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Original Article

Tocilizumab in COVID-19: The Cerrahpaşa-PREDICT score

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ABSTRACT

Background: Cytokine release syndrome (CRS), characterized by overproduction of proinflammatory cytokines in the course of severe coronavirus disease 2019 (COVID-19), has been suggested as the major cause of mortality. Tocilizumab, a recombinant humanized monoclonal antibody against human IL-6 receptor, poses a therapeutic option for the treatment of CRS leading to severe acute respiratory syndrome in coronavirus-2 (SARS-CoV-2) infection.

Methods: We performed a single-center retrospective study to reveal the outcome of COVID-19 patients on tocilizumab and proposed "the Cerrahpaşa-PREDICT score", a new clinical scoring system using clinical and laboratory parameters that would help predicting the 28-day mortality of COVID-19 patients receiving tocilizumab.

Results: Eighty-seven patients (median age: 59 years) were included of whom 75.8% were male. Tocilizumab use significantly improved clinical and laboratory parameters. The 28-day mortality rate on tocilizumab was 16.1%. The Cerrahpaşa-PREDICT score, consisting of platelet counts, procalcitonin, D-dimer levels, SO_2R and the time from symptom onset to tocilizumab administration had a positive predictive value of 94.5% and negative predictive value of 92.9% for anticipating 28-day mortality.

Conclusions: Severe COVID-19 should closely be monitored for the signs of hyperinflammation. We showed that administration of tocilizumab early in the course of the disease (prior to ICU admission) resulted in a favorable outcome. Close monitoring usually aids identifying patients who would benefit from tocilizumab. In this regard, the Cerrahpaşa-PREDICT score might serve as a practical tool for estimating the 28-day mortality in COVID-19 patients who received tocilizumab and would facilitate timely recognition of fatal cases to be evaluated for other therapeutic options.

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1. Introduction

An outbreak of a novel coronavirus disease (COVID-19) caused by severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) has started in China in December 2019 and spread globally [1]. In about 80% of the cases, the disease presents with mild symptoms and has a good prognosis, while in the remaining 20%, it usually progresses to severe pneumonia and acute respiratory distress syndrome (ARDS), resulting in multiple organ failure (MOF) and death [2]. Cytokine release syndrome (CRS) caused by the overproduction of proinflammatory cytokines including interleukin (IL)-1 and IL-6 has been suggested to underlie the secondary hemophagocytic lymphohistiocytosis (sHLH) and the subsequent fatal lung involvement observed in severe COVID-19 [3–5].

IL-6 plays a central role in the pathogenesis of CRS, thus, blocking IL-6 receptors (IL-6Rs) might be beneficial and lifesaving in patients with COVID-19 experiencing CRS [6]. Tocilizumab (ACTEMRA®), a recombinant humanized monoclonal antibody against human IL-6R, has been included in the Turkish COVID-19 Management Guidelines as a therapeutic option for the treatment of severe SARS-CoV-2 infection [7,8].

There are studies published on the impact of tocilizumab use in COVID-19 [9–16], and we aimed to report our experience on tocilizumab therapy in this single-center retrospective study. Herewith, we also propose a new scoring system predicting 28-day mortality in COVID-19 patients receiving tocilizumab.

2. Methods

2.1. Patients

Adult patients with SARS-CoV-2 infection who received tocilizumab at Cerrahpaşa Faculty of Medicine between 16 March and May 01, 2020 were included. Diagnosis of COVID-19 was made on the basis of clinical, laboratory, and radiological findings and confirmed by the detection of SARS-CoV-2 RNA in oro-nasopharyngeal swab samples using reverse transcriptase – polymerase chain reaction (RT-PCR) [17,18]. In patients with initial RT-PCR negativity, sequential testing was performed especially in cases with typical clinical or radiological findings suggesting COVID-19.

The presenting signs and symptoms, vital signs and oxygen saturation on room air (SO2R), and laboratory results including complete blood count, C-reactive protein (CRP), procalcitonin, ferritin, lactate dehydrogenase (LDH), fibrinogen and D-dimer levels together with information on comorbidities and medications were obtained from patient files. Patients were classified as mild/moderate, severe, and critical as described by the WHO [2].

