of death or still intubated at 28 days, our analysis revealed that receiving TCZ results in a statistically significant SHR of 2.7 (95% CI: 1.2–6.3; $p = 0.02$), which means that it increased the proportional "hazard" of being alive and extubated at day 28 by 170% compared to patients who did not receive TCZ. The term "hazard" is a technical term that is interpreted as an increased chance. Our sensitivity analysis in the form of Cox regression supports our findings; the HR of the Cox regression model (for the hazard of death) was 0.49 (95% CI: 0.25–0.97; log rank $p = 0.04$). In agreement with the primary outcome, the results of Cox regression indicated that receiving TCZ reduced the relative hazard of death by 51% (Table 2). The Kaplan–Meier survival curves of both groups are depicted in Fig. 2.

The secondary outcomes show that 11 (37.9%) patients in the TCZ group died within 28 days, while 18 patients (62%) in the control group died within the same period; although numerically lower, the difference in mortality rate between groups was not statistically significant (95% CI of difference: −3.9% to 48.5%; $p = 0.1$). All occurrences of death occurred in the ICU, and none of the patients was spontaneously breathing at the time of death. We recorded similar results for the subgroup analysis of ICU mortality of patients on steroids. The aVFD, however, was statistically higher in the TCZ group; the median (IQR) of aVFD in the TCZ group was 10 (0–13) compared to 0 (0–2.25) in the control group (mean difference 4.7, 95% CI of difference:1.1–8.3; $p = 0.02$). In the TCZ group, 16 patients (55.2%) had positive cultures during the study period, whereas only 10 patients (34.5%) in the control group had positive cultures. The higher rate in the TCZ group was not statistically significant (95% CI of difference: -7.11% to 45.4%; $p = 0.1$). Table 3 presents the results of secondary outcomes.

Table 2
Results of competing risk analysis, and Cox proportional regression.

	Sample statistic (95% CI)	P value
Competing Risk Regression	SHR: 2.7 (1.2–6.3)	0.02
Cox Proportional Hazard	HR: 0.49 (0.25–0.97)	0.04

Competing risk regression: Event of interest is alive and extubated at day 28, competing risk is death or still intubated at day 28. Cox proportional hazard for the risk of death.

Discussion

The primary outcome in this analysis was the composite outcome VFD on day 28, which encompasses both the duration of mechanical ventilation and mortality. Our competing risk analysis indicates that those receiving TCZ had a significantly higher chance of being alive and extubated at day 28 than those who did not receive TCZ. The components of the composite outcome showed significantly higher aVFD and a trend of reduced mortality in general and for the subgroup of patients on steroids without an increase in positive cultures. Sensitivity analysis supported the primary outcome, showing a better survival rate in the intervention group.

This type of composite outcome is common in trials of ARDS in critically ill patients[19–21] owing to several advantages; for example, it penalizes mortality, making it a plausible trial endpoint, while including the continuous variable of ventilator days adds to statistical power, in addition to being realistic, since a single intervention in ARDS is unlikely to impact mortality. However, it may shorten the duration of ventilation if it improves the lung condition, because, as is the case in SARS-CoV-2 infection, ARDS is heterogeneous and mortality is usually multifactorial.[15]

Very few studies[14] performed competing risk analysis on similar patients, and the study by Mohzari et al demonstrated the potential benefit of TCZ in successful extubation of critically ill patients with SARS-CoV-2 infection, while lacking a statistically significant mortality benefit. The evidence from both studies may be regarded collectively in view of the similarities in the analysis; however, our study may have a stronger indication of extubation benefit since the competing risk was continuation of mechanical ventilation, whereas it was death on mechanical ventilation in Mohzari et al's study. This means that our analysis penalized extubation failure even if the patient was still alive. Another reason to examine the results of both studies collectively is that some of our patients may have been included in Mohzari et al's study; however, we cannot be sure of their

