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Research Article

The Relationship Between Frailty, Hematological Parameters, and Mortality in Older Adults with COVID-19

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Abstract

Objectives: Frailty is a geriatric syndrome characterized by a decrease in physical and physiological reserve and increased vulnerability and susceptibility to external stressors. In this study, we aimed to investigate the relationship between mortality, hematological parameters, and frailty in hospitalized older adults with COVID-19.

Methods: In this prospective study, 154 patients who were hospitalized between 01.11.2020 and 31.12.2020 at the Şişli Hamidiye Etfal Health Practice and Research Center COVID-19 inpatient clinics were included. Frailty was evaluated with the FRAIL scale. Complete blood count, CRP, ferritin, D-dimer, and troponin T levels were included as hematological parameters.

Results: Forty-one of the 154 patients (26.6%) were categorized as frail. Troponin T levels were significantly higher in the frail patients compared with the non-frail patients ($p<0.001$). There was a statistically significant relationship between elevated troponin levels and mortality (1-month $p=0.015$, 3-month $p=0.011$).

Conclusion: In this study, there was no significant relationship between mortality and frailty status. A statistically significant relationship between elevated troponin levels and frailty was observed. There was also a significant relationship between elevated troponin levels and mortality in our study.

Keywords: COVID-19, frailty, laboratory, mortality

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The novel coronavirus infection has been affecting many people around the world for a few years. This impact is particularly greater in elderly patients. Morbidity and mortality due to coronavirus infection increase in elderly patients and those with chronic diseases.[1]

Frailty is a geriatric syndrome characterized by physiological decline in multiple systems and an increased susceptibility to adverse outcomes caused by stressors.[2] Frailty is most often seen in elderly patients, but it may not always be associated with age. Mortality is increased for many diseases and medical conditions in the frail population.

In this study, we aimed to prospectively screen patients over 60 years of age hospitalized due to COVID-19 and investigate whether there is a relationship between frailty, hematological parameters, and mortality.

Methods

This research included patients aged 60 years and over who were hospitalized in our hospital's COVID clinics between 10/11/2020 and 03/12/2020. Patients in intensive care, those who could not be contacted, and those who did not agree to participate in the study were excluded. The study

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was conducted prospectively. The protocol was approved by the Ethics Committee of Şişli Hamidiye Etfal Research and Education Hospital with decision number 2796 dated 12/05/2020.

Patients' demographic information, comorbidities, chronic medications they were using, COVID-19 treatments administered in the hospital, and hematological parameters were recorded.

Hematological parameters used included WBC, neutrophil, lymphocyte count and percentage, hemoglobin, CRP, ferritin, D-dimer, and troponin. Hemogram parameters were measured using a Mindray BC-6800 Plus device, D-dimer levels using a Coulter AU480 device, and CRP, ferritin, and troponin levels using Roche Diagnostics Cobas 8000 and Cobas 6000 Modular Analyzer devices.

The FRAIL frailty questionnaire was used to assess frailty. [3] Patients scoring 0 on the questionnaire were considered robust, those scoring 1–2 were considered pre-frail, and those scoring 3 and above were considered frail (Table 1). This study was conducted according to the Declaration of Helsinki.

Results

A total of 175 patients over 60 years of age were admitted to the COVID wards; 21 were excluded due to the inability to contact them, and 154 patients were included in the study. Our diagnostic criteria/inclusion criteria were being over 60 years of age, having ground-glass opacities consistent with COVID-19 pneumonia on chest CT, and/or having a positive SARS-CoV-2 PCR result. Mortality data were obtained from the hospital information management system and via telephone at the 1st and 3rd months.

The mortality rate at the 1st month was 19.6% (n=30), and at the 3rd month was 24.03% (n=37).

Cutoff values for hematological parameters were accepted as follows: lower limit for leukopenia, 4000×10^6/L; lower limit for platelet count, 150000×10^6/L; lower limit for lymphopenia, 800×10^6/L; lower limit for elevated CRP, 5 mg/L; lower limit for elevated ferritin, 500 µg/L; lower limit for elevated D-dimer, 1000 µg/L; and lower limit for elevated troponin T, 0.014 ng/L.

Statistical Analysis

Statistical analyses were performed using IBM SPSS version 17.0 (Illinois, USA). The normality of the variables was examined using histogram graphs and the Kolmogorov-Smirnov test. Descriptive analyses were presented using mean, standard deviation, median, minimum, and maximum values. Categorical variables were compared using the Pearson chi-square test. In cases where the data did not show a normal distribution, groups of two were evaluated using the Mann-Whitney U test, and groups of more than two were evaluated using the Kruskal-Wallis test. Spearman's correlation test was used to analyze the relationship between the measurement data. Kaplan-Meier analysis was used to determine the factors affecting patient survival. Cox regression analysis and binary logistic regression analysis, whichever was appropriate, were used to analyze the independent variables related to mortality. Cases where the p-value was below 0.05 were considered statistically significant.

