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Prognostic performance of ferritin in combination with CT-SS and NEWS, to predict ICU admission and mortality in COVID-19

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Abstract
Introduction: The coronavirus disease 2019 (COVID-19), caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), has created significant challenges in predicting severe disease outcomes. This study evaluates the combined prognostic performance of serum ferritin, national early warning score (NEWS), and computed tomography severity score (CT-SS) in predicting intensive care unit (ICU) admission and 30-day mortality.
Methodology: This retrospective study included 693 COVID-19 patients with confirmed RT-PCR results and complete medical records. Demographic, clinical, and laboratory data, including ferritin levels, NEWS, and CT-SS, were analyzed. Statistical analyses were conducted to evaluate their individual and combined predictive capabilities.
Results: Elevated ferritin levels, higher NEWS, and greater CT-SS were significantly associated with increased ICU admission and mortality risks. Receiver operating characteristic (ROC) analysis revealed excellent predictive accuracy for mortality: ferritin (area under the receiver operating characteristic curve [AUROC]: 0.916), NEWS (AUROC: 0.927), and CT-SS (AUROC: 0.881). Integrating ferritin into NEWS and CT-SS models enhanced predictive precision, with combined scoring systems yielding the highest odds ratios for adverse outcomes. Patients with a NEWS ≥ 5 and ferritin level ≥ 275.8 had a 151-fold increased risk of mortality, while those with a CT-SS ≥ 9 and ferritin level ≥ 275.8 had a 72-fold increased risk.
Conclusions: Combining ferritin with NEWS and CT-SS improves the prognostic accuracy for predicting severe outcomes in COVID-19 patients. This study emphasizes the value of integrating laboratory markers with established scoring systems to optimize clinical decision-making. The findings can guide early interventions, reduce mortality, and improve resource utilization during pandemics.

Key words: COVID-19; ferritin; prognosis; mortality; tomography; severity.

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Introduction

The novel coronavirus disease (coronavirus disease 2019, COVID-19), resulting from the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) virus, was initially detected in China in December 2019 [1]. Although the majority of individuals experience mild to moderate symptoms, a significant portion progresses to a more severe form of COVID-19, necessitating intensive care unit (ICU) admission due to acute respiratory failure [2,3]. Many prognostic models have been proposed for better clinical management to analyze clinical follow-up and predict mortality to optimize treatment approaches.

Early warning scores (EWS) are among the best-known risk stratification tools and are generally used in acute care settings for the rapid assessment of patients. The national early warning score (NEWS) is the most widely used EWS and has been demonstrated to be effective in predicting both ICU admission and mortality in COVID-19 [4,5]. NEWS comprises 7 physiological parameters, including respiratory rate, oxygen saturation, requirement for supplemental oxygen, body temperature, systolic blood pressure, heart rate, and consciousness level [6]. A high NEWS score is proposed to be associated with increased ICU admission and mortality. Another important parameter for predicting mortality due to COVID-19 is the computed tomography severity score (CT-SS), which evaluates the extent of lung involvement using a semi-quantitative method [7,8].

During the pandemic, numerous studies evaluated the prognostic performance of distinct risk-stratifying scoring systems, either alone or combined. Although some of these scoring systems were classified as good or excellent in the early stages of the pandemic, they later failed to maintain sufficient discriminatory performance. Therefore, over time, the need for a novel combined predictive scoring system emerged. This study aimed to evaluate the performance of combined parameters such as ferritin, NEWS, and CT-SS in predicting 30-day mortality and the need for ICU admission in COVID-19 patients. Additionally, the effectiveness of these parameters as independent prognostic markers was investigated. The findings of this study aim to provide valuable insights into the use of these parameters in routine clinical practice.

Methodology

Study design and patient eligibility

This study has been approved by the Institutional Ethics Committee of Çanakkale Onsekiz Mart University (COMU) (Approval No: 2011-KAEK-27/2020-E.2000070224, dated 01/07/2020). Informed consent was waived due to the retrospective nature of the study.

Patients were included if they were 18 years of age or older, had laboratory-confirmed SARS-CoV-2 infection in a respiratory specimen verified by real-time reverse transcription polymerase chain reaction (RT-PCR), and had a baseline computed tomography (CT) scan performed within the first 24–48 hours of hospital admission. Complete baseline clinical data, including vital signs and laboratory results required to calculate early warning scores and other study predictors, as well as complete outcome data for the defined follow-up period, were also required for inclusion. Criteria for exclusion were: (1) being pregnant; (2) had a prior history of lung surgery such as pneumonectomy or lobectomy; (3) had active malignant disease or multiorgan failure at admission, as these conditions could substantially influence prognosis independent of COVID-19; (4) transfer from another hospital without accessible baseline CT or clinical data, or absence of a diagnostic-quality chest CT; (5) missing essential baseline variables despite reasonable attempts at retrieval.

