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Original Article

Evaluation of Clinics and Prognoses of COVID-19 Patients with Ferritin, D-Dimer, FAD-85 Score in Intensive Care Unit

COVID-19 Hastalarının Yoğun Bakıma Yatış Sırasında Ferritin, D-Dimer Değerleri ve FAD-85 Skorları ile Klinik Seyir ve Prognozları Arasındaki İlişkinin Değerlendirilmesi

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ABSTRACT

Objective: COVID-19 is a serious disease that can cause severe acute respiratory distress syndrome and end-stage organ failure. Clinicians need early and effective indicators to evaluate prognosis and prevent mortality in such infections. The FAD-85 score is used as an early marker calculated by the patient's age, ferritin level, and D-dimer level. This study aimed to investigate the effects of the FAD-85 score, D-dimer, and ferritin values on prognosis and mortality during admission to the intensive care unit (ICU).

Material and Methods: The data of 204 patients hospitalized with the diagnosis of COVID-19 in the tertiary ICU between April 1, 2021-March 31, 2022 were retrospectively analyzed. Demographic characteristics of the patients, invasive/non-invasive mechanical ventilator or high flow oxygen requirement and duration, tracheostomy and intubation status, length of stay in hospital and ICU and 1-month mortality were evaluated. From laboratory parameters, leukocyte, lymphocyte, ferritin, D-dimer, procalcitonin, C-reactive protein (CRP), lactate dehydrogenase levels were recorded. Age + 0.01 x ferritin + D-dimer formula was used for the FAD-85 score.

Results: In this study, in which 204 COVID-19 patients were examined, the conditions predicting 1-month mortality: male gender (p=0.029), presence of intubation (p<0.001), increased CRP (p=0.002), low lymphocyte levels (p=0.009), FAD-85>85 (p=0.001) and high ferritin (p= 0.044) were found. In addition, the presence of intubation [odds ratio (OR) 95% confidence interval (CI): 3.941 (2.115-7.343)], high CRP [OR (95% CI): 1.004 (1.000-1.008)], and FAD-85>85 [OR (95% (CI) (2.462 (1.313-4.617)] were found to predict mortality.

It has been determined that the FAD-85 score, a simple metric, is effective in forecasting mortality among COVID-19 patients. It was observed that patients with a FAD-85 score greater than 85, patients with elevated CRP, and patients requiring intubation have higher mortality rates.

Conclusion: Elevated FAD-85 scores, increased CRP levels, and the necessity of intubation all serve as significant indicators of the severity and prognosis for ICU-admitted COVID-19 patients.

Keywords: COVID-19, D-dimer, FAD-85 score, ferritin

ÖZ

Amaç: COVID-19 sadece birkaç gün içerisinde şiddetli akut respiratuar distress sendromuna ve son dönem organ yetmezliğine neden olabilen ciddi bir hastalıktır. Bu nedenle hastalığın erken evrelerinde prognozu değerlendirmek için kolayca erişilebilen göstergeler, doktorların hastalığın alevlenmesini veya ölüm oranını önlemek için zamanında ve etkili önlemler almasını sağlar. Bu çalışmada yoğun bakıma yatış sırasında bakılan FAD-85 skoru, D-dimer ve ferritin değerlerinin prognoz ve mortalite üzerine etkisinin araştırılması amaçlandı.

Gereç ve Yöntemler: Erişkin 3. basamak genel yoğun bakımda 1 Nisan 2021-31 Mart 2022 tarihleri arasında COVID-19 tanısı ile yatmış 204 hastanın verileri retrospektif olarak incelendi. Hastaların yaşı, cinsiyeti, altta yatan hastalıkları, Charlson Komorbidite İndeksi, akut fizyoloji ve kronik sağlık değerlendirmesi skoru, aşı durumu, SARS-CoV-2 PCR testi, beslenme durumu (parenteral, enteral), yoğun bakımda takipleri sürecince kan, idrar ve trakeal aspirat kültürlerinde üreme durumları, trakeostomi ve entübasyon durumu, invaziv/non-invaziv mekanik ventilatör ihtiyacı ve süresi, yüksek akım oksijen ihtiyacı ve süresi, yoğun bakımda ve hastanede kalış süresi ve 1 aylık mortaliteleri değerlendirildi. Laboratuvar parametrelerinden yoğun bakım ünitesine yatış sırasında lökosit, lenfosit, ferritin, D-dimer, prokalsitonin, C-reaktif protein (CRP), laktat dehidrogenaz düzeyleri kaydedildi. FAD-85 skorunun hesaplanması için yaş + 0,01 x ferritin + D-dimer formulü kullanıldı.

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ÖZ

Bulgular: İki yüz dört COVID-19 hastasının incelendiği bu çalışmada, 1 aylık mortaliteyi öngören faktörler; erkek cinsiyet (p=0,029), entübasyon varlığı (p<0,001), CRP artışı (p=0,002), lenfosit düşüklüğü (p=0,009), FAD-85 değerinin 85'in üstünde olması (p=0,001) ve ferritin yüksekliği (p=0,044) olarak bulunmuştur. Ayrıca entübasyon varlığı [odds oranı (OR) (%95 güven aralığı (GA): 3,941 (2,115-7,343)], CRP yüksekliği [OR (%95 GA): 1,004 (1,000-1,008] ve FAD-85 değerinin 85'in üstünde olmasının (OR (%95 GA): 2,462 (1,313-4,617) mortaliteyi öngördüğü anlaşılmıştır. Basit bir şekilde hesaplanabilen FAD-85 skorunun COVID-19 hastalarında mortaliteyi öngörmede etkin olduğu anlaşılmıştır. FAD-85>85 olan, CRP yüksekliği olan ve yoğun bakımda yatış sırasında entübe takip edilen hastalarda mortalite oranı daha yüksek olduğu için bu hastalarda zamanında ve etkin tedavi son derece önemlidir.

