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Tocilizumab Therapy in Critically Ill Patients with Coronavirus Disease-2019 Pneumonia – A Propensity Score-Adjusted Analysis

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Abstract

BACKGROUND: Tocilizumab, an interleukin-6 receptor monoclonal antibody, has been proposed as a therapeutic option to mitigate coronavirus disease 2019 (COVID-19)-associated cytokine storm.

AIM: We investigated whether tocilizumab therapy is associated with the risk of death and major complications in critically ill patients with COVID-19 pneumonia admitted to the intensive care unit (ICU).

METHODS: We retrospectively included 160 patients with COVID-19 admitted to two ICUs of a university hospital in Egypt. A propensity score-adjusted multivariable Cox proportional hazard analysis with in-hospital death as the dependent variable was performed, in addition to a weighed Cox proportional hazard analysis according to inversed probability treatment weights (IPTWs) of the propensity score.

RESULTS: Tocilizumab was given to 107 patients; 84 patients within 48 h (early) and 23 patients after 48 h (late) of ICU admission. ICU/hospital mortality rate was higher in patients with than those without tocilicumab therapy (30.8 vs. 11.3%, $p < 0.001$). After propensity score-adjustment, tocilizumab therapy was not associated with the risk of in-hospital death (relative hazard: 0.67, 95% confidence interval: 0.23–1.93, $p = 0.454$). However, it was associated with high risk of acute kidney injury (AKI) in the ICU (kidney disease improving global outcomes stage 2–3, relative hazard: 3.14, 95% confidence interval: 1.1–8.98, $p = 0.033$) in an IPTW-weighed Cox proportional hazard analysis.

CONCLUSION: Our data do not support the routine use of tocilizumab therapy in critically ill patients with COVID-19 pneumonia. As it did not influence the risk of in-hospital death but was associated with high risk of AKI in the ICU.

Introduction

Since the emergence of coronavirus disease 2019 (COVID-19) due to infection with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), the available therapeutic options remain limited. In these patients, dysregulated immune response and hyperinflammation, the so called “cytokine storm,” plays a pivotal role in disease progression [1], [2]. Increased levels of interleukin-6 (IL-6) were reported in patients with COVID-19 [3], [4], [5], were correlated with viral load [6], and were shown to be associated with disease severity and poor prognosis [4], [7]. IL-6 is a proinflammatory cytokine with multiple biological functions [1]. Increased IL-6 levels were observed in patients with respiratory dysfunction, suggesting a possible role of this mediator in the cytokine-mediated lung damage [8]. Taken together, these observations [1], [2], [3], [4], [5], [6], [7], [8] provide a plausible rationale for the use of IL-6 receptor monoclonal antibody “tocilizumab” in patients with severe COVID-19 pneumonia. Nonetheless, universally accepted definitions for cytokine storm are lacking and the distinction between cytokine storm and a physiologic inflammatory response remains unclear [1]. It is also not clear whether the severity of illness in COVID-19 patients is related to immune hyperactivity or immune dysregulation. The circulating levels of several cytokines, such as IL-6, as well as other inflammatory markers, such as ferritin, are less severely elevated in COVID-19 than in some of the other cytokine storm disorders [1], [9] Although several observational studies have reported favorable outcomes of tocilizumab therapy in patients with COVID-19 [10], [11], [12], [13], [14], [15], [16], randomized control trials (RCTs) did not confirm the expected survival benefit [17], [18], [19], [20]. In fact, IL-6 is a key mediator in the antimicrobial response and blocking cytokine signaling, especially in the early

phase of the disease, may impair viral clearance and increase the risk of secondary infections [1], [21]. This may outweigh the potential beneficial effects of IL-6 blockade in some patients. Although RCTs provide the best evidence in terms of establishing treatment safety and efficacy, inconsistent and conflicting results can arise due to differences in case-mix and trial design. In the absence of gold standards to define the disease trajectory and therapeutic targets in patients with COVID-19, observational trials may provide additional insight to identify possible subgroups that may profit from specific therapies, understand the possible interference with concomitant therapeutic interventions, and set the stage for future RCTs on the subject. In particular, critically ill patients with COVID-19 represent a considerable therapeutic challenge due to the advanced and complex patterns of organ injury in these patients.

The aim of this study was, therefore, to investigate whether treatment with tocilizumab is associated with the risk of death and major complications in critically ill patients with COVID-19 pneumonia admitted to the intensive care unit (ICU) or not. Our hypothesis was that tocilizumab therapy would improve outcome and decrease the rate of major complications during the ICU stay in these patients.

