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Factors Affecting Mortality in COVID-19 Patients Treated with Tocilizumab

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ABSTRACT

The aim of our study was to evaluate the risk factors associated with mortality in COVID-19 patients.
During March 2020 to March 2022, 136 patients who were treated with tocilizumab in the service and intensive care unit due to Covid-19 pneumonia confirmed by Reverse-Transcriptase Polymerase Chain Reaction (RT-PCR) were retrospectively analyzed.
While the mean age of the surviving group (n:70) was 54.4 years, for the dying group (n:66) it was 67.4 years. There was no significant difference in terms of gender in the surviving and dying patient groups (p:0.761). The time from hospitalization to tocilizumab treatment was significantly shorter among survivors (p=0.004), while patients who received tocilizumab in the intensive care unit exhibited a higher mortality rate. While the median Charlson Comorbidity Index (CCI) score was 0 in the surviving patients, it was 2 in the dying group. It was found that a 1-unit increase in CCI increased the mortality rate 1.416 times. Age, CCI, neutrophil, neutrophil-lymphocyte ratio (NLR), urea, and C reactive protein (CRP) were found to be independent risk factors for mortality. Patients with high white blood cell, lactate dehydrogenase, troponin, d-dimer, and low lymphocyte, total protein, albumin, and glomerular filtration rates had higher mortality rate.
CCI, white blood cell, NLR, urea, LDH, troponin, d-dimer, CRP, lymphocyte, GFR, albumin and total protein basal values can be used as risk factors for death from Covid -19 disease. In addition, early initiation of tocilizumab therapy may reduce mortality rates.

Keywords: Covid-19, Charlson comorbidity index, mortality, risk factors, tocilizumab

Introduction

After Covid-19 emerged in China in December 2019, it spread to millions of people around the world, causing many deaths. Although mild symptoms occur in the majority of patients affected by SARS-COV-2, life-threatening severe respiratory failure (ARDS), shock, and organ failure are seen in some (1). One factor that causes severe disease in COVID-19 is the immune response of the host in an irregular and excessive manner known as cytokine storm syndrome (2). Cytokine storm is characterized by intense inflammation, hyperferritinemia, disruption of hemodynamics, and multi-organ failure. Although the pathogenesis is not fully understood, cytokine storms occur as a result of the sudden increase in the circulation of various proinflammatory cytokines including interleukin (IL)-6, IL-1, tumor necrosis factor (TNF)-alpha, and interferon (3). Among these cytokines, IL-6 and other inflammation markers, C-reactive protein (CRP), and ferritin are closely associated with mortality (4,5). IL-6 activates many cells and has a key role in the cytokine storm (6). Tocilizumab, which is used in the treatment of many inflammatory diseases, is a monoclonal anti-interleukin-6 receptor antibody. It was shown that tocilizumab treatment reduced mortality and the need for mechanical ventilation application in severe COVID-19 patients (7). COVID-19 patients with comorbidities are disproportionately associated with worse outcomes. The Charlson Comorbidity Index (CCI) is a simple, easy-to-perform, and valid method to estimate the risk of death related to comorbid diseases. Classical CCI includes 19

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medical conditions weighted 1-6 with total scores ranging from 0 to 33. There are many studies in the literature on the factors affecting mortality in patients with COVID-19 (8,9).

The aim of our study was to evaluate the risk factors associated with mortality in COVID-19 patients.

Materials and Methods

During March 2020 to March 2022, 136 patients who were hospitalized in the service and intensive care unit due to Covid-19 pneumonia and needed tocilizumab treatment and were treated were retrospectively analyzed. Our study's ethics committee approval was obtained from Recep Tayyip Erdoğan University Faculty of Medicine, non-interventional clinical research ethics committee chairmanship. The study was conducted according to the Declaration of Helsinki. Ethical approval no:2022/119.

