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Effect of Tocilizumab in Mortality among Patients with Severe and Critical COVID-19: Experience in a Third-Level Medical Center

Bernardo A. Martínez-Guerra[1], Nereyda A. de-León-Cividanes[1], Karla M. Tamez-Torres[2], Carla M. Román-Montes[1], Sandra Rajme-López[1], Edgar Ortiz-Brizuela[1], Carlos A. Aguilar-Salinas[3], Juan Sierra-Madero[1], José Sifuentes-Osornio[4], Alfredo Ponce-de-León[1], and María F. González-Lara[2]*

[1]Department of Infectious Diseases, [2]Clinical Microbiology Laboratory, [3]Department of Nutrition, and [4]Department of Medicine. Instituto Nacional de Ciencias Médicas y Nutrición Salvador Zubirán, Mexico City, Mexico

ABSTRACT

Background: Trials evaluating safety and efficacy of tocilizumab in coronavirus disease 19 (COVID-19) show contradictory results. **Objective:** The objective of the study was to evaluate the effect of tocilizumab in hospital mortality among patients with severe COVID-19 in a third-level medical center. **Methods:** This prospective cohort study included patients with severe and critical COVID-19. Primary outcome was death during hospitalization. Secondary outcomes included invasive mechanical ventilation (IMV), days on IMV, ventilator-free days (VFDs), length of hospital stay (LOS), and development of hospital-acquired infections (HAIs). Bivariate, multivariate, and propensity score matching analysis were performed. **Results:** During the study period, 99/794 (12%) patients received tocilizumab. Male patients, health care workers, and patients with increased inflammatory markers received tocilizumab more frequently. No difference in hospital mortality was observed between groups (34% vs. 34%, p = 0.98). Tocilizumab was not independently associated with mortality. No significant treatment effects were observed in propensity score analysis. IMV was more frequent (46% vs. 11%, p < 0.01) and LOS was longer (12 vs. 7 days, p < 0.01) in the tocilizumab group, reflecting increased severity. Although HAIs were more frequent in the tocilizumab group (22% vs. 10%, p < 0.01), no difference was seen after adjusting for IMV (38% vs. 40%, p = 0.86). **Conclusions:** In our study, tocilizumab was not associated with decreased hospital mortality among patients with severe COVID-19. (REV INVEST CLIN. 2022;74(1):40-50)

Keywords: Tocilizumab. COVID-19. SARS-CoV-2. Mexico.

***Corresponding author:**
María F. González-Lara
E-mail: fergonla@gmail.com

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INTRODUCTION

The lack of effective treatment options to reduce COVID-19 associated mortality, disease progression, and the need for invasive mechanical ventilation (IMV) remains a problem. Severe forms of COVID-19 are associated with an increased systemic inflammation and elevation of markers such as C-reactive protein (CRP), lactate dehydrogenase (LDH), D-Dimer, ferritin, interleukin (IL)-6, IL-8, and TNF-α[1,2]. Since the first descriptions of COVID-19, anti-inflammatory therapies have been explored. The RECOVERY trial demonstrated a mortality reduction with dexamethasone in hypoxic patients[3]. Numerous anti-inflammatory therapies and immunomodulating agents have been proposed to treat severe forms of COVID-19[4].

Tocilizumab is a recombinant anti-IL-6 monoclonal antibody that binds to membrane and soluble IL-6 receptors[5], currently recommended in the treatment of rheumatoid arthritis and cytokine release syndrome[6,7]. Its use for COVID-19 was first described in small case series where clinical and radiographic improvements were observed after the administration of the drug[8,9]. While numerous cohorts have reported successful outcomes, such results have not been consistently observed in randomized control trials (RCTs) and meta-analysis[10-19]. Updated guidelines consider the use of tocilizumab among patients with progressive or critical COVID-19 in addition to corticosteroids[20-23]. Outcomes of tocilizumab administration must be further explored. Therefore, we conducted a cohort study to evaluate the effect of tocilizumab on hospital mortality among patients with severe or critical COVID-19.