Methods

Study design

This retrospective observational cohort study was approved by the Institutional Review Board of Cairo University Hospitals (Research Ethics Committee, Cairo University Hospitals, Kasr-Al-Aini-Street, 11562, Cairo, Egypt, Protocol-ID: N-89-2020). Informed consent was waived by the aforementioned institutional review board due to the retrospective, anonymous nature of data collection. We included adult patients (>18 years) with confirmed SARS-CoV-2 infection who were admitted between April 28 and July 29, 2020 to two ICUs in New Kasr El-Aini University hospital: a 16-bed medical and a 16-bed postoperative ICU. These ICUs were dedicated to the isolation and treatment of patients with suspected or confirmed COVID-19 disease during the study period. SARS-CoV-2 infection was confirmed in all patients using real-time reverse transcription-polymerase chain reaction on respiratory samples. We excluded patients who were admitted to the ICU for medical conditions not related to COVID-19 and those with incomplete records.

Data collection

A senior intensivist (YN, AM, ME, or FM) reviewed patients' records. Demographic data, preexisting comorbid conditions, laboratory parameters, therapeutic interventions, and major complications in ICU stay. The acute physiology and chronic health evaluation II (APACHE II) score was calculated from the data obtained within 24 h of admission to the ICU [22]. Data collection on admission included laboratory parameters of liver and renal functions, complete blood picture, arterial blood gases, inflammatory parameters (C-reactive protein (CRP) and lactate dehydrogenase (LDH)), and D-dimer levels. These parameters were measured on admission to the ICU and at least once daily thereafter (at 7:00 am) in the ICU. Patients were followed up until death, ICU, or hospital discharge, whichever occurred first.

ICU organization

The two ICUs that participated in the study are closed-format ICUs. The intensivists in charge have background of critical care medicine or anesthesiology. Daily rounds were conducted by a team including attending physicians, nursing staff, and physiotherapists. A multidisciplinary taskforce held daily meetings to review, discuss, monitor clinical progress, and advise on individual patient management. Infection control precautions were strictly implemented. Standard health care was applied according to the best-known evidence [23] and the standard operating procedures of the corresponding units, including isolation in single rooms and medical care with a 1:1 nurse: patient ratio.

Patients' management

Criteria for ICU admission in patients with COVID-19 pneumonia included persistent hypoxemia (SO_2 <90% for >1 h, despite O_2 supplementation using 10 L/min non-rebreathing oxygen face mask), an imminent indication for organ support therapy (invasive mechanical ventilation, vasopressor therapy, or renal replacement therapy), or the need for close monitoring (e.g., severe metabolic derangements or hemorrhagic complications). Antiviral therapies were prescribed at the discretion of the attending physician. Ventilatory parameters were adjusted according to the protective lung ventilation strategy [24]. Prone positioning was performed in all patients, unless hemodynamically unstable or during sessions of non-invasive mechanical ventilation or high flow nasal oxygen therapy. In patients with suspected secondary respiratory infections, deep respiratory and blood samples (tracheal aspirates or bronchoalveolar lavage fluid) were obtained and processed using BioFire® FilmArray® Panels (BioFire Diagnostics, Salt Lake City, Utah 84108 USA).

Definitions

Acute kidney injury (AKI) was defined according to the Kidney Disease Improving Global

Outcomes (KDIGO) criteria [25]; liver dysfunction as a two-fold (moderate) and five-fold (severe) increase of liver enzymes (alanine aminotransferase or aspartate transaminase (AST)) and/or serum bilirubin levels compared to baseline values; thrombocytopenia as platelet counts <100 × 10^9/L; and secondary bacterial respiratory infection as clinical suspicion (purulent expectorations or pulmonary infiltrates in chest X-ray or computed tomography, suggesting bacterial rather than SARS-CoV-2-related infection), together with confirmed microbiologic evidence of pathogenic bacterial infection on respiratory samples. Early tocilizumab therapy was defined as that given within 48 h of admissions in the ICU and late therapy was defined as that given thereafter.

Outcome parameters

The primary outcome parameter was in-hospital mortality. Secondary outcome parameters included major complications during the ICU stay; the need for mechanical ventilation, the need for vasopressor therapy, the occurrence of AKI (KDIGO stage 2–3), liver dysfunction (moderate to severe), thrombocytopenia, and secondary respiratory bacterial infections.