Clinical data assessment

Two authors (Bardakcı O, Akdur G) independently analyzed the electronic and physical records of the study participants. Demographic parameters, clinical and biochemical values, and patient outcomes were noted. Discharge status (home, ICU admission, and mortality) was also extracted. Clinical assessments and initial laboratory evaluations were performed within the first hours of ICU admission. The patients were monitored continuously from admission through either hospital discharge or death.

Thin section CT imaging and scoring

Patients who underwent radiologic imaging using a CT scanner (Asteion TSX-021B; Toshiba Corporation, Tokyo Japan) in COMU hospital radiology clinic and met the inclusion criteria were enrolled for the present study. To assess the severity of the disease, a semi-quantitative scoring system was applied to evaluate pulmonary involvement according to the extent of abnormalities [9]. The CT severity score (CT-SS) was determined by assessing each of the five lung lobes on a scale from 0 to 5, where 0 represented no involvement, 1 indicated less than 5% involvement, 2 corresponded to 5–25% involvement, 3 to 26–49% involvement, 4 to 50–75% involvement, and 5 to more than 75% involvement. The overall CT-SS was calculated by summing the scores of all 5 lobes, yielding a total score ranging from 0 (no lung involvement) to 25 (maximum lung involvement).

Defining screening tools and outcome measures

Clinical acuity was assessed using NEWS, which ranged from 0 to 20, with higher scores indicating increased severity. It included seven physiological variables: respiratory rate, oxygen saturation, supplemental oxygen, temperature, systolic blood pressure, heart rate, and level of consciousness [10].

Statistical analysis

Continuous variables were reported as medians along with interquartile ranges (IQRs), whereas categorical variables were summarized using frequencies and percentages. Group comparisons for continuous variables were conducted using the Mann-Whitney U test, given that the data did not follow a normal distribution, as confirmed by the Shapiro-Wilk test. Univariate and multivariate logistic regression analyses were performed to identify predictors of ICU admission and 30-day mortality. Odds ratios (ORs) with 95% confidence intervals (CIs) were calculated to evaluate the strength of associations. Moreover, covariate adjusted receiver operating characteristic (ROC) curve analysis using multivariable logistic regression was performed to identify diagnostic accuracy measures and calculate the areas under the ROC curve (AUROC). Additionally, associations between illness severity scores (NEWS and CT-SS) and clinical endpoints (ICU admission and mortality) were analyzed. The sensitivity, specificity, and predictive values of these parameters were assessed using ROC analysis to further validate their clinical utility. All statistical analyses were performed using SPSS 20.0 for Windows (IBM Corp., Armonk, NY, USA) and a *p* value < 0.05 was considered as statistical significance.

Results

This study included 693 patients [322 males (46.5%) and 371 females (53.5%)]. Median age of the study participants was 51 years (IQR 37.0–63.0 years), ranging from 18.0 to 91.0 years. The most frequently observed comorbidities were hypertension (23.5%, n = 163), diabetes mellitus (15.2%, n = 105), cardiovascular disease (7.1%, n = 49), and respiratory disease (7.8%, n = 54) (Table 1).

A comparison of baseline demographic and laboratory characteristics between the primary and secondary outcome groups revealed that advanced age was a significant predictor of mortality (72.0 years in the deceased group [IQR 63.0–78.0] compared to 49.0 years in the surviving group [IQR 36.0–61.0], $p < 0.001$). Ferritin levels were also elevated in both the ICU admission group (708.0 vs. 121.9, $p < 0.001$) and the deceased group (850.8 vs. 122.1, $p < 0.001$). NEWS and CT-SS were found to be elevated in the deceased group compared to the survivor group (Table 2).

Univariate and multivariate analyses revealed that male gender ($p = 0.001$), respiratory rate, ferritin, D-dimer, NEWS, and CT-SS were significant predictors of both ICU admission and mortality (Table 3). A 1-point increase in CT-SS and NEWS scores in COVID-19 patients was associated with a 32.2% and 49.8% increased ICU admission rate and a 30.6% and 51.9% increased mortality rate, respectively. The predictive value of ferritin, D-dimer, and other study variables for

Table 1. Comparison of baseline characteristics of COVID-19 patients.