Electronic file data of the patients were reviewed. Patients older than 18 years of age who received tocilizumab treatment were included in the study. The patients were divided into two groups as survivors and non-survivors. Data included comorbidities, age, and gender of the patients were determined. Laboratory tests; white blood cell, platelet, lymphocyte, neutrophil, neutrophil-lymphocyte ratio (NLR), aspartate aminotransferase test (AST), alanine aminotransferase (ALT), urea, creatinine, glomerular filtration rate (GFR), glucose, total protein, albumin, lactate dehydrogenase (LDH), fibrinogen, C-reactive protein (CRP), ferritin, creatine kinase (CK), troponin, d-dimer, procalcitonin and arterial blood gas parameters such as pH, pCO2, PO2, HCO3, lactate levels analyzed before hospitalization were recorded. The association with mortality was evaluated by the Charlson Comorbidity Index (CCI) score. The time elapsed before receiving tocilizumab treatment and the length of hospital stay were determined. Genentech company's commercial drug Actemra (tocilizumab 8mg/kg) was administered to the patients at a maximum dose of 800mg/day intravenous (IV) single dose infusion. Prednol (methylprednisolone) 250 mg and 100 mg IV, and immune plasma prepared from patients who received 300 ml/day infusion therapy, who needed nasal cannula, reservoir mask, and high flow oxygen at the time of admission to the hospital and in clinical follow-up, who applied continuous positive airway pressure (CPAP), and intubated patients were identified.

Statistical Analysis: Statistical analyses were performed by using the SPSS program (IBM, SPSS Inc., Version 23.0, Chicago, USA). Kolmogorov-Smirnov or Shapiro-Wilk test was used to evaluate the distribution of the numerical data. Categorical variables were expressed as frequency and percentage (%), and numerical variables were expressed as mean ± standard deviation or median (minimum to maximum) where appropriate. The relationship between categorical variables with survival was evaluated with the Chi-Square test (Pearson chi-square and Fisher's Exact Test) considering the size of the patient groups in the categories. In group comparisons, Student's T-Test or Mann-Whitney U test was used to compare continuous numerical variables. Receiver operating characteristic (ROC) analysis was performed to determine the laboratory findings' cut-off values, as well as their sensitivity and specificity. Biochemical, clinical, and therapeutic prognostic variables for predicting in-hospital survival were investigated by univariate and multivariate Cox regression analysis, and a hazard ratio (HR) with 95% CI is presented. Kaplan-Meier plots and Log-rank tests were carried out to analyze the relation of variables with survival. A p-value of <0.05 was considered for statistical significance.

Results

While the mean age of the surviving group (n:70) was 54.4 years, for the dying group (n:66) it was 67.4 years. There was no significant difference in terms of gender in the surviving and dying patient groups (p:0.761). The mortality rate was higher in patients who started tocilizumab treatment in the intensive care unit ($p<0.001$). Detailed demographic data and therapy status of the patients are shown (Table 1). Data on age, biochemical parameters, hemogram, and arterial blood gas values of patients who survived and died are given in table 2.

ROC analysis was executed for in-hospital survival evaluation. Urea was found to have 70,8% sensitivity and 72,5% specificity at a cut-off value of 54,5 mg/dL (AUC:0.788; p:0,001). Neutrophils count was found to have 60% sensitivity and 63,8% specificity at a cut-off value of 9425 (AUC:0,665; p:0.001). CRP was found to have 67,7% sensitivity and 55,1% specificity at a cut-off value of 76,9 mg/L (AUC:0,641; p:0,005). Age was found to have 77,3% sensitivity and 64,3% specificity at a cut-off value of 60 years (AUC:0,793; p:0.001). CCI was found to have

Table 1: Demographic Data and Therapy Status of The Patients

		Survivor		
		Survivor	Non-survivor	
		n (%)	n (%)	p
Gender	Female	21 (30)	20 (30,3)	0.969
	Male	49 (70)	46 (69,7)	
Nasal Cannula	Not used	20 (28,6)	48 (72,7)	<0.001
	Used	50 (71,4)	18 (27,3)	
Reservoir Mask	Not used	4 (5,7)	5 (7,6)	0.663
	Used	66 (94,3)	61 (92,4)	
High Flow Oxygen Therapy	Not used	49 (71)	19 (29,7)	<0.001
	Used	20 (29)	45 (70,3)	
Intubation	Not Intubated	65 (92,9)	5 (7,6)	<0.001
	Intubated	5 (7,1)	61 (92,4)	
CPAP	Not used	59 (84,3)	44 (66,7)	0.017
	Used	11 (15,7)	22 (33,3)	
Immune plasma therapy	Not given	58 (82,9)	53 (80,3)	0.701
	Given	12 (17,1)	13 (19,7)	
IVIG	Not given	64 (91,4)	55 (83,3)	0.154
	Given	6 (8,6)	11 (16,7)	
Vitamin Status	Not given	47 (67,1)	53 (80,3)	0.082
	Given	23 (32,9)	13 (19,7)	
Tocilizumab	Intensive care unit	26 (37,1)	46 (69,7)	<0.001
	Clinic	44 (62,9)	20 (30,3)	

