**Tocilizumab effectiveness in mechanically ventilated COVID-19 patients (T-MVC-19 Study): a multicenter real-world evidence**

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**ABSTRACT**

**Background:** This study aimed to evaluate the effectiveness of tocilizumab in mechanically ventilated patients with coronavirus disease 2019 (COVID-19).

**Research design and methods:** This retrospective multicenter study included adults (≥18 years) diagnosed with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) by real-time polymerase chain reaction (RT-PCR) from nasopharyngeal swab, and requiring invasive mechanical ventilation during admission. Survival analyses with inverse propensity score treatment weighting (IPTW) and propensity score matching (PSM) were conducted. To account for immortal bias, we used Cox proportional modeling with time-dependent covariances. Competing risk analysis was performed for the extubation endpoint.

**Results:** A total of 556 (tocilizumab = 193, control = 363) patients were included. Males constituted the majority of the participants (69.2% in tocilizumab arm, 74.1% in control arm). Tocilizumab was not associated with a reduction in mortality with hazard ratio (HR) = 0.82 (95% CI: 0.62–1.10) in the Inverse propensity score weighting (IPTW) analysis and (HR = 0.86 (95% CI: 0.64–1.16) in the PSM analysis. However, tocilizumab was associated with an increased rate of extubation (33.6%) compared to the control arm (11.9%); subdistributional hazards (SHR) = 3.1, 95% CI: 1.86–5.16.

**Conclusions:** Although tocilizumab was not found to be effective in reducing mortality, extubation rate while on mechanical ventilation was higher among tocilizumab treated group.

1. Introduction

In December 2019, a series of pneumonia cases secondary to severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and what is currently known as the novel coronavirus disease 2019 (COVID-19) were reported from Wuhan, China [1]. Owing to its nature of high and quick transmissibility, by March 11th, 2020, COVID-19 had become a pandemic disease [2,3]. As of June 2021, more than 180 million patients globally have been
infected with SARS-CoV-2 and 3.9 million deaths have been reported [4]. In Saudi Arabia, 480,000 confirmed COVID-19 cases in 100 cities were reported, of which 7,744 patients have died [5].

COVID-19 is characterized by fever, cough, fatigue, shortness of breath, pneumonia, and other respiratory tract symptoms [6,7]. However, the severity of the disease can range from mild flu-like symptoms to a devastating course of disease requiring respiratory support and Intensive Care Unit (ICU) admission [8]. The binding of the virus to the airway epithelial cells in COVID-19 patients results in the activation and up-regulation of the innate and adaptive immune response and releases a large number of cytokines, including Interleukin-6 (IL-6) [8,9]. A correlation between COVID-19 and levels of IL-6 has been reported [10,11], suggesting the possibility of repurposing IL-6 inhibitors in the management of severe COVID-19.

Tocilizumab, a recombinant humanized anti-IL-6 receptor monoclonal antibody, has been approved for the treatment of severe chimeric antigen receptor T cell-induced cytokine release syndrome [12]. Several studies have demonstrated the clinical benefit of tocilizumab in severe COVID-19 cases [13–18], though this has not been consistent [15,16]. In the RECOVERY trial, the allocation to tocilizumab was associated with a significant reduction in 28-day mortality compared with usual care alone in patients on non-mechanical ventilation [rate ratio (RR) = 0.85; 95% confidence interval (CI): 0.76–0.94; p = 0.003] but not in patients on invasive mechanical ventilation; [RR = 0.93. 95% CI, 0.74 – 1.18] [18]. More generally, studies were limited due to heterogeneity in study designs, small sample sizes, diversity of study populations, variations in disease severity spectrum, wide ranges of dose regimen, and its frequency, differences in timing of starting tocilizumab therapy, and limiting results to pooled crude unadjusted estimates.

A recent meta-analysis of 25 trials revealed an association of tocilizumab with a reduction in overall mortality [odds ratio (OR) = 0.70, 95% CI, 0.54–0.90, P = 0.007], and mechanical ventilation requirement [OR = 0.59, 95% CI, 0.37–0.93, P = 0.02] [19]. These studies were conducted in different countries including the United States, United Kingdom, Canada, Italy, and Spain, but none of these studies were conducted in Saudi Arabia or the Middle East. Additionally, the contradicting data challenge the decision-makers in determining optimal clinical practice for tocilizumab. In this study, we aimed to evaluate the effectiveness of tocilizumab in COVID-19 mechanically ventilated patients in daily clinical practice in Saudi Arabia at the height of the early pandemic.

2. Patients and methods

2.1. Study design and setting

This was a retrospective study conducted in six centers in three cities in Saudi Arabia: King Saud Medical City Hospital (KSMC) in Riyadh, King Fahad Medical City (KFMC) in Riyadh, King Saud University Medical Center (KSUMC) in Riyadh, Prince Mohammad bin Abdulaziz Hospital (PMAH) in Riyadh, King Faisal Specialist Hospital and Research Center (KFSH&RC) in Jeddah, and Almoosa Specialist Hospital in Al-Ahsa.

The study was approved by the following Institutional Review Board Committees (IRB) with waived informed consent: King Saud Medical City (IRB# H-01-R-053), Second Health Cluster Institutional Review Board (IRB# H-01-R-012), King Saud Medical University Institutional Review Board (IRB# E-20-5527) and Almoosa Specialist Hospital Institutional Review Board (IRB# ARC-20.10.2). We followed the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) Statement checklist in our report [20]. All methods were carried out in accordance with relevant guidelines and regulations.

2.2. Participant selection

We obtained lists of severely/critical ill COVID-19 patients or those who received tocilizumab treatment between March 2020 to January 2021. Through a random-selection process, we screened patients for eligibility. The random selection would minimize sampling bias and provide an equal opportunity for the patient’s record to be selected and coded [21]. Inclusion criteria were as follows: age ≥18 years, diagnosis of SARS-CoV-2 by real-time polymerase chain reaction (RT-PCR) from nasopharyngeal swab, and requiring invasive mechanical ventilation at admission. Patients were excluded if they were outside the study period, did not require mechanical ventilation, or received tocilizumab treatment for an indication other than COVID-19.

2.3. Tocilizumab dosing

Tocilizumab was dosed according to Saudi Ministry of health (MOH) protocols version 2.0 updated in June 2020. The adult dosing for tocilizumab was 4–8 mg/kg (usual dose 400 mg; maximum 800 mg) by IV infusion; repeated within 12 hours for a maximum of 2 doses [22].

2.4. Data collection

Data were manually extracted from electronic health records (EHRs) and then entered into the Research Electronic Data Capture (REDCap) system in a de-identified manner [23]. A trained team of data managers ensured the quality of data collection and resolved any discrepancies.

