Impact of Age on Predictive Capabilities of Ferritin, Ferritin-Hemoglobin Ratio, IL-6, and sIL-2R for COVID-19 Severity and Mortality

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ABSTRACT

The study aimed to establish the impact of age on the predictive capability of ferritin, ferritin-hemoglobin ratio (FHR), IL-6, and sIL-2R in COVID-19 patients. Compared to patients with moderate condition, patients with severe condition had higher ferritin level (441.0 [188.0–829.8] ng/mL vs 281.0 [172.0–388.0] ng/mL, p = 0.002), sIL-2R level (6.0 [4.7–9.0] pg/mL vs 5.3 [3.7–6.9] pg/mL, p = 0.020), FHR (38.4 [15.1–63.4] vs 22.0 [12.1–32.1], p = 0.002). The area under the curves (AUC) for discriminative capabilities of the following biomarkers for severe condition were assessed in patients aged <65 years and patients aged ≥65 years: ferritin (AUC = 0.585, p = 0.309 vs AUC = 0.683, p = 0.002), FHR (AUC = 0.589, p = 0.302 vs AUC = 0.688, p = 0.002), IL-6 (AUC = 0.503, p = 0.972 vs AUC = 0.647, p = 0.019), and sIL-2R (AUC = 0.549, p = 0.552 vs AUC = 0.646, p = 0.017). Also AUCs for discriminative capabilities for in-hospital mortality were compared in patients aged <65 years and ≥65 years: ferritin (AUC = 0.607, p = 0.628 vs AUC = 0.661, p = 0.105), FHR (AUC = 0.612, p = 0.621 vs AUC = 0.688, p = 0.002), IL-6 (AUC = 0.580, p = 0.724 vs AUC = 0.695, p = 0.016), and sIL-2R (AUC = 0.620, p = 0.491 vs AUC = 0.695, p = 0.029). Thus, ferritin, FHR, IL-6, and sIL-2R didn't show acceptable predictive value for severe condition and lethal outcome in patients aged <65 years but had high predictive value for lethal outcome in patients aged ≥65 years.

KEYWORDS

COVID-19; ferritin; IL-6; soluble IL-2 receptors; age; prediction; severity; mortality

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INTRODUCTION

COVID-19 pandemic significantly impacted the social, health, and economic spheres of human life (1). According to WHO reports, as of 12 October 2023, there were over 771 million confirmed cases of COVID-19 and almost 7 million deaths related to this disease worldwide (2). Globally, the case-fatality rate is 0.90% (3). Among hospitalized patients, the death rate at 30 days is almost 6.0% (4). However, the full impact of COVID-19 seems to be much more significant, than reported deaths, as excessive mortality is found to be significantly higher (5).

COVID-19 leads to a hyperinflammatory state resulting in lung damage, acute respiratory distress syndrome, as well as multi-organ failure (6). There are multiple biomarkers that reflect systemic inflammation. Serum ferritin is one of them (7–9). Many studies showed that serum ferritin level is a predictor of severe COVID-19 and lethal outcomes (10–13). However, several studies showed that ferritin is an insufficiently accurate predictor of adverse outcomes in patients with COVID-19 (14, 15). Predictive abilities of ferritin-hemoglobin ratio (16), ferritin-lymphocyte percentage ratio (17, 18), and ferritin-albumin ratio (19) were studied to improve ferritin role in the prediction of severe COVID-19 and mortality. Higher predictive accuracy of the abovementioned ratios compared to single ferritin is explained by the fact that severe COVID-19 is accompanied by an increase in ferritin level (20, 21), a decrease in hemoglobin (22) and albumin (23, 24) levels, as well as lymphocyte count (25–27). However, age has a great effect on ferritin levels in COVID-19 patients (28)

Soluble interleukin-2 receptors (sIL-2R) and interleukin-6 (IL-6) are other important predictors of adverse outcomes in patients with COVID-19 (29, 30). It's known that age impacts levels of both IL-6 (31) and sIL-2R (32) too.

Therefore, given that age impacts levels of serum ferritin, IL-6, and sIL-2R, it's important to establish whether age impacts the predictive capability of these biomarkers. So, this study aims to establish the influence of age on the predictive capability of ferritin, ferritin-hemoglobin ratio, IL-6, and sIL-2R in patients hospitalized for pneumonia associated with COVID-19.

