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Austin R. Morrison

Joseph M. Johnson

Kristin M. Griebe

Mathew C. Jones

John J. Stine

See next page for additional authors

Authors

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Clinical characteristics and predictors of survival in adults with coronavirus disease 2019 receiving tocilizumab

Austin R. Morrison[a], Joseph M. Johnson[a], Kristin M. Griebe[a], Mathew C. Jones[a], John J. Stine[a], Laura N. Hencken[a], Long To[a], Monica L. Bianchini[b], Amit T. Vahia[c], Jennifer Swiderek[d], Mayur S. Ramesh[c], Michael A. Peters[a], Zachary R. Smith[a,*]

[a] Department of Pharmacy, Henry Ford Hospital, 2799 West Grand Blvd, Detroit, MI, 48202, USA
[b] Department of Clinical Pharmacy, University of Colorado Anschutz Medical Campus, 13001 E 17th Pl, Aurora, CO, 80045, USA
[c] Division of Infectious Diseases, Henry Ford Hospital, 2799 West Grand Blvd, Detroit, MI, 48202, USA
[d] Division of Pulmonary & Critical Care Medicine, Henry Ford Hospital, 2799 West Grand Blvd, Detroit, MI, 48202, USA

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ABSTRACT

Coronavirus disease 2019 (COVID-19) can progress to cytokine storm that is associated with organ dysfunction and death. The purpose of the present study is to determine clinical characteristics associated with 28 day in-hospital survival in patients with coronavirus disease 2019 (COVID-19) that received tocilizumab. This was a retrospective observational cohort study conducted at a five hospital health system in Michigan, United States. Adult patients with confirmed COVID-19 that were admitted to the hospital and received tocilizumab for cytokine storm from March 1, 2020 through April 3, 2020 were included. Patients were grouped into survivors and non-survivors based on 28 day in-hospital mortality. Study day 0 was defined as the day tocilizumab was administered. Factors independently associated with in-hospital survival at 28 days after tocilizumab administration were assessed. Epidemiologic, demographic, laboratory, prognostic scores, treatment, and outcome data were collected and analyzed. Clinical response was collected and defined as a decline of two levels on a six-point ordinal scale of clinical status or discharged alive from the hospital. Of the 81 patients included, the median age was 64 (58–71) years and 56 (69.1%) were male. The 28 day in-hospital mortality was 43.2%. There were 46 (56.8%) patients in the survivors and 35 (43.2%) in the non-survivors group. On study day 0 no differences were noted in demographics, clinical characteristics, severity of illness scores, or treatments received between survivors and non-survivors. C-reactive protein was significantly higher in the non-survivors compared to survivors. Compared to non-survivors, recipients of tocilizumab within 12 days of symptom onset was independently associated with survival (adjusted OR: 0.296, 95% CI: 0.098–0.889). SOFA score ≥ 8 on day 0 was independently associated with mortality (adjusted OR: 2.842, 95% CI: 1.042–7.753). Clinical response occurred more commonly in survivors than non-survivors (80.4% vs. 5.7%; $p < 0.001$). Improvements in the six-point ordinal scale and SOFA score were observed in survivors after tocilizumab. Early receipt of tocilizumab in patients with severe COVID-19 was an independent predictor for in-hospital survival at 28 days.

1. Introduction

As of June 3, 2020 over 1.8 million cases of coronavirus disease 2019 (COVID-19) have been identified in the United States with over 105,000 deaths reported [1]. The severity of COVID-19 ranges from asymptomatic to severe disease [2–4]. Severe disease often requires admission to the intensive care unit (ICU) [4–6]. Mortality rates of critically ill patients with COVID-19 range from 16 to 78% [7]. Pharmacologic treatment options have been proposed for COVID-19, including antivirals and immunomodulators [8]. Antivirals have not demonstrated reductions in mortality to date [9–12]. Immunomodulators remain a possible therapeutic option based on the pathophysiologic understanding of COVID-19 [13–15].

COVID-19 can progress in two overlapping phases described as an initial viral response followed by a host inflammatory response [16]. The host response includes an unregulated pro-inflammatory cytokine storm resulting in lung injury, development of acute respiratory distress syndrome (ARDS), and death [16,17]. Interleukin-6 (IL-6) is theorized

* Corresponding author. Department of Pharmacy, Henry Ford Hospital, 2799 West Grand Boulevard, Detroit, MI, 48202, USA.
E-mail address: zsmith1@hfhs.org (Z.R. Smith).

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to play a significant role in the COVID-19 related cytokine storm [13–16]. Tocilizumab, an IL-6 receptor antagonist, has garnered interest as a possible treatment option [8,14,18]. The use of IL-6 receptor antagonists is recommended in the setting of clinical trials [19,20]. Risks of immunomodulator use include propagation of COVID-19 progression by interfering with innate antiviral immunity, development of secondary infections, and adverse drug effects [21–24]. Given the high mortality rates observed in severe COVID-19, clinicians have used off-label tocilizumab and other immunomodulatory agents in practice in select cases [25–29].