2.5. Objectives/study outcomes

The aim was to assess tocilizumab effectiveness in mechanically ventilated COVID-19 patients as compared to a control group that did not receive tocilizumab. The primary endpoint was mortality after mechanical ventilation (referred to here as overall mortality). The secondary endpoint was the rate of extubation. Subgroup analyses for the mortality outcome based on baseline characteristics were explored. We also explored the association between time of tocilizumab administration and mortality.
2.6. Sample size calculation

Assuming a – 10% risk difference in the overall mortality between the tocilizumab and control arms, a sample size of 489 (166 patients who received tocilizumab and 332 who were unexposed to tocilizumab with an estimated ratio of 1:2) assured a power of 80% after applying continuity correction. A significance level (α, type 1 error rate) of 5% was applied.

2.7. Statistical analysis

2.7.1. Statistical software used

We used R Core Team (2020) software (R Foundation for Statistical Computing, Version 4.0.1, Vienna, Austria. The following packages in the R interface were used to conduct the analyses: survival [24], ggplot2 [25], survminer [26], survey [27], mice [28], matchThem [29], cobalt [30], crrSC [31].

Descriptive statistics was used to present baseline characteristics. Continuous data were presented as means with standard deviations (±SD) and medians with interquartile ranges (IQRs). Student’s t-test or Mann–Whitney U test was used for between-arm comparison.

Categorical data were reported as frequencies and percentages and analyzed using either the Chi-square test for nxm tables or Fisher’s exact test for 2×2-table group comparisons. Missing data were determined to be missing at random (MAR) and handled by Multiple Imputation by Chained Equations (MICE) procedure with Nelson Aalen estimator [28,32]. We only considered variables that had <15% of their data missing. Fifty imputations were obtained for the missing value (5 imputed datasets with 10 iterations).

Due to the observational design and the presence of many confounders, we implemented propensity score-based methods to estimate the marginal treatment effect. First, we carried out the inverse propensity score treatment weighting (IPTW) procedure. In IPTW, propensity scores (probability of getting a treatment) were calculated from a multivariable logistic regression model that included all the covariates of interest. Correlation testing was conducted to avoid the inclusion of highly correlated variables in the models. Next, propensity scores were used to calculate weights based on Desai and Franklin formulas [33] using the average treatment effect among the treated (ATT) as the target estimand (i.e. the ‘ideal’ patients for tocilizumab treatment based on specific characteristics). Balance between arms was achieved by creating a pseudo-population in which treatment allocation was independent of the observed covariate. To handle extreme weights, we utilized weight trimming (truncation) and stabilization. Balance of the covariates was checked by standardized mean difference (SMD) and love plots. SMD values <0.2 indicated a good balance. Propensity scores distributions were illustrated by mirror diagrams. As weighting may inflate or deflate the sample size relative to the original population, therefore, a robust sandwich-type estimator for variance estimation was calculated using ‘survey’ package in R for the treatment effect estimates [34].

After weighting and using this package, we fitted an adjusted (weighted) Kaplan-Meier (KM) model to estimate the probability of survival after mechanical ventilation (time 0) in both arms. Events were censored if patients were discharged alive or were still intubated at the time of data collection. A log rank test that accounted for the weighted data was applied to detect differences in survival curves.

To estimate the relative treatment effect, a Cox proportional model was fitted on the weighted data with the arm as a single covariate using the ‘survey’ package for robust variance estimation. The estimate was subsequently pooled across the imputed datasets. Proportional hazard assumption was checked by Schoenfeld residuals plots and statistical testing.

2.7.2. Sensitivity analyses

2.7.2.1. Propensity score matching. Propensity scores matching (PSM) was performed to confirm the results from the IPTW analysis. Propensity scores were generated from the same logistic regression model used in the IPTW model, which included all variables of interest. We then used the nearest-neighbor matching within the imputed datasets approach (using Rubin’s rules) [35] and 1:2 ratio with a caliper of 0.2 [36] and no replacement. Adequate balance of the data was checked by SMD (<0.2 desirable). Visual diagnostics such as love plots for covariate balance and mirror plots for propensity score distributions were generated. Next, we fitted a KM model to the matched data to compare survival probabilities after mechanical ventilation. To test for the statistical difference in the survival curves, we performed a stratified log rank test [37]. For relative treatment effect, a Cox proportional hazard model was fitted using the matched dataset. To account for the paired nature of the data, we stratified on the matched pairs and a robust variance was estimated using the ‘survey’ package.

2.7.2.2. Immortal time bias. The study design may entail a potential immortal time bias. In randomized control trials, the time of treatment assignment and time 0 is aligned. This was not possible in our case as patients may have started tocilizumab treatment after a few days of mechanical ventilation (time 0). During this period, the patient must be alive to receive the treatment later (i.e. immortal bias). The person-days during which patients in the tocilizumab arm did not receive treatment should be accounted toward the untreated group. A Cox proportional hazard model with time dependency covariance was used to evaluate a possible immortal time bias. We performed these analyses with the propensity score-based procedures (IPTW and PSM).

2.7.2.3. Competing risk analysis. For the secondary outcome (extubation), we performed a competing risk analysis for death while on mechanical ventilation; specifically, patients who die while on mechanical ventilation cannot experience the extubation event. The cumulative incidence function (CIF) was estimated using a cluster Fine-Gray model to derive the subdistribution hazard ratio (SHR): the instantaneous risk of failure from an event in subjects who have not failed that type of an event [38]. In the case of the extubation outcome, a SHR>1 indicated a higher incidence probability of the event occurring in tocilizumab. Following the recommendation by Austin et al.,
we conducted the analysis on the matched dataset using the CrsSC package in R to account for the matched pairs [39]. The cause-specific hazard ratio (CSHR) was also estimated as part of the competing risk analysis as suggested by Latouche et al. by fitting Cox proportional models on the matched dataset [40]. Cause specific hazards refers to the instantaneous rate of the outcome of interest in subjects who are event-free. In the case of extubation outcome, a cause specific hazard ratio (CSHR) values of >1 meant a relative increase in the instantaneous rates of extubation rates favoring the tocilizumab arm. The CIF was plotted for each arm and competing risk.

2.7.2.4. Additional analyses. We investigated the association between the time of tocilizumab administration and overall mortality. Using both propensity score approaches (IPTW and PSM), a logistic regression model was fitted that included time of administration as a covariate (prior mechanical ventilation, or within 48 hours and >48 hours of mechanical ventilation) versus control as a reference. We also conducted subgroup analyses to examine the baseline characteristics as treatment effect modifiers of overall mortality using the matched dataset.