MATERIALS AND METHODS

One hundred thirty-five patients hospitalized for pneumonia associated with COVID-19 between March and June 2021 were included in this study. SARS-CoV-2 was confirmed in each patient with PCR or ELISA test (IgM levels). Pneumonia was confirmed in each patient radiologically (either X-ray or chest computed tomography). Levels of ferritin, IL-6, and sIL-2R were assessed at the moment of hospital admission. To calculate the ferritin-hemoglobin ratio, the serum ferritin level (ng/mL) was divided by hemoglobin level (g/dL).

COVID-19 severity was established according to the Protocol of Medical Care of Coronavirus Disease (COVID-19) (33). A severe clinical condition was diagnosed in patients with at least one of the following signs: oxygen saturation ≤93%, respiratory rate ≥30 breaths per minute, and radiologically established pulmonary infiltrates involving >50% of the lung area. The critical clinical condition was established in patients with at least one of the following conditions: altered consciousness (≤14 points according to Glasgow Coma Scale), acute respiratory distress syndrome, sepsis-III criteria, and multiple organ dysfunction syndrome. The moderate clinical condition was diagnosed in COVID-19 patients with pulmonary involvement confirmed radiologically who don't meet criteria of severe or critical clinical conditions.

An informed consent was signed by each potential patient before enrollment into the research. The approval of the Ethics Committee of Ivano-Frankivsk National Medical University (No 134/23) has been acquired. The study has been performed according to the Declaration of Helsinki.

Software MedCalc and MS Excel were used for statistical processing. The distribution of variables was evaluated Shapiro-Wilk test. The variables with abnormal distribution were shown as a median and interquartile range. Categorical variables were presented as a total count accompanied by a corresponding percentage. Mann-Whitney U test, Chi-squared test, and Spearman's rank correlation were used. Receiver operating characteristic (ROC) curves were constructed and the area under the curve (AUC) was computed. Sensitivity, specificity, and Youden index were determined. Also, a comparison of two AUCs was performed. P-values less than 0.05 were considered to be statistically significant.

RESULTS

Participants characteristics. The participants had a median age of 67.0 (61.0–74.0) years. The median value of body mass index in enrolled patients was 27.0 (24.6–31.8) kg/m^2. The median oxygen saturation in patients at the moment of admission was 95.0 (93.0–96.0)%. Among the participants, there were 53 (39.3%) men and 82 (60.7%) women. The median hemoglobin level at the moment of hospital admission was 13.1 (12.2–14.2) g/dL. The median ferritin level at admission was 349.0 (183–595.8) ng/mL. The median ferritin-hemoglobin ratio was 25.7 (13.3–45.8). The median IL-6 level at the moment of hospital admission was 44.4 (13.0–91.8) pg/mL. The median sIL-2R level at the moment of hospital admission was 5.6 (4.2–7.7) ng/mL.

Severe/critical conditions during the in-patient stay developed in 72 (53.3%) patients, and moderate condition was diagnosed in 63 (46.7%) patients. Supplemental oxygen was used in 62 (45.9%) patients. During the in-hospital stay, 14 (10.4%) patients died. Laboratory parameters in accordance with COVID-19 severity and mortality are shown in table 1. Ferritin, ferritin-hemoglobin ratio, and sIL-2R at admission were higher in patients with severe/critical conditions than in patients with moderate conditions. Non-survivors had a higher ferritin-hemoglobin ratio at hospital admission.

Discriminative and predictive capabilities of ferritin, ferritin-hemoglobin ratio, IL-6, and sIL-2R. Discriminative capabilities of ferritin, ferritin-hemoglobin ratio, IL-6, and sIL-2R for severity and mortality are shown in table 2

Tab. 1 Laboratory parameters in the enrolled patients at the moment of hospital admission.