The study was approved by the local ethics committee for clinical trials (Date: April 21, 2020 and Number: 83045809-604.01.02) and the Review Board of the Turkish Ministry of Health.

2.2. Chest CT protocol

Chest computerized tomography (CT) scan was performed in all patients with risk factors or clinical evidence of pneumonia, unless contraindicated. All CT images were retrospectively reevaluated and scored using a revised CT scoring criteria [18] by a radiologist, who was blinded to the RT-PCR results and clinical status of the patients.

2.3. Initial COVID-19 treatment

Patients were managed according to the recommendations of Turkish Ministry of Health [8]. An initial treatment with hydroxychloroquine (±azithromycin) was given to all patients usually for 5–10 days depending on the clinical severity. A course of favipiravir for 5–10 days was added in high risk patients or in cases with progressive disease [8].

Evaluation of response to initial treatment and tocilizumab administration.

Patients with a progression to CRS despite antiviral treatment were considered as candidates for tocilizumab. Since IL-6 levels were not routinely measured, consecutive CRP measurements were used as a surrogate marker to trace the course of IL-6 levels. In patients showing clinical and laboratory deterioration with persistent fever and hypoxia despite hydroxychloroquine and favipiravir treatment 8 mg/kg of tocilizumab (max. per dose 400 mg) was administered intravenously in 100 mL saline over 60 min as recommended [8]. The same dose was repeated, if necessary, within 12–24 h, based on clinical and laboratory response. A rapid rise in CRP, ferritin and fibrinogen levels indicated the appropriate time for initiation of tocilizumab treatment.

2.4. Statistical analysis

All analyses were performed using IBM SPSS V.21. Mann-Whitney *U* test and paired samples T-test were used for the comparison of continuous variables where applicable. Chi-square test was used for comparing categorical variables. A p value less than 0.05 was considered statistically significant.

Uni- and multivariate regression were performed while inventing the proposed scoring system. Diagnostic significance of continuous clinical parameters was assessed by using receiver-operator characteristic (ROC) curve analysis. Youden's J Index was calculated to identify optimal cut-off point for each parameter. To combine parameters which were found significant in univariate analysis according to the cut-off points, multivariate logistic regression analysis with forward variable selection approach was carried out. Due to high standard error estimates, Firth's method was preferred to obtain coefficient estimations in multivariate logistic regression model [19–22]. For each variable that was statistically significant in the Firth's model, a score was obtained, as described elsewhere [23]. ROC curve analysis was performed for probability, and the cut-off was determined. The accuracy of the prediction model was tested by calculating the area under the curve (AUC). In the calculator-development process, after logistic regression analysis, predicted probability was calculated for each patient by using the following formula: probability $= \exp(\sum \beta \times X)/[1+ \exp(\sum \beta \times X)]$.

After applying logistic regression model, the estimated beta coefficients were used to assign score points. The beta coefficients in the model were multiplied by 10. Then, the value was rounded off to the nearest integer. After calculating the score, this variable was used to construct multivariate logistic regression model to obtain probabilities which were used as a combined diagnostic variable to assess diagnostic performance of the new score through ROC curve analysis. Finally, the AUC was calculated for the score. After obtaining the optimal cut-off point using Youden's J Index the score was further evaluated in terms of sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) associated with the 28-day survival following tocilizumab treatment.

3. Results

3.1. Baseline characteristics

Eighty-seven patients with a median age of 59 years (range, 24–92 years) were included in the study, constituting 10.6% (87/814) of all adult patients hospitalized for COVID-19 and 5.5% (87/1577) of those diagnosed with COVID-19 between 16 March and May 01, 2020 (Fig. 1). Patient characteristics on admission are displayed in Table 1.

Hypertension was the most common comorbidity (31%). SARS-CoV-2 RNA was isolated from the oro-nasopharyngeal samples in 58 of the cases (66.7%). Median time from symptom onset to admission was 4 days (range, 1–15 days), and the median duration of hospitalization was 15 days (range, 6–36 days) (Table 1).