Descriptive Statistics

A total of 154 patients were included in the study, 45.45% (n=70) of whom were female. The average age of the patients was 72±8.4 years.

Overall, 65% (n=102) of the patients had hypertension, 40% (n=62) had diabetes mellitus, 31.6% (n=49) had ischemic heart disease, 20% (n=31) had chronic kidney disease, and 14.2% (n=22) had chronic lung disease.

The median number of chronically used medications was 5 (min: 0, max: 14).

In total, 17.4% (n=27) of patients were using ACE inhibitors, 29% (n=45) ARBs, 37.4% (n=58) aspirin, 2.6% (n=4) warfarin, and 7.7% (n=12) NOACs.

Overall, 86.36% (n=133) of the patients included in the study tested positive for SARS-CoV-2 PCR.

In 77.92% (n=120) of the patients, chest CT scans showed

Table 1. FRAIL Questionnaire

1.	Fatigue	How much of the last 4 weeks did you feel tired?	Most of the time: 1, Other: 0
2.	Resistance	Do you have any difficulty walking up 10 steps without resting, alone and without assistance?	Yes: 1, No: 0
3.	Ambulation	Do you have any difficulty walking approximately 200 meters alone, without assistance and without difficulty?	Yes: 1, No: 0
4.	Illnesses	Presence of more than 5 of the following 11 diseases: HT, DM, COPD, MI, CHF, Angina, Asthma, Arthritis, Kidney Disease, Cancer (excluding minor skin cancers)	Yes: 1, No: 0
5.	Loss of weight	Have you lost 5% of your body weight in the last 1 year?	Yes: 1, No: 0

infiltration suggestive of COVID pneumonia. According to the FRAIL frailty questionnaire, 26.6% (n=41) of the patients were assessed as robust, 46.75% (n=72) as pre-frail, and 26.62% (n=41) as frail.

As part of COVID-19 treatment, 92.16% (n=141) of patients received enoxaparin, 96.03% (n=145) received favipravir, 55.2% (n=85) received dexamethasone, 4.5% (n=7) received methylprednisolone (1 mg/kg), 1.3% (n=2) received 250 mg methylprednisolone, 61% (n=94) received any steroid treatment, and 33.33% (n=51) received any quinolone during their hospitalization.

The median WBC count of the patients was 6560×10^6/L (min: 480, max: 116270), the median lymphocyte count was 930×10^6/L (min: 240, max: 100590), the median neutrophil count was 4870×10^6/L (min: 20, max: 28150), the median hemoglobin value was 12.2 g/dL (min: 5.4, max: 17.2), the median CRP value was 93 mg/L (min: 0.4, max: 706), the median ferritin value was 502 µg/L (min: 15, max: 25130), the median D-dimer value was 904 µg/L (min: 155, max: 10003), and the median troponin T value was 0.02 ng/L (min: 0, max: 2.75) (Table 2).

The mean follow-up period for patients was 81 days (min: 1, max: 97).

The median follow-up period in the hospital was 8.5 days (min: 1, max: 35).

The mortality rate at the 1st month was found to be 19.6% (n=30). The mortality rate at the 3rd month was calculated as 24.03% (n=37).

Frailty and Mortality-Related Factors (Univariate Analysis Results)

When the relationship between these groups and 1-month mortality was examined, no significant relationship was found between 1-month mortality and any group (p>0.05 for each group).

No statistically significant relationship was found between 1-month mortality and frailty status (robust, pre-frail, or frail) or frailty score (p=0.658 for frailty status, p=0.312 for frailty score).

No statistically significant relationship was found between mortality at 3 months and frailty status (robust, pre-frail, or frail) (p=0.173). A statistically significant relationship was found between frailty score and 3-month mortality (Table 3). Frailty score was higher in patients who died at 3 months compared with those who survived [median FRAIL score in deceased and surviving patients: 2 (1–3) vs. 1 (0–3); p=0.041].

When the relationship between frailty status and laboratory parameters was examined, a significant relationship was found between elevated troponin levels and frailty (p<0.001). As the level of frailty increased, a significant increase in troponin values was observed [median troponin values for robust, pre-frail, and frail groups, respectively: 0 (0–0.02), 0.02 (0–0.04), and 0.03 (0.02–0.05)]. No statistically significant relationship was found between frailty and other parameters.

Mortality and laboratory parameters were measured at 1 month and 3 months. Of the groups, only troponin elevation and mortality showed a significant correlation (p=0.015 for 1-month mortality, p=0.011 for 3-month mortality). No significant correlation was found between other parameters and mortality at months 1 and 3 (Table 3).

While a statistically significant relationship was found between frailty status and advanced age (p=0.001), no significant relationship was found between frailty status and sex, CT involvement, or PCR status.

Overall, 17.4% of the patients (n=27) were using ACE inhibitors, 29% (n=45) ARBs, 37.4% (n=58) aspirin, 2.6% (n=4) warfarin, and 7.7% (n=12) NOACs. When frailty status and chronically used drug groups were examined, no statistically significant relationship was found between drug groups and frailty.

