Clinical Research

Factors Associated with Mortality in COVID-19 Infection: Sanko University Experience

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ABSTRACT

Objective: Cytokine storm and macrophage activation were shown to be important factors in the pathogenesis of SARS-CoV-2 infection. We aimed to investigate the factors associated with mortality in patients with COVID-19 infection.

Material and Method: We grouped the adult patients followed-up with COVID-19 infection: Group A,outpatient (mild symptoms of COVID-19 infection, but no CT findings); Group B,mild/moderate illness (fever and respiratory tract symptoms of COVID-19 infection together with pneumonia on CT); Group C,severe (respiratory rate >30/minute, or oxygen saturation at room air of <93%, or PaO2/FiO2 of <300, or increase in CT findings more than 50% in 1-2 days) or critical illness (shock, or respiratory insufficiency requiring mechanical ventilation, or organ failure necessitating intensive care).

Results: Of total (n =166), 38.6%(n =64) were female. Mean age was 57.69(±9.8). Group A comprises of 22.9% (n =38), Group B 59.0% (n =98), and Group C 18.1% (n =30) of the patients. 8.4% of the patients (n =14) were died. ROC analysis revealed that age (>61-year), CRP (>62 mg/dL), ferritin (>385 ng/mL), D-dimer (>0.8 ng/mL), lymphocyte (≤850/mm3), procalcitonin (>0.08 µg/L), fibrinogen (>538 mg/dL), LDH (>469 U/L), AST (>39 U/L), SaO2 (≤87%), and duration of hospitalization (>7 days) predicted the mortality. Kaplan-Meier analysis also showed that age (>61 year), smoking (present), SaO2, procalcitonin (>0.08 µg/L), LDH (>469 U/L) were associated with mortality. Cox regression analysis revealed that age (>61), CRP (>62), and LDH (>469) were positive predictors for mortality.

Conclusion: We made an extensive analysis in a small patient population with a diagnosis of COVID-19 infection, and found a high rate of mortality. Older age, inflammatory biomarkers, mainly CRP and LDH, were associated with the mortality.

Keywords: *COVID-19, SARS-CoV-2, Coronavirus, Mortality, Marker.*

ÖZ

COVID-19 Hastalığında Enfeksiyonunda Mortalite ile İlişkili Faktörler: Sanko Üniversitesi Deneyimi

Amaç: Sitokin fırtınası ve makrofaj aktivasyonunun SARS-CoV-2 enfeksiyonu patogenezinde önemli faktörler olduğu gösterilmiştir. Çalışmamızda, COVID-19 enfeksiyonu olan hastalarda mortalite ile ilişkili faktörleri araştırmayı amaçladık.

Gereç ve Yöntem: COVID-19 enfeksiyonu ile takip ettiğimiz erişkin hastaları gruplara ayırdık: Grup A, ayaktan hasta (hafif COVID-19 enfeksiyonu semptomları var fakat tomografi bulgusu yok); Grup B, hafif/orta hastalık (ateş, COVID-19 enfeksiyonu solunum yolu semptomları ile birlikte tomografide pnömöni bulguları); Grup C, ciddi (solunum hızı >30/dk, oda havasında oksijen satürasyonu <%93, veya PaO2/FiO2 <300 veya 1-2 gün içinde tomografi bulgularında %50'den fazla artış) veya kritik hastalık (şok, mekanik ventilasyon gerektiren solunum yetmezliği veya yoğun bakım gerektiren organ yetmezliği).

Bulgular: Toplam 166 hastanın 64'ü (%38.6) kadındı. Ortalama yaş 57.69 (±9.8) idi. Grup A'da 38, Grup B'de 98 ve Grup C'de 30 hasta vardı. Hastaların %8.4' ü (n =14) öldü. ROC analizinde yaş (>61-yıl), CRP (>62 mg/L), ferritin (>385 ng/mL), D-dimer (>0.8 ng/mL), lenfosit (≤850/mm3), prokalsitonin (>0.08 µg/L), fibrinojen (>538 mg/dL), LDH (>469 U/L), AST (>39 U/L), SaO2 (≤%87) ve hastanede yatış süresi (>7 gün) mortaliteyi predikte ettirdi. Kaplan-Meier analizinde yaş (>61-yıl), sigara, SaO2, prokalsitonin (>0.08 µg/L), LDH (>469 U/L) mortaliteyle ilişkili bulundu. Cox regresyon analizinde yaş (>61), CRP (>62) ve LDH (>469) mortalite için pozitif prediktörlerdi.

Sonuç: COVID-19 enfeksiyonu tanısı alan küçük bir hasta grubunda geniş bir analiz yaptık ve mortalite oranını yüksek bulduk. İleri yaş, inflamatuar biyobelirteçler, esas olarak CRP ve LDH, mortalite ile ilişkili bulundu.