Coughing, dyspnea, fever, and myalgia were detected in 67 (77%), 48 (55.2%), 37 (42.5%), and 30 (34.5%) patients, respectively. Median

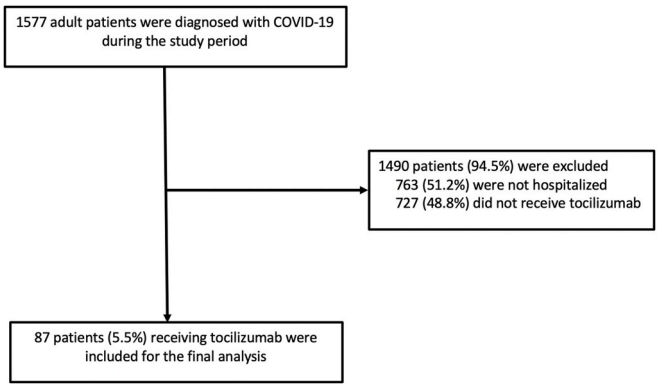


Fig. 1. Study design.

Table 1
Characteristics of the entire cohort on admission (CPAP, continuous positive airway pressure; F, female; M, male; SO_2R, oxygen saturation on room air).

Characteristic	Patients (n = 87)
Age [years - median (range)]	59 (24–92)
Sex [M/F – n (%)]	66 (76)/21 (24)
Comorbidities [n (%)]	
Hypertension	27 (31)
Diabetes	15 (17.2)
Cancer	10 (11.5)
Chronic lung disease	3 (3.4)
None	28 (32.2)
RT-PCR positivity [n (%)]	58 (66.7)
Duration of symptoms prior to admission [days – median (range)]	4 (1–15)
Initial signs/symptoms on admission [n (%)]	
Coughing	67 (77)
Shortness of breath	48 (55.2)
High fever	37 (42.5)
Myalgia[a]	30 (34.5)
Headache	8 (9.2)
Diarrhea	8 (9.2)
Laboratory tests on admission [median (range)]	
Neutrophil count [x 10^9/L]	4.3 (0.7–22.7)
Lymphocyte count [x 10^9/L]	0.9 (0.3–6.1)
Neutrophil/lymphocyte ratio	4.23 (0.77–30)
Platelet count [x 10^9/L]	185.5 (34–418.7)
C-reactive protein [mg/L]	75 (1–396)
D-dimer [mg/L]	0.68 (0.19–6.14)
Ferritin [ng/mL][b]	482 (71–2000)
Fibrinogen [mg/dL]	489 (173–875)
Procalcitonin [ng/mL][c]	0.09 (0.03–2.11)
Lactate dehydrogenase [IU/L]	341 (145–1118)
Alanine aminotransferase [IU/L]	25.5 (3–135)
Creatinine [mg/dL]	0.96 (0.44–8.48)
SO_2R [%]	94 (75–99)
Types of oxygen therapy on admission [n (%)][d]	
No oxygen support	34 (39.5)
Nasal cannula	47 (54)
Mask	3 (3.4)
High-flow nasal therapy	2 (2.3)
CPAP	1 (1.1)
Intubation	1 (1.1)
Severity of disease [n (%)]	
Mild/moderate	26 (29.9)
Severe	58 (66.7)
Critical	3 (3.4)

[a] There were 4 cases with no data available.
[b] There were 44 patients with no ferritin result on admission.
[c] There were 48 patients with no data available.
[d] There was no data for one patient.

SO_2R was 94% (range, 75%–99%). In 34 patients (39%), no oxygen support was needed, whereas the remaining 52 received various modes of oxygen therapy (Table 1). On admission, 29.9%, 66.7%, and 3.4% of the patients had mild/moderate, severe, and critical disease, respectively.

CT scoring was available for 86 patients (99%). Detailed information on the chest CT findings is given in Supplementary Fig. 1. Eighty-two patients (95.4%) had typical CT findings for COVID-19 pneumonia at diagnosis.

