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ORIGINAL ARTICLE

Is Hyperferritinemia Reliable in Determining the Severity of COVID-19 in Older Patients?

COVİD-19'lu İleri Yaşlı Hastalarda Hiperferritinemi Hastalık Şiddeti Yönünden Güvenilir midir?

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ABSTRACT

Aim: To determine whether ferritin levels among elderly patients inflicted with Covid-19 are superior to several types of disease severity indicators.
Methods: A retrospective and cross-sectional analysis was conducted on patients who were admitted to the emergency department of Ordu University Training and Research Hospital between September 2020 and January 2021, with a suspected or confirmed diagnosis of Covid-19. Patients had to be 18 years of age or older and have a glomerular filtration rate greater than 30 ml/min/1.73 m2 in order to meet the basic inclusion criteria. In addition, the data pertaining to the patients' chronic diseases, mortality status, hemogram, blood gas, ferritin, c-reactive protein, and vital signs were recorded alongside the information regarding the tests and examinations conducted for the diagnosis of Covid-19. The data set is divided into two parts: <65 years ≥65 years.
Results: Four hundred sixteen patients were identified as meeting the criteria for the study. Out of the total number of patients, 321 were under the age of 65, while 95 were 65 years of age or older. The under-65 group's mean age was 42.50±12.73 while the older group was 77.89±7.34 years. The mean ferritin of patients 65 and older (249.59±261.45 ng/mL) was significantly more than the patients under 65 (169.76±210.44 ng/mL) (p=0.001). Only mortality differed between older and younger patients (p=0.049). The AUC value of ferritin in older patients was 0.700 (95% CI, 0.482-0.919), and the cut-off value was 231.55 ng/mL in the mortal group (sensitivity=66.7%, specificity=67.4%). Only ferritin levels were significant in older patients' AUC scores of mortality stats among the other biomedical markers.
Conclusions: Some well-known severe disease blood markers, including c-reactive protein, are not as significant as ferritin in older patient mortality ROC curve analyses. Ferritin may be the strongest mortality predictor in older Covid-19 patients.

Keywords: Covid-19, age, older, ferritin, illness severity, mortality.

ÖZ

Amaç: Covid-19'a yakalanmış yaşlı hastalarda ferritin düzeylerinin çeşitli hastalık şiddeti göstergelerinden daha üstün olup olmadığını belirlemek.
Yöntem: Eylül 2020 ile Ocak 2021 tarihleri arasında Covid-19 şüphesi veya tanısı ile Ordu Üniversitesi Eğitim ve Araştırma Hastanesi acil servisine başvuran hastalar retrospektif ve kesitsel olarak incelendi. Temel dahil etme kriterleri hastaların 18 yaş ve üzeri olması ve glomerüler filtrasyon hızının 30 ml/dk/1,73 m2 idi. Hastalara ait kronik hastalık öyküsü, mortalite durumu, hemogram, kan gazı, ferritin, c-reaktif protein ve vital bulgularına ilişkin veriler ile Covid-19 tanısı için yapılan test ve tetkiklere ilişkin veriler kaydedilmiştir. Veri seti iki bölüme ayrılmıştır: <65 yaş ≥65 yaş.
Bulgular: Kriterleri karşılayan 416 hasta çalışmaya dahil edilmiştir. Toplam hasta sayısının 321'i 65 yaşın altında, 95'i ise 65 yaş ve üzerindeydi. Yaş ortalamaları 65 yaş altı grup için 42.50±12.73, yaşlı hasta grubu için 77.89±7.34 idi. Ortalama ferritin düzeyi, 65 yaş ve üzeri hastalarda (249.59±261.45 ng/mL) 65 yaş altı hastalara (169.76±210.44 ng/mL) göre anlamlı düzeyde yüksekti (p=0.001). Ferritin düzeyleri sadece mortalite yönünden iki grup arasında farklılaştı (p<0.037). Yaşlı hastalara ait mortal seyreden alt grupta ferritine ait AUC değeri 0.700 (%95 GA, 0.482-0.919) ve cut-off değeri 231.55 ng/mL idi (duyarlılık=%67.7, özgüllük=%67.4) ve tüm biyobelirteçler içinde yalnızca ferritin seviyeleri anlamlı olarak farklılaşma gösterdi.
Sonuç: C-reaktif protein de dahil olmak üzere iyi bilinen şiddetli hastalık serum belirteçleri, yaşlı hastaların Covid-19 yönünden mortalite tahmininde ferritin kadar değerli değildir. Ferritin, yaşlı Covid-19 hastalarında en güçlü mortalite belirleyicisi olabilir.