Characteristics	COVID-19 patients (n = 693)
Age, median (25%–75%)	51.0 (37.0–63.0)
Gender	
Female, n (%)	371 (53.5)
Male, n (%)	322 (46.5)
Chronic disease, n (%)	
Hypertension	163 (23.5)
Diabetes mellitus	105 (15.2)
Cardiovascular disease	49 (7.1)
Respiratory disease	54 (7.8)
Vital parameters	
SBP (mmHg)	127.0 (119.0–137.0)
DBP (mmHg)	78.0 (71.0–86.0)
Heart rate (/minute)	85.0 (78.0–96.0)
Respiratory rate (/minute)	18.0 (16.0–20.0)
SpO_2 (%)	98.0 (96.0–99.0)
Laboratory parameters	
WBC (x 10^3/µL)	5.87 (4.80–7.50)
Hgb (g/dL)	13.7 (12.6–14.8)
PLT (x 10^3/µL)	200.0 (165.0–240.0)
ALT (U/L)	21.1 (14.9–32.9)
AST (U/L)	23.5 (18.1–33.4)
Amylase (U/L)	60.0 (46.0–78.0)
Lipase (U/L)	34.1 (25.8–44.9)
Ferritin (ng/mL)	133.4 (60.4–279.9)
D-dimer (µg/mL FEU)	310.0 (200.0–540.0)
Illness severity assessment tools	
NEWS	1.0 (0.0–4.0)
CT-SS	3.0 (0.0–9.0)
Disposition, n(%)	
Discharge	491 (70.9)
Regular ward	151 (21.8)
ICU	51 (7.4)
30-day-mortality, n(%)	50 (7.2)

COVID-19: coronavirus disease 2019; SBP: systolic blood pressure; DBP: diastolic blood pressure; SpO_2: oxygen saturation; WBC: white blood cell; Hgb: hemoglobin; Plt: platelet; ALT: alanine aminotransferase; AST: aspartate aminotransferase; NEWS: national early warning score; CT-SS: computed tomography severity score; ICU: intensive care unit.

Table 2. Comparison of baseline characteristics of COVID-19 patients according to both admission and survival status.

Characteristics	Ward admission and discharge (n = 642)	ICU admission (n = 51)	*p* value	Patients alive (n = 643)	Patients deceased (n = 50)	*p* value
	Median (IQR)/n (%)	Median (IQR)/n (%)		Median (IQR)/n (%)	Median (IQR)/n (%)	
Age (years)	50.0 (36.0–61.0)	67.0 (61.0–77.0)	< 0.001	49.0 (36.0–61.0)	72.0 (63.0–78.0)	< 0.001
Male	286 (44.5)	36 (70.6)	< 0.001	286 (44.5)	36 (72.0)	< 0.001
Vital signs at triage						
Saturation (%)	98.0 (96.0–99.0)	89.0 (83.5–94.5)	< 0.001	98.0 (96.0–99.0)	89.0 (82.0–95.0)	< 0.001
Heart rate (beat/min)	84.0 (77.0–95.0)	96.0 (85.0–102.5)	< 0.001	84.0 (77.0–95.0)	89.5 (85.0–101.0)	< 0.001
Respiratory rate (min)	18.0 (16.0–20.0)	22.0 (18.0–25.5)	< 0.001	18.0 (16.0–20.0)	24.0 (20.0–27.0)	< 0.001
SBP (mmHg)	127.0 (119.0–137.0)	132.0 (118.5–142.0)	0.245	127.0 (119.0–137.0)	132.0 (116.0–142.0)	0.231
DBP (mmHg)	78.0 (71.0–85.0)	77.0 (68.0–89.5)	0.559	78.0 (71.0–85.0)	77.5 (68.0–88.0)	0.259
Laboratory parameters						
WBC (x 10^3/µL)	5.8 (4.7–7.3)	9.2 (6.6–12.3)	< 0.001	5.8 (4.7–7.3)	9.0 (6.0–11.5)	< 0.001
Hgb (g/dL)	13.7 (12.7–14.9)	12.5 (11.4–13.8)	< 0.001	13.7 (12.7–14.9)	12.5 (11.3–13.8)	< 0.001
Plt (x 10^3/µL)	200.0 (166.0–239.0)	216.0 (153.0–248.5)	0.889	200.0 (166.0–239.0)	193.5 (145.0–242.0)	0.205
ALT (U/L)	20.9 (14.7–32.6)	23.4 (18.6–44.8)	0.013	21.0 (14.9–32.6)	23.0 (17.6–45.7)	0.119
AST (U/L)	23.1 (17.9–31.6)	42.0 (28.7–61.1)	< 0.001	23.1 (17.9–31.7)	39.4 (26.8–64.4)	< 0.001
Amylase (U/L)	60.0 (46.5–78.0)	63.5 (46.0–83.0)	0.574	60.0 (47.0–78.9)	59.5 (43.0–75.5)	0.750
Lipase (U/L)	33.8 (25.9–44.1)	36.8 (23.5–59.8)	0.493	33.8 (25.9–44.1)	41.3 (23.8–55.4)	0.303
Ferritin (ng/mL)	121.9 (55.1–238.0)	708.0 (421.05–1197.65)	< 0.001	122.1 (55.2–237.3)	850.8 (449.3–1231.4)	< 0.001
D-dimer (µg/mL FEU)	300.0 (180.0–500.0)	780.0 (474.0–1875.0)	< 0.001	300.0 (180.0–505.0)	835.1 (460.0–1950.0)	< 0.001
Illness severity assessment tools						
NEWS	1.0 (0.0–3.0)	9.0 (6.0–11.5)	< 0.001	1.0 (0.0–3.0)	9.0 (6.0–12.0)	< 0.001
CT-SS	2.0 (0.0–8.0)	14.0 (10.0–19.5)	< 0.001	2.0 (0.0-8.0)	14.0 (10.0–19.0)	< 0.001