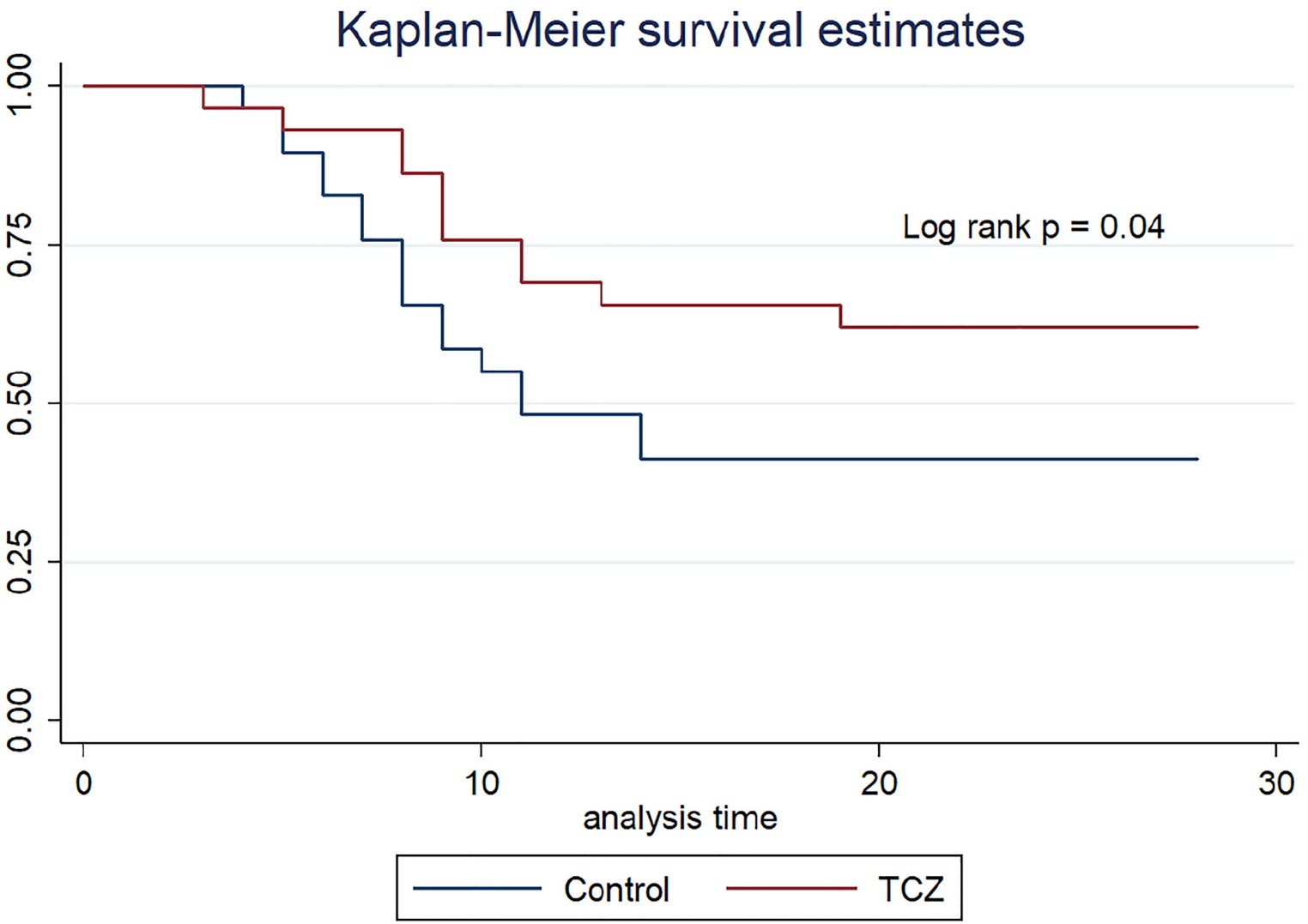

Fig. 2. Kaplan Meier survival curve: Survival of patients in both groups up to 28 days, evaluated by Log – Rank test showing significant difference ($p = 0.04$).

Table 3
Results of secondary outcomes.