Anahtar Kelimeler: Covid-19, yaş, yaşlı, ferritin, hastalık şiddeti, mortalite

Introduction

Two and a half years have passed since the onset of the Covid-19 pandemic, and its presence is still felt globally. While new mutations and strains of SARS-CoV-2 (1) continue to be discovered, the World Health Organization reports that as of 23 September 2022, the total number of confirmed cases exceeds 610 million, and the number of recorded deaths exceeds six million (2). As with other systems, aging is accompanied by significant immunological changes in human physiology (3). These immunological alterations may impact the older differently by weakening the immune system against infection. According to clinical studies and research, it has a more severe course and causes a greater fatality rate, particularly in older patients with Covid-19 illness or pneumonia (4). Certain clinical, laboratory, and imaging results are crucial for the management of Covid-19 patients and the assessment of disease severity, regardless of age. In the diagnostic, triage, and prognosis algorithms of Covid-19, vital signs, serum c-reactive protein (CRP), lymphocyte

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count, and a few other data have a prominent and critical role (5). Increased ferritin levels as a result of inflammation, also known as hyperferritinemia, have been extremely notable in Covid-19 (6). The literature on the hyperferritinemia seen in Covid-19 continues to increase. In the meta-analyses, the link between ferritin elevation, illness severity, and age could not be shown conclusively (7,8). The lack of clarity between ferritin elevation and age in Covid-19 necessitates more research into diagnostic techniques and illness severity evaluation.

In this retrospective study, the difference of ferritin levels with age in the management of Covid-19, similarities and/or variations between age groups, and superiority, if any, were analyzed. In particular, we aimed to evaluate the clinical validity and reliability of ferritin levels in older patients as a predictor of illness severity and diagnostic ability.

Methods

For this retrospective-cross-sectional study, patients admitted to the Emergency Department of "…" University Training and Research Hospital between September 2020 and January 2021 with a Covid-19 suspicion or a Covid-19 diagnosis were analyzed. The physical records of emergency department patients, the hospital information management system (HIMS), and the public health management system (PHMS) of the Ministry of Health served as data sources.

Patients under the age of 18 who did not have the diagnosis and/or symptoms of Covid-19 and those who lacked baseline exams were excluded from the research. In addition, the data set excluded causes of significant hyperferritinemia, particularly advanced renal failure with a glomerular filtration rate of less than 30 ml/min.

The patients' demographic data (gender, age), disease histories, vital signs (oxygen saturation, body temperature, blood pressure, pulse), hemogram, liver function tests, kidney function tests, c-reactive protein (CRP), ferritin, d-dimer, lactate dehydrogenase (LDH), lactate, venous blood gas (VBG), lung tomography and comments, and Covid-19 polymerase chain reaction (PCR) test results were recorded. COVID-19 Reporting and Data System (CO-RADS) was chosen for the imaging-based diagnosis of Covid-19 (9). The CO-RADS categories ranged from very low to very high (1–5), while category 0 indicates negative. Finally, hospitalization status, length of hospital stay, and mortality were documented.

Data Analysis:

Categorical data were expressed as frequency (n) and percentage (%). Continuous variable expressed as mean ± standard deviation (SD). The data were checked for normal distribution with the Kolmogorov-Smirnov test. To compare the two independent groups, Mann-Whitney U-test was used. Pearson's chi-square test was used to determine the relationship between the categorical variables. Correlation analysis was performed by Spearman's rank correlation coefficients. ROC curve analysis was used to determine some study variables' diagnostic value, sensitivity, specificity, and an optimal cut-off value. The optimal cut-off value was acquired using the Youden index (sensitivity + specificity−1). A p-value less than 0.05 was considered statistically significant. All statistical analyses were performed using the SPSS v28 (IBM Inc., Chicago, IL, USA) statistical software.

Results

Between September 2020 and January 2021, the total count of patient submissions to the emergency department of our hospital amounted to 26,584. A total of 416 patients who fulfilled our patient selection criteria, either suspected or diagnosed with Covid-19, were included in the study. The mean age of the patients was 50.58±18.93 years (18-94), and 188 (45.2%) were female while 228 (54.8%) were male.