Sonuç: Yoğun bakımda takip edilen COVID-19 hastalarında FAD-85 skoru ve CRP yüksekliği ile entübasyon varlığı hastalığın şiddeti ve prognozu hakkında önemli bilgiler sağlar.

Anahtar Kelimeler: COVID-19, D-dimer, FAD-85 skoru, ferritin

INTRODUCTION

COVID-19, a severe disease that has rapidly spread across numerous countries, was declared a global pandemic by the World Health Organization in 2020. This infection can result in severe acute respiratory distress syndrome (ARDS) and terminal organ failure (1). Patients diagnosed with COVID-19 pneumonia can experience a rapid escalation in symptoms within just a few days, potentially progressing to ARDS. Therefore, readily available early-stage indicators allow physicians to implement timely and effective strategies to mitigate disease progression and reduce mortality rates.

Existing literature has indicated that elevated levels of ferritin and D-dimer, which signify the thrombo-inflammatory nature of COVID-19, are associated with increased mortality and morbidity rates, as well as prolonged hospital stays (2-4). Nevertheless, the prognosis and mortality of patients cannot be solely determined by ferritin and D-dimer levels. Factors such as patient age and comorbid conditions also significantly influence the outcome.

Numerous factors have been assessed for their ability to predict mortality in COVID-19 patients. The FAD-85 score, comprising D-dimer, ferritin, and age, has been identified as highly predictive when investigating the efficacy of various combinations of variables in predicting mortality. The FAD-85 score demonstrated a sensitivity, specificity, positive predictive value, negative predictive value, false-positive rate, and false-negative rate of 86.4%, 81.8%, 39.6%, 97.7%, 16.0%, and 13.6%, respectively (5).

In the case of COVID-19 patients, assessing predictive factors upon admission to the intensive care unit (ICU) can aid in predicting mortality, facilitating the introduction of suitable measures to reduce them. Consequently, the objective of this study was to explore the influence of the FAD-85 score, D-dimer, and ferritin levels, evaluated upon ICU admission, on the prognosis and mortality of COVID-19 patients.

MATERIALS and METHODS

This study encompassed a total of 204 adult patients who were admitted to the adult general ICU with a diagnosis of COVID-19 between April 1, 2021, and March 31, 2022. Following approval from the Institutional Ethics Committee, the patients' data were retrospectively reviewed. The approval of the Clinical Research Ethics Committee of Ankara Atatürk Sanatorium Training and Research Hospital has been obtained (decision number: 2012-KAEK-15/2666, date: 08.03.2023).

The patients' age, gender, pre-existing conditions, Charlson Comorbidity Index Score (CCIS), acute physiology and chronic health evaluation II (APACHE-II) score, nutritional status (parenteral, enteral), tracheostomy and intubation status, necessity invasive mechanic ventilation (IMV), non-invasive mechanic ventilation (NIMV) and the duration thereof, high flow nasal oxygen ($HFNO_2$) requirement and its duration, duration of ICU and hospital stays, and one-month mortality rates were all recorded.

The patients' COVID-19 vaccination status was reviewed, and they were subsequently categorized as either vaccinated or unvaccinated. For the vaccinated group, the first and second doses of the COVID-19 vaccine were noted and categorized as either inactive or active vaccines.

The diagnosis of COVID-19 was established based on clinical symptoms, contact history, SARS-CoV-2 PCR tests, and typical COVID-19 findings on chest computed tomography. In cases where the SARS-CoV-2 PCR test was negative, but there was clinical suspicion of COVID-19 based on other diagnostic methods, patients were admitted to the COVID ICU and subsequent SARS-CoV-2 PCR tests were conducted. Consequently, patients who initially tested negative on the SARS-CoV-2 PCR test but later tested positive or were diagnosed with COVID-19 based on other diagnostic methods were also included in the study.

Cultures of blood, urine, and endotracheal aspirate samples collected upon ICU admission and throughout the ICU stay were examined. Instances of positive growth in the cultures and the specific microorganisms isolated were documented.

Laboratory parameters, including white blood cell count, lymphocyte count, ferritin, D-dimer, procalcitonin, C-reactive protein (CRP), and lactate dehydrogenase (LDH) levels, were recorded upon ICU admission. Given that the reference range for ferritin in our hospital is 4.6-274 µg/L, the values above 274 µg/L were considered as high ferritin levels. For D-dimer, the reference range is below 550 ng/mL, so values above

550 ng/mL were considered high D-dimer levels. The FAD-85 score was computed using the formula: age + 0.01 x ferritin + D-dimer patients with an FAD-85 score below 85 were classified as low-risk, while those with scores above or equal to 85 were considered high-risk.

Statistical Analysis

Data analyses were performed using SPSS for Windows, version 22.0 (SPSS Inc., Chicago, IL, United States). The normality of the distribution of continuous variables was assessed by the Kolmogorov-Smirnov test. The Levene test was used to evaluate the homogeneity of variances. Unless specified otherwise, continuous data were presented as mean±SD and median (interquartile range). Categorical data were presented as the number of cases (%). Differences in normally distributed variables between two independent groups were compared using Student's t-test, while the Mann-Whitney U test was used for comparisons of non-normally distributed data. Categorical variables were compared using Pearson's chi-square test or Fisher's exact test, with a $p<0.05$ accepted as the level of significance in all statistical analyses.