A positive correlation was found between frailty score and age, number of chronic diseases, and number of chronically used medications, respectively (p=0.001, 0.001, and 0.001; r values: 0.322, 0.262, and 0.266, respectively).

Chronic diseases and frailty status (robust/pre-frail/frail) of the patients were examined. In these analyses, it was observed that patients with cerebrovascular disease (CVA) and dementia were more frail (p=0.001 and p<0.001, respectively). When the frailty status of the patients was categorized into two groups as frail and pre-frail/robust, patients with dementia, cerebrovascular disease (CVD), and

Table 2. Patients' laboratory values

	Mean
WBC (x10^6/L) (Min.-Max.)	8474.68 (480-116270)
Lymphocyte count (x10^6/L) (Min.-Max.)	1906.30(240-100590)
Lymphocyte % (Min.-Max.)	18.65(3-94)
Neutrophil count (x10^6/L) (Min.-Max.)	5823.05(20-28150)
Neutrophil % (Min.-Max.)	73.79 (4-95)
Hemoglobin (g/dL) (SD)	12.09±1.99
Platelet (x10^6/L) (Min.-Max.)	191798.70(700-476000)
CRP (mg/L) (Min.-Max.)	108.74(0.4-706)
Ferritin (µg/L) (Min.-Max.)	867.25(15-25310)
D-Dimer (µg/L) (Min.-Max.)	1276.54(155-10003)
Troponin T (ng/L) (Min.-Max.)	0.65(0-40)

Table 3. Relationship between laboratory parameters and 1-month and 3-month mortality

	1-month mortality		p
	No	Yes	
	Median (IQR)	Median (IQR)	
WBC (x10⁶/L)	6560 (5030-8960)	6825 (5530-9780)	0.475
Lymphocyte count (x10⁶/L)	940 (680-1410)	905 (590-1410)	0.613
Lymphocyte %	16.5 (11-22)	14.75 (9-23)	0.518
Neutrophil count (x10⁶/L)	4720 (3410-7210)	5165 (4480-7470)	0.180
Neutrophil %	76 (68-84)	79.5 (70-86)	0.323
Hemoglobin (g/dL)	12.2 (11.1-13.4)	12.45 (10.8-13.6)	0.925
Platelet (x10⁶/L)	183000 (145000-236000)	167000 (123000-210000)	0.177
CRP (mg/L)	90 (50-154)	105.5 (54-181)	0.388
Ferritin (µg/L)	462.5 (238-995)	621 (352-1426)	0.139
D-Dimer (µg/L)	839 (462-1530)	1027.5 (501-1700)	0.252
Troponin T (ng/L)	0.02 (0-0.04)	0.03 (0.02-0.07)	**0.015**
	3- month mortality		**p**
	No	**Yes**	
	Median (IQR)	**Median (IQR)**	
WBC (x10⁶/L)	6450 (5030-8580)	6930 (5530-10040)	0.277
Lymphocyte count (x10⁶/L)	930 (690-1390)	910 (590-1460)	0.779
Lymphocyte %	17 (11-22)	14,5 (9-22)	0.423
Neutrophil count (x10⁶/L)	4560 (3410-7030)	5170 (4480-7840)	0.105
Neutrophil %	76 (68-84)	79 (70-85)	0.317
Hemoglobin (g/dL)	12.2 (11.1-13.4)	12.3 (10.9-13.5)	0.973
Platelet (x10⁶/L)	183000 (149000-234000)	166000 (123000-210000)	0.145
CRP (mg/L)	85 (50-154)	111 (54-157)	0.387
Ferritin (µg/L)	480.5 (226.5-1009.5)	583 (347-1028)	0.203
D-Dimer (µg/L)	839 (462-1466)	1044 (501-1700)	0.202
Troponin T (ng/L)	0.02 (0-0.04)	0.03 (0.02-0.05)	**0.011**

chronic lung disease were found to be more frail (p<0.001, p<0.001, and p=0.031, respectively).

When the COVID-19 treatment received by patients during hospitalization was examined in relation to their frailty status, it was observed that non-frail patients received steroids more frequently (p=0.024).

When the relationship between sex and mortality was examined, no significant relationship was found between sex and 1-month or 3-month mortality.

Mortality Analysis

When the relationship between sex and mortality was examined, no significant relationship was found between sex and 1-month or 3-month mortality.

When the relationship between patients' chronic diseases and mortality was examined, it was observed that 1-month and 3-month mortality were higher in patients with hematological malignancies.

No significant relationship was found between mortality and other chronic diseases (for hematological malignancy, p=0.021 and p=0.003 for 1-month and 3-month mortality, respectively) (Table 4).

When the relationship between prognostic hematological parameters and mortality was examined, it was found that 3-month mortality was higher in patients with elevated troponin levels, while no significant relationship was found between mortality and other prognostic parameters (for troponin, p=0.022) (Table 4).