Literature to date on tocilizumab in COVID-19 has described outcomes at 14 days, predominately in those with less severe disease, and with limited descriptions of adverse effects. The factors associated with a beneficial response from tocilizumab are unknown. We report the clinical characteristics associated with in-hospital survival at 28 days in patients with COVID-19 receiving off-label tocilizumab.

2. Materials and methods

2.1. Study design and participants

This was a retrospective cohort study of patients admitted to a five-hospital health system in southeast and south-central Michigan. The study was approved by Henry Ford Health System's Institutional Review Board (IRB #13809) with waiver of consent.

Patients hospitalized from March 1, 2020 through April 3, 2020 were eligible for inclusion if they were 18 years of age or older, had confirmed COVID-19 infection, and received tocilizumab. Patients were excluded if they were transferred from an out-of-system hospital, had a positive microbiologic culture 24 h prior to or 48 h after tocilizumab administration that was treated with an antimicrobial, were pregnant, or incarcerated. A confirmed case of COVID-19 was defined as a patient with positive reverse-transcriptase–polymerase-chain-reaction (RT-PCR) assay for severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) in a nasopharyngeal sample tested by the Michigan Department of Health and Human Services or the health system's centralized clinical microbiology laboratory.

Patients were risk stratified by symptoms prior to tocilizumab administration as mild, moderate, or severe COVID-19. Patients without hypoxia or exertional dyspnea were considered to have mild COVID-19. Patients who presented with infiltrates on chest radiography and required supplemental oxygen by nasal cannula or high-flow nasal cannula (HFNC) were classified as having moderate COVID-19. Patients who had respiratory failure requiring invasive mechanical ventilation were classified as having severe COVID-19 [30]. All patients were followed for up to 28 days from the first dose of tocilizumab. Patient data was censored on April 30, 2020.

2.2. Study procedures

Hospitalized patients with COVID-19 received supportive care comprised of supplemental oxygen, HFNC, invasive mechanical ventilation, antibiotics, vasopressors, and renal-replacement therapy, as determined by the primary team. Patients who progressed to ARDS were managed with lung protective ventilation strategies [19]. An institutional treatment COVID-19 guideline was developed that included lopinavir-ritonavir with ribavirin or hydroxychloroquine monotherapy based on disease severity. Intravenous (IV) remdesivir was available for compassionate use or within a clinical trial. The institutional guidelines were developed by consensus, and based on the available literature, experience from Wuhan, China and other centers around the world affected by COVID-19 before Michigan. On March 17, 2020 lopinavir-ritonavir with ribavirin was removed [9]. A short course of corticosteroids was added to the institutional guideline for patients with moderate to severe COVID-19 on March 20, 2020 [19,30]. Tocilizumab was used on a case-by-case basis for patients exhibiting symptoms of cytokine storm, as described below, when assessed by the primary and infectious disease physician.

Patients were eligible for tocilizumab if exhibiting persistent fevers (38.0 °C for greater than 6 h), had a partial pressure of oxygen to fraction of inspired oxygen ratio less than 200, and exhibited persistently rising inflammatory laboratory parameters (ferritin, D-dimer, and lactate dehydrogenase (LDH)) or an elevated inflammatory laboratory parameter defined as a ferritin ≥1000 μg/L, D-dimer ≥ 5 mg/mL, or LDH ≥ 500 U/L. An IL-6 level ≥ five times the upper limits of normal (≤5 pg/ml) was assessed in addition to the above parameters. Bacterial, fungal, and alternate viral infections were to be ruled out prior to tocilizumab administration. Tocilizumab was administered as an 8 mg/kg IV dose using actual body weight with a maximum dose of 800 mg. Doses were rounded to 400 mg, 600 mg, or 800 mg. Patients were eligible for a second dose if persistently febrile despite treatment. Due to medication shortages the tocilizumab dose was changed to a fixed 400 mg IV dose for all patients on March 30, 2020.

2.3. Data collection

Data was ascertained from the health system's electronic medical record and recorded in a standardized electronic case report form. Demographic data, information on clinical symptoms at presentation, vital signs, laboratory tests, chest radiograph results, COVID-19 treatments received prior to tocilizumab, length of stay, and discharge disposition were collected. Baseline data was defined as information collected within 24 h from emergency department presentation. Study day 0 was defined as the first day tocilizumab was administered.