METHODS

Patients and setting

This prospective cohort study was conducted in a tertiary care center in Mexico City that was converted into a COVID-19 dedicated facility since March 16, 2020. Reorganization included expansion of the intensive care unit (ICU) and redistribution of nursing and medical staff. Data from all consecutive patients admitted with severe and critical COVID-19 between March 20 and June 10 were registered. Patients were followed up from admission to death or discharge. A severe case was defined by the presence of any of the following: respiratory rate ≥ 30 breaths per minute, SpO_2 < 93%, PaO_2/FiO_2 ratio < 300, or ≥ 50% lung involvement by chest computed tomography (CT). A critical case was considered when IMV, shock, or multiorgan failure were present[24]. Demographic, clinical, laboratory, imaging, and outcome data were obtained from the electronic medical record. Among patients who received tocilizumab, laboratory test results from 24 h before and 48 h after the first dose of tocilizumab were registered. Previously validated severity and prognostic scores (MLS-COVID-19[25] and NutriCoV score[26]) were registered retrospectively. Primary outcome was death during hospitalization. Secondary outcomes included IMV, days on IMV, ventilator-free days (VFDs) at 28 days, length of stay (LOS), and development of a culture-proven hospital-acquired infection (HAI). VFDs was defined as the number of days being alive and free of IMV for 24 h; patients discharged from the hospital before 28 days were considered alive and free of IMV at day 28. Patients with moderate disease or a LOS < 24 h were excluded from the study. The study was approved by the Institutional Review Board (Ref. number 3333). Written informed consent was waived because of the observational nature of the study.

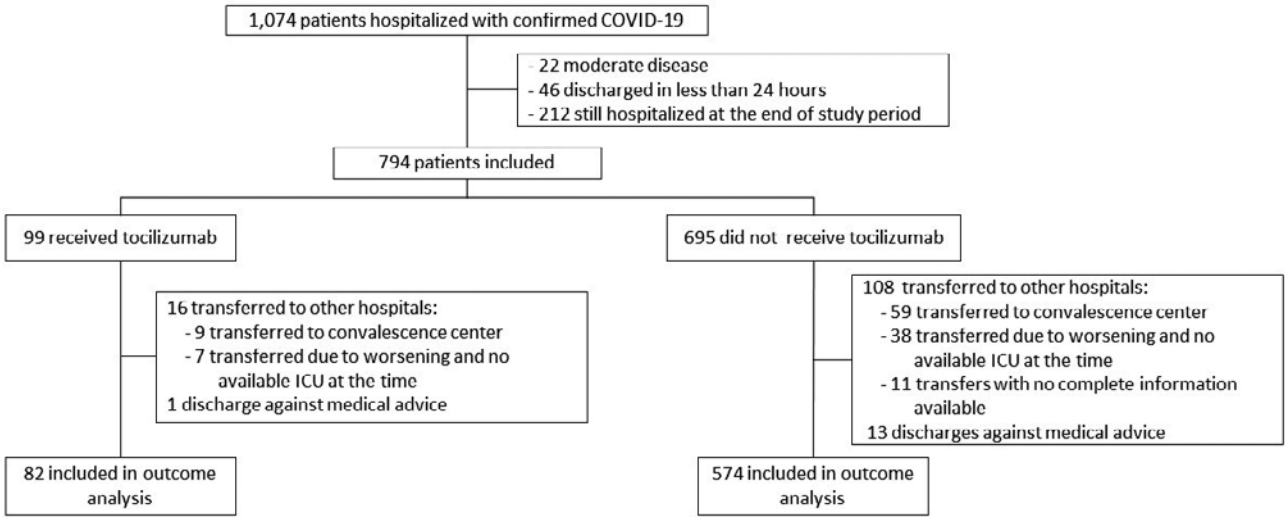
Laboratory procedures

SARS-CoV-2 testing was performed on nasopharyngeal swab samples. NucliSens easyMAG system (bioMérieux, Boxtel, the Netherlands) was used for nucleic acid extraction. Real-time reverse transcription-polymerase chain reaction was processed on Applied Biosystems 7500 thermocycler (Foster City, CA, USA) using primers and conditions described elsewhere[27].

Tocilizumab administration

Intravenous administration of tocilizumab was prescribed by the treating physicians after evaluation of each case, considering possible contraindications (e.g., documented infection other than COVID-19 and known hypersensitivity to tocilizumab). All patients signed an informed consent addressing the potential risks and benefits of tocilizumab therapy known at the time. Because tocilizumab was not widely available in our center, dosing was variable according to

Figure 1. Number of subjects included in the study and follow-up.



local availability and individual patient's resources. All patients received the standard of care. Of note, dexamethasone was not a standard of care in this center during the study period.