RESULTS

This retrospective study involved 204 patients diagnosed with COVID-19 who were admitted to a level 3 adult ICU. Of these, 92 were female and 112 were male, with a mean age of 68.27±13.92.

When the relationship between the demographic characteristics, clinical findings, treatments, laboratory values and one-month mortality was analyzed, male sex ($p=0.028$), intubation rate ($p<0.001$), FAD-85 (both continuous and categorical) ($p<0.001$), ferritin (both continuous and categorical) ($p=0.001$), APACHE-II score ($p=0.013$), leukocyte ($p<0.001$), procalcitonin ($p=0.001$), LDH ($p=0.001$), CRP ($p=0.001$), and D-dimer (both continuous) value ($p=0.031$) were statistically significantly higher in patients with and without one-month mortality. Notably, hospital stay duration ($p<0.001$), oral feeding status ($p=0.001$), history of a previous cerebrovascular event ($p=0.046$), duration of $HFNO^2$ application ($p=0.013$), duration of NIMV application ($p=0.007$), and lymphocyte count ($p<0.001$) were significantly lower in patients with one-month mortality (Table 1).

Table 1. The relationship between demographic characteristics, clinical findings and laboratory values of the patients and 1-month mortality

		1 month mortality				p-value
		Yes (n=113)		No (n=91)		
		$\bar{X}$±SD/n	Med (IQR)/(%)	$\bar{X}$±SD/n	Med (IQR)/(%)	
Gender$^{\Phi}$	Female	43	(38.4%)	49	(53.8%)	**0.028**
	Male	70	(61.6%)	42	(46.2%)	
Age (year)$^{\beta}$		69.75±13.47	71 (20)	66.44±14.31	67 (22)	0.091
Length of stay ICU (day)*		7.75±6.77	6 (8)	10.87±11.58	6 (13)	0.366
Length of stay in hospital (day)*		12.91±7.92	11 (11)	24.21±18.68	21 (24)	**<0.001**
DM$^{\Phi}$	No	71	(62.8%)	68	(74.7%)	0.070
	yes	42	(37.2%)	23	(25.3%)	
HT$^{\Phi}$	No	64	(56.6%)	55	(60.4%)	0.840
	Yes	49	(43.4%)	36	(39.6%)	
CAD$^{\Phi}$	No	97	(85.8%)	83	(91.2%)	0.237
	Yes	16	(14.2%)	8	(8.8%)	
CHF$^{\Phi}$	No	105	(92.9%)	85	(93.4%)	0.891
	Yes	8	(7.1%)	6	(6.6%)	
CKD$^{\Phi}$	No	111	(98.2%)	90	(98.9%)	0.692
	Yes	2	(1.8%)	1	(1.1%)	
Parenteral nutrition$^{\Phi}$	No	92	(81.4%)	81	(89.0%)	0.133
	Yes	21	(18.6%)	10	(11.0%)	
Oral nutrition$^{\Phi}$	No	30	(26.5%)	11	(12.1%)	**0.010**
	Yes	83	(73.5%)	80	(87.9%)	
Intubation$^{\Phi}$	No	33	(29.2%)	59	(64.8%)	**<0.001**
	Yes	80	(70.8%)	32	(35.2%)	
Previous PTE	No	107	(94.7%)	87	(95.6%)	0.999
	Yes	6	(5.3%)	4	(4.4%)	

Table 1. Continued

		1 month mortality				p-value
		Yes (n=113)		No (n=91)		
		±SD/n	Med (IQR)/(%)	±SD/n	Med (IQR)/(%)	
Previous CVD	No	112	(99.1%)	85	(93.4%)	0.046
	Yes	1	(0.9%)	6	(6.6%)	
1st dose vaccine$^{\Phi}$	No	62	(54.9%)	51	(56.0%)	0.240
	Inactivated vaccine	39	(34.5%)	36	(39.6%)	
	Active vaccine	12	(10.6%)	4	(4.4%)	
2nd dose vaccine$^{\Phi}$	No	67	(59.3%)	54	(59.3%)	0.971
	Inactivated vaccine	31	(27.4%)	24	(26.4%)	
	Active vaccine	15	(13.3%)	13	(14.3%)	
PCR test$^{\Phi}$	PCR +	105	(92.9%)	82	(90.1%)	0.470
	PCR -	8	(71%)	9	(9.9%)	
FAD-85$^{\Phi}$		86.81±16.31	88.18 (18.85)	77.78±16.71	78.39 (22.29)	**<0.001**
	No	48	(42.5%)	61	(67.0%)	**<0.001**
	Yes	65	(57.5%)	30	(33.0%)	
Ferritin (μg/L)$^{\Phi}$		969.9±579.32	906(1182)	682.17±546.66	551.5 (760.78)	**0.001**
	No	10	(8.8%)	17	(18.7%)	**0.039**
	Yes	103	(91.2%)	74	(81.3%)	
D-dimer (ng/mL)$^{\Phi}$		7.37±10.6	2.46 (4.89)	4.89±8.05	1.96 (2.76)	**0.031**
	No	7	(6.2%)	12	(13.2%)	0.081
	Yes	106	(93.8%)	79	(86.8%)	
High Flow O_2 days*		3.5±4.27	2 (4)	5.47±6.56	4 (5)	**0.013**
NIMV days*		3.42±4.24	2 (3)	5.48±6.56	4 (5)	**0.007**
CCIS*		4.15±2.12	4 (2)	3.7±2.43	4 (3)	0.220
APACHE-II*		24.77±8.47	23 (11)	21.33±7.92	19 (12)	**0.013**
Leukocyte (x10^3 / mL)*		14.21±6.51	13.3 (7.55)	12.56±7.37	10.66 (6.66)	**<0.001**
Lymphocyte (%)*		6.21±5.82	4.38 (4.77)	8.68±6.77	6.42 (7.55)	**<0.001**
Procalcitonin (ng/mL)*		7.97±31.46	0.53 (2.26)	1.6±6.66	0.11 (0.34)	**0.001**
LDH (IU/L)*		716.37±856.46	551 (363)	482.2±217.86	457 (286)	**0.001**
CRP (mg/L)*		143.79±87.16	135.44 (108.94)	104.34±82.93	87.36 (124.54)	**0.001**