3. Results
A total of 899 patients were screened for inclusion eligibility (Figure 1). We excluded 334 patients for various reasons, the most common one was not being on mechanical ventilation at admission (n = 231). We included 193 patients in the tocilizumab and 363 patients in the control arm.

Overall, there were no differences in the baseline characteristics of age, gender, weight, body mass index (BMI), kidney function and comorbid conditions such as hypertension, diabetes, cardiovascular disease. However, differences were observed in terms of ethnicity (P = 0.044); solid organ transplant (P = 0.025); medication used in the hospital prior to ICU admission such as favipiravir (P < 0.001), hydroxychloroquine (<0.001), therapeutic anticoagulation (<0.001), and convalescent plasma therapy (P < 0.001). More patients in the tocilizumab arm had a fever at the time of intubation (P = 0.030) and presented with a lower median partial oxygen pressure to fractional inspired oxygen (paO2/Fio2) ratio (71.1 versus 102.0 in the control arm). Arms also differed in terms of the following laboratory variables: albumin, aspartate aminotransferase, lactate dehydrogenase, ferritin, sodium, potassium, and magnesium. Variables with the highest missing data were alkaline phosphatase (35%) and erythrocyte sedimentation rate (41.2%) (see Table 1 footnote)

The IPTW and PSM mirror plots for propensity score distribution were presented in Figures S1 and S2 and the Love plots for covariate balance for both IPTW and PSM in Figure S3 and Table S1, all showing adequate balance. Of the patients in the tocilizumab arm, 21.2% of received the treatment within

![Flowchart](https://via.placeholder.com/150)

**Figure 1.** Patients selection flowchart.

COVID-19: coronavirus disease 2019. RT-PCR: real-time polymerase chain reaction.
Table 1. Baseline characteristics.

| Characteristic                        | Tocilizumab (n = 193) | Control (n = 363) | P value |
|---------------------------------------|-----------------------|-------------------|---------|
| Age, mean (±SD)                       | 59.3 (14.2)           | 58.5 (13.7)       | 0.515   |
| Female, n (%)                         | 61 (30.8)             | 91 (25.1)         | 0.143   |
| Ethnicity, n (%)                      |                       |                   | 0.044   |
|  Middle Eastern                       | 137 (69.2)            | 230 (63.4)        |         |
|  East/Southeast Asian                 | 14 (7.1)              | 15 (4.1)          |         |
|  South Asian                          | 39 (19.7)             | 86 (23.7)         |         |
|  African                              | 5 (2.5)               | 28 (7.7)          |         |
|  Unknown/other                        | 3 (1.5)               | 4 (1.1)           |         |
| Weight (kg), median (IQR)             | 80.0 (70.0–95.0)      | 80.0 (70.0–92.0)  | 0.514   |
| BMI (kg/m²), median (IQR)             | 29.4 (26.0–34.3)      | 29.1 (25.0–33.2)  | 0.059   |
| Scr (mg/dl), median (IQR)             | 0.98 (0.76–1.62)      | 1.04 (0.77–1.81)  | 0.314   |
| CKD-EPI (mL/min/m²), median (IQR)     | 77.7 (42.1–98.9)      | 75.3 (37.9–97.8)  | 0.539   |
| CKD stage, n (%)                      |                       |                   | 0.884   |
|  Normal/Stage1                        | 75 (37.9)             | 123 (33.9)        |         |
|  Stage 2                              | 49 (24.7)             | 92 (25.3)         |         |
|  Stage 3A                             | 20 (10.1)             | 37 (10.2)         |         |
|  Stage 3B                            | 16 (8.1)              | 30 (8.3)          |         |
|  Stage 4                              | 24 (12.1)             | 39 (10.7)         |         |
|  Stage 5                              | 14 (7.1)              | 35 (9.6)          |         |
|  Keeping                              | 0 (0.0)               | 7 (1.9)           |         |
| Respiratory diseases, n (%)           | 18 (9.1)              | 43 (11.8)         | 0.316   |
| Established cardiovascular diseases, n (%) | 21 (10.6)           | 45 (12.4)         | 0.529   |
| Atrial fibrillation, n (%)            | 6 (3.0)               | 10 (2.8)          | 0.851   |
| History of VTE, n (%)                 | 3 (1.5)               | 5 (1.4)           | 1.000   |
| Type 1 or 2 Diabetes, n (%)           | 107 (54.0)            | 207 (57.0)        | 0.496   |
| Hypertension, n (%)                   | 117 (59.1)            | 196 (54.0)        | 0.245   |
| Dyslipidemia, n (%)                   | 12 (6.1)              | 34 (9.4)          | 0.172   |
| Liver disease, n (%)                  | 3 (1.5)               | 6 (1.7)           | 1.000   |
| History of cancer, n (%)              | 7 (3.5)               | 7 (3.5)           | 0.243   |
| Solid organ transplant, n (%)         | 6 (3.0)               | 2 (0.6)           | 0.025   |
| HIV, n (%)                            | 1 (0.5)               | 0 (0.0)           | 0.352   |
| ECMO, n (%)                           | 4 (2.0)               | 13 (3.6)          | 0.440   |
| Time of mechanical ventilation relative to admission, n (%) | 45 (22.7) | 77 (21.2) | 0.122 |
|  <24 hours                            | 45 (22.7)             | 77 (21.2)         |         |
|  24–48 hours                          | 29 (14.6)             | 66 (18.2)         |         |
|  >48 hours                            | 118 (59.6)            | 194 (53.4)        |         |
| Outside transfer on mechanical ventilation | 6 (3.0)      | 26 (7.2)          |         |

Medication use during hospitalization, n (%) |
| ACEI or ARB                             | 31 (15.7)             | 63 (17.4)         | 0.607   |
| Statins                                | 72 (36.4)             | 102 (28.1)        | 0.043   |
| Azithromycin                           | 142 (71.7)            | 279 (76.9)        | 0.178   |
| Faviopiravir                            | 103 (52.0)            | 60 (16.5)         | <0.001  |
| Hydroxychloroquine                     | 20 (10.1)             | 14 (3.9)          | 0.003   |
| Lopinavir/Ritonavir                    | 16 (8.1)              | 31 (8.5)          | 0.851   |
| Ribavirin                              | 14 (7.1)              | 24 (6.6)          | 0.836   |
| Interferon B                           | 9 (4.5)               | 18 (5.0)          | 0.827   |
| Steroid                                | 192 (97.0)            | 347 (95.6)        | 0.421   |
| Vitamin C                              | 102 (51.5)            | 203 (55.9)        | 0.316   |
| Thiamine                               | 45 (22.7)             | 172 (47.4)        | <0.001  |
| Vitamin D                              | 126 (63.6)            | 228 (62.8)        | 0.846   |

(Continued)
48 hours and 25.7% received the treatment after 48 hours of mechanical ventilation. Proportionately more patients (60.6%) received two doses of tocilizumab with a median dose of 8 mg/kg/day (Table S2).