Statistical analysis

Descriptive analysis was made through mean, standard deviation, median, and interquartile range (IQR), as appropriate. Comparative analysis was made using χ^2, Fisher's exact test, *t*-test for independent samples, two-sample rank sum tests, and sign-rank tests. Relative risk (RR) for hospital mortality and 95% confidence interval (95%CI) were calculated for each variable in the bivariate analysis. Multivariate analysis using multiple regression was made; variables with $p < 0.05$ in bivariate analysis and those with biological plausibility (e.g., administration of tocilizumab) were included. To estimate treatment effects and minimize selection bias, a propensity score analysis using a matching method was performed. To estimate the propensity score, the treatment received was regressed in a logistic regression model. Baseline variables that could affect the outcome and influence the treatment selection were included in the model. Patients were matched on the logit of the propensity score using calipers of width of 0.1 or less of the standard deviation of the estimated propensity score and on a 1:1 ratio using control replacements if needed. To adequately specify the model, a comparison between variances of continuous variables and standardized means in the matched sample was made. A regression analysis within the matched sample was performed. Finally, the average treatment effect was estimated. A two-tailed $p < 0.05$ was considered statistically significant. The analyses were performed using STATA version 15.1 (Texas, USA).

RESULTS

A total of 794 patients with severe or critical COVID-19 were included, of whom 99 (12%) received tocilizumab (Fig. 1). Median age was 52 (IQR 43-62) years and 489 (62%) were male. The median body mass index (BMI) was 29.7 (IQR 26.7-33.2) kg/m^2, 364 (46%) had a BMI > 30 kg/m^2, 216 (27%) had type 2 diabetes mellitus (DM), 253 (32%) hypertension, and 45 (6%) were immunocompromised. The most common cause of immunosuppression was pharmacological in 25/45 (56%). Very high-risk category on MLS-COVID-19 and Nutri-CoV scores was observed in 166 (21%) and 366/768 (48%), respectively, and no differences between groups were observed. Patients on tocilizumab were more frequently male (74 [74%] vs. 416 [60%], $p < 0.01$), health care workers (12 [12%] vs. 31 [5%], $p < 0.01$), and less likely to have hypertension (19 [19%] vs. 234 [34%] $p < 0.01$). No other differences were observed between groups (Table 1).

Table 1. Baseline demographic and treatment characteristics

Characteristic	All patients, (n=794) (100%)	Received tocilizumab, (n=99) (12%)	Did not receive tocilizumab, (n=695) (88%)	p
Male sex, n (%)	489 (61.6)	73 (73.7)	416 (59.9)	0.008
Age, years, median (IQR)	52 (43-62)	51 (43-61)	52 (43-62)	0.54
Body mass index, kg/m^2, median (IQR) n=755	29.7 (26.7-33.2)	26.7 (27.0-33.9)	29.7 (26.7-33.2)	0.7059
Obesity, n (%)	364 (46.1)	48 (48.5)	316 (45.7)	0.607
Diabetes mellitus, n (%)	216 (27.2)	25 (25.3)	191 (27.5)	0.641
Arterial hypertension, n (%)	253 (31.9)	19 (19.2)	234 (33.7)	0.004
Chronic obstructive pulmonary disease, n (%)	9 (1.1)	2/99 (2.0)	7/695 (1.0)	0.312
Asthma, n (%) n=793	9 (1.1)	2/98 (2.0)	7/695 (1.1)	0.308
Cardiovascular disease, n (%) n=793	36 (4.5)	6/98 (6.1)	30/695 (4.3)	0.43
Immunosuppression, n (%)	45 (5.7)	2 (2.0)	43 (6.2)	0.106
Chronic kidney disease, n (%)	24 (3.0)	0	24 (3.5)	0.06
Current smokers, n (%) n=785	117 (14.9)	10/97 (10.3)	107/688 (15.6)	0.175
Healthcare worker, n (%) n=792	43 (5.4)	12/99 (12.1)	31/693 (4.5)	0.007
Charlson comorbidity index ≥2, n (%)	328 (41.3)	36 (36.4)	292 (42.0)	0.285
SpO_2 ≤90%, n (%) n=770	721 (93.6)	89/94 (94.7)	632/676 (93.5)	0.823
Nutri-CoV category, n (%) n=768				
Low risk	28 (3.7)	2/94 (2.1)	26/674 (3.9)	0.114
Moderate risk	131 (17.1)	12/94 (12.8)	119/674 (17.7)	
High risk	243 (31.6)	40/94 (42.6)	203/674 (30.1)	
Very high risk	366 (47.7)	40/94 (42.6)	326/674 (48.4)	
Lymphopenia <800 cells/μL, n (%) n=788	426 (54.1)	62/99 (62.6)	364/689 (52.8)	0.067
C-reactive protein >10 mg/dL, n (%) n=766	553 (72.2)	76/97 (78.4)	477/669 (71.3)	0.148
D-dimer >1000 ng/mL, n (%) n=762	272 (35.7)	25 (26.6)	247 (37.0)	0.049