Statistical analysis

Data were analyzed using IBM® SPSS® Statistics software, v.21 for Windows (IBM, Somers, NY, USA) and R® Project, v. 4.0.4 (The R Foundation for Statistical Computing Platform). Summary statistics were computed using means with standard deviation, medians and interquartile ranges (IQ), or numbers and percentages. Difference testing between groups was performed using Student's t-test, Mann–Whitney test, Chi-square test, or Fisher's exact test, as appropriate. Detailed statistical analysis is described below.

Propensity scores [26] were obtained through multivariable logistic regression of patient characteristics, baseline laboratory parameters of organ function, and inflammatory parameters (on admission to the ICU in patients who were not treated with tocilizumab and on the day of initiation of tocilizumab therapy in patients who received this therapy), APACHE II score on admission to the ICU, and concomitant therapeutic interventions according to tocilizumab therapy, that is, tocilizumab therapy as the dependent variable. Covariates were selected for inclusion in the multivariable analysis based on a univariate logistic regression analysis with tocilizumab as the dependent variable, with $p < 0.2$ as a cutoff point for inclusion. The propensity score was calculated as the conditional probability based on the multivariable model. To assess the performance of the generated propensity scores in term of discrimination between patients who received tocilizumab and those who did not, we performed a receiver operating curve analysis and the area under the curve (AUC) with 95% confidence interval (CI) was computed.

We used two propensity score-based statistical techniques to assess the possible association between tocilizumab therapy and in-hospital death. First, we performed a propensity score adjusted multivariable Cox proportional hazard analysis with in-hospital death as the dependent variable, including tocilizumab therapy, age, APACHE II score, and the degree of hypoxemia as assessed by PaO_2/FiO_2 ratio on admission to the ICU. The multivariable model was stratified according to admission site. Tocilizumab therapy was included as a time dependent variable. Second, we calculated the inversed probability treatment weights (IPTWs) based on the propensity score [27]. Weighed Cox proportional hazard models were computed using the IPTW according to the propensity score and stratified according to the inclusion site. Tocilizumab therapy was included as a time-dependent variable and the hazard ratio (HR) of in-hospital death in association with tocilizumab therapy was computed.

To assess the possible association between tocilizumab therapy and major complications during the ICU stay, we performed IPTW-weighed Cox proportional hazard analyses as described above with the time to occurrence of the respective complication after tocilizumab therapy as the dependent variable. Tocilizumab therapy was introduced in this analysis as a time-dependent covariate.

All reported p values are two-sided and $p < 0.05$ was considered to indicate statistical significance.

Results

Characteristics of the study group

One hundred and sixty patients were included in the analysis (males: 67.5%, mean age: 60 ± 14 years, Figure 1). Tocilizumab was given to 107 patients (66.9%) during the ICU stay; 84 patients (52.5%) within 48 h (early tocilizumab) and 23 patients (14.4%) after 48 h (late tocilizumab). A fixed dose was used for all patients, consisting of two intravenous injections of 400 mg each, 12 h apart (Actemra®, Hoffmann-La Roche AG, Basel, Switzerland). Tocilizumab was given at a median of 1 (1–2) days (range: 1–6 days) of admission to the ICU Demographic characteristics and preexisting comorbid conditions were similar; however, baseline lymphocyte count, PaO_2/FiO_2 ratio, ferritin levels, and SO_2 were lower in patients who were treated with tocilizumab than those who were not (Tables 1 and 2). Baseline LDH, D-dimer levels, and SO_2 were higher, whereas hemoglobin concentration was slightly lower in patients who received late tocilizumab than early tocilizumab therapy (Tables 1 and 2).