Anahtar Sözcükler: *COVID-19, SARS-CoV-2, Coronavirus, Mortalite, Belirteç.*

Bu makale atıfta nasıl kullanılır: Tanrıverdi M, Gündoğdu N. COVID-19 Hastalığında Enfeksiyonunda Mortalite ile İlişkili Faktörler: Sanko Üniversitesi Deneyimi. Fırat Tıp Dergisi 2023; 28(3): 205-212.

How to cite this article: Tanriverdi M, Gundogdu N. Factors Associated with Mortality in COVID-19 Infection: Sanko University Experience. Firat Med J 2023; 28(3): 205-212.

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COVID-19 pandemic has affected about 550 million people worldwide since first declaration of the pandemic by World Health Organization (WHO) up to July 2022 (1). Several studies have shown that SARS-CoV-2 infection led a high mortality in general population (1, 2). According to data declared by Ministry of Health of Türkiye, more than 15 million People have been affected by SARS-CoV-2 infection, and approximately 99000 people were died up to July 2022 in Türkiye (3). More than 145 million doses of COVID-19 vaccine were performed against COVID-19 infection in our country since January 2021 (3). Mass vac-

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Geliş Tarihi/Received: 22.11.2022 Kabul Tarihi/Accepted: 08.03.2023

cination programs, which attend to prevent SARS-CoV-2 infection, has become effective worldwide in terms of disease severity and mortality due to the infection (1, 4-9). The mortality rates were found as especially higher in specific population such as in those with obesity, diabetes mellitus, cancer, or in older patients (4, 10-12).

Cytokine storm and macrophage activation were shown to be important factors in the pathogenesis of SARS-CoV-2 infection (13). Inflammatory markers were studied as regards to the severity of the infection, or intensive care unit (ICU) admission or mortality (14-17). In previous reports, mortality in COVID-19 infection was shown to be associated with various factors such as oxygen saturation at admission, C-reactive protein (CRP), procalcitonin, D-dimer, ferritin, or lymphocyte counts, neutrophil to lymphocyte ratio, or ischemia-modified albumin levels (14, 15, 17-19). Hospitalization in the intensive care unit due to COVID-19 was also found to be associated with poor clinical findings and biomarkers and mortality, similar to our study (15,16,18,19).

In the meta-analysis of studies with a significant number of patients diagnosed with COVID-19; CRP, D-dimer, procalcitonin and ferritin levels were found to be associated with severe infection, intensive care unit admission, and increased mortality (17).

We aimed to investigate the clinical, demographic and biochemical factors associated with mortality in patients diagnosed with COVID-19 in the period before the vaccination program started.

MATERIAL AND METHOD

Study Design

This retrospective cross-sectional study was conducted in Sanko University Medical Faculty Hospital, and approved by the local Ethics Committee of Sanko University Medical Faculty with approval number, 2021/03. The study was conducted in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments. Written informed consent was obtained from all of the participants.

The adult patients diagnosed and followed-up with COVID-19 infection in Department of Infectious Diseases Sanko University Medical Faculty Hospital between July 2020 and December 2020 were analyzed retrospectively. COVID-19 diagnosis was made by PCR test analyzed from nasal swab samples taken from patients in whom there was a suspicion of COVID-19 infection. All patients underwent clinical and radiological evaluation. A total of 252 patients were screened. Those for whom data were missing, or those which bacterial cultures were positive were not included in the study. As a result, a total of 166 patients were included and analyzed. No patients were treated with anti-interleukin agents or JAK-inhibitors. Glucocorticoid treatment was given, if necessary, according to the national guideline (3). The patients were treated according Ministry of Health to the guideline (3).

Data Collection

Demographic parameters (age, sex, and body mass index (BMI), blood group), smoking status, clinical parameters (symptoms, chronic illnesses (hypertension, type 2 diabetes mellitus, asthma, chronic obstructive pulmonary disease, and coronary artery disease), oxygen saturation (SaO_2, %) duration of hospitalization (days)), and laboratory findings (C-reactive protein (CRP), ferritin, D-dimer, procalcitonin, fibrinogen, alanine transaminase (ALT), aspartate aminotransferase (AST), lactate dehydrogenase (LDH) and troponin levels, lymphocyte, neutrophil and leukocyte counts) were recorded by using electronic and written patient files. Laboratory parameters and cytokines were measured at the admission of patients to the hospital. Complete blood count was studied with an automated analyzer.

Patient Groups

The patients were grouped based on clinical symptoms and pulmonary imaging findings on thorax computed tomography (CT) on admission. We grouped them according to the severity of the infection as Group A - outpatient (mild symptoms of COVID-19 infection, but no CT findings); Group B - mild/moderate illness (fever and respiratory tract symptoms of COVID-19 infection together with pneumonia on CT); Group C - severe (respiratory rate >30/minute, or oxygen saturation at room air of <93%, or PaO2/FiO2 of <300, or increase in CT findings more than 50% in 1-2 days) or critical illness (shock, or respiratory insufficiency requiring mechanical ventilation, or organ failure necessitating intensive care).

The patients, who were grouped in Group A at diagnosis, but who developed a more severe disease later in the disease course were re-classified different as Group B or C.