The comorbidity, age, lymphocyte, and LDH (CALL) score was calculated at baseline [31]. The score ranges from 4 to 13, with increased values predicting higher likelihood of progressing to severe COVID-19. The sequential organ failure assessment (SOFA) score and a six-point ordinal scale of clinical status (as recommended by the World Health Organization R&D Blueprint Group) were collected at baseline and after tocilizumab administration [10,32]. The six-category scale consists of the following categories: 1, not hospitalized; 2, hospitalized, not requiring supplemental oxygen; 3, hospitalized, requiring supplemental oxygen; 4, hospitalized, requiring HFNC, non-invasive mechanical ventilation, or both; 5, hospitalized, requiring invasive mechanical ventilation, ECMO, or both; and 6, death. The American Society for Transplantation and Cellular Therapy (ASTCT) consensus grading for cytokine release syndrome (CRS) used for chimeric antigen receptor T-cell therapy was collected prior to tocilizumab [33]. The ASTCT grading ranges from 1 to 5 and has three features including temperature, blood pressure, and oxygenation support to denote CRS grade. ARDS was diagnosed and classified according to the Berlin Definition [34]. Adverse effects observed in practice and those known to be associated with chronic tocilizumab use were collected. Infection after tocilizumab was defined as a positive microbiologic assay that prompted antimicrobials for the identified pathogen.

2.4. Outcome measures

Characteristics of non-survivors, defined as in-hospital death within 28 days of tocilizumab administration, were compared to survivors. Comparisons included assessment of demographics, time from symptom onset to tocilizumab administration ≤12 days, laboratory parameters, alternative treatments received, and prognostic scores collected [9]. Other endpoints evaluated included clinical response to tocilizumab, defined as a decline of two levels on the six-category scale or discharged alive from the hospital [10]. A comparison of laboratory parameters, SOFA score, six-category scale, and severity of ARDS in survivors and non-survivors from days 0–15 was completed. The six-category scale was also assessed at study day 28.

Table 1
Clinical characteristics and treatment prior to tocilizumab on day zero.

Characteristics	Total (n = 81)	Survivor (n = 46)	Non-Survivor (n = 35)	*p*-value
Demographics				
Median age (IQR) - yr	64 (58–71)	64 (59–70)	67 (51–72)	0.702
Male sex – no. (%)	56 (69.1)	29 (63.0)	27 (77.1)	0.174
Race – no. (%)				0.616
African American	52 (64.2)	29 (63.0)	23 (65.7)	
Caucasian	24 (29.6)	13 (28.3)	11 (31.4)	
Other	5 (6.2)	4 (8.7)	1 (2.9)	
Median weight (IQR) - kg	102.1 (88.5–117.9)	101.4 (89.1–117.9)	104.3 (87- 119.8)	0.853
Median body mass index (IQR) - kg/m^2	33.2 (28.8–39.1)	34.2 (29.2–39.3)	31.4 (28.3–38.9)	0.341
Comorbidities – no. (%)				
Asthma	11 (13.6)	6 (13.0)	5 (14.3)	1.00
Chronic obstructive pulmonary disease	4 (4.9)	4 (8.7)	1 (2.9)	0.383
Congestive heart failure	8 (9.9)	3 (6.5)	5 (14.3)	0.281
Coronary artery disease	15 (18.5)	9 (19.6)	6 (17.1)	0.781
Diabetes	37 (45.7)	23 (50.0)	14 (40.0)	0.371
End stage renal disease	1 (1.2)	1 (2.2)	0 (0)	1.00
Hypertension	60 (74.1)	35 (76.1)	25 (71.4)	0.636
Clinical characteristics				
Inpatient disposition – no. (%)				0.693
General medical ward	7 (8.6)	5 (10.9)	2 (5.7)	
Intensive care unit	74 (91.4)	41 (89.1)	33 (94.3)	
COVID-19 classification – no. (%)				0.602
Mild	1 (1.2)	1 (2.2)	0 (0)	
Moderate	10 (12.3)	7 (15.2)	3 (8.6)	
Severe	70 (86.4)	38 (82.6)	32 (91.4)	
Treatment prior to tocilizumab – no. (%)				
Empiric antibiotics	58 (71.6)	35 (76.1)	23 (65.7)	0.305
Corticosteroids	57 (70.4)	31 (67.4)	26 (74.3)	0.501
Hydroxychloroquine	74 (91.4)	42 (91.3)	32 (91.4)	1.00
Lopinavir/ritonavir with ribavirin	4 (4.9)	2 (4.4)	2 (5.7)	1.00
Remdesivir	2 (2.5)	0 (0)	2 (5.7)	0.184
Prone mechanical ventilation	22 (27.2)	10 (21.7)	12 (34.3)	0.209
Neuromuscular blockade	14 (17.3)	6 (13.0)	8 (22.9)	0.247
Renal replacement therapy	1 (1.2)	1 (2.2)	0 (0)	1.00
Propofol sedation	50 (61.7)	27 (58.7)	23 (65.7)	0.520
Tocilizumab characteristics				
Median days of symptoms to tocilizumab (IQR)	10 (8–13)	9 (7–11)	11 (9–15)	0.038
≤12 days – no. (%)	60 (74.1)	38 (82.6)	22 (62.9)	0.0445
Number of doses – no. (%)				0.140
One	62 (76.5)	38 (82.6)	24 (68.6)	
Two	19 (23.5)	8 (17.4)	11 (31.4)	
First tocilizumab dose (mg)				
Median mg/kg dose (IQR)	6.8 (5–7.8)	7.4 (5.5–8.0)	6.1 (4.6–7.6)	0.074
Median dose (IQR)	800 (400–800)	800 (600–800)	800 (400–800)	0.212
Second tocilizumab dose (mg)				
Median mg/kg dose (IQR)	6.4 (4.4–7.8)	7.6 (5.4–8.1)	5.5 (4.4–6.9)	0.104
Median dose (IQR)	600 (400–800)	700 (500–800)	400 (400–800)	0.465
Median cumulative mg/kg dose (IQR)	7.6 (5.9, 8.8)	7.6 (6.2, 8.8)	7.6 (5.1, 9.1)	0.791
Median cumulative dose (IQR)	800 (600–800)	800 (600–800)	800 (600–800)	0.786
Laboratory results, median (IQR)				
Interleukin-6 (pg/mL)	22 (7.0–62) (n = 38)	12 (5–32) (n = 22)	47.5 (15.5–82) (n = 16)	0.126
C-reactive protein (mg/dL)	16.8 (11.2–27.2) (n = 67)	13.8 (9.5–21.5) (n = 37)	19.0 (14.4–32.7) (n = 30)	0.010
Ferritin, serum (ng/mL)	1470 (885–2543) (n = 71)	1066 (668–2041) (n = 37)	1923 (1332–3000) (n = 34)	0.141
Lactate dehydrogenase, serum (units/L)	462 (363.5–647.8) (n = 70)	431 (359–534) (n = 37)	485 (378–756) (n = 33)	0.301
D-dimer (mg/mL)	3.1 (1.9–10.9) (n = 58)	2.9 (1.8–9.2) (n = 34)	5.1 (2.3–20) (n = 24)	0.211
Clinical scores				
Median SOFA (IQR)	9 (6–11)	8 (5–10)	9 (7–11)	0.065
Median change in SOFA from baseline (IQR)	5 (2–8)	4 (1–8)	5 (3–8)	0.364
Six-category scale – no. (%)				0.755
2–Hospital admission, no supplemental oxygen	1 (1.2)	1 (2.2)	0 (0)	
3–Hospital admission, supplemental oxygen	3 (3.7)	2 (4.4)	1 (2.9)	
4–Hospital admission, requiring high-flow nasal cannula or non-invasive mechanical ventilation	7 (8.6)	5 (10.9)	2 (5.7)	