Data is represented by median IQR (inter quartile range) or n (%); WBC, white blood cell; Hgb: hemoglobin; SBP: systolic blood pressure; DBP: diastolic blood pressure; ICU: intensive care unit; NEWS: national early warning score; CT-SS: computed tomography severity score.

Table 3. Univariate and multivariate logistic regression analysis for the prediction of ICU admission and 30 days' mortality in COVID-19 patients.

	ICU Admission (n = 51)				30 days mortality (n = 50)			
	Univariate analysis		Multivariate analysis		Univariate analysis		Multivariate analysis	
	OR (95% CI)	***p***	**OR (95% CI)**	***p***	**OR (95% CI)**	***p***	**OR (95% CI)**	***p***
Age (years)	1.037 (1.018–1.057)	< 0.001			1.051 (1.030–1.072)	< 0.001		
Gender (ref: female)	2.987 (1.604–5.565)	0.001	2.485 (1.028–6.007)	0.043	3.210 (1.698–6.067)	< 0.001	3.942 (1.243–12.499)	0.020
Chronic disease	3.834 (2.145–6.851)	< 0.001			6.316 (3.459–11.535)	< 0.001	4.981 (1.622–15.296)	0.005
Vital signs at triage								
Saturation (%)	0.850 (0.814–0.888)	< 0.001			0.857 (0.821–0.894)	< 0.001		
Heart rate (beat/min)	1.033 (1.017–1.049)	< 0.001			1.028 (1.012–1.044)	0.001		
Respiratory rate (min)	1.463 (1.330–1.610)	< 0.001	1.230 (1.105–1.368)	0.009	1.626 (1.450–1.825)	< 0.001	1.221 (1.027–1.450)	0.023
Laboratory parameters								
WBC (x 10^3/μL)	1.372 (1.252–1.504)	< 0.001			1.285 (1.183–1.395)	< 0.001		
Hgb (g/dL)	0.717 (0.614–0.837)	< 0.001			0.693 (0.592–0.810)	< 0.001	0.685 (0.511–0.917)	0.011
Ferritin (ng/mL)	1.003 (1.002–1.004)	< 0.001	1.002 (1.001–1.003)	< 0.001	1.003 (1.003–1.004)	< 0.001	1.002 (1.001–1.003)	< 0.001
D-dimer (μg/mL FEU)	1.001 (1.001–1.001)	< 0.001	1.000 (1.000–1.001)	0.003	1.001 (1.001–1.001)	< 0.001	1.000 (1.000–1.001)	< 0.001
Illness severity assessment tools								
NEWS	1.498 (1.381–1.626)	< 0.001	1.384 (1.004–1.526)	< 0.001	1.519 (1.396–1.653)	< 0.001	1.414 (1.271–1.572)	< 0.001
CT-SS	1.322 (1.245–1.403)	< 0.001	1.202 (1.124–1.286)	< 0.001	1.306 (1.232–1.384)	< 0.001	1.172 (1.095–1.254)	< 0.001

ICU, intensive care unit; OR, odds ratio; CI, confidence interval; ref, reference; WBC, white blood cell; Hgb, hemoglobin; FEU, fibrinogen equivalent units; NEWS, national early warning score; CT-SS, computed tomography severity score.