Table 4. Relationship between chronic disease, prognostic laboratory parameters, COVID-19 treatment administered during hospitalization and 1- month and 3-month mortality

Relationship between chronic diseases and mortality											
		1-month mortality				**p**	**3-month mortality**				**p**
		No		**Yes**			**No**		**Yes**		
		n	**%**	**n**	**%**		**n**	**%**	**n**	**%**	
CAD	No	84	(68.29)	21	(70.00)	0.857	78	(66.67)	27	(72.97)	0.473
	Yes	39	(31.71)	9	(30.00)		39	(33.33)	10	(27.03)	
HT	No	42	(34.15)	11	(36.67)	0.795	41	(35.04)	12	(32.43)	0.771
	Yes	81	(65.85)	19	(63.33)		76	(64.96)	25	(67.57)	
DM	No	74	(60.16)	18	(60.00)	0.987	69	(58.97)	23	(62.16)	0.730
	Yes	49	(39.84)	12	(40.00)		48	(41.03)	14	(37.84)	
COPD	No	106	(86.18)	25	(83.33)	0.690	101	(86.32)	31	(83.78)	0.700
	Yes	17	(13.82)	5	(16.67)		16	(13.68)	6	(16.22)	
Hematological malignancy	No	121	(98.37)	27	(90.00)	0.021	116	(99.15)	33	(89.19)	0.003
	Yes	2	(1.63)	3	(10.00)		1	(0.85)	4	(10.81)	
CKD	No	102	(82.93)	22	(73.33)	0.229	97	(82.91)	27	(72.97)	0.184
	Yes	21	(17.07)	8	(26.67)		20	(17.09)	10	(27.03)	
Relationship between prognostic laboratory parameters and mortality											
		1-month mortality				**p**	**3-month mortality**				**p**
		No		**Yes**			**No**		**Yes**		
		n	**%**	**n**	**%**		**n**	**%**	**n**	**%**	
Lymphopenia (<800 x 10^6/L)	No	78	(63.41)	18	(60.00)	0.729	74	(63.25)	22	(59.46)	0.678
	Yes	45	(36.59)	12	(40.00)		43	(36.75)	15	(40.54)	
At least a 10-fold increase in CRP	No	31	(25.20)	6	(20.00)	0.551	31	(26.50)	7	(18.92)	0.351
	Yes	92	(74.80)	24	(80.00)		86	(73.50)	30	(81.08)	
Ferritin>500 (µg/L)	No	64	(52.46)	12	(40.00)	0.221	60	(51.72)	16	(43.24)	0.369
	Yes	58	(47.54)	18	(60.00)		56	(48.28)	21	(56.76)	
D-Dimer> 1000 (µg/L)	No	72	(58.54)	14	(46.67)	0.240	69	(58.97)	17	(45.95)	0.164
	Yes	51	(41.46)	16	(53.33)		48	(41.03)	20	(54.05)	
Troponin T (ng/L)	Normal	43	(36.13)	6	(21.43)	0.137	43	(38.05)	6	(17.14)	0.022
	High	76	(63.87)	22	(78.57)		70	(61.95)	29	(82.86)	
Relationship between COVID-19 treatment administered during hospitalization and mortality											
		1-month mortality				**p**	**3-month mortality**				**p**
		No		**Yes**			**No**		**Yes**		
		n	**%**	**n**	**%**		**n**	**%**	**n**	**%**	
Enoxaaparin	No	8	(6.56)	4	(13.33)	0.218	8	(6.90)	4	(10.81)	0.441
	Yes	114	(93.44)	26	(86.67)		108	(93.10)	33	(89.19)	
Favipravir	No	5	(4.17)	1	(3.33)	0.835	5	(4.39)	1	(2.70)	0.649
	Yes	115	(95.83)	29	(96.67)		109	(95.61)	36	(97.30)	
Dexamethasone	No	57	(46.72)	11	(36.67)	0.321	56	(48.28)	12	(32.43)	0.091
	Yes	65	(53.28)	19	(63.33)		60	(51.72)	25	(67.57)	

Table 4. Continue

Relationship between COVID-19 treatment administered during hospitalization and mortality		1-month mortality				p	3-month mortality				p
		No		Yes			No		Yes		
		n	%	n	%		n	%	n	%	
1 mg/kg methylprednisolone	No	116	(95.08)	28	(93.33)	0.701	110	(94.83)	35	(94.59)	0.956
	Yes	6	(4.92)	2	(6.67)		6	(5.17)	2	(5.41)	
250 mg methylprednisolone	No	122	(100.00)	28	(93.33)	0.004	116	(100.00)	35	(94.59)	0.012
	Yes	0	(0.00)	2	(6.67)		0	(0.00)	2	(5.41)	
Did the patient receive steroids?	No	51	(41.80)	8	(26.67)	0.127	50	(43.10)	9	(24.32)	0.041
	Yes	71	(58.20)	22	(73.33)		66	(56.90)	28	(75.68)	
Did the patient receive any quinolone during admission?	No	84	(68.85)	17	(56.67)	0.205	80	(68.97)	22	(59.46)	0.285
	Yes	38	(31.15)	13	(43.33)		36	(31.03)	15	(40.54)	