(Continues)

Table 1. Baseline demographic and treatment characteristics *(continued)*

Characteristic	All patients, (n=794) (100%)	Received tocilizumab, (n=99) (12%)	Did not receive tocilizumab, (n=695) (88%)	p
Empiric antibiotic treatment, n (%)	744 (93.7)	95 (96)	649 (93.4)	0.505
Treatment with hydroxychloroquine, n (%)	219 (27.6)	33 (33.3)	186 (26.8)	0.171
Adjuvant steroids, n (%)	73 (9.2)	9 (9.1)	64 (9.2)	0.97
ICU care on admission, n (%)	112 (14.1)	17 (17.2)	95 (13.7)	0.349
Use of invasive ventilation at admission, n (%)	103 (13.0)	17 (17.2)	86 (12.4)	0.184

ICU: intensive care unit; IQR: interquartile range; kg: kilogram; m: meter; mg/dL: milligram per deciliter; ng/mL: nanogram per deciliter; µL: microliter.

On admission, the median oxygen saturation was 83% (IQR 70-88), a NEWS score ≥ 7 was found in 580 (87%), a MuLBSTA score ≥ 11 in 156 (20%), and 785 (99%) had multiple lobe involvement in the initial chest CT scan. There were no differences among severity scores between groups. The median time from symptom onset to hospital admission was shorter in the tocilizumab group (7 [IQR 5-9] days vs. 8 [IQR 6-10] days, $p < 0.05$) (Table S1, Supplementary material). Laboratory test results on admission did not differ between groups, except for D-dimer (Table S2). Median PaO_2/FiO_2 was 197 in 766 patients. Interferon-gamma release assay (IGRA) for latent tuberculosis was positive more frequently among patients who received tocilizumab (11/74 [15%] vs. 9/138 [7%], $p < 0.05$).

On admission, 103/794 patients (13%) were placed on IMV. Chloroquine/hydroxychloroquine and steroids were used in 219/794 (28%) and 73/794 (9%) patients, respectively. Among patients who received steroids, 40/73 (55%) received hydrocortisone for refractory circulatory shock, 17/73 (23%) received methylprednisolone, and 16/73 (22%) received low-dose prednisone due to prior chronic steroid treatment. Empiric antibiotic treatment was prescribed in 744/794 (94%) patients, and β-lactams were the most commonly prescribed agents. Therapeutic anticoagulation during follow-up was more commonly used in the tocilizumab group (40/99 [40%] vs. 66/695 [10%], $p < 0.01$).

Hospital follow-up and tocilizumab administration

At 72 h after hospital admission, the median lymphocyte count was 901 cells/µL and the median PaO_2/FiO_2 ratio was 115.4; no differences between groups were observed. Patients who received tocilizumab had higher median concentrations of CRP (17.8 vs. 11.3 mg/dL, $p < 0.01$), LDH (409 vs. 314 U/L, $p < 0.01$), ferritin (983 vs. 659 ng/mL, $p < 0.01$), and procalcitonin (0.52 vs. 0.26 ng/mL, $p < 0.05$). No differences were seen in liver function tests, blood cell counts, D-dimer, creatine phosphokinase, and troponin I (Table S3).