(*continued on next page*)

Table 1 (*continued*)

Characteristics	Total (n = 81)	Survivor (n = 46)	Non-Survivor (n = 35)	*p*-value
5–Hospital admission, requiring invasive mechanical ventilation or extracorpeal membrane oxygenation	70 (86.4)	38 (82.6)	32 (91.4)	
6–Death	0 (0)	0 (0)	0 (0)	
Acute respiratory distress syndrome – no. (%)	67 (82.7)	35 (76.1)	32 (91.4)	0.083
Acute respiratory distress syndrome severity – no. (%)				0.062
Mild	9 (13.4)	8 (22.9)	1 (3.3)	
Moderate	33 (49.3)	15 (42.9)	18 (56.3)	
Severe	25 (37.3)	12 (34.3)	13 (40.6)	
ASTCT cytokine release syndrome grading – no. (%)				0.592
Criteria not met	12 (14.8)	8 (17.4)	4 (11.4)	
Grade 1	1 (1.2)	1 (2.2)	0 (0)	
Grade 2	2 (2.5)	2 (4.4)	0 (0)	
Grade 3	6 (7.4)	4 (8.7)	2 (5.7)	
Grade 4	60 (74.1)	31 (67.4)	29 (82.9)	

*IQR denotes interquartile range, COVID-19 denotes coronavirus disease 2019, SOFA denotes sequential organ failure assessment, ASTCT denotes American Society for Transplantation and Cellular Therapy.

Table 2
Multivariate analysis of independent risk factors for in-hospital 28 day mortality.

Variable	Adjusted Odds Ratio	95% Confidence interval	*p*-value
Tocilizumab within ≤12 days of symptom onset	0.296	0.098–0.889	0.030
Male sex	2.363	0.809–6.903	0.116
SOFA score ≥8	2.842	1.042–7.753	0.041

The following variables were assessed for goodness of fit within the multivariate analysis and did not fit the model: age > 60, presence of acute respiratory distress syndrome, use of prone mechanical ventilation, body mass index greater than 30, CALL score ≥7, African American, presence of infection.
*SOFA denotes sequential organ failure assessment.

Table 3
Clinical outcomes at the end of the study day 28.