3.1. Overall mortality outcome

The overall death rate in the control arm (81.1%) was higher compared to the tocilizumab arm (62.6%). The IPTW analysis examining the two adjusted survival curves showed a difference in the absolute effect (log rank test, \( P = 0.033 \); Figure 2a). As for the relative treatment effect, tocilizumab was associated with a lower incidence of mortality with HR = 0.73 (95% CI 0.55–0.96, \( P = 0.026 \)). However, the PSM analyses did not confirm the IPTW results. No differences between the survival curves (Figure 2b, stratified log rank test \( P = 0.900 \)) and in the relative treatment effects was observed (HR = 0.80, 95% CI 0.57–1.12, \( P = 0.192 \)). When accounting for immortal time bias with Cox time dependent covariance, both the IPTW (HR = 0.82, 95% CI 0.62–1.10, \( P = 0.190 \)) and the PSM (HR = 0.86, 95% CI of 0.64–1.16, \( P = 0.349 \)) analyses showed no difference in overall mortality between the two arms (Table 2; Figure 3).

3.2. Competing risk analysis

A higher percentage of patients experienced extubation in the tocilizumab arm (33.6%) versus the control arm (11.9%). When compared to the control, the CSHR for the extubation outcome for tocilizumab was 2.72 (95% CI 1.56–4.76, \( P < 0.001 \)) and the subdistribution hazard ratio (SHR) was 3.1 (95% CI 1.86–5.16, \( P < 0.001 \)) from the Fine-Gray model. Whereas there was no significant result for death on the mechanical ventilation outcome with CSHR of 0.98 (95% CI 0.70–1.38, \( P = 0.927 \)) but a significant result for the Fine-Gray model with a SHR of 0.68 (95% CI 0.51–0.901, \( P = 0.007 \)). The results of the competing risk analysis were presented in Table 3 and the cumulative incidence function visualized in Figure 2c.

3.3. Subgroup analysis results

No association between the time of tocilizumab administration and overall mortality was found (Table S3). The subgroup analyses for effect modifiers based on baseline characteristics showed interaction effects only for chronic kidney disease stage, angiotensin converting enzyme inhibitor (ACEIs) or angiotensin receptor blocker use (ARBs), and Pao2/Fio2 ratio (>100 versus <100), but not for any other variables (see Figure S4).

4. Discussion

Therapeutic management of COVID-19 is evolving and expanding, with several treatments having been approved, mainly under the emergency use authorization provision (EUA) [41–43]. Among them, only dexamethasone and tocilizumab have shown survival benefits, yet not consistently so across disease spectrums nor across studies [6,44–46]. The association between cytokine release syndrome and COVID-19 severity sparked an interest in the three available anti-IL-6 monoclonal antibodies (tocilizumab, sarilumab, and siltuximab) [47,48]. Of these, tocilizumab has received the most interest due to its availability and the experience gained since its approval in 2008 [49]. Considering the accumulated evidence, tocilizumab was authorized for the treatment of COVID-19 in a special patient population and has been incorporated in the treatment guidelines, including for patients with rapid respiratory decompensation [22]. Our study differs from prior published studies in that it included only mechanically intubated and examined whether tocilizumab is effective in reducing mortality and increasing ventilator independence (extubation) compared to standard care. Although both the IPTW and PSM analyses showed that tocilizumab was effective in reducing mortality, this statistical significance was lost when we accounted for immortal time bias. These findings are in

| Table 2. Overall mortality outcome after mechanical ventilation. |
|---------------------------------------------------------------|
| Analysis | Propensity Score Weighting (Trimmed IPTW ATT) | Propensity Score matching |
| **Overall deaths, n (%)** | 122 (62.6) vs 269 (81.1) | 82 (59.9) vs 125 (72.2) |
| **Adjusted log-rank test/statrafied log-rank test†** | 0.033 | 0.900 |
| **Overall Mortality, HR (95%CI)†** | 0.73 (0.55–0.96, \( P = 0.026 \)) | 0.80 (0.57–1.12, \( P = 0.192 \)) |
| **Overall mortality when accounting for immortal bias, HR (95%CI)†** | 0.82 (0.62–1.10, \( P = 0.190 \)) | 0.86 (0.64–1.16, \( P = 0.349 \)) |
| IPTW: Inverse propensity score weighting. |
| ATT: Average treatment effect on the treated |
| PSM: Propensity score matching |
| CI: Confidence interval |
| HR: Hazard ratio |
| † Survey package (svykm function) used to estimate the survival function with weighted Kaplan-Meier estimator (adjusted curves). For the stratified log-rank test, we performed the analysis on the matched dataset stratifying on the matched pairs. |
| † Extended cox time dependency models that accounted for immortal bias by using \( T_{\text{merge}} \) function in the survival package. |

| Table 3. Competing risk analysis for the clinical outcomes. |
|-------------------------------------------------------------|
| **Crude outcomes** | Tocilizumab (\( n = 137 \)) vs control (\( n = 176 \)) |
| Extubation events, n (%) | 46 (33.6) vs 21 (11.9) |
| Death on MV, n (%) | 79 (57.7) vs 122 (69.3) |
| **Cause specific hazard regression model** | |
| Extubation, CSHR (95%CI), P value | 2.72 (1.56–4.76, \( P < 0.001 \)) |
| Death on MV, CSHR (95%CI), P value | 0.98 (0.70–1.38, \( P = 0.927 \)) |
| **Fine-Gray model †** | |
| Extubation, SHR (95%CI), P value | 3.1 (1.86–5.16, \( P < 0.001 \)) |
| Death on MV, SHR (95%CI), P value | 0.68 (0.51 to 0.90, \( P = 0.007 \)) |
| All analyses were conducted on the matched dataset. |
| † Competing risk analysis conducted using Fine-Gray model on the matched dataset using crrSC package to account for the matched pairs. |
| MV: Mechanical Ventilation |
| CSHR: Cause specific hazard ratio |
| SHR: Subdistribution hazard ratio |
concordance with several recent studies [18,46,50–52]. Conversely, in a study in mechanically intubated COVID-19 patients, Somers and colleagues found that exposure to tocilizumab was associated with a reduction in mortality by 45% [53]. However, more than 40% of patients in the tocilizumab arm were treated 24 hours after intubation, which may have introduced a misclassification bias [54]. Similar to our study, the authors balanced the tocilizumab and control groups using IPTW [53]. In other studies with analyses similar to ours, neither steroids nor PaO2/FiO2 were included in the propensity score model [55]; or patients who died before receiving tocilizumab were excluded, thus possibly inducing selection bias [54]. Further, and although their study was not restricted to mechanically ventilated patients, Biran and colleagues [56] observed that tocilizumab was associated with a reduction in mortality by 29%. Here too, the mortality benefit was lost after adjusting for immortal time bias. A recent meta-analysis published by the World Health Organization (WHO) Rapid Evidence Appraisal for COVID-19 Therapies (REACT) Working Group aimed to synthesize the evidence on

![Kaplan Meier curves for overall mortality](image)

**Figure 2.** Kaplan Meier curves for overall mortality. (a) Inverse propensity score treatment weighting. (b) Propensity score matching. (c) Cumulative incidence function for the competing risks while on mechanical ventilation.