Table 4. Predictive value of ferritin, D-dimer and other study variables for ICU admission and 30 days mortality prediction according to ROC analysis in COVID-19 patients.

	Cut-Off	AUROC (95% CI)	Sensitivity (%) (95% CI)	Specificity (%) (95% CI)	NPV (%) (95% CI)	PPV (%) (95% CI)	Accuracy (%) (95% CI)
ICU admission							
Ferritin	≥ 244.5	0.904 (0.855–0.934)	90.2 (78.6–96.7)	76.1 (72.5–79.3)	98.9 (97.7–99.6)	23.0 (20.2–26.1)	77.1 (73.7–80.1)
D-Dimer	≥ 535.0	0.799 (0.731–0.867)	72.6 (58.3–84.1)	78.1 (74.6–81.2)	97.3 (95.8–98.3)	20.8 (17.4–24.7)	77.6 (74.3–80.7)
NEWS	≥ 5	0.925 (0.898–0.952)	80.4 (66.9–90.2)	85.8 (82.9–88.4)	98.2 (96.9–99.0)	31.1 (23.3–36.3)	85.4 (82.6–88.0)
CT-SS	≥ 7	0.895 (0.855–0.934)	90.2 (78.6–96.7)	69.5 (65.8–73.1)	98.9 (97.5–99.5)	20.0 (16.8–21.5)	71.0 (67.5–74.4)
30 days mortality							
Ferritin	≥ 275.8	0.916 (0.879–0.953)	92.0 (80.1–97.8)	79.6 (76.3–82.7)	99.2 (98.1–99.7)	26.0 (22.8–29.5)	80.5 (77.4–83.4)
D-Dimer	≥ 435	0.803 (0.737–0.868)	73.6 (59.7–84.7)	67.8 (64.1–71.4)	96.9 (95.2–98.0)	15.9 (13.5–18.7)	68.3 (64.6–71.7)
NEWS	≥ 5	0.927 (0.899–0.954)	80.0 (66.3–89.9)	85.7 (82.7–88.3)	98.2 (96.9–98.9)	30.3 (25.6–35.5)	85.3 (82.4–87.8)
CT-SS	≥ 8.5	0.881 (0.832–0.930)	82.0 (68.6–91.4)	78.4 (75.0–81.5)	98.3 (96.9–99.0)	22.8 (19.5–26.4)	78.6 (75.4–91.6)

ICU: intensive care unit; NEWS: national early warning score; CT-SS: computed tomography severity score; AUROC: area under curve receiver operating characteristics; CI: Confidence interval; PPV: positive predictive value; NPV: negative predictive value.

Table 5. Analysis of ICU admission and 30 days mortality in COVID-19 patients based on ferritin in association with NEWS and CT-SS.

	ICU admission				
	n ICU admission / n Total	**OR (95% CI) Crude model**	***p***	**OR (95% CI) Adjusted model [a]**	***p***
NEWS │ Ferritin					
NEWS 0–4 │ Ferritin < 244.5	1 / 440	Reference	-		-
NEWS 0–4 │ Ferritin ≥ 244.5	9 / 121	35.277 (4.423–281.350)	0.001	48.655 (3.595–658.475)	0.003
NEWS ≥ 5 │ Ferritin < 244.5	4 / 52	36.586 (4.007–333.974)	0.001	56.036 (3.802–825.982)	0.003
NEWS ≥ 5 │ Ferritin ≥ 244.5	37 / 80	377.744 (50.572–2821.517)	< 0.001	460.786 (37.836–5611.729)	< 0.001
CT-SS │ Ferritin					
CT-SS 0–6 │ Ferritin < 244.5	2 / 392	Reference	–		–
CT-SS 0–6 │ Ferritin ≥ 244.5	5 / 60	17.727 (3.357–93.602)	0.001	22.435 (3.150–159.806)	0.002
CT-SS ≥7 │ Ferritin < 244.5	5 / 103	9.949 (1.902–52.049)	0.007	13.834 (1.994–95.963)	0.008
CT-SS ≥7 │ Ferritin ≥ 244.5	39 / 138	76.818 (18.237–323.583)	< 0.001	89.205 (15.448–515.105)	< 0.001
	30 days mortality				
	n 30 days mortality / n Total	**OR (95% CI) Crude model**	***p***	**OR (95% CI) Adjusted model [a]**	***p***
NEWS │ Ferritin					
NEWS 0-4 │ Ferritin < 275.8	3 / 458	Reference	-		-
NEWS 0-4 │ Ferritin ≥ 275.8	7 / 103	11.059 (2.809–43.534)	0.001	11.815 (2.589–53.928)	0.001
NEWS ≥5 │ Ferritin < 275.8	5 / 62	13.304 (3.097–57.150)	0.001	15.437 (3.196–74.574)	0.001
NEWS ≥5 │ Ferritin ≥ 275.8	35 / 70	151.667 (44.412–517.946)	< 0.001	139.454 (35.504–547.751)	< 0.001
CT-SS │ Ferritin					
CT-SS 0-8 │ Ferritin < 275.8	3 / 447	Reference	-		-
CT-SS 0-8 │ Ferritin ≥ 275.8	9 / 69	22.200 (5.847–84.289)	< 0.001	25.780 (5.484–121.183)	< 0.001
CT-SS ≥9 │ Ferritin < 275.8	4 / 74	8.457 (1.853–38.591)	0.006	10.649 (1.946–58.276)	0.006
CT-SS ≥9 │ Ferritin ≥ 275.8	34 / 103	72.928 (21.804–243.924)	< 0.001	72.743 (17.311–305.683)	< 0.001