Median neutrophil and lymphocyte counts were 4.3 × 10^9/L and 0.9 × 10^9/L, respectively. Median platelet count was 185.5 × 10^9/L including 7 cases (8%) with a platelet count < 100 × 10^9/L. Median CRP, LDH, and D-dimer levels were 75 mg/dL, 341 IU/L, and 0.68 mg/L, respectively (Table 1).

Treatment for COVID-19 given prior to and/or during tocilizumab therapy were listed in Supplementary Fig. 2. All patients received hydroxychloroquine with a median of 10 days (range, 2–19 days), while 81 patients (93%) received favipiravir with a median of 5 days (range, 3–10 days) before and/or at the time of tocilizumab use.

Median durations from symptom onset and hospital admission to tocilizumab administration were 10 days (range, 3–24 days) and 6 days (range, 1–17 days), respectively. Seventy-five patients (86.2%) received tocilizumab in the COVID-19 wards, whereas in 12 cases (13.8%) tocilizumab was given in the ICU. Sixty-five patients (74.7%) received 2 doses of tocilizumab.

Comparison of baseline, tocilizumab administration, and post-tocilizumab Day 7 (D_7) parameters.

Percentage of patients who needed oxygen support was significantly higher at tocilizumab use than on admission, and similarly percentage of patients free of oxygen support on D7 post-tocilizumab was significantly higher than that at tocilizumab administration (Supplementary Figure 3). On D7 of tocilizumab therapy, 63 patients were still in hospital, 20 had been discharged and 4 had died.

Table 2 summarizes the laboratory parameters on admission, at tocilizumab administration, and on D7 of tocilizumab. Median SO2R on admission was significantly higher than that at tocilizumab use, and this was 95% on D7 of tocilizumab, which was significantly higher than those observed on admission and at tocilizumab infusion (Table 2).

Neutrophil and platelet counts, and NLR on admission were significantly lower than those at tocilizumab administration. On the contrary, lymphocyte counts were significantly lower, and the CRP and D-dimer levels were significantly higher at tocilizumab therapy when compared to levels on admission Table 2. Similarly, ferritin and LDH levels at tocilizumab administration were significantly higher than those on admission.

On D7 of tocilizumab, lymphocyte and platelet counts were significantly higher, whereas CRP, ferritin, and fibrinogen levels were significantly lower when compared to those at tocilizumab administration Table 2.

Lymphocyte and platelet counts were found significantly higher than baseline on D7 post-tocilizumab Table 2. CRP and fibrinogen levels were significantly lower, but D-dimer levels were significantly higher than those observed on admission (Table 2).

Out of the 13 patients who were intubated on D7 post-tocilizumab, eight (61.5%) died and 5 (38.5%) recovered during follow-up. Two additional patients were intubated after D7 of tocilizumab and died, making a total of 14 deaths (16.1%) within 28 days (Supplementary Fig. 4). Median durations from symptom onset and tocilizumab administration to death were 20.5 days (range, 10–31 days) and 9 days (range, 3–17 days), respectively. Of these 14 patients, 10 died due to secondary ventilator-associated pneumonia (VAP) accompanying ARDS, three died because of cardiovascular diseases and one patient with myelodysplastic syndrome died due to intracranial bleeding.

Table 2
Parameters on admission, at TCZ administration, and on the D7 of TCZ treatment.