Student's t-test $^{\beta}$ or the Mann-Whitney U test*, Pearson's chi-square test or Fisher's exact test $^{\Phi}$.
Statistically significant p-values are in bold.
DM: Diabetes mellitus, HT: Hypertension, CAD: Coronary artery disease, CHF: Congestive heart failure, CKD: Chronic kidney disease, PTE: Pulmonary thromboembolism, CVD: Cerebrovascular disease, NIMV: Non-invasive mechanical ventilation, CCIS: Charlson Comorbidity Index, APACHE-II: Acute physiology and chronic health assessment score, LDH: Lactate dehydrogenase, CRP: C-reactive protein, IQR: Interquartile range,
PCR: Polymerase chain reaction, ICU: Intensive care unit, SD: Standard deviation

FAD-85 score. it is calculated using the formula age + 0.01 x ferritin + D-dimer. In patients with FAD-85>85, advanced age (p<0.001), second dose vaccine inactivity (p=0.011), CCIS (p<0.001), APACHE-II score (p<0.001), leukocyte count (p=0.017), procalcitonin (p=0.001) and CRP (p=0.009) values were statistically significantly higher than those with FAD-85<85. Compared to those with FAD-85<85, patients with FAD-85>85 had lower rates of oral feeding (p=0.002) and shorter durations of HFNO[2] (p=0.006) and NIMV (p=0.002) (Table 2).

For patients with ferritin levels above 274 μg/L, significantly higher values of procalcitonin (p=0.026) and LDH (p=0.008) were observed. In contrast, the rate of inactivated vaccination (p=0.011, p=0.013) was significantly lower compared to those with ferritin levels below 274 μg/L (Table 3).

In patients with a D-dimer level above 550 ng/mL, female sex (p=0.026), age (p=0.013), CCIS (p=0.012), APACHE-II score (p=0.011), procalcitonin (p=0.03), LDH (p=0.003), and CRP (p=0.002) levels were found to be statistically significantly higher, and the oral feeding rate (p=0.009) was lower than those with a D-dimer level below 550 ng/mL (Table 4).

Table 2. Evaluation of the factors affecting the FAD-85 result of the patients

		FAD-85				p-value
		>85 (n=95)		<85 (n=109)		
		X̄±SD/n	Med (IQR)/(%)	X̄±SD/n	Med (IQR)/(%)	
Gender$^{\Phi}$	Female	38	(40.0%)	54	(50.0%)	0.153
	Male	57	(60.0%)	54	(50.0%)	
Age (year)$^{\beta}$		76.69±10.95	79 (13)	60.94±11.95	61 (16)	**<0.001**
Length of stay ICU (day)*		8.91±9.4	6 (9)	9.35±9.31	6 (9)	0.826
Length of stay in hospital*		17.34±13.01	15 (14)	18.49±16.35	14 (18)	0.969
DM$^{\Phi}$	No	69	(72.6%)	70	(64.2%)	0.198
	Yes	26	(27.4%)	39	(35.8%)	
HT$^{\Phi}$	No	53	(55.8%)	66	(60.6%)	0.491
	Yes	42	(44.2%)	43	(39.4%)	
CAD$^{\Phi}$	No	82	(86.3%)	98	(89.9%)	0.427
	Yes	13	(13.7%)	11	(10.1%)	
CHF$^{\Phi}$	No	87	(91.6%)	103	(94.5%)	0.411
	Yes	8	(8.4%)	6	(5.5%)	
CKD$^{\Phi}$	No	93	(97.9%)	108	(99.1%)	0.599
	Yes	2	(2.1%)	1	(0.9%)	
Parenteral nutrition$^{\Phi}$	No	77	(81.1%)	96	(88.1%)	0.164
	Yes	18	(18.9%)	13	(11.9%)	
Oral nutrition$^{\Phi}$	No	28	(29.5%)	13	(11.9%)	**0.002**
	Yes	67	(70.5%)	96	(88.1%)	
Intubation$^{\Phi}$	No	36	(37.9%)	56	(51.4%)	0.054
	Yes	59	(62.1%)	53	(48.6%)	
Previous PTE$^{\Phi}$	No	91	(95.8%)	103	(94.5%)	0.754
	Yes	4	(4.2%)	6	(5.5%)	
Previous CVD$^{\Phi}$	No	92	(96.8%)	105	(96.3%)	0.999
	Yes	3	(3.2%)	4	(3.7%)	
1st dose vaccine$^{\Phi}$	No	48	(50.5%)	65	(59.6%)	0.195
	Inactivated vaccine	41	(43.2%)	34	(31.2%)	
	Active vaccine	6	(6.3%)	10	(9.2%)	
2nd dose vaccine$^{\Phi}$	No	50	(52.6%)	71	(65.1%)	**0.011**
	Inactivated vaccine	35	(36.8%)	20	(18.3%)	
	Active vaccine	10	(10.5%)	18	(16.5%)	
PCR test$^{\Phi}$	PCR +	90	(94.7%)	97	(89.0%)	0.139
	PCR -	5	(5.3%)	12	(11.0%)	
High flow O_2 days*		3.54±4.76	2 (5)	5.11±5.98	3 (5)	**0.006**
NIMV days*		3.45±4.75	2 (5)	5.11±5.96	3 (5)	**0.002**
CCIS*		4.93±2.04	5 (2)	3.1±2.13	3 (4)	**<0.001**
APACHE-II*		26.03±8.14	26 (11)	20.8±7.85	19 (6)	**<0.001**
Leukocyte (x10^3 / mL)*		14.74±7.82	13.3 (8.26)	12.37±5.89	11.09 (6.49)	**0.017**
Lymphocyte (%)*		6.16±4.46	4.42 (4.83)	8.32±7.53	6.3 (6.83)	0.053
Procalcitonin (ng/mL)*		8.34±33.56	0.46 (1.57)	2.3±8.93	0.13 (0.73)	**0.001**
LDH (IU/L)*		692.66±911.3	509 (366)	543.46±315.77	(5028290)	0.287
CRP (mg/L)$^{\beta}$		143.12±94.4	135.44 (125.58)	111.44±78.14	98.16 (114.67)	**0.009**