![Forest plot](image)

**Figure 3.** Forest plot of hazard ratios with their corresponding 95% confidence interval obtained from the conducted analyses.

IPTW: Inverse propensity score treatment weighting. PSM: Propensity score matching. HR: Hazard ratio.
IL-6 inhibitors exposure and mortality [57]. While the overall analysis showed that IL-6 inhibitors were associated with reduction in mortality, the subgroup analysis of mechanically ventilated patients didn’t favor IL-6 inhibitors when compared to control.

The absence of an unequivocal mortality benefit in our study may be explained by two factors. First, initiating an immunomodulator at a later stage of the cytokine release syndrome may be less effective than initiating it at an earlier stage. The mortality benefit observed with tocilizumab was observed mainly in patients with moderate to severe COVID-19 who did not require mechanical ventilation [56,58–61]. Russell and colleagues in a multicenter retrospective study comparing early (prior to or within 24 hours of intubation) versus late tocilizumab (more than 24 hours after intubation) administration, found that early administration was associated with a 85% reduction in mortality when compared to no tocilizumab [62]. In addition to the small sample size, it is worth noting that the matching model included only a few variables, which could have decreased the precision of the exposure effect [63,64]. In our study, the majority (72%) received tocilizumab within 48 hours of intubation (Table S2) with no differences in mortality regardless of the timing of administration (Table S3). Though subject to further investigation in a randomized controlled trial, because of its larger sample size and the rigorous differentiated statistical analyses, our study provides initial evidence of no mortality benefit with early tocilizumab administration. Second, despite the evidence of IL-6 as a proinflammatory cytokine involved in cytokine release syndrome, other proinflammatory cytokines may also be involved and might mediate or moderate outcomes in worsening COVID-19 patients [48]. The potential benefit of using other immunomodulators against these cytokines should be examined under controlled conditions as well as in the setting of daily clinical practice.

With regard to our results related to the extubation rate, we performed a competing risk analysis to account for events that might compete with this secondary study outcome (i.e. death on mechanical ventilation). The addition of tocilizumab reduced the hazard of COVID-19 patients to remain intubated by 172% (CSHR: 2.72). Our findings differ from those of a retrospective study by Fisher and colleagues in which the extubation rate in tocilizumab arm was similar to that in the control arm (OR 1.53; 95% CI, 0.71 – 3.30) [52]. An important difference in our study is that patients treated with tocilizumab received more concurrent medications (notably, favipiravir and convalescent plasma) compared to those in the study by Fisher and colleagues. Despite the equivocal results on the primary outcome of interest, our study underscores the importance of a number of methodological and analytical issues that need to be addressed, especially in critical care studies. One is the importance of sensitivity analyses. Our IPTW analysis on the primary outcome was subjected to a sensitivity analysis using PSM – which, in fact, failed to confirm the IPTW results. This discrepancy could be attributed to several factors. The IPTW analysis included more observations compared to the PSM analysis. It yielded a much narrower 95% CI and therefore greater precision of the estimate. It is also possible that the IPTW analysis may have been prone to model misspecification compared to PSM model. However, covariate balance diagnostics showed that all variables in IPTW analysis had adequate balance as indicated by the SMD, yet that the PSM model had less bias for the overall distance.

Further, we accounted for immortal time bias by counting the person-days where no treatment was received in the tocilizumab group toward the untreated group using Cox time dependent covariance. Here, neither the IPTW nor the PSM analyses found a difference in the overall mortality. Immortal bias is an analytical procedure common in observational studies [65]. It refers to a period of time in which patients must be alive to receive the treatment. If our study were a randomized control trial, the time of tocilizumab administration (i.e. treatment allocation) should be aligned with the mechanical ventilation (day 0) to avoid misclassification of the exposure. However, in observational studies, patients may start their treatment at different time points after day 0. Consider, for instance, the scenario where time 0 for the tocilizumab group is when treatment is started and time 0 for the control group is the time of starting mechanical ventilation. Excluding immortal time induces selection bias in that person days that should have been counted as untreated are excluded, shortening the person days for the untreated, and thus biasing the estimate. To avoid the ensuing misclassification of the exposure, treatment should be considered a time-dependent rather than a fixed-time covariate to ensure that all person days will be correctly counted toward the treated or untreated arms [54]. Our decision to control for immortal time bias is underscored by a study by Shinati et al. in mechanically ventilated ICU patients. Fixed time analysis yielded a strong association of ICU length stay and delirium but this association was not found when considering delirium as a time dependent covariate.

A competing risk analysis was conducted for our secondary extubation outcome. Koller and colleagues reviewed 50 publications in high-impact journals and reported that 70% of these publications were susceptible to competing risk problems [66]. Competing risks occur when the occurrence of an event may prevent the occurrence of the primary event of interest [38]. In critical care settings, the extubation endpoint, while an important marker of patient improvement, may also be affected by rapidly changing changes in status due to new events occurring that are unrelated to the treatments of interest. Further, there is a common misconception that hazard ratios derived from competing risk models convey the same information (Fine-Gray Model versus Cause-specific hazard (CSH) model); while, in fact, this is not the case. The CSH model evaluates a binary event of interest over time, considers all other events as non-relevant, therefore censors these events, and thus violates the assumption of non-informative censoring. When there are no competing risks, the survival function can be linked directly with the hazard function and the CIF can be calculated as ‘one minus survival function.’ However, in the case of competing risks, there is no direct one-to-one link between survival and hazard function. Therefore, a naïve KM estimator will be larger than an
estimator that accounts for other competing risks. To estimate the impact of covariate of interest on CIF in the presence of competing risks, the use of Fine-Gray models is recommended [38,67]. In our CSH analysis, the extubation rate was much higher in the tocilizumab arm. Likewise, the probability of event occurrence was also higher in our Fine-Gray model. However, the event of death on mechanical ventilation had a statistical non-significant CSHR result but a statistically significant SHR result. One interpretation, though an erroneous one, would be that patients treated with tocilizumab treatment have a lower probability of death while on mechanical ventilation. There was indeed a seemingly greater impact of extubation events on the CIF, which in turn had an indirect impact on the CIF for the competing risk outcome of death on mechanical ventilation. This made it appear that tocilizumab had an exclusive protective effect against death while on mechanical ventilation (MV) – when, in fact, extubated patients cannot experience death while on MV. That is why Latouche and colleagues recommend to report both CSH and Fine-Gray models side by side for competing risk analysis. This allows transparency and facilitates interpretation of the results [40]. One caveat for using Fine-Gray models is that statistical methods accounting for time varying covariance are not well established yet and need further research [68].