Laboratory parameter	Severity			Mortality		
	Moderate condition	Severe/critical condition	p	Survivors	Non-survivors	P
Hemoglobin, g/dL	130.5 (123.0–140.0)	131.0 (121.0–142.0)	0.986	131.0 (123.5–142.0)	122.0 (112.8–141.5)	0.237
Ferritin, ng/mL	281.0 (172.0–388.0)	441.0 (188.0–829.8)	0.002	337.0 (179.0–549.0)	467.5 (397.0–1008.0)	0.066
FHR	22.0 (12.1–32.1)	38.4 (15.1–63.4)	0.002	24.5 (13.1–44.6)	40.1 (29.9–95.3)	0.047
IL-6, pg/mL	36.2 (8.1–71.4)	56.4 (16.2–105.3)	0.055	40.4 (11.5–81.7)	80.4 (26.8–153.7)	0.063
sIL-2R, ng/mL	5.3 (3.7–6.9)	6.0 (4.7–9.0)	0.020	5.4 (3.9–7.6)	7.1 (5.0–9.5)	0.094

Abbreviations: FHR, ferritin-hemoglobin ratio; IL-6, interleukin-6; sIL-2R, soluble interleukin-2 receptors.

Tab. 2 Discriminative capabilities of laboratory parameters for the disease severity and mortality.

Laboratory parameter	Severity			Mortality		
	AUC	SE	p	AUC	SE	p
Ferritin	0.653	0.049	0.002	0.651	0.087	0.083
FHR	0.658	0.049	0.001	0.668	0.094	0.075
IL-6	0.596	0.049	0.052	0.652	0.078	0.052
sIL-2R	0.616	0.048	0.016	0.637	0.083	0.100

Abbreviations: AUC, area under the curve; FHR, ferritin-hemoglobin ratio; IL-6, interleukin-6; SE, standard error; sIL-2R, soluble interleukin-2 receptors.

and fig. 1. Ferritin, ferritin-hemoglobin ratio, and sIL-2R had poor but statistically significant discriminative capabilities for severe/critical condition.

Optimal cut-off values for the prediction of severe/critical condition and lethal outcome are shown in table 3. Only ferritin and ferritin-hemoglobin ratio had acceptable Youden indexes for the prediction of lethal outcome.

Effect of elderly on predictive capabilities of ferritin, ferritin-hemoglobin ratio, IL-6, and sIL-2R. There were 53 (39.3%) patients aged <65 years and 82 (60.7%) patients aged ≥65 years. There was no statistically significant difference between participants aged <65 years and participants aged ≥65 years in ferritin level, ferritin-hemoglobin ratio, IL-6, sIL-2R (table 4).

Correlation analysis between the age and laboratory parameters was performed. There was no correlation between age and ferritin level (r = 0.116, p = 0.182), ferritin-hemoglobin ratio (r = 0.140, p = 0.110), IL-6 level