The median time from symptom onset to tocilizumab administration was 11 (IQR 9-13) days and the median time from admission to tocilizumab 4 (IQR 2-6) days. Thirty patients (30%) received the drug 24 h or more after IMV onset. The median total dose was 400 mg (range: 200-800 mg). Five patients received two doses of tocilizumab within the first 24 h after the first dose. After tocilizumab, the median CRP level decreased from 19.2 to 4.8 mg/dL ($p < 0.01$), and median alanine aminotransferase (ALT) and aspartate aminotransferase (AST) levels increased from 40.3 to 58.5 and 47.7 to 70.6 U/L ($p < 0.01$), respectively. The median lymphocyte count increased from 756.8 to 916.8 cells/µL ($p < 0.05$) while the median neutrophil count decreased from 6483 to 4415 cells/µL ($p < 0.01$). No differences were seen in other

Table 2. Severe and critical COVID-19 patients' outcomes regarding tocilizumab use

Outcomes	All patients, (n=656) (100%)	Received tocilizumab, (n=82) (12%)	Did not receive tocilizumab, (n=574) (88%)	p
Discharge, n (%)	433 (66.0)	54 (65.9)	379 (66.6)	0.975
Death, n (%)	223 (34.0)	28 (34.2)	195 (34.0)	
ICU admission during follow-up, n (%) (n=547)	89 (16)	30/65 (46)	59/482 (12)	<0.0001
Use of invasive mechanical ventilation during follow-up, n (%) (n=555)	82 (15)	30/65 (46)	52/490 (11)	<0.0011
Duration of mechanical ventilation in survivors, days, median (IQR) (n=87)	13 (11-18)	13 (11-21) n=27	14 (11-18) n=60	0.9267
Ventilator-free days in IMV survivors, median (IQR) (n=87)	12 (7-17)	10 (6-16) n=27	12 (8-17) n=60	0.361
Length of stay median in survivors, days, median (IQR) (n=433)	8 (5-14)	16 (10-30) n=54	7 (5-12) n=379	<0.0001
Hospital-acquired infection, n (%)	74 (11.3)	18 (22.0)	62 (9.8)	0.001
HAP/VAP, n (%)	49 (7.5)	13 (15.9)	36 (6.3)	0.002
Bloodstream infection, n (%)	28 (4.3)	7 (8.5)	21 (3.6)	0.041
Hospital-acquired infection in patients who received mechanical ventilation, n (%)	72/183 (39.3)	18/47 (38.3)	54/136 (39.7)	0.865
Circulatory shock, n (%) (n=653)	169 (25.9)	41 (50)	128 (22.5)	<0.0001
Renal replacement therapy, n (%) (n=563)	31 (4.8)	1 (1.2)	30 (5.3)	0.161

ICU: intensive care unit; IMV: invasive mechanical ventilation; IQR: interquartile range; HAP/VAP: hospital-acquired pneumonia/ventilator-associated pneumonia.

laboratory tests, including PaO_2/FiO_2 ratio (116 vs. 116, p = 0.95) (Table S4).

At 7 days after hospital admission, patients who received tocilizumab had lower CRP levels (3.0 vs. 10.5 mg/dL, p < 0.01) and higher median transaminase levels (72.9 vs. 41.6 U/L for ALT and 52.9 vs. 68 U/L for AST, p < 0.01). The median PaO_2/FiO_2 ratio was similar between groups (122 vs. 132, p = 0.22) (Table S5). No cases of fulminant hepatitis, intestinal perforation, or febrile neutropenia were observed.

Outcomes

Among 656/794 (85%) patients with complete follow-up, 223/656 (34%) died and 433/656 (66%) were discharged. Among patients with incomplete follow-up, 124/138 (90%) were transferred to another facility and 14/138 (10%) were discharged against medical advice for unspecified reasons (Fig. 1).

Outcomes are described in Table 2. No difference in hospital mortality was seen between groups (28/82