There was statistically no significant difference between the mean age of females (50.68±18.06yrs) and males (50.50±19.660yrs) (p=0.738). The patients were divided into two groups as young/middle-aged group (<65 years) and older group (≥65 years) and compared for study variables. There was no significant difference between gender distributions across the two age groups (p=0.802). In the young/middle-aged group, there was no significant difference between the female (43.08±12.62) and male (42.03±12.82) patients in terms of age mean (p=0.483). On the other hand, in the older group, the mean age of males (79.90±6.35) was significantly higher than that of females (75.57±7.77) (p=0.003) (Table 1).

The frequency data for oxygen saturation (sPO2), fever, heart rate, length of hospitalization (LoS), hospitalization status (HS), PCR test positivity, and mortality, which are among the parameters indicating the severity of the illness, are provided in Table 2. The distribution of the existence of chronic illness in the patient's medical history by age is shown in the same table. Except for fever and PCR, all parameters showed significant age-related variations. Patients aged 65 and older varied considerably from the young-to-middle-aged group with regard to all chronic disorders.

There was significant difference between CO-RADS distributions across the two age groups (p<0.001, □2= 29.6). In the young/middle-aged group, half of the patients (50.2%) were CO-RADS category 0. The rate of those with CO-RADS category 0 was lower in the older group (26.3%). While the rate of patients with CO-RADS category 1 was higher in the young/middle-aged group (21.2% vs 17.9%), the rate of patients with CO-RADS category 2 was higher in the older group (16.2% vs 23.2%). The rate of patients with CO-RADS 3-4 categories was higher in the older group (5.6% vs 12.6% and 3.4% vs 10.5%, respectively). Similarly, the rate of patients with CO-RADS category 5, implies a very high probability for COVID-19 pneumonia, was also higher in the older group (3.4% vs 9.5%). In the last step, CO-RADS was separated into two major groups. The first group has scores lower than 3 while the second group contains scores of 3 and above. While patients

with CORADS scores below 3 were more prevalent in the young-to-middle age group (87.6% vs 67.4%, respectively), those with scores of 3 and above were more common in the older group (32.6 percent vs 12.5 percent, respectively).

The descriptive statistics for ferritin levels (ng/mL) in patients were as follows: in under-65 age group (n=321), the mean ferritin value was 170 (SD=210), the median value was 95.3, the interquartile range (IQR) 158, the minimum value 5.91 and the maximum value was 1584.00. For patients aged 65 and older (n=95), the mean ferritin value was 250 (SD=261), the median value 148.4, the interquartile range 267, the lowest value 6.20, and the highest value was 1356.00. These differences were statistically significant (p<0.001, Z=11943).

Table 3 shows the serum ferritin levels of patients with some variables. The study found significant differences in ferritin levels among patients under 65 years of age based on several parameters, including PCR positivity, hospitalization status, length of stay, oxygen saturation, and CO-RADS. However, only mortality and CO-RADS parameters showed a significant difference in ferritin levels among patients older than 65. On the other hand, while the serum ferritin levels of patients with and without mortality was not significantly different in the young/middle-aged group (p=0.519), it was higher in patients with mortality in the older group (p=0.049).

Also we evaluated the correlation between the ferritin levels and age, saturation (sPO2), fever, pulse, white blood cell (WBC), hemoglobin (HGB), platelet (PLT), neutrophil (NEU), lymphocyte (LYM), neutrophil-to-lymphocyte ratio (NLR), aspartate transaminase (AST), alanine transaminase (ALT), blood urea nitrogen (BUN), creatinine (CRE), lactate dehydrogenase (LDH), c-reactive protein (CRP), glomerular filtration rate (GFR), lactate (LAC), troponin (TROP) and d-dimer (DD) in each group. The results revealed a significant positive correlation between the ferritin and age in the <65 years group (r =0.351, p<0.001). There was no correlation between age and ferritin level in those older than 65.