Student's t-test $^{\beta}$ or the Mann-Whitney U test*, Pearson's chi-square test or Fisher's exact test $^{\Phi}$.
Statistically significant p-values are in bold.
DM: Diabetes mellitus, HT: Hypertension, CAD: Coronary artery disease, CHF: Congestive heart failure, CKD: Chronic kidney disease, PTE: Pulmonary thromboembolism, CVD: Cerebrovascular disease, NIMV: Non-invasive mechanical ventilation, CCIS: Charlson Comorbidity Index, APACHE-II: Acute physiology and chronic health assessment score, LDH: Lactate dehydrogenase, CRP: C-reactive protein, IQR: Interquartile range, PCR: Polymerase chain reaction, ICU: Intensive care unit, SD: Standard deviation

Table 3. Evaluation of the factors affecting the ferritin result of the patients

		Ferritin				p-value
		>274 mg/L (n=177)		<274 mg/L (n=27)		
		$\bar{X}$±SD/n	Med (IQR)/(%)	$\bar{X}$±SD/n	Med (IQR)/(%)	
Gender$^{\Phi}$	Female	76	(42.9%)	16	(61.5%)	0.075
	Male	101	(57.1%)	10	(38.5%)	
Age (year)$^{\beta}$		67.84±13.89	69 (22)	71.15±13.95	74 (17)	0.250
Length of stay ICU (day)*		8.94±8.96	6 (9)	10.44±11.59	5 (17)	0.905
Length of stay in hospital*		17.34±13.96	14 (14)	21.96±19.69	15 (20)	0.459
DM$^{\Phi}$	No	122	(6.9%)	17	(63.0%)	0.536
	Yes	55	(31.1%)	10	(37.0%)	
HT$^{\Phi}$	No	105	(59.3%)	14	(51.9%)	0.463
	Yes	72	(40.7%)	13	(48.1%)	
CAD$^{\Phi}$	No	158	(89.3%)	22	(81.5%)	0.330
	Yes	19	(10.7%)	5	(18.5%)	
CHF$^{\Phi}$	No	166	(93.8%)	24	(88.9%)	0.405
	Yes	11	(6.2%)	3	(11.1%)	
CKD$^{\Phi}$	No	175	(98.9%)	26	(96.3%)	0.348
	Yes	2	(1.1%)	1	(3.7%)	
Parenteral nutrition$^{\Phi}$	No	153	(86.4%)	20	(74.1%)	0.144
	Yes	24	(13.6%)	7	(25.9%)	
Oral nutrition$^{\Phi}$	No	38	(21.5%)	3	(11.1%)	0.211
	Yes	139	(78.5%)	24	(88.9%)	
Intubation$^{\Phi}$	No	77	(43.5%)	15	(55.6%)	0.241
	Yes	100	(56.5%)	12	(44.4%)	
Previous PTE$^{\Phi}$	No	170	(96.0%)	24	(88.9%)	0.131
	Yes	7	(4.0%)	3	(11.1%)	
Previous CVD$^{\Phi}$	No	171	(96.6%)	26	(96.3%)	0.999
	Yes	6	(3.4%)	1	(3.7%)	
1st dose vaccine$^{\Phi}$	No	105	(59.3%)	8	(29.6%)	**0.013**
	Inactivated vaccine	60	(33.9%)	15	(55.6%)	
	Active vaccine	12	(6.8%)	4	(14.8%)	
2nd dose vaccine$^{\Phi}$	No	112	(63.3%)	9	(33.3%)	**0.011**
	Inactivated vaccine	44	(24.9%)	11	(40.7%)	
	Active vaccine	21	(11.9%)	7	(25.9%)	
PCR test$^{\Phi}$	PCR +	161	(91.0%)	26	(96.3%)	0.706
	PCR -	16	(9.0%)	1	(3.7%)	
High flow O_2 days*		4.28±5.34	3 (5)	5.00±6.46	3 (5)	0.606
NIMV days*		4.25±0.33	3 (5)	4.93±6.44	3 (4)	0.590
CCIS*		3.85±2.25	4 (3)	4.59±2.37	4 (2)	0.136
APACHE-II*		23.36±8.61	21 (11)	22.41±6.81	19 (10)	0.543
Leukocyte (x10^3 / mL)*		13.54±7.04	12.32 (8.03)	13.05±6.35	12.21 (6.5)	0.775
Lymphocyte (%)*		7.13±6.45	5 08(5,2)	8.54±5.79	7.24 (7.32)	0.081
Procalcitonin (ng/mL)*		5.75±25.64	0.32 (1.01)	0.94±2.54	0.11 (0.39)	**0.026**
LDH (IU/L)*		639.59±705.83	520.5 (358)	436.33±193.78	418 (252)	**0.008**
CRP (mg/L)$^{\beta}$		130.83±88.07	124.91(124.24)	95.8±77.07	85.07 (132.25)	0.052