CPAP: continuous positive airway pressure, IVIG: intravenous immunoglobulin therapy

89,4% sensitivity and 51,4% specificity at a cut-off value of 1 (AUC: 0,768; p:0.001). CCI was found to have 89,4% sensitivity and 51,4% specificity at a cut-off value of 1 (AUC: 0,768; p:0.001). Neutrophil to lymphocyte ratio (NLR) was found to have 61,5% sensitivity and 79,7% specificity at a cut-off value of 16,15 (AUC: 0,747; p:0.001). It was found that the mortality rate was higher in those with age ≥ 60, CCI ≥ 1, NLR >16.15, neutrophil >9425, urea >54.5, CRP≥ 76.9 (Figure1).

In the multivariate Cox Regression analysis, age, CCI score, neutrophils, urea, and CRP were found to be independent risk factors for mortality. A 1-unit increase in CCI increased the mortality rate 1.416 times (1.092-1.836), HR 95% CI (p:0.009) (Table 3).

Discussion

According to the results of our study, the CCI index can be used as a useful tool to evaluate the risk of comorbidities and predict mortality in COVID-19 patients treated with tocilizumab. CCI, white blood cell, NLR, urea, LDH, troponin, d-dimer, CRP, procalcitonin, lymphocyte, GFR, albumin and total protein baseline values found as risk factors for mortality of COVID -19 disease, together with comorbidities existing before treatment. These results are compatible with the literature (27).

Although most COVID-19 patients have a favorable clinical course, it may result in a negative clinical course and mortality in patients with chronic diseases and elderly patients. In previous studies, advanced age (≥65 years old) was found to be an important risk factor for mortality in SARS, Middle East respiratory syndrome (MERS), and COVID-19 patients. As age progresses, deterioration in the immune system and defects in cytokine secretion negatively affect the reproduction of the virus. Therefore, the disease is more fatal in the elderly (9-11). In our study, the mean age of the non-survivor patient group was found to be higher than the survivors and was consistent with the literature. It has been reported that COVID-19 infection is more severe and mortal in men than in women (12,13). Angiotensin-converting enzyme 2 (ACE 2), which mediates the entry of COVID-19 into the cell, was found to be higher in the blood circulation of men than women (14). However, we found no statistically significant difference between the survivors and the dying group in terms of gender. This situation can be associated with the sample size.

In some studies, it has been reported that tocilizumab treatment reduces mortality, early discharge from the hospital, and the need for mechanical ventilation in severe COVID-19 patients (15,16). The mortality rate of COVID-19 patients treated with tocilizumab in the intensive

Table 2: Demographic Ddata and Laboratory Parameters of The Patients

	Survival		
	Survivor	Non-Survivor	
	Mean ± SD Median (min - max)	Mean ± SD Median (min - max)	p
Age	54.4 ± 12.3	67.4 ± 9.9	<0.001
Hospitalization Duration	15.5 (6 - 86)	16 (1 - 53)	0.976
Tocilizumab (Time between hospitalization and treatment) (Days)	5 (0 - 22)	8 (0 - 33)	0.004
Charlson Comorbidity Index	0 (0 - 3)	2 (0 - 6)	<0.001
White blood cells (109/L)	9969 ± 4535	12953 ± 5899	0.001
Neutrophils (109/L)	8573 ± 4314	11342 ± 5272	0.001
Lymphocytes (109/L)	830 (70 - 3610)	550 (50 - 30560)	<0.001
Neutrophil to lymphocyte ratio	10.6 (1.2 - 106.9)	18.6 (0 - 437)	<0.001
Monocytes (109/L)	370 (20 - 830)	290 (10 - 1180)	0.51
Hemoglobin (g/L)	12.8 ± 1.5	12 ± 1.7	0.007
MCV (fL)	88 (68 - 928)	88 (62 - 99)	0.966
Platelets (109/L)	217 (71 - 536)	211 (62 - 541)	0.606
Urea (mg/dL)	45 (19 - 221)	71 (27 - 272)	<0.001
Glomerular Filtration Rate (GFR)	97.1 ± 20.5	72.3 ± 32.7	<0.001
Creatinine (mg/dL)	0.8 (0.4 - 2.7)	0.9 (0.3 - 7.9)	0.015
AST (U/L)	42 (14 - 283)	35 (12 - 158)	0.258
ALT (U/L)	49 (12 - 466)	26 (9 - 155)	0.001
Total protein (g/L)	61 ± 6	58 ± 7	0.002
Albumin (g/L)	31 ± 4	28 ± 4	<0.001
LDH (U/L)	439.6 ± 171.6	519 ± 255.7	0.038
C reactive protein (mg/L)	71.3 (1.3 - 300)	116 (5.8 - 7595)	0.005
Ferritin (ng/mL)	822 (105 - 4720)	942 (113 - 11487)	0.117
Creatine Kinase	93 (0.4 - 1134)	57 (0.5 - 956)	0.147
Procalcitonin (ng/mL)	0.1 (0.1 - 9.4)	0.2 (0.1 - 9.8)	0.008
Fibrinogen	519.4 ± 134	537 ± 165.3	0.533
Troponin I	6.1 (3.2 - 22)	23.3 (3.2 - 575)	<0.001
D-dimer (mg/L)	0.7 (0.3 - 8)	1.4 (0.3 - 14.3)	0.001
pH	7.44 ± 0.11	7.39 ± 0.13	0.017
SaO2	91.1 (14.3 - 915)	91.7 (30.7 - 961)	0.581
pO2	63.9 (15 - 533)	65.8 (27.9 - 661)	0.37
pCO2	40.7 (28.3 - 415)	39.5 (20 - 525)	0.769
HCO3	27.1 (20.7 - 44)	25.6 (7.8 - 44455)	0.145
Lactate	1.7 (0.6 - 4.6)	1.9 (0.7 - 7.7)	0.077