The following variables exhibited significant correlations in the age group below 65 years (Spearman's rho correlation coefficient (r) values and p values will be provided in order): sPO2 -0.235 (<0.001), pulse -0.134 (0.016), LOS 0.220 (<0.001), HGB 0.302 (<0.001), PLT -0.140 (0.012), NLR 0.148 (0.009), AST 0.327 (<0.001), ALT 0.293 (<0.001), BUN 0.180 (0.007), CRE 0.295 (<0.001), GFR -0.398 (p < 0.001), LDH 0.248 (p < 0.001), CRP 0.429 (p < 0.001), LAC 0.428 (p < 0.001), CO-RADS 0.207 (p < 0.001). The following variables showed significant correlations in older population (Spearman's rho correlation coefficient (r) values and p values will be provided in order): LYM -0.210 (0.041), AST 0.206, (0.043), CRP 0.403 (<0.001), LAC 0.472 (<0.001), D-DIMER 0.319 (0.002), CORADS 0.268 (0.009).

We discovered that the CRP and LAC values had the highest correlation with ferritin in both age groups. Our concluding statistical analysis will focus on ROC curve analyses and will provide two distinct sets of results. The analysis was performed, and area under the curve (AUC), sensitivity, specificity, and 95 % confidence interval (CI) were calculated.

In the first set, ROC curves were used to assess the diagnostic ability and disease severity prediction of serum ferritin level in relation to mortality and PCR positive, hospitalization status, LoS, sPO2, and CO-RADS (Table 4). While the serum ferritin level was found as a diagnosis variable to Covid-19 mortality in older patients (p<0.049), it was not in the young/middle-aged group (p=0.519). The AUC of ferritin level of older patients was 0.700 (95 % CI, 0.482-0.919) and, a cut-off value of ferritin level of older patients was determined as 236.15 in the mortal group (sensitivity = 66.67%, specificity = 68.60%). Therefore, the probability of mortality due to Covid-19 presence may increase significantly when the ferritin level of patients ≥65 years of age level increase above this value.

In the second set, the ROC curve approach was tested exclusively in the older population by comparing serum indicators that may indicate the severity of an illness and help in its diagnosis (Table 5). CRP, LYM, NLR, LDH, and LAC were selected as these serum markers to be tested with serum ferritin. As described before, mortality status, PCR positivity, hospitalization status, LoS, CO-RADS, and sPO2 were chosen as diagnostic

Table-1: The distribution of patients according to gender and age groups. There was no significant difference between gender distributions across the two age groups (p=0.802, χ2=0.063). *Abbreviations:* χ2: Pearson's chi-square test; Z: Mann-Whitney U test; Med: median; Min: minimum; Max: maximum.

	Age < 65				**Age ≥ 65**				***Total***			
	n			**Max**	**n**	**Med**	**Min**	**Max**	***n***	**Med**	**Min**	**Max**
Female	144	42.5	19	64	44	73	65	93	188	50.5	19	93
Male	177	42	18	64	51	81	66	94	228	48	18	94
Total	321	42	18	64	95	79	65	94	416	48.5	18	94
p	0.483 (Z=-0.702)				0.003 (Z=-2.952)				0.738 (Z=-0.334)			
p	0.802 (χ^2=0.063)											

Table 2. The frequency distribution of several parameters based on age and common chronic conditions. The p value reflects the significant difference between age groups. Significant p values are displayed in bold. *Abbreviations:* χ2: Pearson's chi-square test; LR χ2: Likelihood ratio chi-square test; LoS, Length of stay in hospital, PCR, polymerase chain reaction test for Covid-19; sPO2, peripheral oxygen saturation; CO-RADS, COVID-19 Reporting and Data System; CAD, coronary artery disease; DM, diabetes mellitus; HT, hypertension; COPD: chronic obstructive pulmonary disease; CVA, cerebrovascular accident.