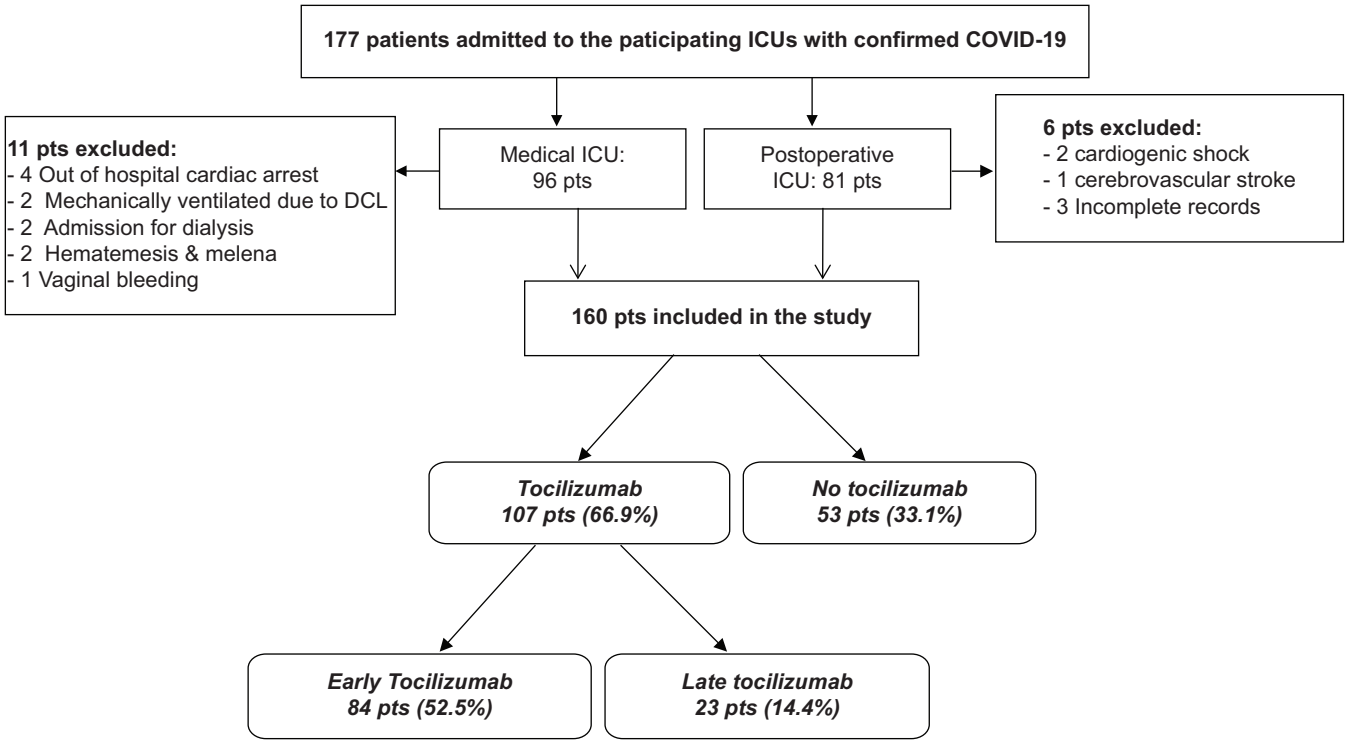

Figure 1: Flow chart showing patient inclusion. DCL: Disturbed conscious level

Concomitant therapies and therapeutic interventions

Concomitant antimicrobial, anticoagulation, and adjunctive therapies are shown in Table 1. Oseltamivir (24.3 vs. 45.3%, p = 0.007) and azithromycin (24.3 vs. 49.1%, p = 0.002) were given less and convalescent plasma (42.1 vs. 7.5%, p < 0.001) was given more frequently in patients who were treated with tocilizumab than who were not. All but one patient were treated with intravenous methylprednisolone (2 mg/kg/day) for a maximum of 10 days and gradually withdrawn over 3 days thereafter. Concomitant medications were similar between patients who were treated with tocilizumab early or late during the ICU stay (Table S1). Overall, patients who were treated with tocilizumab required invasive mechanical ventilation (34.6 vs. 13.2%, p = 0.004), and vasopressor therapy (32.7 vs. 13.2%, p = 0.008) more frequently at any time during the ICU stay than those who were not. Mechanical ventilation and vasopressor therapy were initiated in 29 and 21.5% of patients after tocilizumab therapy, but their rates were not significantly different according to the onset of tocilizumab therapy during the ICU stay (Table S2).

Table 1: Characteristics of the study cohort on admission to the ICU according to tocilizumab therapy