AST: Aspartate aminotransferase, ALT: Alanine aminotransferase, LDH: Lactate dehydrogenase

care unit was likewise found to be higher than those given in the ward, and the mean duration of tocilizumab treatment in the group of patients who died was longer than the group that survived in our study. Factors such as high intubation rate, older patients, disease severity, and high CCI may have played a role in the higher mortality rate in patients using tocilizumab in the intensive care unit compared to the ward.

CCI is mainly used to predict the risk of death within 1 year of hospitalization. One to six points are given according to the severity of the morbidity (17). It is an easy-to-apply method used to evaluate survival and prognosis. The severity and mortality of COVID-19 infection can

Table 3: Risk Factors Associated With Mortality In Cox Regression Analysis

	Univariate Analysis		Multivariate Analysis	
	p	HR (95% CI)	p	HR (95% CI)
Pre Tocilizumab Covid (Duration)	0.127	0.969 (0.932 - 1.009)		
Age	<0.001	1.041 (1.02 - 1.062)	0.024	1.029 (1.004 - 1.055)
Gender	0.761	1.085 (0.641 - 1.838)		
Charlson Comorbidity Index	<0.001	1.677 (1.364 - 2.061)	0.009	1.416 (1.092-1.836)
High Flow Oxygen therapy	0.070	1.659 (0.96 - 2.868)		
CPAP	0.168	1.435 (0.859 - 2.397)		
Immune plasma therapy	0.106	1.665 (0.897 - 3.091)		
Metilprednizolon>250	0.040	0.591 (0.358 - 0.976)		
White blood cells (109/L)	0.078	1 (1 - 1)		
Neutrophils (109/L)	0.100	1 (1 - 1)	0.032	1.000 (1.000 - 1.000)
Lymphocytes (109/L)	0.460	1 (1 - 1)		
Neutrophil to lymphocyte ratio	0.528	1.001 (0.998 - 1.005)		
Monocytes (109/L)	0.729	(0.999 - 1.001)		
Hemoglobin (g/L)	0.469	0.946 (0.813 - 1.1)		
MCV (fL)	0.498	0.987 (0.952 - 1.024)		
Platelets (109/L)	0.783	1 (1 - 1)		
Urea (mg/dL)	<0.001	1.006 (1.003 - 1.01)	0.006	1.007 (1.002-1.011)
Glomerular Filtration Rate (eGFR)	<0.001	0.985 (0.979 - 0.992)		
ALT (U/L)	0.064	0.993 (0.985 - 1)		
AST (U/L)	0.573	0.998 (0.99 - 1.005)		
Total protein (g/L)	0.467	0.865 (0.584 - 1.279)		
Albumin (g/L)	0.143	0.620 (0.326 - 1.176)		
LDH (U/L)	0.092	1.001 (1 - 1.002)		
Creatine Kinase	0.636	1 (0.998 - 1.001)		
C reactive protein (mg/L)	0.012	1 (1 - 1.001)	0.021	1.000 (1.000 - 1.001)
Procalcitonin (ng/mL)	0.855	1.013 (0.883 - 1.161)		
Ferritin (ng/mL)	0.113	1 (1 - 1)		
Fibrinogen	0.604	1 (0.999 - 1.002)		
Troponin I	<0.001	1.006 (1.003 - 1.008)		
D-dimer (mg/L)	0.296	1.05 (0.958 - 1.15)		
Partial thromboplastin time (s)	0.127	1.033 (0.991 - 1.076)		