[34%] vs. 195/574 [34%], p = 0.98), even after excluding those who received the drug ≥ 24 h after IMV (12/52 [23%] vs. 195/574 [34%], p = 0.110). During follow-up, patients who received tocilizumab were more frequently admitted to the ICU (30/65 [46%] vs. 59/482 [12%], p < 0.01) and intubated (40/65 [46%] vs. 52/490 [11%], p < 0.01). IMV duration in survivors was similar between groups (13 vs. 13 days, p = 0.92). No difference in VFDs at 28 days was observed between groups (median of 10 vs. 12 days, p = 0.36). Circulatory shock was more common in the tocilizumab group (41/82 [50%] vs. 128/574 [22%], p < 0.01). The LOS in survivors was longer in the tocilizumab group (16 vs. 7 days, p < 0.01). A total of 110 HAIs were registered in 74 patients. Overall, HAIs were more frequent in the tocilizumab group (18/82 [22%] vs. 62/574 [10%], p < 0.01). Hospital-acquired/ventilator-associated pneumonia (HAP/VAP) and bloodstream infection (BSI) were more frequent in the tocilizumab group, although no difference was seen after adjusting for mechanical ventilation use (18/47 [38%] in the tocilizumab group vs. 54/136 [40%] in the control group, p = 0.87). The most frequent causes of HAP/VAP were Gram-negative bacilli, particularly *Enterobacteriaceae,* in 48/69 isolates (70%). The most frequent causes of BSI were coagulase-negative staphylococci in 14/35 isolates (40%). Invasive fungal infections included six episodes of candidemia and 14 episodes of COVID-19-associated aspergillosis (CAPA). No differences between groups were observed regarding candidemia (0 in the tocilizumab group vs. 6 in the non-tocilizumab group, p = 0.45) or CAPA (3 in the tocilizumab group vs. 11 in the non-tocilizumab group, p = 0.40).

Mortality

Bivariate analysis showed increased hospital mortality with advanced age, male sex, DM, hypertension, higher Charlson score, higher Nutri-CoV category, lower SpO_2 on admission, increased MuLBSTA and NEWS scores, lymphopenia, higher inflammatory marker levels, lower PaO_2/FiO_2 ratio at baseline, use of adjuvant steroids, and IMV. Tocilizumab was not associated with mortality (RR 1.0 [95%CI 0.73-1.39], p = 0.98). When analysis was restricted to patients who received IMV at any point, tocilizumab was not associated with decreased mortality (RR 0.76 [95%CI 0.53-1.10], p = 11). In multivariate analysis, age, male sex, higher Nutri-CoV category, high CRP, and IMV, but not tocilizumab administration, were independently associated with increased mortality (Table 3). Tocilizumab administration before or within the first 24 h after IMV onset was not independently associated with decreased mortality in bivariable or multivariate analysis (RR 0.68 [95%CI 0.41-1.13], p = 0.11). A propensity score analysis using data from 586 patients with complete follow-up was estimated. The baseline variables included in the model were age, sex, DM, obesity, hypertension, chronic obstructive pulmonary disease, immunosuppression, health care worker status, SpO_2 ≤ 90%, lymphopenia < 800 cells/μL, CRP > 10 mg/dL, DD > 1000 ng/mL, steroid use, and mechanical ventilation in the first 24 h after admission. The variance ratio of age (the only continuous variable included) was 1.21. Adequate balance within the matched sample was achieved (Table S6). A total of 73 treated patients were matched with 66 untreated controls. A regression adjustment for in-hospital mortality in the matched sample showed an adjusted odds ratio of 1.22 (95%CI 0.52-2.86, p = 0.66) for tocilizumab treatment. No significant treatment effects were observed (difference 0.014, p = 872) (Table 4).

DISCUSSION

We conducted a cohort study to describe the effect of tocilizumab in hospital mortality of patients with severe COVID-19. After a rigorous comparative analysis between groups, we observed that tocilizumab was not associated with a decrease in hospital mortality in patients with severe or critical COVID-19. Advanced age, male sex, DM, hypertension, increased disease severity, and selected laboratory tests results were associated with increased mortality in the bivariate analysis. After multivariate analysis, age, male sex, and the use of IMV were independently associated with increased mortality, as described in previous reports[28-30]. CRP > 10 mg/dL has been previously related to increased mortality, in agreement with our results[31]. As previously reported[26,32], increasing Nutri-CoV category was also independently associated with mortality.

Numerous studies evaluating the efficacy of tocilizumab for COVID-19 have shown contradictory results. A retrospective cohort study by Biran et al.