Student's t-test $^{\beta}$ or the Mann-Whitney U test*, Pearson's chi-square test or Fisher's exact test $^{\Phi}$.
Statistically significant p-values are in bold.
DM: Diabetes mellitus, HT: Hypertension, CAD: Coronary artery disease, CHF: Congestive heart failure, CKD: Chronic kidney disease, PTE: Pulmonary thromboembolism, CVD: Cerebrovascular disease, NIMV: Non invasive mechanical ventilation, CCIS: Charlson Comorbidity Index, APACHE-II: Acute physiology and chronic health assessment score, LDH: Lactate dehydrogenase, CRP: C-reactive protein, IQR: Interquartile range, PCR: Polymerase chain reactio, ICU: Intensive care uni, SD: Standard deviation

A single-variable logistic regression analysis was performed to identify factors influencing mortality in patients. Variables with a p-value less than 0.05, were identified as having a high likelihood of predicting mortality based on the single-variable analysis. Male sex (p=0.029), intubation (p<0.001), elevated CRP (p=0.002), decreased lymphocyte count (p=0.009), FAD-85 score greater than 85 (p=0.001), and ferritin value above 274 µg/L (p=0.044) were determined to be predictive of mortality. Variables with a p-value less than 0.25 in the single-variable logistic regression analysis were included in the multivariable logistic regression analysis. The Forward LR method was applied. The results of the multivariable logistic regression analysis showed that the presence of intubation odds ratio (OR): (5% confidence interval (CI): 3.941 (2.115-7.343)], elevated CRP levels (OR): (95% CI): 1.004 (1.000-1.008)], and FAD-85 score greater than 85 OR: (95% CI): 2.462 (1.313-4.617)] were predictors of mortality (Table 5).

DISCUSSION

In the study aimed at exploring the prognostic and predictive effects of D-dimer, ferritin levels, and the FAD-85 score at the time of admission to the COVID ICU among 204 patients, findings indicated that male sex, intubation, a high CCIS, increased CRP, decreased lymphocyte count, and an FAD-85 score greater than 85 were predictive of mortality. This study brings valuable insights for healthcare professionals by identifying parameters that can assist in early stratification of patients at higher risk, thus enabling targeted treatment strategies to improve patient outcomes.

The risk of mortality from COVID-19 does indeed increase with age in both genders, but men over the age of 30 have a higher risk of death compared to women (6,7). This discrepancy has been attributed to factors such as differences in sex hormones, variations in immune responses, and disparities in vaccine response (8). The Global Health 50/50 project, the world's most extensive gender-disaggregated database on COVID-19, clearly substantiates the increased case fatality rate in men (9). A study conducted by qeadan and colleagues has also demonstrated that ferritin levels are more elevated in men than in women among COVID-19 patients (4). In line with these findings, the current study also detected higher 1-month mortality rates and elevations in ferritin, in male patients. This highlights the need for potential gender-specific considerations when managing COVID-19 patients and when considering the impact of biomarkers like ferritin on disease severity and prognosis.

COVID-19 patients pose a higher risk of disease transmission to healthcare workers, especially when interventions like $HFNO^2$ or NIMV are used. Elective intubation is often preferred, based on expert recommendations, as a way to minimize clinical risks, including contamination of healthcare workers, when NIMV fails in patients (10).

In Northern Italy, it has been reported that more than 10% of COVID-19 patients experiencing hypoxia were intubated in the ICU (11). The rates of intubation in COVID-19 patients have varied greatly in different studies, with reports ranging from as low as 5% to as high as 88%. This considerable variability can be attributed to differences in the study populations, settings, and criteria for intubation (12).

However, it is generally recognized that the mortality rate is higher in intubated COVID-19 patients than in those who are not intubated (13). This underscores the severity of patients requiring intubation, and the importance of careful patient selection and timing for this intervention. Intubation is a significant procedure that comes with its own risks, and these must be balanced against the potential benefits for each individual patient.

In patients with COVID-19, NIMV has been reported to be associated with lower mortality compared to patients who are not intubated or those who require intubation, suggesting that NIMV may confer survival benefits (14). $HFNO^2$, on the other hand, is currently recommended by clinical practice guidelines for critically ill patients with acute hypoxemic respiratory failure, as it has been shown to decrease the need for intubation compared to standard oxygen (15).

In this study, we found that the duration of $HFNO^2$ and NIMV application was shorter in patients with higher mortality and an FAD-85 score>85, suggesting that these patients were rapidly intubated. In our cohort, the intubation rate was 54.9%, and intubation was found to be a predictive factor for 1-month mortality.