We grouped the patients according to the mortality: alive vs. exitus. We compared demographic, clinical and laboratory parameters between the groups.

Statistical Analysis

Data obtained in the study were analysed statistically using SPSS 26.0 (IBM Corporation, Armonk, New York, United States). The conformity of the data to normal distribution was evaluated using the Shapiro-Wilk francia test. Homogenity of variance was evaluated with the Levene test. When comparing 2 independent groups of quantitative data according to each other, we used nonparametric Mann-Whitney U test with Monte Carlo results. When comparing categorical variables with each other, the Pearson Chi-Square, Fisher Exact and Fisher-Freeman-Holton tests with Monte Carlo simulation technique were used. Comparison of column ratios with each other was expressed by Benjamini-Hochberg corrected p-values. To detect the relationship between the real classification of the procedure's success and the

classification made by the cut-off values, sensitivity and specificity ratios, and positive and negative predictive values were expressed by ROC (Receiver Operating Curve) curve analysis. Kaplan-Meier (product limit method) Log Rank (Mantel-Cox) analysis was used to evaluate the effect of the factors on the survival and mortality. To measure the effects of prognostic variables on the mortality and duration of in-hospital follow-up, Cox Regression Analysis with Backward Stepwise (Wald) Method was used. Quantitative variables were stated as mean (standard deviation), and median (minimum-maximum) values, and categorical variables as number (n) and percentage (%) in the tables. Variables were evaluated at a 95% confidence level, and a value of $p < 0.05$ was accepted as statistically significant.

RESULTS

A total of 166 patients were included, 38.6% (n =64) of them were female. Mean age was 57.69 (±9.8). Fever and cough were detected in 82.5% (n =137) and 86.7% (n =144) of the patients, respectively. Co-existent illness was found in 88.0% of the patients (n =146). Thorax CT revealed normal findings in 22.9% (n =38), mild-moderate disease in 59.0% (n =98), and severe pneumonia in 18.1% (n =30) of the patients. 8.4% of the patients (n =14) were died. Mean duration of hospitalization was 11.14 (±9.24) days (Table 1).

Table 1. *Baseline demographic, clinical and laboratory parameters of the patients.*

	n	**%**
Sex (female)	64	38.6%
Blood group		
0	58	34.9%
A	66	39.8%
B	29	17.5%
AB	13	7.8%
Disease severity		
Group A	38	22.9%
Group B	98	59.0%
Group C	30	18.1%
Smoking	71	42.8%
Mortality	14	8.4%
Co-existent disease	146	88.0%
Hypertension	79	47.6%
T2D	72	43.4%
Asthma	25	15.1%
COPD	6	3.6%
CAD	27	16.3%
Fever	137	82.5%
Cough	144	86.7%
Sputum	4	2.4%
Dyspnea	136	81.9%
Anorexia	127	76.5%
Faintness/Fatigue	155	93.4%
	Mean(SD.)	**Median (Min-Max)**
Age	57.69 (9.8)	57 (38-79)
BMI (kg/m^2)	28.49 (6.56)	27 (22-86)
CRP (mg/L)	91.9 (81.46)	74 (1-350)
Ferritin (ng/mL)	573.67 (551.09)	396 (4-2000)
D-dimer (ng/mL)	0.99 (0.98)	0.57 (0.25-5.54)
WBC (/mm^3)	8280.99 (3491.23)	7610 (1950-23340)
PMNL (/mm^3)	6438.28 (3512.03)	5605 (1000-22590)
Lymphocyte (/mm^3)	1089.35 (726.18)	860 (180-3590)
Procalcitonin (µg/L)	0.15 (0.28)	0.05 (0.01-2)
Fibrinogen (mg/dL)	568.03 (208.64)	554 (202-1200)
LDH (U/L)	405.14 (541.7)	312.5 (132-6980)
Troponin (pg/mL)	11.74 (14.88)	8 (1-120)
AST (U/L)	29.87 (20.51)	26 (3-152)
ALT (U/L)	37.78 (29.05)	30.5 (8-308)
SaO2 (%)	90.66 (4.38)	89 (78-99)
Duration of hospitalization (day)	11.14 (9.24)	11 (0-43)

Age was higher, but smoking rate was lower in exitus group than in alive group ($p = 0.003$ and $p = 0.004$, respectively).

Comorbidities were detected at a similar rate among the groups. CT findings in the exitus group revealed mild-moderate disease. CRP (0.004), ferritin (0.001), D-dimer (0.002), procalcitonin (0.001), fibrinogen (0.032), LDH (<0.001) and AST (0.003) levels, and duration of hospitalization were higher, but SaO2 and lymphocyte count were lower in exitus group (Table 2).