Parameter [Median (range)]	On admission	At TCZ administration	Day 7 of TCZ treatment	p value
SO_2R [%]	94 (75–99)	92.5 (73–99)	95 (89–99)	0.029[a] 0.001[b] 0.012[c]
Neutrophil count [x 10^9/L]	4.3 (0.7–22.7)	5.1 (0.5–27.5)	4.9 (0.3–27.2)	**0.045**[a] NS[b] NS[c]
Lymphocyte count [x 10^9/L]	0.9 (0.3–6.1)	0.9 (0.1–4.8)	1.3 (0.3–5.9)	**0.016**[a] **< 0.001**[b] **0.001**[c]
Neutrophil/ lymphocyte ratio	4.23 (0.77–30)	5.12 (0.64–116)	3.36 (0.3–52)	**0.032**[a] NS[b] NS[c]
Platelet count [x 10^9/L]	185.5 (34–418.7)	228 (21–541)	361 (43–623)	**< 0.001**[a] **< 0.001**[b] **< 0.001**[c]
C-reactive protein [mg/L]	75 (1–396)	154 (4–399)	4.9 (0.8–470)	**< 0.001**[a] **< 0.001**[b] **< 0.001**[c]
D-dimer [mg/L]	0.68 (0.19–6.1)	1.3 (0.26–80)	2.4 (0.2–37)	**0.019**[a] NS[b] **0.011**[c]
Ferritin [ng/mL]	482 (71–2000)	801 (68–2447)	644 (112–4666)	**0.004**[a] **0.048**[b] NS[c]
Fibrinogen [mg/ dL]	489 (173–875)	563 (163–900)	259 (50–893)	NS[a] **< 0.001**[b] **< 0.001**[c]
Procalcitonin [ng/ mL]	0.09 (0.03–2.11)	0.2 (0.03–4.65)	0.05 (0.02–10.78)	NS[a] NS[b] NS[c]
Lactate dehydrogenase [IU/L]	341 (145–118)	424 (191–1183)	396 (183–1387)	**< 0.001**[a] NS[b] NS[c]
Alanine aminotransferase [IU/L]	25.5 (3–135)	30 (4–232)	82 (18–394)	**0.002**[a] **< 0.001**[b] **< 0.001**[c]
Creatinine [mg/dL]	0.96 (0.44–8.48)	0.9 (0.4–3.24)	0.86 (0.56–3.09)	NS[a] NS[b] NS[c]

[a] Represents the difference between the values at baseline and tocilizumab administration.
[b] Represents the difference between tocilizumab administration and post-TCZ D_7 values.
[c] Represents the difference between the baseline and post-TCZ D_7 values. (NS, not significant; TCZ, tocilizumab) (Paired sample T-test was used for these comparisons).

3.2. Comparison of survived and dead patients

Patients who died were significantly older than those who survived (Table 3). The frequency of ARDS was 78.5% in non-survivors, whereas this was 8.7% in patients who survived. SO2R also differed significantly between survivors and non-survivors. In patients who died neutrophil counts and NLR were significantly higher at tocilizumab administration (Table 3). Platelet counts were significantly lower in non-survivors, whereas lymphocyte counts were comparable. CRP, D-dimer, procalcitonin, and LDH levels were significantly higher in patients who died

Table 3
The comparison of parameters at the time of TCZ therapy between the surviving patients and the cases who died (Chi-square test is used for comparing the categorical variable and independent samples T-test (for normally distributed) and Mann-Whitney *U* test (for not normally distributed) were used for comparing continuous variables).

Parameters at TCZ administration [Median (range)]	Patients who survived (n = 73)	Patients who died (n = 14)	p value
Sex [M/F – n (%)]	55/18 (75.3)	11/3 (78.6)	NS
Age [years]	58 (24–92)	65.5 (43–83)	**0.017**
Days from symptom start to TCZ therapy	10 (4–24)	12 (3–18)	NS
Percentages of patients receiving two doses of TCZ [%]	72.6	71.4	NS
Percentages of cases with ARDS [%]	8.7	78.5	**< 0.001**
SO_2R [%]	93 (73–99)	89.5 (80–98)	**0.045**
Neutrophil count [x 10^9/L]	4.8 (0.5–15)	8.8 (1.4–27.5)	**0.019**
Lymphocyte count [x 10^9/L]	0.9 (0.2–4.8)	0.8 (0.1–1.9)	NS
Neutrophil/lymphocyte ratio	4.85 (0.81–70)	10 (0.64–116)	**0.015**
Platelet count [x 10^9/L]	237 (39–541)	158 (21–531)	**0.042**
C-reactive protein [mg/L]	136 (4.0–399)	202.5 (73–356)	**0.024**
D-dimer [mg/L]	1.16 (0.26–80)	4.78 (0.53–80)	**0.001**
Ferritin [ng/mL]	795 (68–2296)	1412.5 (84–2447)	NS
Fibrinogen [mg/dL]	563.5 (163–900)	568.5 (356–900)	NS
Procalcitonin [ng/mL]	0.16 (0.03–2.9)	0.84 (0.18–4.65)	**< 0.001**
Lactate dehydrogenase [IU/L]	408 (191–1035)	587 (237–1183)	**0.003**
Alanine aminotransferase [IU/L]	31 (8–232)	25 (4–120)	NS
Creatinine [mg/dL]	0.86 (0.4–2.51)	1.18 (0.6–3.24)	NS

