Received: 12 May 2021 | Accepted: 21 July 2021

DOI: 10.1111/ijcp.14642

ORIGINAL PAPER

Infectious Diseases

THE INTERNATIONAL JOURNAL OF CLINICAL PRACTICE WILEY

Application of CALL score for prediction of progression risk in patients with COVID-19 at university hospital in Turkey

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Abstract

Background: The CALL score was developed as a predictive model for progressive disease. We aimed to validate and/or improve the performance of CALL score in our hospital settings.

Methods: Adult patients with polymerase chain reaction-confirmed COVID-19 were included in this retrospective observational study. Clinical and laboratory characteristics (including complete blood count, CRP, ferritin, LDH, fibrinogen, d-dimer) were obtained. ROC analysis was used for the evaluation of CALL score's performance. Cox regression analyses were performed for the selection of new parameters for improving CALL score.

Results: Overall, 256 patients were enrolled in the study. The median age was 54 (IQR, 22.5), 134 (52%) were women, 155 (61%) had at least one comorbidity, 60 (23%) had severe disease. The AUC value for CALL score for predicting progression to severe COVID-19 was 0.59 (95% CI 0.50-0.66). D-dimer on admission was associated with progressive disease (HR = 1.2 CI 95% 1.02-1.40), ($P < .027$).

Conclusion: The performance of the CALL score in our patient population was low compared with the original study. We found an additional parameter for predicting progressive COVID-19 disease, D-dimer, which may guide future studies to develop new scoring systems for predicting progressive disease.

1 | INTRODUCTION

Coronavirus Disease 2019 (COVID-19), caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), usually causes asymptomatic or mild disease, while approximately 10%-15% of patients had severe disease.[1,2] Severe cases increase the demand for hospital beds and may lead to a shortage of medical care. The prediction models to estimate the risk of progressive disease can assist the healthcare system in this situation. The early identification of patients who have high risk may decrease the need for hospitalisation, mechanical ventilation and even mortality by early management.[3] For this purpose, many risk factors, including patient characteristics (age, underlying conditions) and laboratory parameters (C-reactive protein (CRP), ferritin, lymphocyte count, neutrophil/lymphocyte ratio), were identified for prediction of disease severity in previous studies.[4,5]

In the early pandemic period, various prediction models were developed. The CALL score, based on four clinical parameters (Comorbidity-Age-Lymphocyte count-Lactate dehydrogenase [LDH]), was claimed as an optimal estimate of progression with an AUC value of 0.91 (with 95% CI of 0.86-0.94) by distinguishing hospitalised COVID-19 patients with stable (n = 168) and progressive diseases (n = 40) This study was one of the earliest and most known studies for creating predictive model for hospitalised COVID-19 patients.[6] We aimed to evaluate the performance of the CALL score

in patients with COVID-19 in our hospital setting. We also aimed to improve the CALL score's performance by modifying its components according to our findings.

What's known

- Prediction of progressive disease is vital for healthcare professionals for better management of COVID-19 patients.
- The early identification of patients who have high risk may decrease the need for hospitalisation, mechanical ventilation and even mortality by early management.

What's new

- Because of the relatively low performance of CALL score in our patient population, we recommend using of D-dimer as a component of future predictive scoring systems for severe COVID-19 disease.

2 | METHODS

2.1 | Study population

Adult patients (18 years of age or older) confirmed with real-time reverse transcriptase-polymerase chain reaction (RT-PCR) COVID-19 were included in this retrospective, a non-interventional study from 19 March 2020 to 5 June 2020 (the last visit was on 22 June 2020). The patients were followed up until 14 days after discharging. A waiver of informed consent was issued by the Marmara University School of Medicine Institutional Ethical Review Board (Reference number: 09.2020.723). The patients were stratified into disease categories as mild, moderate or severe based on the National Institutes of Health.[7]

Severe cases were defined as at least one of the following, respiratory rate ≥30 breaths/min, resting oxygen saturation <94%, PaO2/FiO2 ≤300 mmHg or requirement of mechanical ventilation.[7] We excluded patients who had severe disease on admission or in the first 24 hours after admission.

Progression to severe COVID-19 was defined as appearing one or more of the parameters mentioned above 24 hours from admission.

Assessed comorbidities included hypertension, diabetes, cardiovascular disease, liver disease, asthma, chronic lung disease and malignancies.

2.2 | Data collection

We obtained the patients' characteristics (age, sex, comorbidities), vital signs and the laboratory parameters, including complete blood count, CRP, ferritin, LDH, fibrinogen, d-dimer, from electronic patient records. These laboratory parameters were assessed at admission and every other day during hospitalisation. The O2 saturation of the patient was measured by pulse oximetry on room air and confirmed by arterial blood gas analysis. Progression of illness was assessed by attending infectious disease specialists daily during hospitalisation.