Our study has some limitations. It was observational and may have included potential confounders. Hence our decision to apply two propensity score methods to control for bias reduced unmeasured confounding [69]. Although we included many variables in our propensity score models, variables that predict ICU mortality such as the Sequential Organ Failure Assessment (SOFA) or the Acute Physiologic Assessment and Chronic Health Evaluation II (APACHEII) scores were not available in or calculable from the medical records. Having these aggregate metrics available, as opposed to using the individual components of these scores (in as far as available, as we did), places the propensity score models at risk of overfitting. The competing risk analysis did not consider immortal time bias as the inclusion of time-dependent variables in Fine-Gray models is less established and is an area of ongoing statistical research. The recent evidence suggests that clinical improvement or reduction in mortality following exposure to tocilizumab could be seen in patients with elevated IL-6 levels [70,71]. In our institutions, IL-6 levels were not readily available; however, the following biomarkers were measured: ferritin, c-reactive protein (CRP), and D-Dimer (Table 1). Importantly, CRP levels are predictive of IL-6 mediated disease severity [72,73], hence absence of IL-6 levels should not adversely impact the findings of our study. As shown in figure S4 subgroup analysis, we found no interaction in patients with CRP (mg/dl) ≥75 or <75. Additionally, and per MOH COVID-19 treatment guidelines, one or more of the aforementioned biomarkers could be used to predict cytokine syndrome and thus indication for tocilizumab [74].

5. Conclusions
This current study suggests that tocilizumab was not effective in reducing mortality. After accounting for immortal time bias, there were no differences between IPTW and PSM in terms of the absolute effect. However, extubation rate while on mechanical ventilation was higher among tocilizumab-treated patients, indicating a possible benefit in this patient population. A randomized controlled trial evaluating tocilizumab against standard of care in critically ill mechanically ventilated patients is needed.

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Authors Contributions
Conceptualization was by Y.A.M; A.A (Ahmad Alamer); A.A.A (Ahmed A Alrashed); A.S.A Statistics, methodology, software and interpretation of the results was done by A.A (Ahmad Alamer). Consultation on statistics was provided by I.A. The first draft of the paper was done by A.A, Y.A.M., and D.A. Abstract was drafted by N.A and. All named authors meet the International Committee of Medical Journal Editors (ICMJE) criteria for authorship for this article, declare their responsibility for the integrity of the work as a whole, and have given their approval for this version to be published.

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References
Papers of special note have been highlighted as either of interest (+) or of considerable interest (+++) to readers.