n	Tocilizumab	No tocilizumab	p-value	Early tocilizumab	Late tocilizumab	p-value
	107	53		84	23	
Age, years, mean ± SD	61 ± 14	60 ± 15	0.711	60 ± 13	64 ± 15	0.50
Sex, male, n (%)	71 (66.4)	37 (69.8)	0.660	56 (66.7)	15 (65.2)	0.896
BMI, kg/m^2, mean ± SD	28.3 ± 3.9	27.4 ± 3.8	0.256	28.7 ± 4.1	27 ± 2.9	0.088
APACHE II score , mean ± SD	10.6 ± 5.9	8.8 ± 5.2	0.051	10.5 ± 6.1	10.9 ± 5.2	0.613
Referral from another hospital	16 (15)	5 (9.4)	0.457	12 (14.3)	4 (17.4)	0.744
Onset of symptoms prior to hospital admission, days, median (IQ)	7 (5–10)	7 (5–10)	0.932	7 (5–10)	7 (4–9)	0.735
Initial symptoms, n (%)						
Fever	96 (89.7)	46 (86.8)	0.581	77 (91.7)	19 (82.6)	0.205
Dyspnea	78 (72.9)	36 (67.9)	0.513	62 (73.8)	16 (69.6)	0.792
Cough	58 (54.2)	27 (50.9)	0.697	44 (52.4)	14 (60.9)	0.469
Fatigue	9 (8.4)	4 (7.5)	1.000	5 (6.0)	4 (17.4)	0.097
Diarrhea	5 (4.7)	2 (3.8)	1.000	5 (6.0)		0.583
Anosmia	1 (0.9)	1 (1.9)	1.000	1 (1.2)	-	1.000
Hospital LOS prior to ICU admission, days, median (IQ)	0 (0–1)	0 (0–1)	0.289	0 (0–1)	0 (0–1)	0.322
Comorbidities, n (%)						
Systemic hypertension	62 (57.9)	27 (50.9)	0.402	48 (57.1)	14 (60.9)	0.748
Diabetes mellitus	51 (47.7)	22 (41.5)	0.462	42 (50.0)	9 (39.1)	0.355
Ischemic heart disease	23 (21.5)	10 (18.9)	0.699	17 (20.2)	6 (26.1)	0.545
Chronic lung disease	9 (8.4)	8 (15.1)	0.197	7 (8.3)	2 (8.7)	1.000
Chronic renal disease	9 (8.4)	6 (11.3)	0.552	9 (10.7)	-	0.200
Smoking	8 (7.5)	9 (17.0)	0.066	4 (4.8)	4 (17.4)	0.063
Arrhythmia	6 (5.6)	2 (3.8)	1.000	6 (7.1)	-	0.337
Immunosuppresssion	5 (4.7)	3 (5.7)	1.000	3 (3.6)	2 (8.7)	0.292
Cancer	3 (2.8)	2 (3.8)	1.000	2 (2.4)	1 (4.3)	0.520
Chronic liver disease	3 (2.8)	1 (1.9)	1.000	3 (3.6)	-	1.000
Comorbidities, n, median (IQ)	2 (1-3)	2 (1-3)	0.910	2 (1–3)	2 (1–2)	0.972

APACHE II: Acute physiology and chronic health evaluation, BMI: Body mass index, IQ: Interquartile range, ICU: Intensive care unit, SD: Standard deviation.

Table 2: Baseline inflammatory parameters, arterial blood gases, blood picture, and parameters of organ function*

n	Tocilizumab	No tocilizumab	P-value	Early tocilizumab	Late tocilizumab	p-value
	107	53		84	23	
Inflammatory parameters						
CRP, mg/L	151 (69–232)	92 (38.8–231.5)	0.085	149 (70–213)	153 (69–328)	0.335
Ferritin, ng/L	960 (537–1774)	655 (375–1500)	0.041	946 (601–1575)	1326 (427–2058)	0.519
LDH, IU/L	611 (432–846)	555 (392–776)	0.286	533 (403–788)	755 (579–1178)	0.005
Arterial blood gases						
pH	7.41 (7.39–7.46)	7.43 (7.39–7.46)	0.814	7.43 (7.38–7.46)	7.42 (7.4–7.46)	0.858
HCO_3, mmol/L	23 (21–26)	23 (20–26)	0.729	23 (21–26)	23 (22–25)	0.358
SO_2, %	91 (89–93)	87 (80–89)	0.002	91 (89–93)	93 (92–98)	0.004
PCO_2, mmHg	35 (30–42)	33 (28–40)	0.067	35 (30–42)	34 (31–41)	0.797
PO_2, mmHg	108 (69–154)	126 (72–163)	0.283	123 (68–160)	100 (74–137)	0.464
Blood picture, median (IQ)						
Hemoglobin g/dl	12.7 (11.0–14.0)	13.4 (11.7–14.5)	0.077	13 (11.1–14)	12 (11–12.8)	0.048
WBC, $\times 10^9$/L	9.0 (6.0–13.0)	9.4 (7.6–13.5)	0.664	9 (6.3–12)	9 (6–16)	0.676
Neutrophil count, $\times 10^9$/L	8.0 (5.0–11.4)	8.1 (5.3–11)	0.752	8 (5–10)	9 (5–14)	0.412
Lymphocyte count, $\times 10^9$/L	1.0 (0.6–1.0)	0.9 (0.6–1.6)	0.004	1.0 (0.7–1.0)	1.0 (0.1–1.0)	0.459
Platelets, $\times 10^9$/L	227 (152–276)	246 (190–319)	0.098	223 (151–280)	232 (169–275)	0.930
Parameters of organ function						
Creatinine, mg/dL	1.0 (1.0–1.2)	1.1 (0.85–1.4)	0.588	1.0 (1.0–1.3)	1.0 (0.8–1.0)	0.055
Urea, mg/dL	51 (34–70)	39 (27–63)	0.055	50 (34–73)	51 (35–65)	0.930
Bilirubin, mg/dL	1.0 (0.3–1.0)	0.6 (0.4–1.1)	0.471	1.0 (0.1–1.0)	0.8 (0.4–1.0)	0.947
ALT, IU	40 (27–59)	45 (35–63)	0.145	39 (25–58)	46 (30–60)	0.192
AST, IU	37 (25–60)	39 (28–58)	0.530	37 (27–57)	38 (20–62)	0.888
PaO_2/FiO_2 ratio	150 (95–193)	188 (105–237)	0.053	150 (85–190)	167 (125–198)	0.103
D–Dimer	1.0 (0.4–3.3)	0.6 (0.4–1.8)	0.096	1 (0.2–2)	5 (1–16)	<0.001