Clinical endpoints	Total (n = 81)	Survivor (n = 46)	Non-Survivor (n = 35)	*p*-value
Outcomes				
Clinical improvement per six-category scale with tocilizumab – no. (%)	39 (48.1)	37 (80.4)	2 (5.7)	< 0.001
Six-category scale by day 28 – no. (%)				< 0.001
1–Discharge (alive)	32 (39.5)	32 (65.6)	0 (0)	
2–Hospital admission, no supplemental oxygen	2 (2.5)	2 (4.4)	0 (0)	
3–Hospital admission, supplemental oxygen	4 (4.9)	4 (8.7)	0 (0)	
4–Hospital admission, requiring high-flow nasal cannula or non-invasive mechanical ventilation	0 (0)	0 (0)	0 (0)	
5–Hospital admission, requiring invasive mechanical ventilation or extracorpeal membrane oxygenation	8 (9.9)	8 (17.4)	0 (0)	
6–Death	35 (43.2)	0 (0)	35 (100)	
Hospitalization and disposition characteristics				
Mechanical ventilation at any time – no. (%)	77 (95.1)	43 (93.5)	34 (97.1)	0.630
Median days of mechanical ventilation (IQR)	10 (6–16)	10 (5–23)	9 (7–15)	0.157
Median days of intensive care unit (IQR)	12 (7–20)	12 (6–27)	11 (8–18)	0.181
Median days of hospitalization (IQR)	18 (13–29)	27.5 (14–31)	14 (9–20)	< 0.001
Hospital discharge disposition – no. (%)				
Still hospitalized	14 (17.3)	14 (30.4)	0 (0)	
Home	18 (22.2)	18 (39.1)	0 (0)	
Long term care facility	14 (17.3)	14 (30.4)	0 (0)	

*IQR denotes interquartile range.

2.5. Statistical analysis

Continuous variables were reported as median and interquartile range (IQR) and compared using the Mann-Whitney *U* test or student t-test, as appropriate. Categorical data was reported as number and percentage (no., %) and compared using the chi-squared test or Fisher's exact test, as appropriate. No imputations were made for missing data points. The sample size was derived from all eligible consecutive hospitalized patients during the study period. A two-sided $\alpha < 0.05$ was considered statistically significant. Bivariate and multivariate logistic regression analysis were planned a-priori to identify independent predictors associated with 28 day in-hospital survival. Covariates in the bivariate analysis with a *p*-value < 0.2 and clinical rationale were included in a multivariate regression model that was restricted to a subject-to-variable ratio of 10:1. Statistical analysis was performed using IBM SPSS version 25 (Chicago, IL) and SAS 9.4 (Cary, NC).

3. Results

A total of 92 patients with an order for tocilizumab were identified. Eleven were excluded, leaving 81 available for analysis in the study (Supplemental Fig. 1). The median age was 64 (58–71) years and 69.1% were male. The median time from COVID-19 symptom onset to hospital admission was 5 (3–7) days. The 28 day in-hospital mortality was 43.2%, leaving 46 patients in the survivors and 35 in the non-survivors group. On study day 0 patients were classified as having mild,