The relationship between COVID-19 treatment received by patients during hospitalization and mortality was examined. It was observed that 1-month and 3-month mortality were higher in patients receiving 250 mg of prednisolone (p=0.004 and p=0.012 for 1-month and 3-month mortality, respectively). While no significant increase in 1-month mortality was detected in patients receiving steroids, 3-month mortality was found to be higher in patients receiving steroids (p=0.127 and p=0.041 for 1-month and 3-month mortality, respectively) (Table 4).

When the relationship between chronically used medication groups and mortality was examined, no association was found between any medication group and mortality (Table 4).

When the relationship between the number of chronic diseases, the number of chronically used medications, and mortality was examined, no significant relationship was found between mortality and the number of medications or diseases.

When the relationship between patients' age and mortality was examined, it was observed that 3-month mortality increased as patient age increased (p=0.220 and p=0.029 for 1-month and 3-month mortality, respectively).

Factors Independently Associated with Survival and Mortality (Kaplan-Meier and Regression Analysis Results)

Binary logistic regression analysis was performed to determine the factors affecting 1-month and 3-month mortality. According to the binary logistic regression analysis, age, frailty, elevated troponin, and the presence of hematological malignancy were not found to have a significant effect on 1-month mortality. However, a significant relationship was found between the presence of hematological malignancy and 3-month mortality (p=0.02) (Table 5).

Patients were divided into three categories based on their frailty status, and survival analysis was performed: Group 1: robust/pre-frail/frail; Group 2: robust or pre-frail/frail; Group 3: robust/pre-frail or frail.

Kaplan-Meier analysis was performed between 1-month mortality and frailty status, sex, prognostic parameters, and the presence of hematological malignancy. According to the results of the analysis, while survival was observed to be lower in patients with hematological malignancy (p=0.042), no statistically significant relationship was found for the other parameters (Table 6).

Kaplan-Meier analysis was performed between 3-month mortality and frailty status, sex, prognostic parameters, and the presence of hematological malignancy. According to the results of the analysis, it was observed that survival at 3 months was lower in the presence of hematological malignancy and elevated troponin (p<0.001 and p=0.024 for hematological malignancy and troponin, respectively) (Table 6).

When the effect of hematological malignancy on 1-month mortality was examined using Cox regression analysis, it was found that it had no statistically significant effect on mortality.

Table 5. Binary logistic analysis for 3-month mortality

	p	Exp(B)	95% CI for EXP(B)	
			Lower	Upper
Hematological malignancy	**0.020**	0.061	0.006	0.640

Table 6. Relationship between 1-month and 3rd-month mortality and frailty status, sex, prognostic parameters, and the presence of hematological malignancy

1-month mortality		Estimate	Std. error	95% Confidence interval		p
				Upper bound	Lower bound	
Sex	Male	21.712	1.677	18.425	24.998	0.833
	Female	20.282	1.894	16.570	23.995	
	All	21.072	1.265	18.593	23.552	
1.group	Robust	19.865	2.427	15.109	24.622	0.908
	Pre-frail	22.125	1.978	18.248	26.002	
	Frail	20.607	2.110	16.471	24.743	
	All	21.072	1.265	18.593	23.552	
2.group	Robust or pre-frail	21.416	1.578	18.322	24.510	0.774
	Frail	20.607	2.110	16.471	24.743	
	All	21.072	1.265	18.593	23.552	
3.group	Robust	19.865	2.427	15.109	24.622	0.834
	Pre-frail or frail	21.434	1.450	18.593	24.275	
	All	21.072	1.265	18.593	23.552	
Lymphopenia (<800 x 10^6)	No	20.247	1.709	16.898	23.597	0.448
	Yes	21.779	1.909	18.038	25.520	
	All	21.072	1.265	18.593	23.552	
Hematological malignancy	No	21.411	1.310	18.843	23.980	**0.042**
	Yes	14.800	6.172	2.704	26.896	
	All	21.072	1.265	18.593	23.552	
Increased CRP (>10 fold)	No	20.359	2.507	15.447	25.272	0.787
	Yes	21.117	1.434	18.307	23.927	
	All	21.072	1.265	18.593	23.552	
Ferritin > 500 µg/L	No	22.206	1.778	18.722	25.691	0.247
	Yes	20.150	1.738	16.744	23.556	
	All	21.066	1.265	18.586	23.546	
D-Dimer>1000 µg/L	No	20.050	1.792	16.537	23.564	0.636
	Yes	21.078	1.766	17.617	24.540	
	All	21.072	1.265	18.593	23.552	
Troponin T	Normal	21.236	2.818	15.713	26.759	0.651
	High	21.153	1.430	18.350	23.956	
	All	21.328	1.275	18.830	23.826	
3-month mortality		**Estimate**	**Std. Error**	**95% Confidence Interval**		**p**
				Lower Bound	**Upper Bound**	
Sex	Male	81.744	3.425	75.031	88.458	0.753
	Female	79.410	4.071	71.431	87.390	
	All	80.716	2.631	75.560	85.873	