Values are presented in median (25–75% interquartile range). *On admission to the ICU in patients who were not treated with tocilizumab and on the day of initiation of tocilizumab therapy in patients who received this therapy. ALT: Alanine aminotransferase, AST: Aspartate transaminase, FiO_2: Fraction of inspired oxygen, IU: International unit, SaO_2: Arterial oxygen concentration, PO_2: Partial pressure of oxygen, PCO_2: Partial pressure of carbon dioxide. CRP: C-reactive protein, LDH: Lactate dehydrogenase

Morbidity and mortality

AKI (KDIGO 2–3) occurred after tocilizumab therapy or during the ICU stay in patients who were not treated with tocilizumab in 28 (17.5%) patients, thromboctytopenia in 31 (19.4%) patients, and secondary bacterial respiratory infections in 31 (19.4%) patients. Severe AKI, secondary bacterial pneumonia, and thrombocytopenia were more common in patients treated with tocilizumab than those who were not (Table S3). However, the prevalence of other major complications was similar between patients who were treated with tocilizumab and those who were not, irrespective of the time of tocilizumab therapy (Table S3). The overall ICU/hospital mortality rate was 24.4% (n = 39). ICU and hospital lengths of stay were 7 (IQ: 4–10) and 10 (IQ: 7–14) days, respectively. Mortality rate was higher (30.8 vs. 11.3, p < 0.001) and ICU (8 (6–12) vs. 4 (3–6), <0.001) and hospital (12 [9–16] vs. 8 [6-19], p < 0.001) lengths stay were longer in patients who were treated with tocilizumab than those who were not.

Propensity score adjustment

Sixteen variables were included in the logistic multivariable analysis used to determine the propensity score (Table S3). The performance of the computed propensity score was good in terms of discriminating between patients who received tocilizumab therapy and those who did not (AUC: 0.824; 95% CI: 0.756–0.891, p < 0.001, Figure 1). The distribution of the propensity score according to treatment with tocilizumab is shown in Figure S2. Table S4 demonstrates the distribution of the covariates included in computing the propensity score after IPTW according to tocilizumab therapy.

In a multivariable Cox proportional hazard with in-hospital death as the dependent variable, the propensity score based on the likelihood of being treated with tocilizumab was independently associated with higher risk of in-hospital death (Table 3). However, treatment with tocilizumab was not associated with the risk of death (HR: 2.01, 95% CI: 0.33–12.19, p = 0.666). Likewise, in IPTW-weighed Cox proportional hazard analysis, tocilizumab therapy was not associated with the risk of in-hospital death (HR: 0.81, 95% CI: 0.33–2.0, p = 0.642) (Table 4).

Table 3: Summary of multivariable Cox proportional hazard analyses with in-hospital death as the dependent variable, stratified according to the inclusion site

Variable	Relative hazard (95% confidence interval)	p-value
Age (per year)	1.00 (0.97–1.02)	0.710
APACHE II (per point)	1.1 (1.05–1.56)	<0.001
PaO_2/FiO_2 ratio (per mmHg)	0.99 (0.98–0.99)	0.003
Propensity score (per point %)	2.01 (0.33–12.19)	0.003
Tocilizumab therapy*	0.67 (0.23–1.93)	0.454

APACHE: Acute physiology and chronic health evaluation. *Included as a time-dependent variable

IPTW-weighed Cox proportional hazard analysis revealed that tocilizumab therapy was independently associated with high risk of moderate to severe AKI (HR: 3.14, 95% CI: 1.1–8.98, 0 = 0.033). Treatment with tocilizumab was not associated with the risk of acquiring bacterial pneumonia, thrombocytopenia, liver dysfunction, the need for mechanical ventilation, or vasopressor therapy during the ICU stay (Table 4).