(Table 3). Although ferritin levels were higher in non-survivors than survivors, the difference was not statistically significant.

3.3. Safety of tocilizumab treatment

A moderate decrease in fibrinogen levels was detected on D7 following tocilizumab (Table 2). Seven patients had fibrinogen levels <100 mg/dL (median, 74 mg/dL – range, 50–99 mg/dL). Median alanine aminotransferase (ALT) level at tocilizumab administration was 30 IU/L, which was 82 IU/L on D7 of tocilizumab (Table 2). Elevation in ALT levels were observed in 42 cases (48.2%) within 7 days following tocilizumab adminstration, of which all returned to normal within 28 days of follow-up.

Of the 12 patients (14%) with secondary bacterial pneumonia (SBP) on D7 post-tocilizumab, 11 had VAP. Nine of those (75%) were diagnosed prior to tocilizumab administration. Three patients acquired SBP after tocilizumab.

3.4. The Cerrahpaşa-PREDICT (*Procalcitonin, RE*spiratory, *D*-dimer, *Interval between onset of symptoms and toCilizumab, Thrombocyte*) score

A total of 24 parameters (age, sex, CT score, number of comorbidities, fever, shortness of breath, coughing, headache, myalgia, diarrhea, neutrophil, lymphocyte and platelet counts, NLR, CRP, D-dimer, ferritin, fibrinogen, procalcitonin, LDH, ALT, AST, creatinine levels, and SO_2R) were first tested in the univariate analysis. Eleven parameters were found to be significant (Table 4A), and then a multivariate analysis was performed, which differentiated 5 parameters (platelet count, procalcitonin, SO_2R, D-dimer, and time from symptom onset to tocilizumab use) to be significantly associated with survival (Table 4B). In our score, we included procalcitonin but not CRP following variable selection methods, which was also supported by another study, in which

Table 4
Uni- (A) and multivariate (B) analyses of factors on survival and the parameters used for the proposed score (C).

(A) Univariate analyses of factors with significant impact on survival

Parameter	Coef.	Std. Err.	p value	95% CI	
				Lower	Upper
D-dimer	2.502197	0.7386195	0.001	1.05453	3.949865
Platelet count	2.340325	0.6597936	<0.001	1.047154	3.633497
Procalcitonin	2.441678	0.8919675	0.006	0.6934535	4.189902
SO2R	1.5058	0.5954439	0.011	0.3387519	2.672849
Time from symptom start to TCZ use	1.17204	0.5843874	0.045	0.0266615	2.317418
Creatinine	1.861573	0.6064267	0.002	0.6729981	3.050147
LDH	2.017651	0.6607062	0.002	0.7226903	3.312611
Ferritin	1.516689	0.5911773	0.01	0.3580024	2.675375
CRP	1.908954	0.7316251	0.009	0.4749956	3.342913
INR	1.892884	0.6585508	0.004	0.6021478	3.183619
Age	1.612271	0.61662917	0.009	0.4043613	2.82018

(B) Multivariate analyses of factors used in the proposed score

Parameter	Coef.Φ	Odds Ratio	Std. Err.	p value	95% CI	
					Lower	Upper
Platelet count	2.452892	11.62191	0.9575447	0.01	0.5761389	4.329645
Procalcitonin	2.560328	12.94007	1.090285	0.019	0.4234088	4.697248
SO2R	1.790459	5.992201	0.8778773	0.041	0.0698508	3.511067
D-dimer	1.997414	7.369973	0.9225326	0.03	0.1892832	3.805545
Time from symptom start to TCZ use	1.762091	5.824604	0.959371	0.066	−0.1182415	3.642424