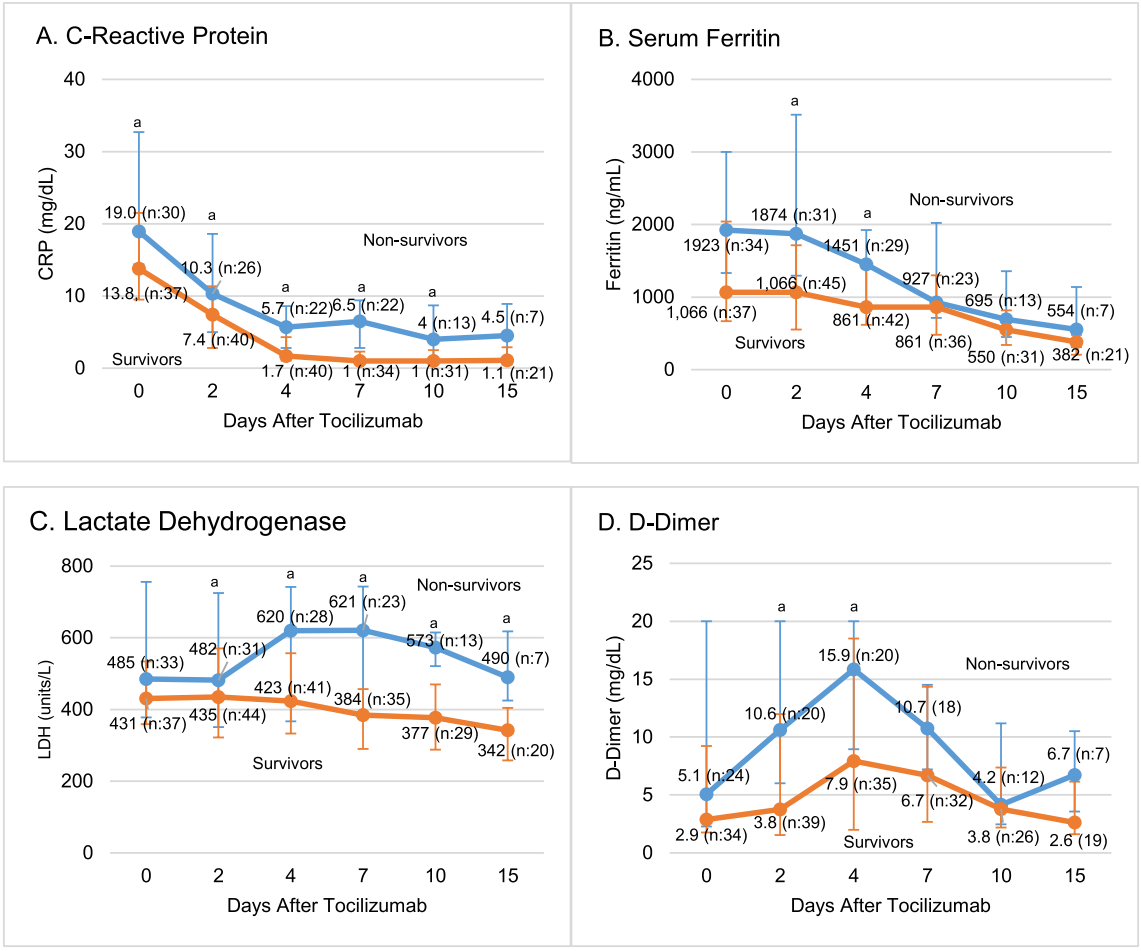

Fig. 1. Temporal changes in laboratory parameters after tocilizumab administration. Fig. 1 shows temporal changes in C-reactive protein, serum ferritin, lactate dehydrogenase, and D-Dimer. The n values in parenthesis represents the evaluable population in the data, if not representative of the entire cohort. Median values are shown by the circles graphed on the line, interquartile range is denoted by the error bars above and below the circles. [a] $p < 0.05$ for non-survivors vs survivors on study day. CRP = C-reactive protein, LDH = lactate dehydrogenase.

moderate, or severe COVID-19 in 1 (1.2%), 10 (12.3%), and 70 (86.4%) of cases, respectively. The median SOFA score was 9 (6–11) on day 0, and the median increase in the SOFA score from baseline was 5 (2–8). The C-reactive protein was higher in non-survivors (13.8 [9.5–21.5] vs. 19 [14.4–32.7] mg/dL; p = 0.01).

There were no differences observed in the prevalence of co-morbidities, rate of obesity, median SOFA score on day 0, or median change in SOFA score from baseline to day 0 between survivors and non-survivors. No other differences were noted between the survivors and non-survivors at baseline or on day 0 (Table 1 and Supplemental Table 1). The median days from symptom onset to tocilizumab administration was 10 (8–13) days. There was a difference in time from symptom onset to tocilizumab administration between survivors and non-survivors (9 [7–11] vs. 11 [9–15]; p = 0.038). There were no differences noted in the COVID-19 treatment characteristics or prognostic scores of survivors and non-survivors (Table 1).

The single independent predictor of 28 day in-hospital survival was receipt of tocilizumab within 12 days of symptom onset (adjusted OR: 0.296, 95% CI: 0.098–0.889). A SOFA score ≥8 was independently associated with 28 day in-hospital mortality (adjusted OR: 2.842, 95% CI: 1.042–7.753) (Table 2). Patients in the survivor group were more likely to have a clinical response to tocilizumab by day 28 (80.4% vs 5.7%; p = < 0.001). The hospital length of stay was longer in the survivors compared to non-survivors (27.5 [14–31] vs 14 [9–20]; p < 0.001). Fourteen (17.3%) patients remained hospitalized at the end of the study (Table 3). Numerical reductions in ferritin and CRP were observed in survivors and non-survivors after tocilizumab administration to study day 15. Lactate dehydrogenase declined in survivors from day 0–15. Significant differences were observed in CRP, LDH, D-Dimer, and ferritin levels when comparing survivors and non-survivors on select study days as depicted in Fig. 1. Improvements were observed in the six-category scale, SOFA score, and ARDS severity when comparing the survivors to non-survivors from study day 0–15 (Fig. 2).

Twenty-nine (35.8%) patients experienced hypertriglyceridemia with levels greater than 500 mg/dL. Of the patients that developed hypertriglyceridemia, eight did not receive propofol. All patients with elevated amylase and lipase levels received concurrent propofol. A total of 18 (22.2%) patients developed an infection. The median time to development of infection from tocilizumab was 9 (6–13) days. No difference was observed in the median time to development of infection between survivors and non-survivors. There was a total of seventeen (21.0%) bacterial infections and three (3.7%) fungal infections. No differences were noted in the occurrence of adverse effects between survivors and non-survivors (Supplemental Table 2).