Table 6. Continue

3-month mortality		Estimate	Std. Error	95% Confidence Interval		p
				Lower Bound	Upper Bound	
1.group	Robust	84.829	4.980	75.069	94.590	0.213
	Pre-frail	81.522	3.756	74.161	88.884	
	Frail	75.438	5.394	64.865	86.012	
	All	80.716	2.631	75.560	85.873	
2.group	Robust or pre-frail	82.684	2.990	76.824	88.544	0.093
	Frail	75.438	5.394	64.865	86.012	
	All	80.716	2.631	75.560	85.873	
3.group	Robust	84.829	4.980	75.069	94.590	0.276
	Pre-frail or frail	79.266	3.104	73.182	85.350	
	All	80.716	2.631	75.560	85.873	
Lymphopenia (<800 x 10^6)	No	81.617	3.339	75.072	88.161	0.662
	Yes	79.316	4.273	70.940	87.692	
	All	80.716	2.631	75.560	85.873	
Hematological malignancy	No	82.108	2.579	77.053	87.162	**<0.001**
	Yes	34.800	17.088	1.308	68.292	
	All	80.716	2.631	75.560	85.873	
Increased CRP (>10 fold)	No	81.184	5.412	70.577	91.792	0.323
	Yes	80.489	3.004	74.601	86.377	
	All	80.716	2.631	75.560	85.873	
Ferritin > 500 µg/L	No	82.793	3.457	76.017	89.569	0.298
	Yes	78.433	3.985	70.622	86.245	
	All	80.611	2.646	75.425	85.797	
D-Dimer>1000 µg/L	No	81.070	3.195	74.808	87.331	0.329
	Yes	78.520	4.259	70.171	86.868	
	All	80.716	2.631	75.560	85.873	
Troponin T	Normal	88.823	3.347	82.262	95.384	**0.024**

When the effects of hematological malignancy and elevated troponin on 3-month mortality were examined using Cox regression analysis, it was found that the presence of hematological malignancy increased 3-month mortality by 4.2 times, and elevated troponin increased it by 2.4 times, with a borderline significant p-value (p=0.02 for hematological malignancy, p=0.05 for elevated troponin) (Table 7).

Discussion

This prospective study included 154 patients with an average age of 72 years.

The average follow-up period for patients was 81 days (min: 1, max: 97). The average hospital stay was 8.5 days. The mortality rate at 1 month was found to be 19.61% (n=30). The mortality rate at 3 months was calculated as 24.03% (n=37).

When the relationship between frailty and mortality was examined, no statistically significant relationship was found between frailty status and mortality, while a statisti-

Table 7. Cox regression analysis for 3-month mortality

	B	SE	p	Exp(B)	95.0% CI for Exp(B)	
					Lower	Upper
Hematological malignancy	1.436	0.616	**0.020**	4.203	1.256	14.063
Troponin T	0.890	0.453	**0.050**	2.434	1.001	5.917

cally significant relationship was found between increased frailty score and 3-month mortality.

When the relationship between frailty status and laboratory parameters was examined, a significant relationship was found between elevated troponin and frailty.

Among the mortality and laboratory parameters examined at 1 and 3 months, only elevated troponin and mortality showed a significant relationship.

When we look at the studies in the literature examining the relationship between frailty and mortality in elderly COVID-19 patients, we see that different frailty scales are used in the studies and that the results are variable. In a study conducted by Kundi et al.[4] in 2020 in our country, using the hospital frailty risk score to examine the relationship between frailty and mortality in 18,234 hospitalized COVID patients, the average age of the patients was reported as 74.1. A total of 12,295 patients were classified as frail. The in-hospital mortality rate was stated as 18.2%. The study concluded that there was a statistically significant relationship between frailty and in-hospital mortality. This study has several weaknesses. The hospital frailty risk score only analyzes frailty based on the diagnoses available in the system. This scoring system evaluates frailty based on the number of illnesses rather than frailty parameters such as ambulation, walking speed, muscle strength, functionality, and malnutrition. Indeed, those with a low number of illnesses may also have higher disease severity, which can negatively affect frailty. Not taking disease severity into account is also among the limitations of the scale. As the authors have stated, the hospital vulnerability risk score is a scoring system that is difficult and inappropriate to apply to all patients and may give misleading results in terms of vulnerability.