(C) Parameters of the proposed score

Parameter	Favorable	Unfavorable[b]	Points (Coef. x 10)[a]
Platelet count	>147 × 109/L	≤147 × 109/L	25
Procalcitonin	<0.3555 ng/mL	≥0.3555 ng/mL	26
SO2R	>91.5%	≤91.5%	18
D-dimer	<2.52 mg/L	≥2.52 mg/L	20
Time from symptom start to TCZ use	≤12 days	>12 days	18

[a] These points were calculated by multiplying the relevant beta coefficients by 10, and then, the value was rounded off to the nearest integer.
[b] Patients get the displayed points for each unfavorable parameter, for example a patient having all unfavorable parameters gets a total of 107 points.

procalcitonin was shown to be associated with mortality [24].

The proposed mortality score was constructed using these 5 parameters, and the points for each parameter were calculated as previously described (Table 4C). Each patient got the related points, if the parameter was unfavorable, and a total score for each patient was calculated. The cut-offs for the calculation (by the formula described in the methods section) and the score were 0.36585 and 62.5 (which was rounded off to 63) defined by the ROC curve analysis (Supplementary Figs. 5 and 6), respectively. The AUCs for the calculation and the score were 0.942 (CI: 0.87–1.00) and 0.954 (CI: 0.908–0.999), respectively, and the PPV and NPV of the score were 94.5% and 92.9%, respectively (Supplementary Table 1). Among the 14 patients who died within the 28-day follow-up, 13 had a score ≥63, whereas only one patient with a score <63.

4. Discussion

In this retrospective cohort study, we analysed the clinical and laboratory characteristics of COVID-19 patients receiving tocilizumab to propose a scoring system for predicting the 28-day survival (the Cerrahpaşa-PREDICT score).

The median age was 59 years and most of the patients were male (76%), which was compatible with the literature [11,16]. On admission, fever, cough, and dyspnea were the most common symptoms, and the most common comorbidity was hypertension, as it was in most of the studies [10,11,15,25].

In our cohort, all patients received intravenous tocilizumab, whereas in some studies, tocilizumab was administered subcutaneously displaying similar efficacy [11]. Median duration from the onset of symptoms to tocilizumab use was 10 days, which was 12–13 days in other studies [12,15,26]. In line with the study by Morrison et al. [16], we showed that a duration of ≤12 days from symptom onset to tocilizumab use was an independent favorable factor predicting 28-day mortality.

Although it was shown that lower doses can also be efficient [10], nearly three-quarter of patients received 2 doses (800 mg total) of tocilizumab as described before [16,27]. Following tocilizumab administration, the need for O_2 therapy and SO_2R values significantly improved, as displayed before [12,15,25,27]. Similarly, significant increases in lymphocyte and platelet counts after tocilizumab therapy were observed, which were compatible with previous studies [12,25]. Inflammatory parameters including CRP, ferritin, and fibrinogen levels significantly decreased following tocilizumab therapy as shown by Toniati and colleagues [15].

Our study showed that administration of tocilizumab early in the course of the disease (prior to ICU admission) resulted in a favorable outcome with a 28-day mortality rate of 16.1%, similar to earlier reports with rates ranging between 16% and 25% [15,26,28]. On the contrary, a recently published placebo-controlled study showed that tocilizumab use did not prevent intubation or death among patients with severe COVID-19 [29]. Similarly, in another randomized placebo-controlled study, tocilizumab use did not demonstrate any significant benefit in hospitalized patients with severe COVID-19 pneumonia [30]. Clinical status and 28-day mortality rates were comparable between the tocilizumab and placebo arms. In our study, the 28-day mortality rate was 16.1%, which were 19.7% and 19.4% in the tocilizumab and placebo arms of the study by Rosas et al. respectively [30].