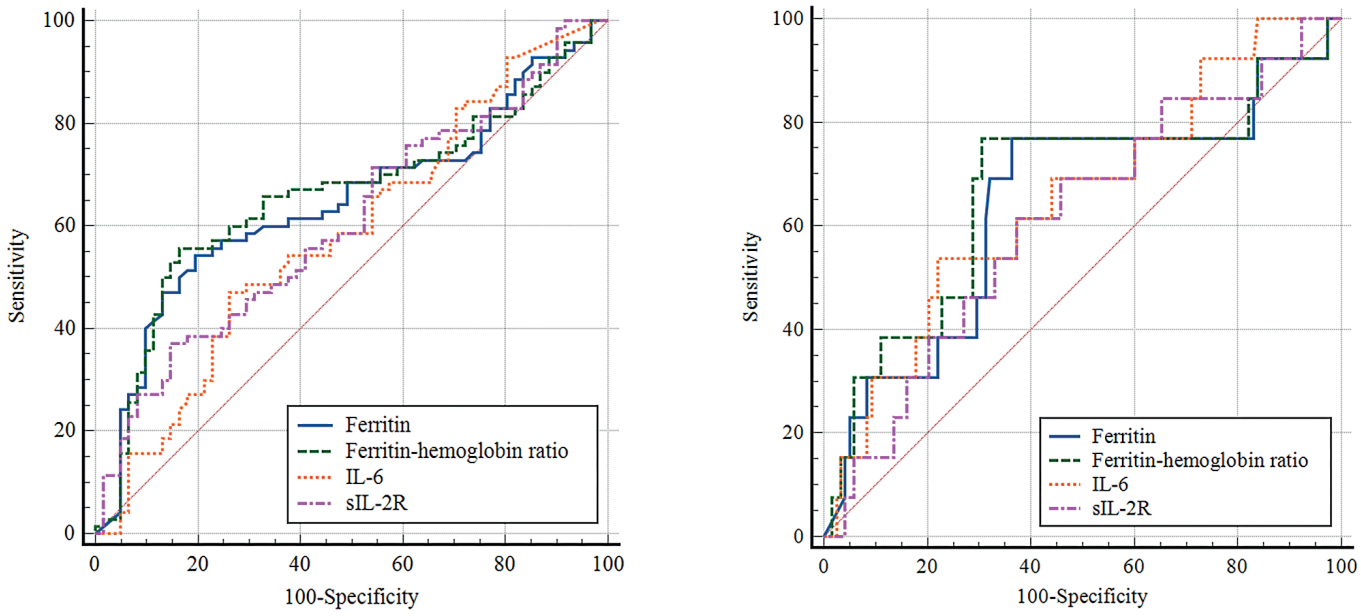

Fig. 1 ROC-curves of discriminative capabilities of ferritin, ferritin-hemoglobin ratio, IL-6, and sIL-2R for severe/critical condition (A) and lethal outcome (B).

Tab. 3 Predictive capabilities of laboratory parameters for the disease severity and mortality.

Laboratory parameter	Severe/critical condition				Lethal outcome			
	Optimal cut-off value	Sensitivity, %	Specificity, %	Youden index	Optimal cut-off value	Sensitivity, %	Specificity, %	Youden index
Ferritin	402.0	54.9	80.6	0.356	396.0	78.6	63.9	0.425
FHR	34.0	55.7	83.6	0.393	35.2	76.9	69.5	0.464
IL-6	62.5	48.6	74.6	0.232	91.0	50.0	77.7	0.277
sIL-2R	7.5	38.9	85.7	0.246	6.2	64.3	62.8	0.271

Abbreviations: FHR, ferritin-hemoglobin ratio; IL-6, interleukin-6; sIL-2R, soluble interleukin-2 receptors.

Tab. 4 Laboratory parameters in patients aged <65 years and patients aged ≥65 years.

Laboratory parameter	Patients aged <65 years	Patients aged ≥65 years	p
Ferritin, ng/mL	285.0 (164.0–549.0)	378.5 (202.5–618.5)	0.336
FHR	22.5 (12.2–43.8)	29.5 (15.5–46.4)	0.284
IL-6, pg/mL	29.9 (11.7–68.8)	56.1 (16.1–98.3)	0.190
sIL-2R, ng/mL	5.1 (3.6–7.3)	5.7 (4.5–8.2)	0.100

Abbreviations: FHR, ferritin-hemoglobin ratio; IL-6, interleukin-6; sIL-2R, soluble interleukin-2 receptors.

(r = 0.154, p = 0.074). A weak but significant positive correlation was seen between age and sIL-2R level at admission (r = 0.230, p = 0.007).

Severe/critical condition was established in 48 (58.5%) patients aged ≥65 years and 24 (45.2%) patients aged <65 years (p = 0.133). 11 (13.4%) patients aged ≥65 years and 3 (5.7%) patients aged <65 years died during in-patient stay (p = 0.151).

Discriminative and predictive capabilities of ferritin, ferritin-hemoglobin ratio, IL-6, and sIL-2R for severe/critical condition and lethal outcomes in patients aged <65 years and patients aged ≥65 years are shown in table 5 and fig. 2. Each laboratory parameter failed to show acceptable discriminative capability for the disease severity and in-hospital mortality in patients aged <65 years. However, ferritin, ferritin-hemoglobin ratio, IL-6, and sIL-2R showed weak discriminative capabilities for the disease severity in patients aged ≥65 years. Ferritin-hemoglobin ratio, IL-6, and sIL-2R had acceptable discriminative capabilities with an acceptable Youden index for in-hospital mortality in patients aged ≥65 years. However, there was no statistical significance comparing AUCs for discriminative capabilities of ferritin, ferritin-hemoglobin ratio, IL-6, and sIL-2R in patients aged ≥65 years and patients aged <65 years.