Parameters/Diseases		Age <65		Age ≥65		p
		n	%	n	%	
sPO2	<93	12	3.7	41	43.2	**<0.001**
	≥93	309	96.3	54	56.8	(χ^2=102.462)
CO-RADS	<3	281	87.5	64	67.4	**<0.001**
	≥3	40	12.5	31	32.6	(χ^2=21.071)
Fever	<38	134	41.7	42	44.2	0.669
	≥38	187	58.3	53	55.8	(χ^2=0.183)
Pulse	<100	167	52.0	34	35.8	**0.005**
	≥100	154	48.0	61	64.2	(χ^2=7.738)
LoS (day)	<5	172	53.6	23	24.2	**<0.001**
	≥5	149	46.4	72	75.8	(χ^2=25.396)
Hospitalization status	No	157	48.9	21	22.1	**<0.001**
	Yes	164	51.1	74	77.9	(χ^2=21.515)
PCR	Negative	116	36.1	31	32.6	0.530
	Positive	205	63.9	64	67.4	(χ^2=0.394)
Mortality	No	314	97.8	86	90.5	**0.003**
	Yes	7	2.2	9	9.5	(LR χ^2=8.693)
CAD	No	312	97.2	68	71.6	**<0.001**
	Yes	9	2.8	27	28.4	(χ^2=60.856)
DM	No	307	95.6	57	60.0	**<0.001**
	Yes	14	4.4	38	40.0	(χ^2=85.125)
HT	No	298	92.8	53	55.8	**<0.001**
	Yes	23	7.2	42	44.2	(χ^2=76.308)
COPD	No	319	99.4	70	73.7	**<0.001**
	Yes	2	0.6	25	26.3	(χ^2=79.731)
Malignancy	No	321	100.0	88	92.6	**<0.001**
	Yes	0	0.0	7	7.4	(LR χ^2=21.086)
CVA	No	321	100.0	87	91.6	**<0.001**
	Yes	0	0.0	8	8.4	(LR χ^2=24.168)

Table 3: Ferritin (ng/mL) distribution based on diagnostic and severity indicators. Significant p values are displayed in bold. *Abbreviations:* SD, standard deviation; MR, mean rank; Z, Mann-Whitney U test; Mort., mortality; PCR, polymerase chain reaction test for Covid-19; sPO2, peripheral oxygen saturation; HS, hospitalization status; LoS, length of stay in hospital; bpm, beats per minute; CO-RADS, COVID-19 Reporting and Data System.

	n	Age <65					Age ≥65				
		Mean	SD	MR	p	n	Mean	SD	MR	p	
Mort.	-	314	170.55	211.38	161.50	0.519	86	221.42	219.00	46.20	**0.049**
	+	7	134.43	171.98	138.64	Z=-0.644	9	518.81	451.14	65.22	Z=-1.970
PCR	-	116	103.61	104.54	131.43	**<0.001**	31	249.88	273.61	49.61	0.691
	+	205	207.19	243.74	177.73	Z=-4.294	64	249.45	257.57	47.22	Z=-0.397
HS	-	157	110.16	111.18	137.24	**<0.001**	21	211.89	246.12	43.57	0.404
	+	164	226.82	261.56	183.74	Z=-4.487	74	260.29	266.27	49.26	Z=-0.834
LoS	<5	172	121.52	137.68	140.66	**<0.001**	23	267.25	334.84	47.00	0.842
(day)	≥5	149	225.45	260.81	184.48	Z=-4.219	72	243.95	235.85	48.32	Z=-0.200
sPO2	<93	12	503.14	466.01	245.58	**0.001**	41	290.20	304.52	51.10	0.340
(%)	≥93	309	156.81	183.73	157.72	Z=-3.218	54	218.76	221.37	45.65	Z=-0.954
Fever	<38	134	174.31	203.02	171.40	0.089	42	257.74	287.84	48.05	0.988
(°C)	≥38	187	166.50	216.08	153.55	Z=-1.699	53	243.13	241.14	47.96	Z=-0.015
Pulse	<100	167	172.97	176.78	169.92	0.073	34	242.38	220.90	47.88	0.975
(bpm)	≥100	154	166.28	242.27	151.33	Z=-1.793	61	253.61	283.21	48.07	Z=-0.031
CO-RADS	<3	281	159.10	193.83	156.24	**0.015**	64	194.12	223.66	42.14	**0.003**
	≥3	43	297.45	345.53	203.44	Z=-2.435	35	465.45	671.19	63.60	Z=-2.977

Table 4. Results of the ROC curve analysis for serum ferritin level (ng/mL) indicating positivity of mortality, PCR, hospitalization status, LoS, sPO2 and CO-RADS in the young/middle-aged and older patient groups. Significant p values are displayed in bold. *Abbreviations:* PCR, polymerase chain reaction test for Covid-19; sPO2, peripheral oxygen saturation; HS, hospitalization status; LoS, length of stay in hospital; CO-RADS, COVID-19 Reporting and Data System; AUC, area under the curve.