Our results were supported by more recently published two randomized controlled studies [31,32]. Among critically ill COVID-19 patients, tocilizumab treatment was shown to improve outcomes, including survival [31]. In the RECOVERY (Randomized Evaluation of COVID-19 Therapy) trial, enrolling more than 2000 patients in each arm, tocilizumab improved survival and clinical outcomes among hospitalized COVID-19 patients with hypoxia and CRS [32]. 28-day mortality was significantly higher in the control arm than that of patients receiving tocilizumab (33% vs. 29%, $p = 0.0066$).

In our cohort, surviving cases were significantly younger, confirming the prior observation that older age was a predictor of death [27]. CRP, LDH, and D-dimer levels were significantly lower in patients who survived, and platelet counts were significantly lower in cases who died. Similarly, Campochiaro and colleagues [28] showed that improving patients had significantly lower CRP levels, while LDH levels did not

differ in their study. However, LDH levels were significantly higher in cases with clinical improvement in the study by Fernández-Ruiz et al. [33], and Quartuccio and colleagues [13] showed that patients receiving tocilizumab who required invasive ventilation had higher LDH levels than non-ventilated patients, which were compatible with our findings. Patients with D-dimer levels >3500 ng/mL were found to have inferior survival rates [14] and NLR was found significantly elevated in patients who died [34], all of which was in line with our results.

Elevation in ALT levels was observed in 48.2% of the cases, which was 44% in the cohort of Alattar et al. [9]. In our cohort, SBP rate was 14%, and it was 16% in one study [9] and bacterial infection rate was 21% in another [16]. In the recently published placebo-controlled studies [29,30], serious infection rates in the tocilizumab and placebo arms were 8.1% and 17.1% and 21% and 25.9%, respectively.

Herein we propose, "the Cerrahpaşa-PREDICT score", for anticipating the 28-day mortality in COVID-19 patients receiving tocilizumab. This is an easy-to-use scoring system composed of 5 parameters including platelet count, procalcitonin, D-dimer levels, SO_2R and the time from symptom onset to tocilizumab use. PPV and NPV of the score were found to be 94.5% and 92.9%, respectively.

Our results should be considered with caution, due to the retrospective nature of our study. The study lacks a control arm, since tocilizumab was available from the first patient on at our center, who met the severity criteria according to the national guidelines. Other limitations include unavailability of viral load measurements and heterogenicity of the cohort, which consists of RT-PCR positive patients and clinically and radiologically proven RT-PCR negative cases and.

Moreover, determination of serum IL-6 levels before and after tocilizumab therapy would have been useful to demonstrate the immune modulating effect. However, in the absence of high-level clinical evidence to guide therapeutic interventions in such a rapidly growing pandemic, the wide off-label use of potentially beneficial agents is understandable. Our results including the proposed Cerrahpaşa-PREDICT score require further confirmation and validation through controlled prospective trials.

In conclusion, patients with severe COVID-19 should closely be monitored for the signs of hyperinflammation. Daily laboratory trends usually help identifying patients who would benefit from an anti-inflammatory intervention. In this regard, the Cerrahpaşa-PREDICT score might serve as a practical tool for estimating the 28-day mortality in COVID-19 patients, who received tocilizumab and would help recognising cases with negative outcome in order to early direct them to other therapeutic options.

4.1. Authorship statement

- AEE, İİB, MCA, RK, and FT developed the trial design and responsible for the organization and coordination of the trial.
- AEE and MCA are the chief investigators and responsible for the data analysis.
- KCD, YS, SM, GYD, FÇ, NÖY, FK, ŞB, SÜ, BM, IB, and YD collected data.
- SAK reevaluated the CT scans.
- MK, DS, GA, and KM performed the RT-PCR testings for the detection of SARS-CoV-2 RNA from the oropharyngeal and nasopharyngeal swab samples.
- All authors contributed to the writing of the final manuscript.
- All authors approved the final draft.

Declaration of competing interest

All authors have no conflict of interest to declare.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jiac.2021.05.007.

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