1. Guan W, Ni Z, and Hu Y, et al. Clinical characteristics of coronavirus disease 2019 in China. N Engl J Med. 2020 Feb 28;382(18):1708-1720.* A good article on the clinical presentation of COVID-19 patients.
2. World Health Organization: Coronavirus Disease 2019 (COVID-19) situation report - 66 [Internet]. World Health Organization; 2020 [cited 2021 Aug 06]. Available from: https://www.who.int/docs/
default-source-coronavirus-situation-reports/20200326-sitrep-66-covid-19.pdf?sfvrsn=81b946e1_2
3. World Health Organization: WHO coronavirus disease (COVID-19) dashboard [Internet]. World Health Organization; 2020 [updated 2021 Dec 10; cited 2021 Aug 06]. Available from: https://covid19.who.int/
4. Macedo A, Gonçalves N, Febara C. COVID-19 fatality rates in hospitalized patients: systematic review and meta-analysis. Ann Epidemiol. 2021 May 1;57:14–21.
5. Yang X, Yu Y, Xu J, et al. Clinical course and outcomes of critically ill patients with SARS-CoV-2 pneumonia in Wuhan, China: a single-centered, retrospective, observational study. Lancet Respir Med. 2020 May 1;8(5):475–481.
6. Chen C, Hu F, Wei J, et al. Systematic review and meta-analysis of tocilizumab in persons with coronavirus disease-2019 (COVID-19). Leuk. 2021 [2021 May 17];35(6):1661–1670.
7. Wang D, Hu B, Hu C, et al. Clinical characteristics of 138 hospitalized patients with 2019 novel coronavirus–infected pneumonia in Wuhan, China. JAMA. 2020 Mar 17;323(11):1061–1069.
8. Al-Dahdah O. Novel Coronavirus HC (COVID-19): a global pandemic. Knee. 2020 Mar 1;27(2):270.
9. Channappanavar R, Perlman S. Pathogenic human coronavirus infections: causes and consequences of cytokine storm and immunopathology. Semin Immunopathol. 2017 2017 May 2;39(5):529–539.
10. Giamarellos-Bourboulis EJ, Netea MG, Rovina N, et al. Complex immune dysregulation in COVID-19 patients with severe respiratory failure. Cell Host Microbe. 2020 Jun 10;27(6):992–1000.e3.
11. Vardhana SA, Wolchok JD. The many faces of the anti-COVID immune response. J Exp Med. 2020;217:6.
12. Xiao-Shan W, Xiao-Rong W, Jian-Chu Z, et al. A cluster of health care workers with COVID-19 pneumonia caused by SARS-CoV-2. J Microbiol Infect Dis. 2021 Feb 1;54(1):54–60.
13. Xiaoling X, Mingfeng H, Tianlan L, et al. Effective treatment of severe COVID-19 patients with tocilizumab. Proc Natl Acad Sci U S A. 2020 May 19;117(20):10970–10975.
14. Shao-Huan L, Chih-Cheng L, and Hui-Ting H, et al. Tocilizumab for severe COVID-19: a systematic review and meta-analysis. Int J Antimicrob Agents. 2020 Sep 1;56(3):106103.
15. Tleyleh IM, Kashour Z, Damlaj M, et al. Efficacy and safety of tocilizumab in COVID-19 patients: a living systematic review and meta-analysis. Clin Microbiol Infect. 2021 Feb 1;27(2):215–227.
16. Aziz M, Haghbin H, Sitta EA, et al. Efficacy of tocilizumab in COVID-19: a systematic review and meta-analysis. J Med Virol. 2021 Mar 1;93(3):1620–1630.
17. Malgie J, Schoones JW, Pijs BG. Decreased mortality in coronavirus disease 2019 patients treated with Tocilizumab: a rapid systematic review and meta-analysis of observational studies. Clin Infect Dis. 2021 Jun 1;72(11):E742–9.
18. Abani O, Abbas A, Abbas F, et al. Tocilizumab in patients admitted to hospital with COVID-19 (RECOVERY): a randomised, controlled, open-label, platform trial. Lancet. 2021 May 1;397(10285):1637–1645.
19. Qiu W, Hua L, Rong-Guo W, et al. Tocilizumab treatment for COVID-19 patients: a systematic review and meta-analysis. Infect Dis Poverty. 2021 [2021 May 18];10(1):1–17.
20. von Elm E, Altman DG, Egger M, et al. The strengthening the reporting of observational studies in epidemiology (STROBE) statement: guidelines for reporting observational studies. In Equator network. 2020.
21. Vassar M, Holzmann M. The retrospective chart review: important methodological considerations. J Educ Eval Health Prof. 2013 Nov;30(10):12.
22. Saudi Ministry of Health: Saudi MoH Protocol for supportive care and antiviral treatment of suspected or confirmed COVID-19 infection (Version 3.1) [Internet]. Saudi Arabia: Saudi Ministry of Health; 2021 [cited 2021 Aug 26]. Available from: https://www.moh.gov.sa/Ministry/MediaCenter/Publications/Documents/MOH-therapeutic-protocol-for-COVID-19.pdf.
23. Harris PA, Taylor R, Minor BL, et al. The REDCap consortium: building an international community of software platform partners. J Biomed Inform. 2019 Jul 1;95:103208.
24. Springer Link: Modeling Survival Data: Extending the Cox Model. [Internet]. New York: Springer Nature; 2000 [cited 2021 Aug 26]. Available from: https://link.springer.com/book/10.1007/978-1-4757-3294-8
25. Springer link: ggplot2: elegant graphics for data analysis [Internet]. New York: Springer Nature; 2016 [cited 2021 Aug 26]. Available from: http://link.springer.com/10.1007/978-3-319-24277-4
26. Survminer: drawing Survival Curves using ‘ggplot2’ [Version 0.4.9] [Internet]. [2021] [cited 2021 Aug 26]. Available from: https://cran.r-project.org/web/packages/survminer/index.html
27. Wiley online library: complex surveys: a guide to analysis using R. biostatistics [Internet]. John Wiley & Sons; 2010 [cited 2021 Aug 26]. Available from: https://onlinelibrary.wiley.com/doi/book/10.1002/9780470580066
28. Buuren SV, Groothuis-Oudshoorn K. mice: multivariate imputation by chained equations in R.J Stat Softw. 2011 Dec 12;45(1):1–67.
29. MatchThem: matching and weighting multiply imputed datasets [R package matchthem version 1.0.0] [Internet]. 2021 [cited 2021 Aug 26]. Available from: https://cran.r-project.org/package=MatchThem
30. Cobalt: covariate balance tables and plots [R package cobalt version 4.3.1] [Internet]. 2021 [cited 2021 Aug 26]. Available from: https://ngreifer.github.io/cobalt/
31. CrsSC: competing risks regression for stratified and clustered data [Version 1.1]. [Internet]. [2015] [cited 2021 Aug 26]. Available from: https://cran.r-project.org/web/packages/crsSC/index.html
32. Sterne JA, White IR, Carlin JB, et al. Multiple imputation for missing data in epidemiological and clinical research: potential and pitfalls. BMJ. 2009 Jul 18;338(7713):157–160.
33. Desai RJ, Franklin JM. Alternative approaches for confounding adjustment in observational studies using weighting based on the propensity score: a primer for practitioners. BMJ. 2019 Oct 23;367.DOI:10.1136/bmj.l5657.
34. Austin PC, Stuart EA. Moving towards best practice when using inverse probability of treatment weighting (IPTW) using the propensity score to estimate causal treatment effects in observational studies. Stat Med. 2015 Dec 10;34(28):3661–3679.
35. Wiley online library: multiple imputation for nonresponse in surveys [Internet]. John Wiley & Sons; 1987 [cited 2021 Aug 26]. Available from: http://doi.wiley.com/10.1002/9780470316696
36. Austin PC. Optimal caliper widths for propensity-score matching when estimating differences in means and differences in proportions in observational studies. Pharm Stat. 2011 Mar;10(2):150–161.
37. Klein JP, Moeschberger ML. Survival analysis: techniques for censored and truncated data. Journal of the Neurological Sciences. 1997;149(2):95.
38. PC A, DS L, JP F. Introduction to the analysis of survival data in the presence of competing risks. Circulation. 2016 Feb 9;133(6):601−609.
39. PC A, JP F. Propensity-score matching with competing risks in survival analysis. Stat Med. 2019 Feb 28;38(5):751–777.
40. Latouche A, Allignol A, Beyersmann J, et al. A competing risks analysis should report results on all cause-specific hazards and cumulative incidence functions. J Clin Epidemiol. 2013 Jun 1;66 (6):648–653.
41. WHO Solidarity Trial Consortium. Repurposed antiviral drugs for Covid-19 — interim WHO solidarity trial results. N Engl J Med. 2020 Dec 2;383(6):497–511.
42. The RECOVERY Collaborative Group. Dexamethasone in hospitalized patients with Covid-19. N Engl J Med. 2020 Jul 17;384(8):693–704.
43. Coronavirus (COVID-19) Update: FDA Authorizes Monoclonal Antibodies for Treatment of COVID-19 [Internet]. Food and Drug Administration; 2020 [updated 2020 Nov 21; cited 2021 Aug 17]. Available from: https://www.fda.gov/news-events/press-announcements/coronavirus-covid-19-update-fda-authorizes-monoclonal-antibodies-treatment-covid-19
44. Fusina F, Albani F, Granato E, et al. Effect of corticosteroids on mortality in hospitalized COVID-19 patients not receiving invasive mechanical ventilation. Clin Pharmacol Ther. 2021 Jun 1;109(6):1660–1667.
45. Salama C, Han J, Yau L, et al. Tocilizumab in patients hospitalized with Covid-19 Pneumonia. N Engl J Med. 2020 Dec 17;384(1):20–30.