Logistic regression was performed, adjusted and unadjusted odds ratios were calculated (table 6). Unadjusted odds ratio showed that ferritin, ferritin-hemoglobin ratio,

Tab. 5 Discriminative and predictive capabilities of laboratory parameters for severity and mortality in patients aged <65 years and patients aged ≥65 years

Laboratory parameter	<65 years old				≥65 years old				Comparison of two AUCs	
	AUC; SE	p	Optimal cut-off value	Youden index	AUC; SE	p	Optimal cut-off value	Youden index	Difference	p
Severe/critical condition										
Ferritin	0.585; 0.084	0.309	463.0	0.279	0.683; 0.060	0.002	396.0	0.405	0.098	0.342
FHR	0.589; 0.087	0.302	25.6	0.369	0.688; 0.059	0.002	35.2	0.436	0.099	0.346
IL-6	0.503; 0.082	0.972	50.6	0.140	0.647; 0.063	0.019	62.5	0.268	0.144	0.164
sIL-2R	0.549; 0.082	0.552	8.3	0.181	0.646; 0.061	0.017	7.3	0.311	0.097	0.343
Lethal outcome										
Ferritin	0.607; 0.220	0.628	391.0	0.347	0.661; 0.099	0.105	438.0	0.470	0.054	0.823
FHR	0.612; 0.227	0.621	34.3	0.381	0.688; 0.059	0.002	35.2	0.436	0.076	0.746
IL-6	0.580; 0.227	0.724	12.7	0.407	0.695; 0.081	0.016	41.4	0.325	0.115	0.633
sIL-2R	0.620; 0.174	0.491	6.3	0.320	0.695; 0.089	0.029	6.6	0.361	0.075	0.701

Abbreviations: AUC, area under the curve; FHR, ferritin-hemoglobin ratio; IL-6, interleukin-6; SE, standard error; sIL-2R, soluble interleukin-2 receptors.