Table 2. *Comparison of demographic, clinical and laboratory parameters among Alive and Exitus groups.*

	Alive (n =152)	Exitus (n =14)	p
	n (%)	n (%)	
Sex (female)	59 (38.8)	5 (35.7)	0.999 [c]
Age	56 (38-79)	67 (46-73)	**0.003** [u]
BMI (kg/m^2)	28 (23-38)	27 (22-86)	0.169 [u]
Blood Group			
0	54 (35.5)	4 (28.6)	
A	60 (39.5)	6 (42.9)	0.529 [ff]
B	25 (16.4)	4 (28.6)	
AB	13 (8.6)	0 (0)	
Disease severity			
Group A	38 (25) [B]	0 (0)	
Group B	84 (55.3)	14 (100) [A]	**0.004** [ff]
Group C	30 (19.7)	0 (0)	
Smoking	70 (46.1)	1 (7.1)	**0.004** [c]
Co-existent disease	133 (87.5)	13 (92.9)	0.999 [fe]
Hypertension	70 (46.1)	9 (64.3)	0.265 [c]
T2D	64 (42.1)	8 (57.1)	0.399 [c]
Asthma	24 (15.8)	1 (7.1)	0.697 [fe]
COPD	5 (3.3)	1 (7.1)	0.416 [fe]
CAD	24 (15.8)	3 (21.4)	0.703 [fe]
Fever	123 (80.9)	14 (100)	0.133 [fe]
Cough	130 (85.5)	14 (100)	0.219 [fe]
Sputum	3 (2)	1 (7.1)	0.299 [fe]
Dyspnea	122 (80.3)	14 (100)	0.076 [fe]
Anorexia	113 (74.3)	14 (100)	**0.042** [fe]
Faintness/Fatigue	141 (92.8)	14 (100)	0.601 [fe]
CRP (mg/L)	71.5 (1-350)	138.5 (40-252)	**0.004** [u]
Ferritin (ng/mL)	336.5 (4-2000)	1007 (205-2000)	**0.001** [u]
D-dimer (ng/mL)	0.53 (0.25-3.99)	1.65 (0.29-5.54)	**0.002** [u]
WBC (/mm^3)	7610 (2630-23340)	7460 (1950-20240)	0.999 [u]
PMNL (/mm^3)	5475 (1180-22590)	6715 (1000-18190)	0.192 [u]
Lymphocyte (/mm^3)	880 (180-3590)	505 (220-1130)	**<0.001** [u]
Procalcitonin (µg/L)	0.05 (0.01-2)	0.17 (0.03-1.07)	**0.001** [u]
Fibrinogen (mg/dL)	535.5 (202-1200)	665.5 (383-921)	**0.032** [u]
LDH (U/L)	297.5 (132-1077)	568 (254-6980)	**<0.001** [u]
Troponin (pg/mL)	8 (1-120)	8.5 (1-70)	0.290 [u]
AST (U/L)	25 (3-152)	44 (17-84)	**0.003** [u]
ALT (U/L)	30.5 (9-308)	37 (8-100)	0.805 [u]
SaO2 (%)	89 (78-99)	86.5 (85-88)	**<0.001** [u]
Duration of hospitalization (day)	10 (0-39)	17 (8-43)	**<0.001** [u]

[u] Mann-Whitney U Test (Monte Carlo); [c] Pearson Chi-Square Test(monte carlo), [ff] Fisher Freeman Halton test(monte carlo); [fe] Fisher Exact Test (monte carlo), Min: Minimum, Max: Maximum, [A] Express significance comparing alive, [B] Express significance comparing comparing exitus.

ROC analysis revealed that age (>61, [AUC±SE.: 0.743±0.064, p<0.001]), CRP (>62, [AUC±SE.: 0.732±0.057, p<0.001]), (>62 mg/L), ferritin (>385, [AUC±SE.: 0.746±0.060, p <0.001]), D-dimer (>0.8 ng/mL) (>0.8, (AUC±SE.: 0.749±0.077, p =0.001)), lymphocyte (≤850, (AUC±SE.: 0.779±0.052, p =0.001)), procalcitonin (>0.08, (AUC±SE.: 0.769±0.065, p <0.001)), fibrinogen (>538 mg/dL) (>538, (AUC±SE.: 0.672±0.066, p =0.009)), , LDH (>469, (AUC±SE.: 0.859±0.047, p <0.001)), AST (>39, (AUC±SE.: 0.740±0.069, p <0.001)), levels, SaO_2 (≤87%, (AUC±SE.: 0.894±0.026, p <0.001)), and duration of hospitalization (>7 days) (>7 (AUC±SE.: 0.763±0.059 , p <0.001)), predicted the mortality (Table 3).