Table 3. Factors associated with mortality

Characteristic	RR (95CI%), p	aOR (95%CI), p
Age	1.06 (1.04-1.08), <0.001	1.07 (1.04-1.09), <0.001
Age >60 years[a]	2.33 (1.9-2.87), <0.0001	–
Male sex	1.34 (1.06-1.69), 0.0112	1.78 (1.12-2.83), 0.015
Diabetes mellitus[a]	1.46 (1.17-1.8), 0.0009	–
Hypertension	1.41 (1.14-1.74), 0.002	1.01 (0.63-1.62), 0.964
Charlson comorbidity index ≥2[b]	2.22 (1.78-2.77), <0.0001	–
Nutri-CoV category	5.37 (3.86-7.47), <0.001	3.48 (2.34-5.15), <0.001
Baseline SpO_2 ≤90%[a]	4.68 (1.57-13.98), 0.0003	–
NEWS score ≥7[b]	1.69 (1.37-2.08), <0.0001	–
MuLBSTA score ≥11[b]	2.00 (1.64-2.45), 0.0001	–
Absolute lymphocyte count <800 cells/µL	1.63 (1.30-2.06), <0.0001	1.41 (0.90-2.21), 0.133
C-reactive protein >10 mg/dL	3.78 (2.51-5.67), <0.0001	2.45 (1.35-4.42), 0.003
Lactate dehydrogenase >245 U/L[c]	8.36 (2.75-25.41), <0.0001	–
Troponin I ≥20 pg/mL[c]	3.00 (2.48-3.63), <0.0001	–
Ferritin >500 ng/mL[c]	1.52 (1.2-1.93), 0.0003	–
D-dimer >1000 ng/mL	1.79 (1.45-2.22), <0.0001	1.46 (0.94-2.27), 0.094
PaO_2/FiO_2 ratio <300[c]	1.62 (1.06-2.51), 0.016	–
Adjuvant steroids	1.77 (1.39-2.26), <0.0001	1.67 (0.85-3.24), 0.130
ICU admission	2.1 (1.71-2.57), <0.0001	–
Use of mechanical ventilation	1.95 (1.6-2.39), <0.0001	3.01 (1.78-5.10), <0.001
Treatment with tocilizumab	1.00 (0.73-1.39), 0.9751	1.09 (0.58-2.06), 0.782
Hospital-acquired infection	1.29 (0.98-1.71), 0.0865	–

N=587. PseudoR2 0.32 Area under the curve 0.86.
[a]Advanced age, diabetes, and baseline SpO_2 were not included in the model because they are included in the Nutri-CoV score.
[b]As Nutri-CoV score was included in the model, Charlson, NEWS, and MuLBSTA scores were not included.
[c]Elevated lactate dehydrogenase, troponin I, ferritin, and PaO_2/FiO_2 ratio were not included in the model to avoid excessive laboratory abnormalities that are known to be present in patients with severe COVID-19.
[d]ICU admission was not included in the model because in our center, ICU admission is highly concordant with the use of mechanical ventilation.
NEWS: National Early Warning Score; FiO_2: fraction of inspired oxygen; mg/dL: milligram per deciliter; ng/mL: nanogram per milliliter; PaO_2: partial pressure of oxygen in arterial blood; pg/mL: picograms per milliliter; U/L: units per liter; µL: microliter.

Table 4. Treatment effect estimation

Sample	Treated	Untreated	Coefficient (SE)	95%CI, p
Treatment effect	0.356	0.342	0.014 (0.085)	–0.153-0.180, 0.872

SE: standard error.

reported lower mortality rates in critically ill patients who received tocilizumab (49% vs. 61%), including those on IMV[10]. Accordingly, two meta-analyses including data from cohort studies concluded that tocilizumab was associated with lower mortality[14,15]. Another meta-analysis reported that tocilizumab decreased the probability of IMV[16]. Results from EMPACTA showed that tocilizumab reduced the likelihood of progression to mechanical ventilation or death[17]. Results from the RECOVERY study group reported lower mortality rates among patients who received tocilizumab[18]. In contrast, results from COVACTA revealed no difference in clinical status or 28-day mortality, but found a shorter median time to hospital discharge in patients who received tocilizumab[11]. Similarly, another multicenter RCT by Stone et al. concluded that tocilizumab did not prevent intubation or death[12]. Recently, an open-label RCT carried out in India reported that tocilizumab did not reduce COVID-19 progression, in a health-care setting which may be more relatable to ours[19]. Furthermore, another meta-analysis using data from five RCT did not find reduced mortality[13]. In our study, patients received tocilizumab after a median of 11 days after symptom onset; so, it is likely that acute respiratory distress syndrome had been already established before the drug administration. We observed a non-significant trend for decreased mortality among patients who received tocilizumab before or within the first 24 h after IMV onset. Since 30% received the drug more than 24 h after IMV onset, it is likely that late treatment had an impact on the outcome, although the optimal timing is yet to be proven[33]. A recently published observational study reported a lower 90-day mortality in patients that received tocilizumab within the first 10 days after symptom onset when compared with those that received the drug after day 11[34]. In our study, the prolonged time from admission to tocilizumab administration was due to low availability and high cost of the drug in our setting. Several differences were noted among patients who received tocilizumab due to the non-randomized nature of the study. Tocilizumab was more frequently used in males who may present with more severe forms of COVID-19[35], and among health care workers, reflecting selection bias. Patients in the tocilizumab group had elevated CRP, LDH, and ferritin levels during follow-up, which are known to be associated with increased mortality and may have led the decision to prescribe the drug[36]. Furthermore, patients who received tocilizumab were more likely to be admitted to the ICU for IMV and had a longer LOS, reflecting increased disease severity during follow-up. In an effort to minimize confounding, a propensity score matching analysis was performed, and no significant treatment effects were observed.