Steinmeyer et al.[5] examined the clinical characteristics and disease outcomes of 94 hospitalized COVID patients in 2020. This retrospective study included patients from three geriatrics clinics. Frailty status was assessed using the Frail Non-Disabled Survey (FIND), which is very similar to the FRAIL questionnaire we used in our study. The mean age of the patients included in the study was 85.5, and 10 patients were classified as frail. According to multivariate regression analysis, increased age (>85 years), lymphopenia (<800), and respiratory failure were associated with mortality, while no significant relationship was found between frailty status and mortality.

Yang et al.[6] examined the relationship between frailty and mortality in hospitalized COVID patients in a meta-analysis in 2021. This meta-analysis included 4324 patients from 16 studies. Fourteen of the studies were retrospective cohorts, and two were prospective cohorts. The meta-analysis included 11 studies using the Clinical Frailty Scale, one using the Frailty Index, one using the FRAIL scale, one using the Palliative Performance Scale, one using the Hospital Frailty Risk Score, and one using the Frail Non-Disabled Survey. The meta-analysis found that frailty was associated with severe illness, prolonged hospital stay, mechanical ventilation, and increased mortality (RR: 1.81, $p<0.001$). One weakness of this analysis is that most of the studies included were retrospective. Furthermore, the mean follow-up period was not specified in the meta-analysis. As the authors also noted, converting OR to RR in the analysis may have contributed to the increased risk ratio.

Zhang et al.[7] conducted a meta-analysis in 2021 involving 23,944 studies to examine the relationship between frailty and mortality in COVID patients. This meta-analysis included 15 studies; seven were prospective and eight were retrospective. Of the studies included, 11 examined in-hospital mortality, three examined 30-day mortality, and one examined 60-day mortality. Thirteen of the patients included in the study were hospitalized, and two were nursing home residents. Eleven studies examined in-hospital mortality, three examined 30-day mortality, and one examined 60-day mortality. In 11 of these studies, the Clinical Frailty Scale was used; in one, the Frailty Index; in one, the Palliative Performance Scale; in one, the Hospital Frailty Risk Score; and in one, the Frail Non-Disabled Survey. As a result of the meta-analysis, frailty was found to be a risk factor for mortality. Of the studies included in the meta-analysis, 10 used OR (2.48) and five used HR (1.99) to examine the relationship between frailty and mortality (p-value not specified).

A meta-analysis conducted by Subramaniam et al.[8] in 2022 examined the relationship between frailty and in-hospital mortality or 30-day mortality and the need for invasive mechanical ventilation in hospitalized COVID patients. A total of 34,628 patients from 25 studies were included. For frailty, the Clinical Frailty Scale was used in 21 studies, the Frailty Index in one study, the Hospital Frailty Risk Scale in two studies, and the Frail Non-Disabled Survey in one study. The mean age of the patients was 73, the frailty rate was 57.9%, and the mortality rate was 26.2%. This meta-analysis found no significant relationship between frail and non-frail populations in terms of mortality. Furthermore, it was noted that frail patients had a lower need for invasive mechanical ventilation compared with non-frail patients and that non-frail patients had a higher rate of admission to the intensive care unit. The lower rate of intensive care unit admission in frail patients may be related to patient, family, or clinician preference. Of the studies included in the analysis, eight indicated mortality using HR, six using OR, and seven using other definitions. Four studies found no asso-

ciation between frailty and mortality. When frail patients were compared with non-frail patients, although univariate pooled mortality was higher in frail patients, frailty did not increase mortality when other covariates were considered (RR: 1.17). Based on 11 studies, it was also reported that the proportion of non-frail patients was higher in patients admitted to the intensive care unit (p=0.011) and that mortality was higher in non-frail patients (RR: 1.63). Although the majority of studies included in the meta-analysis (n=21) used the Clinical Frailty Scale, the large number of patients in studies using the Hospital Frailty Risk Scale may have skewed the results. Finally, the study observed that mortality was higher in patients with dementia, chronic renal failure, heart failure, diabetes mellitus, hypertension, and cerebrovascular disease.

Sablerolles et al.[9] retrospectively examined the relationship between frailty and in-hospital mortality in hospitalized COVID patients in their 2021 study, which included 2434 patients in 63 hospitals across 11 countries. In this study, which used the Clinical Frailty Scale and evaluated patients with an average age of 68 years, it was observed that frail patients had a higher rate of in-hospital mortality and that frailty was associated with increased intensive care unit admission (p<0.0001 for both cases).

Blomaard et al.[10] retrospectively examined the relationship between frailty and in-hospital mortality in 1376 hospitalized COVID patients in 15 hospitals in the Netherlands in 2021. In this study, which used the Clinical Frailty Score to assess frailty, the average age of the included patients was 78 years. As a result of this study, a significant relationship was found between increased frailty score and mortality (p<0.001; mortality was approximately three times higher in patients with Clinical Frailty Score 6–9 compared with patients with Clinical Frailty Score 1–3; OR: 2.8, CI: 1.8–4.3). In addition, it was shown that the time from the onset of symptoms to hospital admission was shortened as the frailty score increased (p<0.001). The authors interpreted this situation as frail patients being less tolerant of disease symptoms.