Advanced age, diabetes mellitus, respiratory rate, increased CRP levels, and oxygen saturation have been found to have significant predictive value for the need for IMV in patients with COVID-19 (16). The research conducted by Alroomi has indicated that individuals with ferritin levels exceeding 1000 ng/mL tend to have higher concentrations of CRP than those with lower levels (3). Research indicates that along with an increase in CRP, other markers associated with COVID-19 include lymphopenia, leukocytosis, elevated levels of procalcitonin, D-dimer, ferritin, and LDH (17,18). Wang et al. (19) highlighted that a significant number of COVID-19 patients experienced a pronounced decrease in lymphocyte count during their hospital stay, and this lymphopenia became more severe over time in those patients who did not survive.

In this study, it was determined that patients with a FAD-85 score greater than 85 and a higher 1-month mortality exhibited leukocytosis, elevated procalcitonin, and CRP levels. Notable associations were discovered between raised ferritin and D-dimer levels, and increased LDH levels, along with increased 1-month mortality. A decrease in lymphocytes and elevated CRP were identified as factors predicting mortality. We think these changes in blood parameters are related to the continued inflammatory response, cytokine storm, and tendency to coagulation disorders.

Hyperferritinemia has been proposed as a mortality indicator in COVID-19 patients (20,21), with studies showing a significant link to the severity of the disease (22). Increased

Table 4. Evaluation of the factors affecting the D-dimer result of the patients

		D-dimer				p-value
		>550ng/mL (n=185)		<550ng/mL (n=19)		
		X̄±SD/n	Med (IQR)/(%)	X̄±SD/n	Med (IQR)/(%)	
Gender$^{\Phi}$	Female	88	(47.8%)	4	(21.1%)	**0.026**
	Male	96	(52.2%)	15	(78.9%)	
Age (year)$^{\beta}$		69.04±13.69	71 (22)	60.79±14.24	67 (25)	**0.013**
Length of stay ICU (day)*		9.38±9.46	6 (9)	6.79±7.89	4 (8)	0.131
Length of stay in hospital*		18.4±15.31	15 (15)	13.58±8.53	10 (12)	0.278
DM$^{\Phi}$	No	124	(67.0%)	15	(78.9%)	0.288
	Yes	61	(33.0%)	4	(21.1%)	
HT$^{\Phi}$	No	106	(57.3%)	13	(68.4%)	0.349
	Yes	79	(42.7%)	6	(31.6%)	
CAD$^{\Phi}$	No	162	(87.6%)	18	(94.7%)	0.706
	Yes	23	(12.4%)	1	(5.3%)	
CHF$^{\Phi}$	No	171	(92.4%)	19	(100.0%)	0.371
	Yes	14	(7.6%)	0	(0.0%)	
CKD$^{\Phi}$	No	182	(98.4%)	19	(100.0%)	0.999
	Yes	3	(1.6%)	0	(0.0%)	
Parenteral nutrition$^{\Phi}$	No	157	(84.9%)	16	(84.2%)	0.376
	Yes	28	(15.1%)	3	(15.8%)	
Oral nutrition$^{\Phi}$	No	39	(21.1%)	2	(10.5%)	**0.009**
	Yes	146	(78.9%)	17	(89.5%)	
Intubation$^{\Phi}$	No	78	(42.2%)	14	(73.7%)	0.501
	Yes	107	(57.8%)	5	(26.3%)	
Previous PTE$^{\Phi}$	No	177	(95.7%)	17	(89.5%)	0.236
	Yes	8	(4.3%)	2	(10.5%)	
Previous CVD$^{\Phi}$	No	179	(96.8%)	18	(94.7%)	0.501
	Yes	6	(3.2%)	1	(5.3%)	
1st dose vaccine$^{\Phi}$	No	101	(54.6%)	12	(63.2%)	0.756
	Inactivated vaccine	69	(37.3%)	6	(31.6%)	
	Active vaccine	15	(8.1%)	1	(5.3%)	
2nd dose vaccine$^{\Phi}$	No	107	(57.8%)	14	(73.7%)	0.235
	Inactivated vaccine	53	(28.6%)	2	(10.5%)	
	Active vaccine	25	(13.5%)	3	(15.8%)	
PCR test$^{\Phi}$	PCR +	169	(91.4%)	18	(94,7%)	0.999
	PCR -	16	(8.6%)	1	(5.3%)	
High flow O_2 days*		4.43±5.66	3 (5)	3.89±3.41	4 (3)	0.670
NIMV days*		4.38±5.66	3 (5)	3.89±3.41	4 (3)	0.630
CCIS*		4.08±2.23	4 (2)	2.68±2.38	3 (4)	**0.012**
APACHE-II*		23.6±8.15	21 (11)	19.68±9.96	18 (6)	**0.011**
Leukocyte (x10^3 / mL)*		13.48±6.83	12.37 (7.95)	13.39±8.14	11.9 (7.09)	0.494
Lymphocyte (%)*		7.12±6.28	4.91 (5.7)	9.15±7.1	6.3 (7.16)	0.139
Procalcitonin (ng/mL)*		5.2±24.62	0.3 (0.95)	4.35±16.55	0.08 (0.31)	**0.030**
LDH (IU/L)*		636.71±691.19	521 (364.5)	378.56±175.19	399 (187)	**0.003**
CRP (mg/L)$^{\beta}$		130.85±88.61	124.91 (122.09)	80.88±57.97	64.4 (90.34)	**0.002**