4. Discussion

In this retrospective cohort study, the clinical characteristics, factors independently associated with survival, and 28 day outcomes in patients with COVID-19 after tocilizumab administration were described. Receipt of tocilizumab within 12 days of symptom onset in patients with COVID-19 was the only factor independently associated with in-

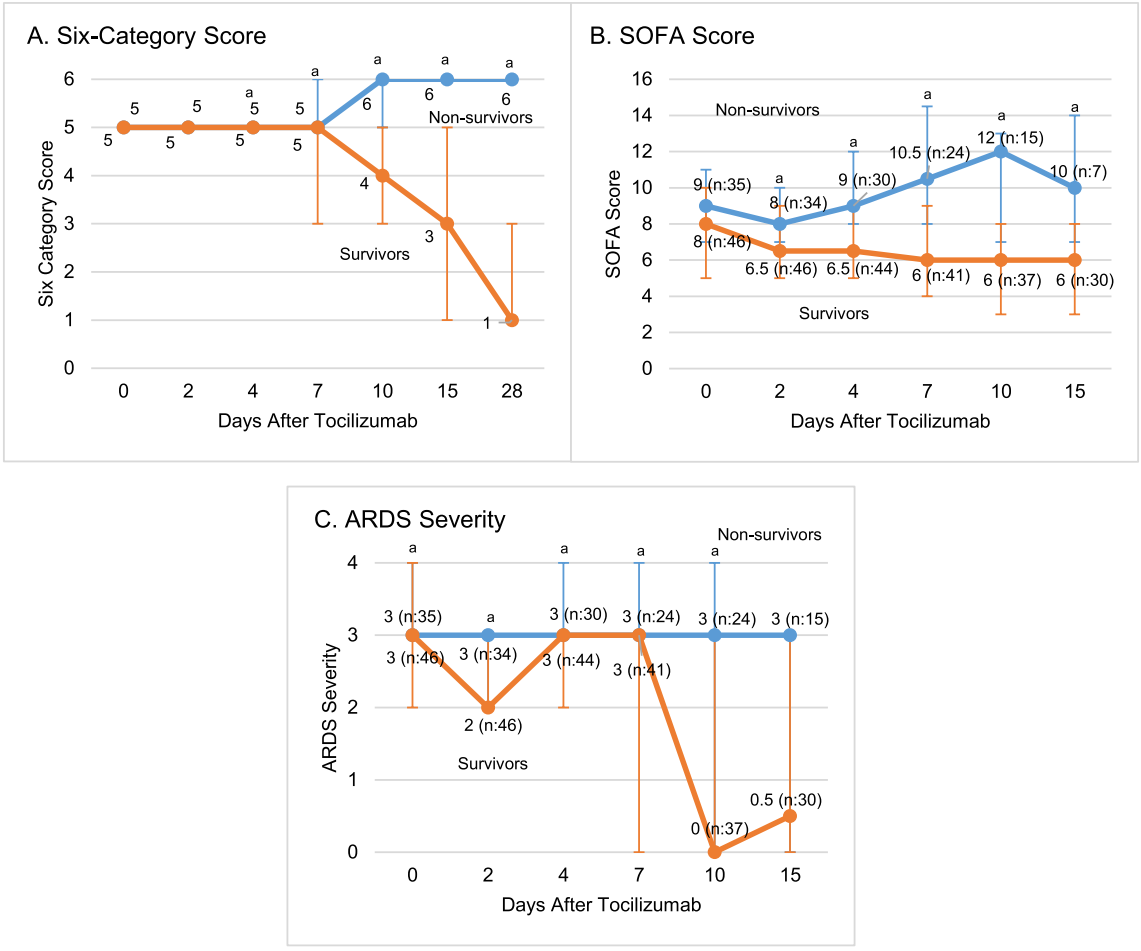

Fig. 2. Temporal changes in clinical scores after tocilizumab administration. Fig. 2 shows temporal changes in six-category score, SOFA score, ARDS severity. Median values are shown by the circles graphed on the line, interquartile range is denoted by the error bars above and below the circles. The n values in parenthesis represents the evaluable population in the data, if not representative of the entire cohort. For ARDS: 4 = severe, 3 = moderate, 2 = mild, 1 = invasive mechanical ventilation without ARDS, 0 = not receiving invasive mechanical ventilation. $_{a}\,p < 0.05$ for non-survivors vs survivors. SOFA = sequential organ failure assessment, ARDS = acute respiratory distress syndrome.

hospital survival at 28 days. A clinical response was more likely to occur in those that survived. The association with improved survival remained intact when adjusting for SOFA score and male sex. COVID-19 progression has been characterized by a biphasic response with the latter phase consisting of an excessive hyper-inflammatory response [16]. Early intervention to mitigate the cytokine storm with an immunomodulator may optimize patient outcomes. This study further supports that intervention timing relative to disease onset is a key factor [27].