Table 3. *Roc analysis demonstrating cut-off values of the clinical and laboratory parameters predicting mortality.*

Mortality	Cut-off	Sensitivity	Specificity	+PV	-PV	AUC±SE.	p value
Age	>61	78.57%	69.74%	19.3	97.2	0.743 ± 0.064	**<0.001**
CRP (mg/L)	>62	92.86%	46.71%	13.8	98.6	0.732 ± 0.057	**<0.001**
Ferritin (ng/mL)	>385	85.71%	53.29%	14.5	97.6	0.746 ± 0.060	**<0.001**
D-dimer (ng/mL)	>0.8	78.57%	67.57%	18.6	97.1	0.749 ± 0.077	**0,001**
Lymphocyte (/mm^3)	≤850	92.86%	55.26%	16	98.8	0.779 ± 0.052	**<0.001**
Procalcitonin (µg/L)	>0.08	78.57%	75.00%	22.4	97.4	0.769 ± 0.065	**<0.001**
Fibrinogen (mg/dL)	>538	78.57%	50.66%	12.8	96.2	0.672 ± 0.066	**0.009**
LDH (U/L)	>469	85.71%	80.92%	29.3	98.4	0.859 ± 0.047	**<0.001**
AST (U/L)	>39	57.14%	85.53%	26.7	95.6	0.740 ± 0.069	**<0.001**
SaO2 (%)	≤87	92.86%	83.55%	34.2	99.2	0.894 ± 0.026	**<0.001**
Duration of hospitalization (day)	>7	100.00%	42.11%	13.7	100	0.763 ± 0.059	**<0.001**

Roc: Receiver Operating Curve, Analysis: Honley&Mc Nell - Youden index J), AUC: Area under the ROC curve, SE: Standard Error.

Kaplan-Meier analysis also showed that age (>61 year) (p =0.021), smoking (present) (p =0.023), SaO2, pro-calcitonin (>0.08 µg/L) (p =0.035), LDH (>469 U/L) (p =0.012) were associated with mortality (Table 4).

Table 4. *Kaplan-Meier analysis demonstrating the factors associated with mortality and estimate survival.*

	Exitus	Alive	Estimate Survival	Estimate Proportion Surviving at the	p value
	n(%)	n(%)	Mean or Median* ± Se.	10 day/20 day/30 day	
Anorexia					
Absent	0(0)	39(100)	-	100/100/100	-
Present	14(11)	113(89)	40.000±7.42*	98/84.6/58.6	
SaO2 (%)					
>87	0(0)	101(100)	-	100/100/100	**0.034**
≤87	14(21.5)	51(78.5)	40.000±6.49*	96.9/78.7/51	
Smoking					
No	13(13.7)	82(86.3)	31.353±2.80	96.9/76.1/41.6	**0.023**
Yes	1(1.4)	70(98.6)	40.000±0.00	100/100/100	
Age (year)					
≤61	4(3.5)	109(96.5)	39.044±2.30	100/97.7/85.5	**0.001**
>61	10(18.9)	43(81.1)	24.954±1.43	95.6/70.1/0	
CRP (mg/L)					
≤62	2(2.7)	71(97.3)	28.500±1.50	100/100/0	0.508
>62	12(12.9)	81(87.1)	35.680±2.11	97.7/83.3/72.9	
Ferritin (ng/mL)					
≤385	2(2.4)	81(97.6)	26.143±1.18	95.2/95.2/0	0.911
>385	12(14.5)	71(85.5)	34.480±2.24	98.8/82.3/62.7	
D-dimer (ng/mL)					
≤0.8	4(3.7)	105(96.3)	39.663±1.88	97.8/93.9/93.9	0.242
>0.8	10(17.5)	47(82.5)	31.255±1.994	94.4/81.2/49.5	
Lymphocyte (/mm^3)					
>850	1(1.2)	84(98.8)	27.000±0.00	100/100/0	0.146
≤850	13(16)	68(84)	33.845±2.29	97.4/79.8/60.8	
Procalcitonin (µg/L)					
≤0.08	3(2.6)	114(97.4)	33.848±2.47	100/97/53.9	**0.035**
>0.08	11(22.4)	38(77.6)	32.376±2.95	95.9/72.4/57.9	
Fibrinogen (mg/dL)					
≤538	3(3.8)	77(96.3)	37.625±3.73	100/100/62.5	0.145
>538	11(12.8)	75(87.2)	33.208±2.33	97.5/80.3/64.3	
LDH (U/L)					
≤469	2(1.6)	123(98.4)	35.528±2.448	100/98.1/65.4	**0.012**
>469	12(29.3)	29(70.7)	31.018±2.80	95.1/70.4/51.3	
AST (U/L)					
≤39	7(5)	132(95)	33.903±1.91	97.4/91.6/64.1	0.193
>39	7(25.9)	20(74.1)	29.473±4.24	100/61/40.6	
Total	14(8.4)	152(91.6)	34.061±2.161	98/84.6/58.6	-

Kaplan Meier Test: Log Rank (Mantel-Cox), SE: Standard Error.

Cox regression analysis revealed that age (>61 year), CRP (>62 mg/L), and LDH (>469 U/L) were positive predictors for mortality (Table 5).