Table 4: Hazard ratios of in-hospital death and major complications, associated with tocilizumab therapy*

Outcome	Time to occurrence after tocilizumab therapy, days, median (IQ)	Hazard ratio (95% Confidence interval)	p-value
In-hospital death	6 (5–10)	0.81 (0.33–2.0)	0.642
Major complications during ICU stay			
Need for mechanical ventilation	3 (1–6)	1.67 (0.55–5.08)	0.370
Need for vasopressor therapy	3 (1–6)	2.11 (0.44–10.08)	0.347
Bacterial pneumonia	5 (2–7)	1.84 (0.69–4.90)	0.222
Acute kidney injury	6 (2–7)	3.14 (1.1–8.98)	0.033
Thrombocytopenia	5 (1–9)	2.44 (0.88–6.75)	0.087
Liver dysfunction	3 (1–7)	1.59 (0.62–4.1)	0.339

IQ: Interquartile range

Based on IPTW-weighed Cox proportional hazard analyses with the respective complication after tocilizumab therapy as the dependent variable, stratified according to the inclusion site. Tocilizumab therapy was included as a time-dependent variable.

Discussion

Despite of the accumulating evidence, suggesting a pivotal role of IL-6 levels in cytokine-induced injury [3], [4], [6] and poor prognosis in patients with COVID-19 [4], [7], our study did not confirm that the routine treatment with the anti-IL-6 monoclonal antibody "tocilizumab" influences the risk of death, the need for mechanical ventilation, or the need for vasopressor therapy in these patients. The discrepancy between the results of our study and that of earlier observational studies, which reported favorable outcomes of tocilizumab therapy in critically ill COVID-19 patients [10], [11], [12] may be attributed to the differences in case-mix and concomitant therapies. Indeed, the severity of illness was more pronounced in the previous observational studies, as evident from the high mortality rates (39–57%) in these studies, compared to ours [10], [11]. In addition, almost all patients in our cohorts have been treated with corticosteroids that may have exerted similar immunomodulatory effects to tocilizumab in the control group. In particular, the use of moderate dose of methylprednisolone in our patients may also have had potential deleterious effects. In the contrary, steroids were used at low rates in the previous cohorts, ranging from 13 to 63% [10], [11], [12]. Since the current evidence supports that the use of glucocorticoids, especially dexamethason, has favorable effects on outcome in the most severe cases of COVID-19 and potentially worsen outcomes in milder cases [28], [29], the increasing use of steroids in these patients will be a major confounding factor that should be considered in the future RCTs.

The efficacy of tocilizumab therapy was inconsistent throughout the published RCTs which did not show survival benefits in mild to moderately severe patients with COVID-19 [17], [18], [19], [20], [30]. A RCT by Veiga *et al*. was stopped early at an interim analysis due excess mortality in patients who were treated with tocilizumab [31]. A press releases of a trial of the IL-6 receptor antagonist, sarilumab, indicated no benefit in the whole population but a trend toward harm in a subgroup not mechanically ventilated [32], [33]. Nonetheless, some potential benefits have been reported, including reduction in the composite outcome of the need for mechanical ventilation or death [18], [20], [30]. Notably, these trials were confined to patients in the early stages of the disease process before ICU admission with relatively low mortality rates [17], [18], [19], [20]. Moreover, the use of concomitant immunomodulatory therapies, such as dexamethason [18] and rescue therapy with tocilizumab [17] in the control groups, may have mitigated potential survival benefits.

More recently, the REMAP-CAP trial evaluated the IL-6 receptor antagonists tocilizumab and sarilumab in an international, multifactorial, adaptive platform trial, including adult patients with COVID-19, within 24 h after starting organ support in the ICU [34]. They found that treatment with the IL-6 receptor antagonists improved outcomes, including survival. However, the trial included patients with higher risk of death as compared to other trials [19], [20], [30], [31] and to those included in our analysis. The early enrollment of patients in REMAP-CAP trial within 24 h after starting organ support in the ICU may have been an important factor to maximize effectiveness and reverse organ dysfunction. The study was limited, however, by the open-label design and the multifactorial design with possible interactions with concomitant therapeutic interventions. Since IL-6 is crucial for both a healthy immune response and a detrimental cytokine storm which may not play the essential role throughout the disease trajectory, timing of therapy and patients' selection are key factors in determining the potential efficacy of tocilizumab. Thus, the variability in timing and case-mix may provide a plausible explanation to the discrepancy between the results of these studies [17], [18], [19], [20], [30], [34]. Immunosuppression may be expected to be beneficial if given to patients with advanced disease process, in whom benefits of therapy may outweigh the potential risks. Initiating therapy too early may impair appropriate antiviral response and negatively influence outcomes, whereas delayed therapy may not be effective due to advanced tissue damage and irreversible organ failure.