The study population had a high likelihood for severe COVID-19 and mortality based on presenting CALL and SOFA scores [31,35]. High rates of obesity, hypertension, and diabetes were observed in the present study relative to previous epidemiologic reports of COVID-19 [5,7]. Rates of mechanical ventilation and mortality were higher compared to previous reports of tocilizumab use in COVID-19. Reasons for this difference in mortality may be explained by a difference in severity of illness, high rates of co-morbidities associated with severe COVID-19, a longer duration of follow-up, a higher rate of invasive mechanical ventilation, and rates of ARDS [25–28]. Mortality rates observed in the present study are similar to those reported for critically ill COVID-19 populations and the general ICU population with ARDS [7,36,37].

A SOFA score of ≥8 on day 0 was independently associated with mortality. A SOFA score of ≥3 on hospital presentation has been described as an independent predictor for mortality in the COVID-19 population [35]. An improvement was noted in survivors for SOFA scores and six-category scale. ARDS severity was also improved in survivors, a finding consistent with other immunomodulatory trials [29]. These findings are important to guide the use of off-label tocilizumab in those with cytokine storm associated with COVID-19 until results of randomized controlled trials are available.

No standard definition for cytokine storm related to COVID-19 exists. Previous studies have defined cytokine storm associated with COVID-19 using various threshold values for vital signs, CRP, IL-6, ferritin, and LDH [25–27,29]. CRP is the only common diagnostic marker amongst all published reports to date with values of 5–10 mg/dL (10–20 times the upper limits of normal) being used to define cytokine storm. Following tocilizumab administration in the present study, CRP was reduced in all patients, as seen in previous reports of tocilizumab and an IL-1 receptor antagonist, anakinra [25–29]. The ASTCT grading for CRS identified 85.2% of patients with cytokine storm, but this may be an imperfect diagnostic tool in the setting of COVID-19. Future research is needed to establish criteria to define cytokine storm associated with COVID-19 and identify progression of disease from the viral phase to the hyper-inflammatory phase [16]. Recent studies have demonstrated the effectiveness of antivirals in limiting disease severity [10,12]. A step-wise treatment approach using antiviral and immunomodulatory agents in succession for patients with

disease progression appears to be a viable therapeutic approach that may warrant research.

Hypertriglyceridemia occurred frequently in the present cohort, irrespective of propofol use. Clinicians should routinely monitor triglyceride levels, markers for pancreatitis, and secondary hemophagocytic lymphohistiocytosis (sHLH) if tocilizumab is administered. Due to the inflammatory markers associated with sHLH, an IL-6 antagonist may not prevent this complication, and continuous monitoring is paramount [23]. Secondary infections were noted in 22.2% of patients, which is higher than a previous report of 16%; however, rates in epidemiologic reports of critically ill COVID-19 populations describe a range of 4.7–32.5% [10,28,35,38,39]. If unable to enroll patients into a clinical trial, clinicians should consider a multidisciplinary approach to weigh the benefits and potential risks of off-label tocilizumab for COVID-19.

This study has several limitations. The study population included is predominately one that is critically ill with severe COVID-19, and results may not be applicable to less severe populations. This study was conducted within a single health system, with a limited sample size, and with no placebo comparator group. The study follow-up period was 28 days after tocilizumab administration which limits the assessment of long term efficacy and adverse effects. However, the follow-up is longer than what has been reported for tocilizumab and is consistent with duration of follow-up for antiviral agents [9,10]. The health system's COVID-19 guideline were modified during the study period, but the treatments received in both survivors and non-survivors was consistent.

5. Conclusion

The receipt of tocilizumab within 12 days of symptom onset may be a key factor independently associated with 28-day survival in COVID-19. Research is needed to define diagnostic criteria for cytokine storm associated with COVID-19, establish the clinical efficacy of tocilizumab in placebo-controlled trials, and further describe which COVID-19 populations may derive clinical benefit from tocilizumab.

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CRediT authorship contribution statement

Austin R. Morrison: Conceptualization, Methodology, Formal analysis, Investigation, Writing - review & editing. **Joseph M. Johnson:** Methodology, Investigation, Writing - original draft, Writing - review & editing. **Kristin M. Griebe:** Methodology, Investigation, Writing - review & editing. **Mathew C. Jones:** Methodology, Investigation, Writing - review & editing. **John J. Stine:** Investigation, Writing - review & editing. **Laura N. Hencken:** Investigation, Writing - review & editing. **Long To:** Investigation, Writing - review & editing. **Monica L. Bianchini:** Formal analysis, Writing - review & editing. **Amit T. Vahia:** Formal analysis, Writing - review & editing. **Jennifer Swiderek:** Writing - review & editing. **Mayur S. Ramesh:** Conceptualization, Methodology, Writing - review & editing, Supervision. **Michael A. Peters:** Conceptualization, Methodology, Formal analysis, Investigation, Writing - review & editing, Supervision. **Zachary R. Smith:** Conceptualization, Methodology, Formal analysis, Investigation, Writing - original draft, Writing - review & editing, Supervision.

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Appendix A. Supplementary data

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