Table 5. *Cox Regression analysis indicating the predictors of mortality according to cut-off values.*

	B	SE	p	HR	95.0% CI for HR	
					Lower	Upper
Age (>61)	-3.482	1.058	**0.001**	**32.5**	4.1	258.3
CRP (>62)	3.166	1.337	**0.018**	**23.7**	1.7	326.0
Ferritin	1.667	1.006	0.098	5.3	0.7	38.0
Fibrinogen	-2.152	1.139	0.059	8.6	0.9	80.2
LDH (>469)	-3.673	1.121	**0.001**	**39.4**	4.4	354.2

10 / 20 / 30 day survival rates (Sh): 99.8 (0.003) / 97.3 (0.021) / 73.4 (0.146) -Base Line Hazard: 0.047. Cox Regression-Backward Stepwise (Wald) Method. C.I.: Confidence interval. B: regression coefficients. SE: Standard error.

DISCUSSION

We showed that older age (>61-year), and inflammatory markers such as CRP (>62) and LDH (>469) strongly predicted the mortality in COVID-19 infection. Kaplan-Meier analysis also showed that smoking, low oxygen saturation, high procalcitonin were associated with mortality.

SARS-CoV-2 belongs to a coronavirus family and binds to angiotensin-converting enzyme 2 for entry into the host cell (24-26). After entry to the cell, viral replication in lower respiratory tract may lead to viremia, the stage at which respiratory epithelial cells, dendritic cells, and macrophages produce an immune reaction via secreting cytokines and chemokines (27). During the transition from early infection to pulmonary involvement, and then to systemic hyperinflammation, levels of pro-inflammatory cytokines and chemokines increase (14). The continuing secretions of pro-inflammatory cells may lead an uncontrolled inflammatory response that may cause a worsening clinical situation and cytokine storm.

Given an overactivation of inflammation in COVID-19 infection, it is not surprising that inflammatory biomarkers may be increased in this infection. In a systematic review of several studies investigating COVID-19 infection, increase in CRP, LDH, ALT, AST, D-

dimer levels and lymphopenia were detected in the infection (28). In various studies, the severity of laboratory abnormalities was shown to be associated with the severity of the infection (29-31). In a small study from Türkiye including 245 patients, increased levels of CRP, D-dimer, ferritin and low lymphocyte counts were found to be significant predictors of the mortality rate in COVID-19 infection (15). In our study, although ferritin (>385), D-dimer (>0.8) or lymphocyte (≤850) levels were shown to be associated with mortality in Roc analysis, they did not reach a strong association with mortality when considering survival time or other factors.

In one study, CRP (>4.76 mg/dL), D-dimer (>0.4 mcg/mL) and procalcitonin (0.01 mcg/dL) levels were found to be associated with more severe course of disease in COVID-19 infection (32). They serially measured laboratory parameters during the course of infection, and also revealed that progressive decrease in lymphocyte or thrombocyte count, increase in CRP, procalcitonin, or liver enzymes was associated with the severity of the infection (32). We could measure the laboratory parameters at the admission, not follow-up them during the course of infection.

In our study, hypertension, type 2 diabetes (T2D), asthma, chronic obstructive pulmonary disease (COPD), or coronary artery disease (CAD) was not associated with mortality in COVID-19. Small sample size might have led such a finding. In a study including a large sample demonstrated that T2D was associated with the severity of and mortality in the COVID-19 (10). Hypertension also was shown to be associated with the prognosis of the infection (10). In a previous study, COPD or asthma were not found as risk factors for SARS-CoV-2 infection (32). Inconsistent findings were reported regarding the association of COPD or asthma with the severity of COVID-19 (33, 34).

We analyzed the association of biomarkers with mortality in COVID-19 infection, but not analyze the factors predicting intensive care unit admission. In one small study including 29 patients, IL-6, CRP and procalcitonin were found as predictors of ICU need (17).

In a meta-analysis analyzing 25 studies, biomarkers were investigated as regards to the prognosis of COVID-19 infection (18). In this report, increased levels of CRP (≥10 mg/L), procalcitonin (≥0.5 ng/mL), D-dimer (>0.5 mg/L) and ferritin were demonstrated to be associated with a poor composite outcome that consists of severe infection, ICU admission, ARDS and mortality (18). In this meta-analysis including a total of 5350 patients, these findings were not modified by age, sex, cardiovascular disease, diabetes, and COPD.

SARS-CoV-2 infection, via entry of the virus to alveolar cells expressing ACE2 and cytokine storm injuring alveolar cells, may result in alveolar edema and acute respiratory distress syndrome (14, 35). Supportive care including supplemental oxygen was the main stay of therapy in COVID-19 patients during the early pandemic before the initiation of vaccination against SARS-CoV-2 infection. In the studies conducted in the pre-vaccination period, more than a half of the patients hospitalized with a diagnosis of COVID-19 infection required oxygen therapy (9, 36). Expectingly, we found that low oxygen saturation was associated with mortality. After the beginning of vaccination against COVID-19 infection, and decreasing pathogenicity of the infection with time, oxygen need in the patients infected with SARS-CoV-2 decreased (37).

In our study, symptoms of COVID-19 infection were similar in alive or exitus groups, with the exception of anorexia which was higher in exitus group. However, even anorexia could not reach a predictive value in further analyses. It may indicate that clinical and laboratory evaluations at baseline, rather than the symptoms, may reflect the mortality in COVID-19 infection. We also showed that longer duration of hospitalization might be associated with mortality. Hence, prompt diagnosis and early initiation of therapy has become prominent.