Tocilizumab was not associated with increased frequency of HAIs after adjusting for IMV, which is compatible with previous RCT results[11,12,17]. Latent tuberculosis screening is not routinely recommended in rheumatological patients, but it has been a concern in countries with a high tuberculosis incidence during the pandemic[37,38]. Screening for latent tuberculosis was done in a low proportion of our patients. No cases of tuberculosis reactivation were diagnosed during follow-up. No other severe adverse events such as gastrointestinal perforation or febrile neutropenia related to tocilizumab were recorded.

During the study period, steroid treatment was not yet part of the standard of care, and those who received them were frequently diagnosed with refractory circulatory shock, explaining the increased mortality seen on bivariate analysis for this subset of patients. Of note, the fact that tocilizumab, in contrast with the EMPACTA and RECOVERY trials[17,18], was not administered with steroids, could have played a role in our results. The COVACTA and BACC Bay trials, which did not find differences in mortality, also reported a lower corticosteroid use in the tocilizumab group[11,12].

Baseline demographic characteristics were consistent with previous reports from our country, which include a high prevalence of obesity, DM, and hypertension in COVID-19 patients and in the general population[39,40]. Alarmingly, a high use of unnecessary antibiotics was found[41-44].

Our study has several limitations. This was an observational cohort study with unbalanced groups even after adjusting for confounders. It is possible that a small sample size rendered insufficient power to detect differences in mortality similar to those reported in clinical trials[11,12,17,18]. Tocilizumab use was not systematic regarding dose and timing, which led to variability of prescriptions, although a response in laboratory results in the first 48 h was seen, as previously described[45]. Furthermore, 17% of patients were lost to follow-up and not included in outcome analysis. The main reasons for this were improvement and transfer to a convalescence center or transfer to other hospitals with available ICU space at the time due to disease progression. ICU unavailability during the peak of the pandemic contributes to mortality[46].

We consider that this study reflects non-systematic and individual physician-based prescription during the early months of the pandemic. This analysis also allows a description of adverse events, including HAIs. The late use of tocilizumab or other immunomodulatory treatments is a real-world situation in countries where drugs are costly and not widely available. We believe that this was a common practice during the study period since high-impact trials were not yet published. This report provides additional evidence about the effect and safety of tocilizumab for COVID-19 in settings outside controlled clinical trials, where the health-care system is constantly overrun, and some treatments may not be widely available.

In conclusion, we did not observe an association between tocilizumab and reduced hospital mortality among patients with severe or critical COVID-19. Advanced age, male sex, elevated inflammatory markers, and mechanical ventilation were associated with increased mortality. Tocilizumab appeared to be safe, as no severe adverse effects were registered. Even though no benefit on mortality was observed, early administration may be beneficial. Physicians should consider setting-specific factors when prescribing tocilizumab. In Mexico, drug availability and cost could represent barriers for optimal drug timing and dosing. The present study, underscores that tocilizumab, if considered for therapy, should be used in strict adherence to current guidelines and high-quality evolving evidence.

SUPPLEMENTARY DATA

Supplementary data are available at DOI: 10.24875/RIC.21000404. These data are provided by the corresponding author and published online for the benefit of the reader. The contents of supplementary data are the sole responsibility of the authors.

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