ICU, intensive care unit; OR, odds ratio; CI, confidence interval; NEWS, national early warning score; CT-SS, computed tomography severity score; [a] The adjusted model included age and gender.

ICU admission and 30-day mortality was also explored according to ROC analysis in COVID-19 patients. For predicting mortality, ferritin (cut-off value: ≥ 275.8; AUROC: 0.904, 95% CI: 0.855–0.934), NEWS (cut-off value: ≥ 5 AUROC: 0.927, 95% CI: 0.899–0.954), and CT-SS (cut-off value: ≥ 8.5, AUROC: 0.881, 95% CI: 0.832–0.930) demonstrated excellent predictive performances (Table 4). Similar analyses were also performed for ICU admission and are presented in Table 4.

Table 5 presents ICU admission and mortality rates among COVID-19 patients based on NEWS and CT-SS levels. Mortality predictions showed notable variation within NEWS and CT-SS subgroups depending on ferritin levels. Additionally, stratifying patients by ferritin levels significantly enhanced the accuracy of predicting ICU admission and mortality across the NEWS and CT-SS subgroups. Patients with a NEWS ≥ 5 and a ferritin level ≥ 275.8 had the highest odds ratio of 151.667 (44.412–517.946) in the crude model and 139.454 (35.504–547.751) in the adjusted model. Patients with a CT-SS ≥ 9 and a ferritin level ≥ 275.8 had an odds ratio of 72.928 (21.804–243.924) in the crude model and 72.743 (17.311–305.683) in the adjusted model for mortality prediction. Similar improvements in the prediction of ICU admission were also observed and are presented in Table 5.

In Table 6, the influence of ferritin, NEWS, and CT-SS on the discriminative accuracy of various models predicting ICU admission and mortality was evaluated. Initially, a base model incorporating high-risk factors such as older age, male gender, presence of comorbidities, low oxygen saturation, and elevated respiratory rate was developed. Pairwise analysis revealed that integrating ferritin levels into the base model significantly improved its accuracy in predicting ICU admission (difference between areas [DBA] = −0.040, $p = 0.001$) and 30-day mortality (DBA = − 0.041, $p = 0.041$). Similarly, incorporating NEWS into the base model significantly enhanced its accuracy for predicting ICU admission (DBA = −0.020, $p = 0.049$) and 30-day mortality (DBA = − 0.022, $p = 0.003$).

Discussion

In this study, the predictive capabilities of ferritin combined with two prognostic scoring systems for 30-day mortality were evaluated and independent mortality predictors were analyzed in a large cohort of COVID-19 patients. As a result, ferritin, NEWS, and CT-SS were significantly associated with both ICU admission and 30-day mortality. Moreover, predictive models incorporating ferritin into both NEWS and CT-SS were more precise than those that did not include serum ferritin levels.

The findings of this study highlight the significance of incorporating validated laboratory markers, such as ferritin, into commonly utilized risk stratification scores to improve the estimation of progression to severe or critical conditions in COVID-19 patients. As COVID-19 spread rapidly, healthcare providers faced challenges in implementing clinical strategies designed to improve outcomes and minimize resource usage. In this context, numerous studies have explored the single or combined effects of multiple risk stratification scores, including ferritin, D-dimer, neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR), procalcitonin, NEWS, and CT-SS [11–17]. Unfortunately, the prognostic performance of these risk

Table 6. Discrimination accuracy of different models on the prediction of ICU admission and 30-days mortality in COVID-19 patients.