We treated the patients with supportive therapy, but not give any specific treatment targeting inflammatory biomarkers. In the literature, a lot of studies have been conducted regarding the effect of therapeutic agents targeting inflammatory pathways on the course of COVID-19 infection. Tocilizumab, monoclonal antibody binding IL-6 receptor and precluding IL-6 signaling, is one of the best-known agents which has been proved to be effective in COVID-19 infection (38).

Strength and Limitations

We analyzed the mortality in the patients with COVID-19 infection both by Roc analysis, Kaplan-Meier and Cox regression analysis. The sample size was small. Small sample size might have led the lack of association between co-existent diseases and mortality. We could not analyze the factors predicting intensive care unit admission, or severity of infection. We did analyze the SaO2 and biomarkers on the admission of hospital, but could not analyze those during the course of the infection.

Conclusion

We made an extensive analysis in a small patient population with a diagnosis of COVID-19 infection, and showed inflammatory biomarkers, mainly CRP and LDH, were associated with the mortality. In large studies analyzing also the other parameters indicating prognosis, such as ICU admission, and measuring the biomarkers also during the course of the infection might be more beneficial. The effects of therapeutic agents on such biomarkers will be clarified in future studies.

REFERENCES

1- World Health Organization (WHO). Clinical management of COVID-19. https://covid19.who.int/ (Access Date: 15 July 2022).
2- Bottle A, Faitna P, Brett S, Aylin P. Factors associated with, and variations in, COVID-19 hospital death rates in England's first two waves: observational study. BMJ Open 2022; 12: e060251.
3- Türkiye Cumhuriyeti Sağlık Bakanlığı. COVID-19 Rehberi Erişkin Hasta Tedavisi Rehberi. https://covid19.saglik.gov.tr/ (Access Date: 15 July 2022).
4- Bajpai J, Kant S, Verma A et al. The Severity of COVID 19 Pneumonia in Vaccinated vs. Non-vaccinated Patients in the Second Wave: An Experience From a Tertiary Care Center in India. Cureus. 202; 14: e25378.
5- Watson OJ, Barnsley G, Toor J, Hogan AB, Winskill P, Ghani AC. Global impact of the first year of COVID-19 vaccination: a mathematical modelling study. Lancet Infect Dis 2022; 22: 1293-302.
6- Wells CR, Galvani AP. The global impact of disproportionate vaccination coverage on COVID-19 mortality. Lancet Infect Dis 2022; 22: 1254-5.
7- Wong CKH, Lau KTK, Xiong X et al. Adverse events of special interest and mortality following vaccination with mRNA (BNT162b2) and inactivated (CoronaVac) SARS-CoV-2 vaccines in Hong Kong: A retrospective study. PLoS Med 2022; 21: e1004018.
8- Lopez Bernal J, Andrews N, Gower C et al. Effectiveness of the Pfizer-BioNTech and Oxford-AstraZeneca vaccines on covid-19 related symptoms, hospital admissions, and mortality in older adults in England: test negative case-control study. BMJ 2021; 13: 373: n1088.
9- Wiersinga WJ, Rhodes A, Cheng AC, Peacock SJ, Prescott HC. Pathophysiology, Transmission, Diagnosis, and Treatment of Coronavirus Disease 2019 (COVID-19): A Review. JAMA 2020; 324: 782-93.
10- Sonmez A, Demirci I, Haymana C et al. Clinical characteristics and outcomes of COVID-19 in patients with type 2 diabetes in Turkey: A nationwide study (TurCoviDia). J Diabetes 2021; 13: 585-95.
11- Sahin I, Haymana C, Demir T et al. Clinical Characteristics and Outcomes of COVID-19 Patients with Overweight and Obesity: Turkish Nationwide Cohort Study (TurCObesity). Exp Clin Endocrinol Diabetes 2022; 130: 115-24.
12- Fattore GL, Olivos NSA, Olalla JEC, Gomez L, Marucco AF, Mena MPR. Mortality in patients with cancer and SARS-CoV-2 infection: Results from the Argentinean Network of Hospital-Based Cancer Registries. Cancer Epidemiol 2022; 79: 102200.
13- Okan F, Okan S, Hanoglu Y. Is Vitamin D Level Associated with COVID-19 Infection? Med J Western Black Sea 2022; 6: 48-52.
14- Choudhary S, Sharma K, Silakari O. The interplay between inflammatory pathways and COVID-19: A critical review on pathogenesis and therapeutic options. Microb Pathog 2021; 150: 104673.
15- Topcu H, Arik YE. The Importance of D-Dimer, Ferritin, CRP and Lymphocyte Values in Determining Mortality in COVID-19 Disease in Turkey. Clin Lab 2022; 1: 68.
16- Tjendra Y, Al Mana AF, Espejo AP et al. Predicting Disease Severity and Outcome in COVID-19 Patients: A Review of Multiple Biomarkers. Arch Pathol Lab Med 2020; 144: 1465-74.
17- Broman N, Rantasärkkä K, Feuth T et al. IL-6 and other biomarkers as predictors of severity in COVID-19. Ann Med 2021; 53: 410-2.
18- Huang I, Pranata R, Lim MA, Oehadian A, Alisjahbana B. C-reactive protein, procalcitonin, D-dimer, and ferritin in severe coronavirus disease-2019: a meta-analysis. Ther Adv Respir Dis 2020; 14: 1753466620937175.
19- Yılmam İ, Gegin S. Evaluation of Patient Characteristics and Pandemic Management in the First Three Months of the COVID-19 Pandemic at the. Med J Western Black Sea 2021; 5: 386-90.
20- Baytar MS, Baytar Ç. Evaluation of readmissions after discharged from ıntensive care unit in patients with coronavirus disease-2019. Med J Western Black Sea 2022; 6: 53-7.
21- Sanchez BG, Gasalla JM, Sánchez-Chapado M, Bort A, Diaz-Laviada I. Increase in Ischemia-Modified Albumin and Pregnancy-Associated Plasma Protein-A in COVID-19 Patients. J Clin Med 2021; 10: 5474.
22- La Torre G, Marte M, Massetti AP et al. The neutrophil/lymphocyte ratio as a prognostic factor in COVID-19 patients: a case-control study. Eur Rev Med Pharmacol Sci 2022; 26: 1056-64.
23- Aslaner Ak M, Sahip B, Çelebi G, Horuz E, Ertop Ş. Abnormalities of Peripheral Blood Parameters in Hospitalized Patients with COVID-19: A Temporal Change Analysis in Relation to Survival. Med J Western Black Sea 2021; 5: 391-400.
24- Yuki K, Fujiogi M, Koutsogiannaki S. COVID-19 pathophysiology: A review. Clin Immunol 2020; 215: 108427.
25- Arshad Ali S, Baloch M, Ahmed N, Arshad Ali A, Iqbal A. The outbreak of Coronavirus Disease 2019 (COVID-19)-An emerging global health threat. J Infect Public Health 2020; 13: 644-6.
26- Zhang C, Shi L, Wang FS. Liver injury in COVID-19: management and challenges. Lancet Gastroenterol Hepatol 2020; 5: 428-30.