Our study demonstrates that tocilizumab therapy may not convey the desirable benefit in patients with similar case-mix as those included in our study, including rather younger patients with moderate risk of death than those seen elsewhere. Accordingly, the routine early use of tocilizumab may not be justified in all ICU patients. Future research resources may be better targeted to understand the mechanistic aspects related to this therapy in COVID-19. In particular, better understanding of patterns of immune hyperreactivity in patients with COVID-19 is crucial to develop effective therapeutic approaches and establish reliable biomarkers to guide therapeutic success. Indeed, local inflammation may play a detrimental role of COVID-19-induced organ dysfunction, irrespective of the circulating cytokine levels. Several studies have shown that systemic levels of cytokines may not be as high as seen with other causes of sepsis and acute respiratory distress syndrome [35], [36], [37]. These findings [35], [36], [37] suggest that COVID-19 may not be characterized, at least in all patients, by a cytokine storm that justifies therapies such as IL-6 antagonists.

In our study, tocilizumab therapy was independently associated with AKI. This may have outweighed the possible favorable effect of tocilizumab therapy on outcome in our patients. The recent RCTs, though including less severely ill patients than ours, did not raise safety concerns in relation to tocilizumab therapy [17], [18], [19], [20], [30], [34]. In the absence of clear survival benefit, it may be prudent to avoid treatment with

tocilizumab in patients with impaired renal dysfunction. Subsequent assessment of the parameters organ function is mandatory in patients who are treated with this therapy.

Our study has some limitations. First, the health-care system in Egypt is not uniform in terms of case-mix, available resources, and quality of care. The results of our analysis may not be, therefore, extrapolated to other critically ill patients with a different case-mix. Second, the propensity score adjustment may be limited by the included variables in the multivariable model used to calculate these scores and the possible influence of unmeasured confounders cannot be excluded. Third, concomitant therapies were given according to the discretion of the attending physician and product availability. A potential bias-by-indication may have resulted in a residual confounding effect, despite of meticulous statistical adjustment. Finally, the relatively small number of patients in our study does not allow detailed subgroup analysis to identify patients in whom tocilizumab therapy may be beneficial or harmful. In addition, we did not measure IL-6 levels in our patients, so that investigating the possible target levels for tocilizumab therapy was not possible.

Conclusion

In this cohort of critically ill patients with COVID-19 pneumonia, tocilizumab therapy was not associated with the risk of in-hospital death but was independently associated with high risk of AKI in the ICU. Our data do not support the routine use of tocilizumab in these patients.

Declarations

Ethics approval and consent to participate

The report was approved by the Institutional Review Board of Cairo University Hospitals, (Research Ethics Committee, Cairo University Hospitals, Kasr-Al-Aini-Street, 11562, Cairo, Egypt, Protocol-ID: N-89 2020) which waived informed consents due to the retrospective and anonymous nature of data collection. All methods were performed in accordance with the relevant guidelines and regulations.

Consent for publication

Not applicable.

Availability of data and material

The dataset used and analyzed during the current report are available from the corresponding author on reasonable request. YN, AM, ME, and FM have complete access to patient data.

Authors' Contributions

YN, AM, FM, AEh, SM, AR, MS, AEd, SG, and YS designed the scientific work. YN, AM, MEs, MS, and FM contributed to data collection. YN, FM, SB, and YS contributed to data handling. SB, YN, and YS performed the statistical analysis. SB, YN, FM, and MS reviewed the literature. YN, SB, and YS wrote the first draft of the manuscript. All the authors reviewed, revised, and approved the submitted manuscript. YN, AM, and FM have complete access to the clinical data of the reported cases and hold responsibility for integrity and correctness of data. SB and YS have access to the data set used for the current analysis.

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Key points

1. In this cohort of critically ill patients with COVID-19 pneumonia, tocilizumab therapy did not show any benefit in terms of reducing in-hospital mortality
2. Tocilizumab therapy may be associated with high risk of AKI in the ICU
3. The routine use of tocilizumab in these patients may not be justified and further studies are warranted to identify subgroups of patients who may benefit from this therapy.

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