	ICU admission						
	Area under the ROC curve (95% CI)	**Area under the ROC curve (95% CI)**	**Pairwise analysis (95% CI)**				
Prognostic model	**Without ferritin**	**With ferritin**	**DBA**	**SE**	**Lower Upper**	**Z statistic**	***p* value**
Base model = age, gender, chronic disease, SO_2, RR	0.902 (0.855–0.949)	0.942 (0.906–0.977)	– 0.040	0.204	(–0.065) – (–0.016)	– 3.254	0.001
NEWS	0.925 (0.898–0.952)	0.953 (0.932–0.973)	– 0.028	0.156	(–0.045) – (–0.011)	– 3.302	0.001
CT-SS	0.895 (0.855–0.934)	0.939 (0.917–0.961)	– 0.045	0.176	(–0.072) – (–0.017)	– 3.216	0.001
Base model with NEWS	0.932 (0.906–0.958)	0.952 (0.928–0.975)	– 0.020	0.159	(–0.040) – (–0.019)	– 1.966	0.049
Base model with CT-SS	0.944 (0.920–0.968)	0.958 (0.938–0.978)	– 0.014	0.129	(–0.033) – (0.004)	– 1.518	0.129
	30 days mortality						
	Area under the ROC curve (95% CI)	**Area under the ROC curve (95% CI)**	**Pairwise analysis (95% CI)**				
Prognostic model	**Without ferritin**	**With ferritin**	**DBA**	**SE**	**Lower Upper**	**Z statistic**	***p* value**
Base model = age, gender, chronic disease, SO_2, RR	0.923 (0.878–0.969)	0.964 (0.941–0.988)	– 0.041	0.188	(–0.081) – (–0.002)	– 2.043	0.041
NEWS	0.927 (0.899–0.954)	0.956 (0.935–0.976)	– 0.029	0.159	(–0.046) – (–0.012)	– 3.281	0.001
CT-SS	0.881 (0.832–0.930)	0.944 (0.918–0.970)	– 0.055	0.197	(–0.087) – (–0.023)	– 3.411	0.001
Base model with NEWS	0.944 (0.918–0.970)	0.966 (0.944–0.987)	– 0.022	0.156	(–0.041) – (–0.002)	– 2.136	0.003
Base model with CT-SS	0.956 (0.935–0.977)	0.968 (0.949–0.988)	– 0.012	0.144	(–0.028) – (0.004)	– 1.476	0.140

ICU: intensive care unit; CI: confidence interval; ROC: receiver operating characteristics; DBA: difference between areas; SE: standard error; ACE: angiotensin converting enzyme; NEWS: national early warning score; CT-SS, computed tomography severity score; RR, respiratory rate; SO_2, saturation oxygen %.

stratification systems varied in their capacity to distinguish between survivors and non-survivors, ultimately being rated as fair or poor, contrary to their initial classification as excellent or good [18]. For this reason, it is not surprising to see novel studies exploring the potential use of these prognostic systems to better distinguish patients likely to require ICU admission or succumb to the disease. In addition to single-center studies, large multicenter investigations provide more robust and generalizable estimates of prognostic performance in COVID-19. For example, Amer *et al*. [19] and Hammad *et al*. [20] conducted multicenter international studies assessing hospitalized patients during the delta variant pandemic and the diagnostic yield of RT-PCR, respectively. Similarly, large-scale multicenter prognostic models such as the ISARIC 4C Mortality Score, the 4C Deterioration model, COVID-GRAM, and the CO-RADS CT assessment scheme have demonstrated the feasibility of reliable risk stratification across diverse healthcare settings [21].

Ferritin is one of the most important laboratory parameters shown to play a role in predicting mortality in patients with COVID-19. This study found that ferritin, both in univariate and multivariate analysis, predicted ICU admission in COVID-19 patients. Furthermore, this study demonstrated that elevated ferritin at admission was linked to increased in-hospital mortality, even with standard treatment for COVID-19-associated pneumonia. These results align with the findings of Rajpoot *et al*. [3] and Raman *et al*. [22], who identified elevated serum ferritin as an independent predictor of mortality. In a recent study, Madian *et al.* [23] offered a simplified model for predicting mortality in COVID-19. The authors created a new predictive model called APRI-plus, which incorporated four key predictors: age, aspartate transferase, platelets, and serum ferritin. The model demonstrated excellent performance for predicting mortality, achieving an AUROC of 0.90. Unfortunately, in this study, the other three parameters (aside from ferritin) lacked predictive capability. For this reason, the aim was to identify whether parameters used alongside ferritin, including NEWS and CT-SS, could more effectively predict mortality.