27- Mehta P, McAuley DF, Brown M, Sanchez E, Tattersall RS, Manson JJ. HLH Across Speciality Collaboration, UK. COVID-19: consider cytokine storm syndromes and immunosuppression. Lancet 2020; 395: 1033-4.
28- Rodriguez-Morales AJ, Cardona-Ospina JA, Gutiérrez-Ocampo E et al. Latin American Network of Coronavirus Disease 2019-COVID-19 Research (LANCOVID-19). Electronic address: https://www.lancovid.org. Clinical, laboratory and imaging features of COVID-19: A systematic review and meta-analysis. Travel Med Infect Dis 2020; 34: 101623.
29- Guan WJ, Ni ZY, Hu Y et al; China Medical Treatment Expert Group for Covid-19. Clinical Characteristics of Coronavirus Disease 2019 in China. N Engl J Med 2020; 382: 1708-20.
30- Huang C, Wang Y, Li X et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. Lancet. 2020; 395: 497-506.
31- Wu C, Chen X, Cai Y, et al. Risk Factors Associated With Acute Respiratory Distress Syndrome and Death in Patients With Coronavirus Disease 2019 Pneumonia in Wuhan, China. JAMA Intern Med 2020; 180: 934-43.
32- Zhang JJ, Dong X, Cao YY et al. Clinical characteristics of 140 patients infected with SARS-CoV-2 in Wuhan, China. Allergy 2020; 75: 1730-41.
33- Xu L, Mao Y, Chen G. Risk factors for 2019 novel coronavirus disease (COVID-19) patients progressing to critical illness: a systematic review and meta-analysis. Aging (Albany NY) 2020; 12: 12410-21.
34- Geifman N, Whetton AD. A consideration of publication-derived immune-related associations in Coronavirus and related lung damaging diseases. J Transl Med 2020; 3; 18: 297.
35- Ye Q, Wang B, Mao J. The pathogenesis and treatment of the `Cytokine Storm' in COVID-19. J Infect 2020; 80: 607-13.
36- Alhazzani W, Møller MH, Arabi YM et al. Surviving Sepsis Campaign: guidelines on the management of critically ill adults with Coronavirus Disease 2019 (COVID-19). Intensive Care Med 2020; 46: 854-87.
37- Flisiak R, Rzymski P, Zarębska-Michaluk D et al. Variability in the Clinical Course of COVID-19 in a Retrospective Analysis of a Large Real-World Database. Viruses 2023; 15: 149.
38- Xu X, Han M, Li T et al. Effective treatment of severe COVID-19 patients with tocilizumab. Proc Natl Acad Sci USA 2020; 117: 10970-5.