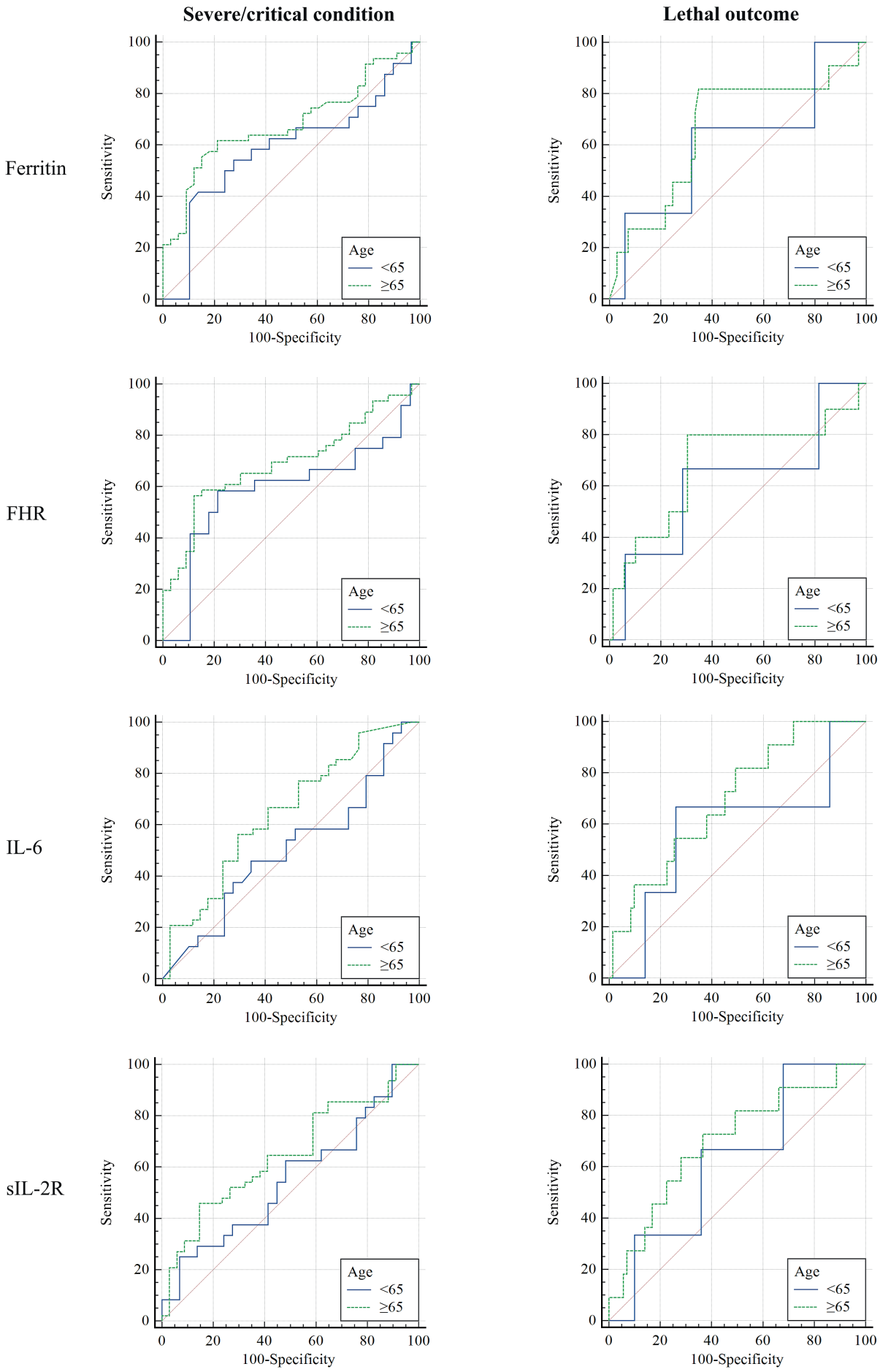

Fig. 2 ROC-curves of discriminative capabilities of ferritin, ferritin-hemoglobin ratio (FHR), IL-6, and sIL-2R for severe/critical condition and lethal outcome in patients aged <65 years and patients aged ≥65 years.

Tab. 6 Odds ratio for prediction of severe/critical clinical condition and lethal outcome in patients aged <65 years and patients aged ≥65 years.

Laboratory parameter	<65 years old		≥65 years old	
	Unadjusted OR (95% CI)	Adjusted OR (95% CI)	Unadjusted OR (95% CI)	Adjusted OR (95% CI)
Severe/critical condition				
Ferritin	1.0001 (0.9995–1.0022)	1.0052 (0.9941–1.0164)	1.0026 (1.0008–1.0045)	1.0016 (0.9960–1.0072)
FHR	1.0094 (0.9911–1.0281)	0.9393 (0.8097–1.0897)	1.0344 (1.0105–1.0589)	1.0093 (0.9391–1.0849)
IL-6	0.9987 (0.9945–1.0030)	0.9986 (0.9937–1.0035)	1.0054 (0.9985–1.0123)	1.0035 (0.9960–1.0110)
sIL-2R	1.1595 (0.9389–1.4318)	1.1149 (0.8820–1.4094)	1.2180 (1.0216–1.4522)	1.1293 (0.9316-1.3688)
Lethal outcome				
Ferritin	1.0009 (0.9983–1.0034)	0.9926 (0.9767–1.0087)	1.0013 (0.9998–1.0029)	1.0001 (0.9958–1.0044)
FHR	1.0134 (0.9801–1.0478)	1.1412 (0.9235–1.4103)	1.0226 (1.0020–1.0435)	1.0150 (0.9578–1.0756)
IL-6	0.9968 (0.9783–1.0156)	0.9941 (0.9717–1.1070)	1.0083 (1.0012–1.0154)	1.0079 (0.9998–1.0161)
sIL-2R	0.7885 (0.4441–1.3999)	0.6136 (0.2665–1.4130)	1.2440 (1.0251–1.5098)	1.1354 (0.8638–1.4923)

Abbreviations: CI, confidence interval; FHR, ferritin-hemoglobin ratio; IL-6, interleukin-6; OR, odds ratio; SE, standard error; sIL-2R, soluble interleukin-2 receptors.

and sIL-2R in patients aged ≥65 years may be used for prediction of severe/critical condition. Also, ferritin-hemoglobin ratio, IL-6, and sIL-2R in patients aged ≥65 years may be used for prediction of mortality according to unadjusted odds ratio. However, all tested biomarkers failed to show enough predictive abilities according to adjusted odds ratio.