	Age group	Cut-off value	Sensitivity (%)	Specificity (%)	AUC (95% CI)	p
Mortality (+)	<65	101.45	57.14	53.18	0.429(0.204-0.654)	0.519
	≥65	236.15	66.67	68.60	0.700(0.482-0.919)	**0.049**
PCR (+)	<65	88.75	59.02	60.34	0.644(0.584-0.705)	**<0.001**
	≥65	151.15	48.44	51.61	0.475(0.355-0.595)	0.691
HS (+)	<65	92.96	62.80	62.42	0.645(0.584-0.706)	**<0.001**
	≥65	147.00	55.41	61.90	0.560(0.425-0.695)	0.404
LoS (≥5)	<65	96.50	62.42	62.21	0.637(0.574-0.699)	**<0.001**
	≥65	147.00	54.17	56.52	0.514(0.378-0.650)	0.842
CO-RADS (≥3)	<65	112.45	60.00	59.07	0.619(0.528-0.709)	**0.015**
	≥65	189.55	64.52	68.75	0.689(0.574-0.804)	**0.003**
sPO2 (<93)	<65	173.50	66.67	71.85	0.774(0.636-0.912)	**0.001**
	≥65	149.20	56.10	55.56	0.557(0.439-0.676)	0.340

Table 5. The combined ROC curve analyzes and results of the disease severity and diagnostic parameters for a variety of conditions that affect the older patients. Here are the AUC values and p-values of six different blood parameters (FER, CRP, LAC, LDH, LYM, and NLR) for nine distinct situations (PCR, CORADS, sPO2, HS, LoS, and mortality). Notable is the fact that the FER value has a high AUC and is more relevant than measures such as CRP and LAC, particularly in terms of mortality. Values of p that are statistically significant are given in bold. *Abbreviations:* PCR, polimerase chain reaction; CORADS, ; sPO2, ; HS, hospitalization status; LoS, lenght of stay; FER, ferritin; CRP, c-reactive protein; LYM, lymphocyte; NLR, neutrophile-lymphocyte ratio; LAC, lactate; LDH, lactate dehydrogenase; Ref., reference line; AUC, area under the curve.

Blood markers		Mortality	LoS	HS	sPO2	CO-RADS	PCR
Ferritin	AUC	0.700	0.514	0.560	0.557	0.689	0.475
	p	**0.049**	0.842	0.404	0.340	**0.003**	0.691
CRP	AUC	0.604	0.629	0.615	0.485	0.693	0.434
	p	0.307	0.068	0.116	0.801	**0.002**	0.303
LAC	AUC	0.660	0.557	0.582	0.617	0.614	0.579
	p	0.115	0.416	0.264	0.052	0.074	0.218
LDH	AUC	0.570	0.500	0.498	0.449	0.603	0.421
	p	0.322	0.996	0.982	0.061	0.106	0.218
LYM	AUC	0.635	0.496	0.525	0.529	0.636	0.631
	p	0.186	0.950	0.732	0.634	**0.032**	**0.042**
NLR	AUC	0.529	0.613	0.589	0.498	0.411	0.672
	p	0.777	0.109	0.224	0.976	0.163	**0.008**

and/or severity indicators of the illness. Consequently, only mortality status (95% CI, AUC=0.700, p=0.049) and CO-RADS (95% CI, AUC=0.689, p=0.003) were shown to have significant AUC values in relation to ferritin levels. While NLR (95% CI, AUC=0.672, p=0.008) and LYM (95% CI, AUC=0.636, p=0.032) in PCR had significantly higher AUC values on its own, no serum markers for LoS, HS and sPO2 had significantly higher AUC values.

Discussion

Due to the toxicity of iron to pathogenic microorganisms, high level of ferritin, an acute phase reactant, is an essential host defense mechanism that inhibits their proliferation, hence inhibiting the spread of pathogenic microorganisms (10). Moreover, serum ferritin levels have been described as an indicator (11) and diagnostic parameter for the severity of infections (12). Therefore, we analyzed serum ferritin levels in elderly Covid-19 patients to evaluate the severity and diagnostic utility of the disease and found a significant association between high ferritin and mortality. In addition, this association was not observed in patients younger than 65 years old.