After the novel coronavirus disease 2019 became a major worldwide health problem, countless attempts were made to develop a prognostic scoring system to predict poor outcomes for COVID-19 patients [24–26]. In this context, NEWS has been found to be significantly higher in deceased patients with COVID-19. NEWS was introduced by the Royal College of Physicians a decade ago, and reportedly outperforms other EWSs in identifying patients at risk of ICU admission and mortality. Akdur *et al.* [5] published one of the most comprehensive studies on this subject in 2021, demonstrating that higher age, NEWS, and CT-SS were significantly associated with time-to-death within 90 days in an adjusted Cox regression model. Unfortunately, the authors did not add a commonly used laboratory tool, such as ferritin, to their prognostic models. In another study by Bardakci *et al*. [4], NEWS was also assessed as a prognostic marker in COVID-19 patients. The authors observed that COVID-19 patients with a NEWS ≥ 7 had an elevated risk of ICU admission, intubation, and mortality in both crude and adjusted models. Furthermore, incorporating the lung ultrasound score into NEWS significantly enhanced its predictive accuracy in identifying high-risk patients. In our study, patients with a NEWS ≥ 5 and ferritin level ≥ 275.8 had a 151.667 times (95% CI: 44.512–517.946) higher risk of mortality compared to patients with a NEWS < 5 and ferritin level < 275.8. This study, to our knowledge, is the first to evaluate the effectiveness of combining ferritin with CT-SS and NEWS in predicting mortality among COVID-19 patients. The choice of a NEWS cut-off value of 5 was based on ROC curve analysis, which identified this threshold as providing the optimal balance between sensitivity and specificity according to the highest Youden Index. This lower cut-off, compared with values such as ≥ 7 reported in previous literature, may allow earlier identification of high-risk individuals and facilitate timely clinical intervention.

This study not only assessed ferritin and NEWS for mortality prediction, but also explored the role of CT as a prognostic method in patients with COVID-19. Being a semi-quantitative scoring method, CT-SS was previously employed by Zhou *et al*. [27] and Abbasi *et al*. [28], and utilized to quantify the extent of CT findings in COVID-19 patients. Integrating CT-SS into a prognostic model targeting high-risk patients significantly improved the identification of individuals at elevated risk for ICU admission and mortality. In this study, the patients with a CT-SS ≥ 9 and ferritin level ≥ 275.8 had a 72.928 times (95% CI: 21.804–243.924) higher risk of mortality compared to patients with a CT-SS < 9 and ferritin level < 275.8. Similar associations between negative outcomes and elevated CT-SS have been consistently reported in recent studies [4,29].

Ferritin and NEWS hold significant value and can have a widespread impact when routinely incorporated as part of screening tools in hospital settings. Unlike thorax CT, which is not advised for regular screening due to infection risks and resource limitations during the COVID-19 pandemic, ferritin and NEWS could provide a practical and efficient alternative. Consequently, integrating ferritin into standard diagnostic and management protocols for future pandemics could offer several benefits, including ease of implementation, cost-effectiveness, and repeatability.

While this study examined the combined predictive value of various laboratory parameters alongside two established risk prediction tools, it is not without limitations. First, the present study was a retrospective single-center study, which may have introduced selection bias and incomplete data. Second, our hospital was the only tertiary-care facility treating COVID-19 patients in the region; for that reason, the findings may not be entirely applicable to all patients within the region. Additionally, due to the retrospective nature of our study and incomplete medical records, data on vaccination status, baseline oxygen support, and treatments such as corticosteroids or antivirals were unavailable for all patients, which may have influenced outcomes. The single-center retrospective design may limit generalizability, and treatment protocols might have varied over the study period. Furthermore, the absence of external validation means that the predictive performance of our models should be confirmed in other cohorts.

Conclusions

Advanced age, increased ferritin levels, elevated NEWS and CT-SS scores, and the presence of multiple comorbidities emerged as important risk factors for negative outcomes in patients with COVID-19. Integrating these parameters could enhance the ability to predict the progression of COVID-19 patients to severe illness or death. This approach enables physicians to make prompt diagnoses and implement timely interventions, potentially resulting in better outcomes and lower mortality. Their role must, therefore, be considered in clinical practice.

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Conflict of interest

No conflict of interest is declared.

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