DISCUSSION

Our study showed acceptable discriminative capabilities of ferritin, ferritin-hemoglobin ratio, sIL-2R for severe/critical condition. IL-6 failed to show sufficient discriminative capabilities for severe/critical condition. However, all these parameters had insufficient discriminative capabilities for lethal outcome. Among all participants, ferritin and ferritin-hemoglobin ratio showed sufficient predictive capabilities for severe/critical condition; the optimal cut-off criteria were 402.0 ng/mL and 34.0, respectively. Despite the fact that multiple studies have evaluated the discriminative and predictive capabilities of these biomarkers, impact of age on discriminative and predictive capabilities of COVID-19 severity and mortality has not been assessed.

There are controversial results of multiple studies regarding the discriminative and predictive capabilities of ferritin, IL-6, and sIL-2R for severe condition and mortality. Cao P. et al (2020) showed a high discriminative capability of ferritin for the severity of COVID-19 (AUC, 0.873) with an optimal cut-off value of 272.5 ng/mL (34). Also, the study performed by Deng F. et al (2021) showed a high discriminative capability for in-hospital mortality in COVID-19 patients treated in ICU (AUC, 0.822) (35). However, some studies showed far lower discriminative capability of ferritin for hospital mortality. Shakaroun D. A. et al. (2023) reported that ferritin for predicting hospital mortality had an AUC of 0.65 with a sensitivity of 65% and specificity of 58% at the optimal cut-off value (36). According to the FerVid study, the AUC of ferritin levels for adverse outcome prediction was 0.617 (21) which corresponds to our results. Some studies showed great variation in the discriminative capability of IL-6 for adverse outcomes. The study performed by Aykal G. et al (2021) showed a high AUC for IL-6 (0.864) (37). Jamoussi A. et al (2023) reported an AUC of 0.805 for ferritin level for mortality in COVID-19 patients managed in ICU (38). According to the study of Arnold D. T. et al (2021) IL-6 had an AUC of 0.77 (0.65–0.88) for the prediction of poor prognosis (39). However, Jang H. J. et al (2021) reported an AUC of 0.687 for the IL-6 level for in-hospital mortality in patients with respiratory failure, an optimal cut-off value of 191 pg/mL with a sensitivity of 50.0% and a specificity of 87.2% (29) that is similar to the results of our study. This study showed that an AUC for the predictive capability of sIL-2R for mortality was 0.718 (29). Such controversy may be explained by the fact that there were differences in studied populations and variability in the severity of COVID-19 at biomarker measurement.

Despite the evidence that levels of ferritin (28), IL-6 (40), and sIL-2R (32) increase with age, comparison of predictive abilities depending on the patients' age was not found. Our study showed the absence of discriminative capabilities of ferritin, ferritin-hemoglobin ratio, IL-6, and sIL-2R for severe/critical condition and lethal outcome in patients aged <65 years. Ferritin-hemoglobin ratio, IL-6, and sIL-2R had acceptable discriminative capabilities for severe/critical condition and lethal outcome in patients aged ≥65 years. Also, ferritin showed acceptable discriminative capabilities for severe/critical condition in patients aged ≥65 years. However, according to adjusted odds ratio, all studied biomarkers didn't show enough predictive abilities.

Further perspectives include the establishment of the influence of different age categories on discriminative and predictive capabilities of laboratory parameters on COVID-19 severity and mortality. Also, a study of other factors (gender, body mass index, comorbidities, etc.) on discriminative and predictive capabilities of laboratory parameters is a perspective.

CONCLUSIONS

Ferritin, ferritin-hemoglobin ratio, IL-6, and sIL-2R didn't show acceptable predictive value for severe condition and lethal outcome in patients aged <65 years. However, ferritin-hemoglobin ratio, IL-6, and sIL-2R have high predictive value for lethal outcome in patients aged ≥65 years. So, age may affect the predictive capabilities of these biomarkers.

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