Age, Charlson Comorbidity Index, Urea (mg/dL), Neutrophils (109/L), C reactive protein (mg/L), Vitamin Status, steroid, White blood cells (109/L), RDW, ALT (U/L), LDH (U/L), High Flow Oxygen Therapy, CPAP, Immune plasma therapy selected as covariate

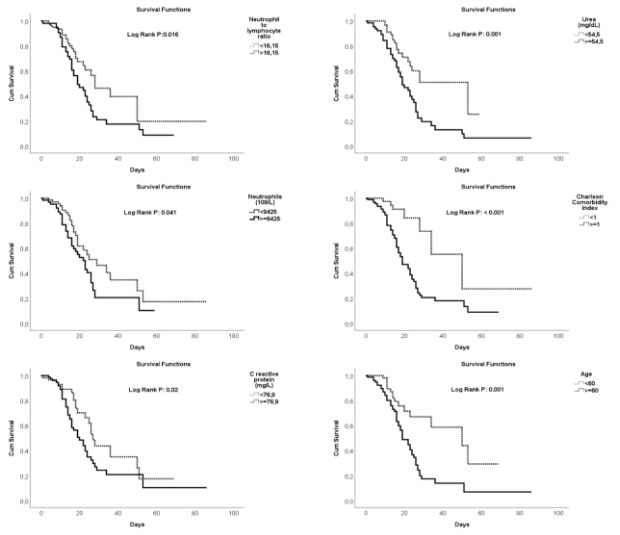

Fig. 1. Kaplan Meier survival curve for NLR, neutrophil count, CRP, Urea, CCI, and age
NLR: neutrophil-lymphocyte ratio, CRP: C reactive protein (CRP), CCI: Charlson Comorbidity Index

generally be predicted by age, gender, and comorbidities such as diabetes, cardiovascular, cerebrovascular, and respiratory diseases (18,19). We determined that there was an increase in mortality in the group with high CCI scores in COVID-19 patients using tocilizumab.

In many studies, it has been determined that an increase in white blood cells and NLR causes the disease to progress with a more severe clinical course and mortality. Lymphocytes have an important function in eliminating virus-infected cells. Insufficient regeneration of lymphocytes infected by the virus and especially a decrease in CD4 count are helpful in predicting the severe and mortal course of the disease (20-22). In our study, an increase in white blood cells and NLR, but a decrease in lymphocytes was found in the patient group who died, which was consistent with the literature.

In severe COVID-19 infections, an increase in troponin level is observed, which indicates viral myocarditis (22). Similarly, we detected higher troponin levels in the non-survival group. Acute respiratory distress and multi-organ failure during COVID-19 infection, an increase in TNF-α, IL-6, IL-8, and IL-12 cytokines occurs because of the uncontrolled immune system response caused by the infection. Evidence from studies that increases in serum ferritin, d-dimer, lactate, LDH, and IL-6 levels are associated with mortality. The release of cytokine, tissue factor, and elevation of d-dimer indicate an increased tendency of blood to clot. In addition, an increase in procalcitonin is one of the laboratory findings showing that the patient will deteriorate (23-25). In line with the literature, CRP, d-dimer, LDH, and procalcitonin were higher in the non-survivors. However, there was no statistically significant difference in ferritin levels between the groups. This may be caused by many factors that affect the ferritin level apart from inflammation.

In a study by Durán-Méndez A et al., it was reported that adding tocilizumab treatment in the early inflammatory period of COVID-19 infection reduced inflammatory markers and mortality (26). Similarly, we observed that delayed tocilizumab treatment was associated with high mortality rates.

Limitation of the Study: Since our study was retrospective, we could not evaluate the important risk factors such as weight, body mass index, smoking and other data of the patients.

The CCI index is a method that can be easily applied in comorbidity risk stratification and in predicting the relationship between mortality in patients who will be treated with tocilizumab in COVID-19 patients. CCI, white blood cell, NLR, urea, LDH, troponin, d-dimer, CRP, procalcitonin, lymphocyte, GFR, albumin and total protein baseline values can be used as risk factors for mortality of Covid -19 disease, together with comorbidities existing before treatment. In addition, early initiation of tocilizumab therapy may reduce mortality rates.

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