	TCZ (n = 29)	Control (n = 29)	95% CI of difference	P value
ICU mortality (n, %)	11 (37.9%)	18 (62%)	-3.9 to 48.5	0.1
Actual VFD: median (IQR)	10 (0–13)	0 (0–2.25)	1.1–8.3	0.02
Positive cultures (n, %)	16 (55.2%)	10 (34.5%)	-7.11 to 45.4	0.1
ICU mortality for patients on steroids (n, %)	4/17 (23.5%)	6/16 (37.5%)	-20.5 to 45.8	0.6

TCZ = Tocilizumab, CI = confidence interval, VFD = ventilator free days, IQR = interquartile range. All comparisons by Wilcoxon Rank-SUM test for continuous data, and Chi^2 test for discrete data.

exact number, as they randomly chose their patients. Nevertheless, Mohzari et al's study remains more powerful owing to the larger sample size and complex statistical analysis, and our study may serve as supporting evidence using a similar analytical technique.

Furthermore, several studies have demonstrated patterns similar to our findings, particularly with regard to the components of the primary outcome. A trend of lower mortality was shown by Klopfenstien et al[22] in a retrospective case-control study with a similar sample size; however, studies with larger sample sizes were able to demonstrate a statistically significant lower mortality rate for patients treated with TCZ,[23,24] which may imply a true clinical effect on mortality that we were not able to demonstrate statistically owing to lack of power. The significantly higher aVFD in the TCZ group in this study supports our intuition of improving lung condition, thus hastening extubation, which was also demonstrated by others.[25]

More recent randomized clinical trials (RCT) have also explored the outcome of ventilator-free days, although in different statistical models. In the REMAP-CAP[26] report of the immune module using Bayesian statistics, respiratory support-free days in the TCZ group had a significantly higher odds ratio than the control, with > 99.9% being superior to the control. In contrast, the mean and median ventilator days were not different between the TCZ and control groups in two other RCTs.[27,28]

The sensitivity analysis in our study seems to support the result of the primary outcome, and in concordance with numerous published articles with different designs, showing a statistically significant HR of survival in Cox regression, and significant log-rank p values for TCZ-treated patients.[5,23,24,29]

A higher rate of positive cultures in the TCZ group was expected owing to the immunomodulatory effect of TCZ; however, it did not reach the level of statistical significance. However, in studies with larger sample sizes, the higher rate of superinfection in the TCZ group was shown to be significant[24,29] in observational studies; RCTs, however, did not show a significant difference between groups in the rate of super-added infection.[27,28] It is not clear in the aforementioned studies and also not accounted for in our study whether those positive cultures were mere counts or actually indicated infection.

The role of TCZ in the management of SARS-CoV-2 has been studied extensively but on a wide spectrum of clinical presentations of the disease. Our results suggest a potential benefit in critically ill or mechanically ventilated patients; accordingly, we suggest further studies with a randomized controlled design in this specific population, with this specific composite outcome as the primary outcome, to ensure adequate power and sample size that may enable the capture of statistical significance. Although our study may not be novel in evaluating the potential role of TCZ in SARS-CoV-2 management, it adds to the compiling evidence of the hypothesized benefit of an infrequently used analytical method. Accordingly, we believe that in view of the evidence Tocilizumab may be considered as an option for the management of critically ill or mechanically ventilated patients.

Our study has several limitations, the first of which is the limitation inherent within its retrospective design and lack of prospective randomization, although propensity score matching partially compensated for this defect. Second, the small sample size in our study definitely renders it underpowered; thus, significant findings should be interpreted cautiously. The insignificant results in our study could also be due to the small sample size. Third, we did not follow the classical method of propensity score matching; however, this was for justifiable reasons, and the resultant matched groups were similar. The matching method, however, could have been better if we matched TCZ patients to controls in a 1:2 ratio, and we recognize the matching ratio of 1:1 as a limitation. Lastly, several details were overlooked in our study, such as the duration of symptoms before hospitalization, mechanical ventilation, and TCZ treatment, since the main focus of the study was the duration of mechanical ventilation itself and ICU outcome, which were published elsewhere,[14] in addition to the lack of differentiation between simple positive cultures and actual infections that required treatment.

Conclusion

Mechanically ventilated patients with SARS-CoV-2 infection treated with TCZ may have a better composite outcome of VFD. TCZ may be associated with significantly longer aVFD but insignificantly lower mortality and higher superinfection on day 28. TCZ treatment may also be associated with better 28-day survival. These findings need to be confirmed in larger prospective randomized trials.

Declaration of Competing Interest

Nothing to declare.

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