46. Rosas IO, Bräu N, Waters M, et al. Tocilizumab in hospitalized patients with severe Covid-19 Pneumonia. N Engl J Med. 2021 Feb 25;384(16):1503–1516.

47. COVID-19 treatment guidelines: interleukin-6 inhibitors [Internet] National Institutes of Health; 2021 [updated 2021 Oct 19; cited 2021 Aug 15]. Available from: https://www.covid19treatmentguidelines.nih.gov/therapies/immunomodulators/interleukin-6-inhibitors/

48. Moore JB, June CH. Cytokine release syndrome in severe COVID-19. Science (80). 2020;368(6490):473–474.

49. FDA briefing document arthritis advisory committee meeting August 2, 2017 [Internet]. Food and Drug Administration; 2017 [cited 2021 Aug 27]. Available from: https://www.fda.gov/media/106325/download

50. Tsai A, Diawara O, Nahass RG, et al. Impact of tocilizumab administration on mortality in severe COVID-19. Sci Rep. 2020 [2020 Nov 5];10(1):1–7.

51. Soin AS, Kumar K, Choudhary NS, et al. Tocilizumab plus standard care versus standard care in patients in India with moderate to severe COVID-19-associated cytokine release syndrome (COVINTOC): an open-label, multicentre, randomised, controlled, phase 3 trial. Lancet Respir Med. 2021 May 1;9(5):511–521.

52. Fisher MJ, Marcos Raymundo LA, Monteforte M, et al. Tocilizumab in the treatment of critical COVID-19 pneumonia: a retrospective cohort study of mechanically ventilated patients. Int J Infect Dis. 2021 Feb 1;103:536–539.

53. Somers EC, Eschenuer GA, Troost JP, et al. Tocilizumab for treatment of mechanically ventilated patients with COVID-19. medRxiv. 2020 Jun 3. DOI:10.1101/2020.05.29.20117358.

54. Lévesque LE, Hanley JA, Kezouh A, et al. Problem of immortal time bias in cohort studies: example using statins for preventing progression of diabetes. BMJ. 2010 Mar 12;340(7752):907–911.

55. Biran N, Ip A, Ahn J, et al. Tocilizumab among patients with COVID-19 in the intensive care unit: a multicentre observational study. Lancet Rheumatol. 2020 Oct 1;2(10):e603.

56. Fernández-Ruiz M, López-Medrano F, Carretero O, et al. Tocilizumab therapy in SARS-CoV-2 pneumonia: a matched retrospective cohort analysis. Med Clin (Barc). 2021. DOI:10.1016/j.medcli.2021.06.014.

57. Group TWREA for C-19 T (REACT) W, Domingo P, Mur I, Mateo GM, et al. Association between administration of IL-6 antagonists and mortality among patients hospitalized for COVID-19: a meta-analysis. JAMA. 2021;326(6):499–518.

58. Rossi B, Nguyen LS, Zimmermann P, et al. Effect of Tocilizumab in hospitalized patients with severe COVID-19 Pneumonia: a case-control cohort study. Pharm. 2020 [2020 Oct 17];13(10):317.

59. Capra R, Rossi ND, Mattioli F, et al. Impact of low dose tocilizumab on mortality rate in patients with COVID-19 related pneumonia. Eur J Intern Med. 2020 Jun 1;76:31.

60. Guaraldi G, Meschian M, Cozzi-Lepri A, et al. Tocilizumab in patients with severe COVID-19: a retrospective cohort study. Lancet Rheumatol. 2020 Aug 1;2(8):e474.

61. Menzel F, Fontana M, Salvarani C, et al. Efficacy of tocilizumab in patients with COVID-19 ARDS undergoing noninvasive ventilation. Crit Care. 2020 [2020 Sep 29];24(1):1–9.

62. Petrak RM, Van Hise NW, Skorodin NC, et al. Early Tocilizumab dosing is associated with improved survival in critically ill patients infected with severe acute respiratory syndrome coronavirus-2. Crit Care Explor. 2021;3(4):e00395.

63. Ellis AG, Trikalinos TA, Wessler BS, et al. Propensity score–based methods in comparative effectiveness research on coronary artery disease. Am J Epidemiol. 2018 May 1;187(5):1064–1078.

64. Brookhart MA, Schneeweiss S, Rothman KJ, et al. Variable selection for propensity score models. Am J Epidemiol. 2006 Jun;163(12):1149.

65. Walraven CV, Davis D, Forster AJ, et al. Time-dependent bias was common in survival analyses published in leading clinical journals. J Clin Epidemiol. 2004 Jul;57(7):672–682.

66. Koller MT, Raatz H, Steyerberg EW, et al. Competing risks and the clinical community: irrelevance or ignorance? Stat Med. 2012 May 20;31(11–12):1089–1097.

67. Zhang Z, Navas T, Herrick WG. Survival analysis in the presence of competing risks. Ann Transl Med. 2017 Feb 1;5:3.

68. Poguntke J, Schumacher M, Beyersmann J, et al. Simulation shows undesirable results for competing risks analysis with time-dependent covariates for clinical outcomes. BMC Med Res Methodol. 2018 [2018 Jul 16];18(1):1–10.

69. Rosenbaum PR, Rubin DB. The central role of the propensity score in observational studies for causal effects. Biometrika. 1983 Apr 1;70(1):41–55.

70. Flisiak R, Jaroszewicz J, Rogalska M, et al. Tocilizumab improves the prognosis of COVID-19 in patients with high IL-6. J Clin Med. 2021;10(8):1583.

71. Salvati L, Occhipinti M, Gori L, et al. Pulmonary vascular improvement in severe COVID-19 patients treated with tocilizumab. Immunol Lett. 2020;228:122–128.

72. Liu F, Li L, and Da XM, et al. Prognostic value of interleukin-6, C-reactive protein, and procalcitonin in patients with COVID-19. J Clin Virol. 2020;127:104370.

73. Herold T, Jurinovic V, Arnreich C, et al. Elevated levels of IL-6 and CRP predict the need for mechanical ventilation in COVID-19. J Allergy Clin Immunol. 2020;146(1):128–136.e4.

74. Saudi Ministry of Health: Saudi MoH protocol for patients suspected of/confirmed with COVID-19; supportive care and antiviral treatment of suspected or confirmed COVID-19 infection (Version 3.4) [Internet]. Saudi Arabia: Saudi Ministry of Health; 2022 [cited 2022 Jan 08]. Available from: https://www.moh.gov.sa/Ministry/MediaCenter/Publications/Documents/MOH-therapeutic-protocol-for-COVID-19.pdf