A literature review revealed that there are very few studies examining the relationship between mortality and laboratory parameters in elderly COVID patients.

In 2020, Wang et al.[11] conducted a study to determine the characteristics and prognostic factors of the disease in elderly COVID patients over a 4-week follow-up period. The study included 339 patients with an average age of 71 years. The results showed that increased WBC and neutrophil counts, decreased platelet count, prolonged aPTT, increased D-dimer, increased AST, increased creatinine, increased CK and troponin, increased CRP and IL-6, decreased CD4 and CD8, and increased procalcitonin were associated with mortality. In the Cox regression analysis performed, it was shown that increased WBC and prolonged aPTT (HR: 1.16 and 1.17, respectively; p<0.001 for both parameters) were associated with increased mortality, and decreased lymphocyte count was a strong factor in predicting poor disease outcome (p<0.001). Factors such as procalcitonin and troponin were also statistically significant, but it was noted that their predictive power was limited because their HR was around 1.

In our study, the only laboratory parameter associated with frailty and mortality was found to be increased troponin levels. Although no research directly investigating the relationship between frailty and troponin levels has been observed in the literature, Ticinesi et al.[12]'s study of elderly individuals presenting to the emergency department with suspected acute coronary syndrome showed that setting higher troponin threshold values (≥141 ng/L) in frail elderly patients with suspected acute coronary syndrome increased specificity (in the study, the upper limit of normal was 17.8 ng/L for men and 10.5 ng/L for women). In other words, it was observed that the relationship between troponin, MI, and frailty increased when the upper limit value for hsTroponin I was set higher. Based on this, it can be concluded that troponin levels may be somewhat higher in frail patients. The fact that no correlation was found between mortality and other laboratory parameters besides troponin in our study may be related to the limitation of evaluating only the parameters at the time of admission.

Our study has several strengths and limitations. Strengths include being one of the few studies to examine the relationship between frailty and mortality in COVID-19 patients using the FRAIL questionnaire, being the first to investigate the relationship between frailty and laboratory parameters, being one of the few studies to examine the relationship between laboratory parameters and mortality in elderly COVID patients, and being a prospective study. Weaknesses include the small number of patients included, the failure to assess vital signs and oxygen requirements upon hospital admission, the inability to examine other elements of a comprehensive geriatric assessment, such as malnutrition and sarcopenia, and being a single-center study. Furthermore, laboratory parameters were recorded upon initial hospitalization, and the analysis was performed only with parameters at admission; follow-up laboratory measurements were not included in the evaluation.

Conclusion

COVID-19 is an infectious disease that causes significant morbidity and mortality. Frailty, on the other hand, is a

condition that usually appears with advancing age, is characterized by decreased resistance to stressors, and is associated with increased mortality. In our study, we investigated whether there is a relationship between frailty and mortality in patients with COVID-19. While no statistically significant relationship was found between frailty status and mortality in patients with COVID-19, a significant relationship was found between frailty score and elevated troponin levels, as well as between mortality and elevated troponin levels. Based on these results, we recommend that frailty status, a significant cause of mortality and morbidity, be assessed and that troponin levels be checked in elderly hospitalized patients with COVID-19.

Abbreviations

ACE: Angiotensin converting enzyme
aPTT: Active partial thromboplastin time
ARB: Angiotensin receptor blocker
ARDS: Acute respiratory distress syndrome
BAL: Bronchoalveolar lavage
CD-3: Cluster of differentiation-3
CD-4: Cluster of differentiation-4
CD-8: Cluster of differentiation-8
CK: Creatinine kinase
COPD: Chronic obstructive pulmonary disease
COVID: Coronavirus disease
COVID-19: Coronavirus disease 2019
CRP: C reactive protein
CT: Computed tomography
CVA: Cerebrovascular accident
DL: Deciliter
DM: Diabetes mellitus
ESR: Erythrocyte sedimentation rate
G: Gram
HARC: Health application and research center
HR: Hazard ratio
HsTroponin: High sensitive troponin
HT: Hypertension
IL-6: Interleukin-6
IL-10: Interleukin-10
CAD: Coronary artery disease
CKD: Chronic kidney disease
L: Liter
LDH: Lactate dehydrogenase
MERS-CoV: Middle east respiratory syndrome–related coronavirus
MCG(µg): Microgram
MG: Milligram
Min: Minimum
Max: Maximum
mRNA: Messenger ribonucleic acid
NG: Nanogram
NOAC: Novel oral anticoagulant
OR: Odds Ratio
PCR: Polymerase chain reaction
RNA: Ribonucleic acid
RR: Risk ratio
SARS-CoV-2: Severe acute respiratory syndrome coronavirus-2
SD: Standard deviation
USA: United States of America
WBC: White blood cell
WHO: World Health Organization

Disclosures

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