Student's t-test $^{\beta}$ or the Mann-Whitney U test*; Pearson's chi-square test or Fisher's exact test $^{\Phi}$.
Statistically significant p-values are in bold.
DM: Diabetes mellitus, HT: Hypertension, CAD: Coronary artery disease, CHF: Congestive heart failure, CKD: Chronic kidney disease, PTE: Pulmonary thromboembolism, CVD: Cerebrovascular disease, NIMV: Non invasive mechanical ventilation, CCIS: Charlson Comorbidity Index, APACHE-II: Acute physiology and chronic health assessment score, LDH: Lactate dehydrogenase, CRP: C-reactive protein, IQR: Interquartile range, PCR: Polymerase chain reactio, ICU: Intensive care uni, SD: Standard deviation

Table 5. Univariate and multivariate logistic regression analysis

	Univariate logistic regression					Multivariate logistic regression (forward LR)				
	Wald	p	OR	95% CI for OR		Wald	p	OR	95% CI for OR	
				Lower	Upper				Lower	Upper
Age	2.836	0.092	1.017	0.997	1.038					
Gender (ref: female)	4.797	**0.029**	1.872	1.068	3.281					
İntubation	24.636	**<0.001**	4.470	2.475	8.073	18.661	**<0.001**	3.941	2.115	7.343
CCIS	1.947	0.163	1.092	0.965	1.235					
Lymphocyte	6.869	**0.009**	0.937	0.892	0.984					
CRP	9.825	**0.002**	1.006	1.002	1.009	4.378	**0.036**	1.004	1.000	1.008
Procalcitonin	2.652	0.103	1.033	0.993	1.074					
Unvaccinated (ref: vaccinated 1)	0.028	0.867	0.953	0.547	1.662					
Unvaccinated (ref: vaccinated 2)	0.001	0.994	0.998	0.569	1.751					
FAD-85 (ref: <85)	11.937	**0.001**	2.753	1.550	4.891	7.884	**0.005**	2.462	1.313	4.617
Ferritin (ref: <274)	4.075	**0.044**	2.366	1.025	5.461					
D-dimer (ref: <550)	2.795	0.095	2.300	0.866	6.108					

Wald: Test statistics, OR: Odds radio, Statistically significant p-values are in bold. CCIS: Charlson Comorbidity Index, CRP: C-reactive protein, CI: Confidence interval

D-dimer levels are thought to help in the early detection of patients who are likely to have a poor outcome (2). Elderly individuals have a higher risk of developing ARDS, and their immune response tends to be less robust, resulting in a more severe progression of the disease (23). The FAD-85 score, a calculation that considers a patient's age, ferritin, and D-dimer levels, serves as an early predictive tool for assessing patient outcomes. The FAD-85 score demonstrates significant predictive power in determining the likelihood of mortality. All the parameters included in the FAD-85 score are easily attainable through standard clinical procedures, and it is recommended that these lab tests are carried out upon a patient's admission to the hospital (5). In our research, we observed a substantial association between increased levels of ferritin and D-dimer, and mortality at one month. Additionally, we identified a FAD-85 score exceeding 85 as an indicator of mortality risk. This score, which is simple to calculate, can provide early indications about the severity and potential fatality of a COVID-19 case.

Besides laboratory parameters, the presence of comorbidities is another crucial aspect to consider in patients with COVID-19. A study involving 134.209 patients hospitalized due to COVID-19 revealed that individuals with obesity and diabetes experienced higher mortality rates. Additionally, the need for IMV was more prevalent among patients who were obese, diabetic, and hypertensive (24).

CCIS, which is an indicator of multiple comorbidities, has been consistently demonstrated to be a potent predictor of mortality in various studies (25). In the context of this study, it was observed that patients with a FAD-85 score exceeding the threshold of 85 and those exhibiting elevated D-dimer levels, had notably higher CCIS.

Another frequently employed scoring system in the ICU is the APACHE-II score. Studies have demonstrated that the APACHE-II score is a more reliable indicator of illness severity and mortality when compared to MuLBSTA (multi-lobar infiltrates, hypo-lymphocytosis, bacterial co-infection, smoking history, hypertension, and age) and CURB-65 (confusion, uremia, respiratory rate, blood pressure, age≥65 years) in COVID-19 patients (26). In this study, it was observed that patients with increased 1-month mortality, elevated d-dimer levels, and FAD-85>85 also exhibited higher APACHE-II scores. These findings suggest that the APACHE-II score can be reliably utilized as a scoring system for predicting mortality in COVID-19 patients.

Study Limitation

There are some limitations to our study. It is a single-center retrospective study with a small number of patients, which limits the generalizability of our findings. We used only admission laboratory values to evaluate the clinical prognosis and mortality of patients. The consequences of fluctuations in laboratory values during the follow-up in the ICU were not studied. Complications such as thrombotic events and sepsis, that might emerge as a result of the increase in laboratory markers, were not examined. Because our hospital is a tertiary care center with multiple COVID ICUs, and because our study was carried out in a third-level COVID ICU, these factors could potentially contribute to the elevated mortality rate.

CONCLUSION

In summary, COVID-19 is characterized by a rapidly evolving clinical course, underscoring the importance of early prognostic markers. Such markers play a vital role in risk prediction and guiding the implementation of prophylactic treatments to prevent complications. We propose that the FAD-85 score can serve as a valuable predictive factor for the clinical prognosis of COVID-19. However, the FAD-85 score is not widely utilized currently, and to strengthen the evidence for its utility, additional multicenter studies are warranted. These future investigations will help corroborate and validate our findings, leading to more informed and effective management strategies for COVID-19 patients.

Ethics

Ethics Committee Approval: The approval of the Clinical Research Ethics Committee of Ankara Atatürk Sanatorium Training and Research Hospital has been obtained. (decision number: 2012-KAEK-15/2666, date: 08.03.2023).

Informed Consent: Retrospective study.

Footnotes

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