In the literature, there are insufficient studies evaluating the relationship between ferritin and Covid-19 patient age, particularly for geriatric patients. Rather, it was observed that the severity of the disease and the diagnostic value of ferritin were determined by including all ages.

One study particularly caught our attention. The investigation conducted by Avci and Gursoy, encompassing a sample size of 1820 individuals, did not place emphasis on ferritin. However, their findings indicated a statistically significant elevation in ferritin levels among the elderly population compared to the younger cohort, which is consistent with the outcomes of our own study. The study in question reported a mean age of 76.1±7.4 years for the geriatric population, which is comparable to the findings of our own study. In the same study, the mean ferritin in Covid patients

aged 65 and over was calculated as 325.1±993.7. The AUC value for ferritin with regards to mortality was not disclosed (13).

Ahmed et al. reported that the AUC of ferritin in terms of mortality in a group of patients they analyzed (n=157) was 0.69, and the mean age of the non-survivor group was 65.5 years (14).

Jonathan et al. performed a retrospective study (n=942) and found that the AUC value for predicting mortality in patients younger than 60 years was 0.730 (15). It was reported by Onur et al. that the AUC for ferritin was 0.762 (sensitivity=70%, specificity=70%) in their research (n=301, median age=57) (16). In another study conducted in patients with Covid-19 (n=264, mean age of 47.4 ± 15.3 years), the ROC analysis results of ferritin in terms of mortality (AUC=0.703, sensitivity=69%, specificity=63.7%, p=0.001) (17).

In fact, in our analysis, the mortality rate of older patients was significantly different from that of patients under sixty-five. Our data indicate that hyperinflammatory response and its negative impacts are better managed in younger patients and suggest that the appropriate immune system's responsiveness decreases with age (18).

In a study with a mean age of 44.5±17.1 years (n=1338), there was no significant difference between CO-RADS scores <3 and ≥3 regarding ferritin levels (19). In our study, however, there was a significant difference between the ferritin levels of younger and older patients with low and high CO-RADS scores. Thus, after its relationship with mortality, ferritin levels in older patients also shown diagnostic significance in terms of CO-RADS.

C-reactive protein, lactate, lymphocyte, lactate dehydrogenase, and neutrophil-lymphocyte ratios are not as significant as ferritin in ROC curve analyses for mortality in older patients, which is an unexpected finding. In a study involving 386 patients with a mean age of 54 years and a patient sample, Yousaf et al. (20) discovered considerably greater AUC mortality values for LDH, CRP, and D-Dimer in addition to ferritin (0.74, 0.73, 0.737, 0.758).

Whereas, older patients might exhibit elevated C-reactive protein levels in the absence of illness (21). On the other hand, it has been shown that elevated CRP levels in older patients are also associated with poor outcomes such as short-term mortality, regardless of the presence of acute infection (22). However, studies has also documented a correlation between CRP and fatality among geriatric individuals (23).

Finally, a systematic review that examined aged Covid-19 patients found that the levels of D-dimer, CRP, lymphocytes, and lactate dehydrogenase were an increased risk of mortality in the elderly (24).

Conclusion

In terms of the lung involvement and mortality that are characteristic of the disease, we observed that ferritin levels in older patients with Covid-19 were remarkable. However, we found that it was unable to predict disease severity metrics in older patients, such hospitalization status, length of stay, and oxygen saturation. These are all measures of how severely the illness affects the patient. The fact that hyperferritinemia and its severity are lower in patients under 65 years of age and that this is not associated with mortality, whereas the opposite situation exists in older patients, demonstrates that the immune response balance is lost with age, which may lead to results such as death replacing it more easily. Nevertheless, comprehensive research on older populations is required in order to determine whether or not hyperferritinemia is the first step in the death cascade or only a sign of hyperinflammation.

Limitations

The cases of hyperferritinemia that were identified in emergency services during the chaotic time characterized by the severe progression of the pandemic and limited access to comprehensive etiological investigations were predominantly associated with Covid-19. Nonetheless, in order to establish a more definitive perspective on the correlation between Covid-19, hyperferritinemia, and age, it is required that other potential factors be carefully assessed and eliminated through comprehensive examination. Additionally, our study has basic limitations such as its retrospective nature and single-institution context. Therefore, more multicenter, comprehensive studies are required to confirm the conclusions of this research.

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