2.3 | Statistical analysis

The distribution of numerical variables was tested with Kolmogorov Smirnov, Skewness kurtosis tests and histogram plots. The numerical variables without normal distribution were reported with median, interquartile range, minimum and maximum values. Categorical variables were reported with frequencies and percentages. The categorical variables were analysed with Chi-Square or Fisher's exact tests. The distribution of numerical variables among independent groups was compared with Mann-Whitney U test. The CALL score was calculated with the number of comorbidities, age, LDH and lymphocyte count variables, according to the study Ji et al.[6] The ability of CALL score for prediction of progressive COVID-19 was tested with receiver operating characteristic (ROC) analysis, where the area under curve (AUC) value was reported with a 95% confidence interval. Two distinct threshold values (including CALL score = 6 and 9) were used, and sensitivity, specificity, negative and positive predictive values and likelihood ratios were reported with a 95% confidence interval. The independent variables were used in univariate Cox regression models, where the dependent variable was the progressive disease. A p-value less than 0.05 was considered statistically significant. All analyses were executed with Stata 15.1 software.

3 | RESULTS

3.1 | Clinical characteristics of patients

Overall, 256 patients with PCR-confirmed COVID-19 included in the study. The median age was 54 (IQR, 22.5), 134 (52%) patients were women, 83 (32%) were older than 60 years. Of 256 patients, 155 (61%) had at least one comorbidity, and the most common comorbidities were hypertension (n = 94, 37%) and diabetes (n = 62, 24%). The median hospitalisation day was 6 (IQR, 5) days, and death was observed in only 5 (2%) patients. Progression to severe disease was observed in 60 (23%) patients. When stable and progressive groups were compared, sex, lymphocyte count, ferritin, CRP and fibrinogen levels were found significantly different between groups ($P < .05$ for all) (Table 1).

We categorised lymphocyte count (>1.0 and ≤1.0 × 109/L), LDH (≤250, 250-500, >500 U/L) and age (≤ 60 and >60 years) according to original CALL score thresholds, and additionally we added dichotomised D-dimer value (≤0.55 and >0.55 mg/L) to compare stable and progressive (Table 1). We did not find any significant difference among these groups, except D-dimer categories ($P = .012$).

TABLE 1 Characteristics of patients on admission

	Overall N = 256	Stable group N = 196	Progressive group N = 60	*P* value
Age, y, median (IQR)	54 (22.5)	54 (24.5)	57 (19)	.072
	20-91	20-91	20-87	
Male sex (n, %)	122 (47.66)	84 (42.86)	38 (63.33)	**.005**
Comorbidity (n, %)	155 (60.55)	115 (58.67)	40 (66.67)	.208
> 2 comorbidities (n, %)	84 (32.81)	61 (31.12)	23 (38.33)	.298
Lymphocyte, $\times 10^9$/L	1200 (800)	1300 (900)	1100 (700)	**.036**
	100-17000	100-17000	200-2900	
D-dimer, mg/L	0.495 (0.57)	0.48 (0.58)	0.615 (0.655)	.164
	0.12-11.78	0.12-9.34	0.19-11.78	
LDH, U/L	233 (107)	229 (105.5) 132-	241 (115)	.0927
	132-1194	1194	142-611	
Ferritin, μg/L	113.5 (175)	103 (151)	157 (237)	**.0015**
	1.8-2403	1.8-2403	5.2-1557	
CRP, mg/L	16 (34)	14 (29)	27 (48)	**.0007**
	0.3-177	0.3-177	3-164	
Fibrinogen, mg/dL	423 (133)	410 (133.5)	459 (123)	**.0031**
	141-795	141-767	294-795	
D-dimer, mg/L (n, %)				**.012**
≤ 0.55	139 (57.44)	115 (61.83)	24 (42.86)	
> 0.55	103 (42.56)	71 (38.17)	32 (57.14)	
Lymphocyte, $\times 10^9$/L (n, %)				.270
>1.0	148 (58.73)	117 (60.62)	31 (52.54)	
≤ 1.0	104 (41.27)	76 (39.38)	28 (47.46)	
Age, y (n, %)				.264
≤ 60	173 (67.58)	136 (69.39)	37 (61.67)	
> 60	83 (32.42)	60 (30.61)	23 (38.33)	
LDH, U/L (n, %)				.399
≤250	148 (59.92)	117 (62.23)	31 (52.54)	
250-500	87 (35.22)	62 (32.98)	25 (42.37)	
>500	12 (4.86)	9 (4.79)	3 (5.08)	
Hospitalisation (d)	6 (5)	5 (3)	11 (6.5)	**<.001**
	0-59	0-22	4-59	
Death (n, %)	5 (1.95)	1 (0.51)	4 (6.67)	**.011**

Abbreviations: CRP, C-reactive protein; LDH, lactate dehydrogenase. IQR, interquartile range.

Comorbidities; Hypertension, diabetes, cardiovascular system disease, chronic lung disease, chronic liver disease, chronic renal disease and immunosuppression.

P <.05 considered significant (in bold).

3.2 | Performance of CALL score for prediction of progressive disease

The AUC value for CALL score for predicting progression to severe COVID-19 was 0.59 (95% CI 0.50-0.66) with an AUCROC (Figure 1). When the cut-off point was selected as 6, the positive predictive value was 26.6% (95% CI 20.7-33.2), and the negative predictive value was 90% (95% CI 76.3-97.2) for disease progression. When the cut-off point was selected as 9, the positive and negative predictive values were 26.5% (95% CI 18.2-36.1) and 78% (95% CI 70.3-84.5), respectively (Table 2).

3.3 | COX regression analysis of clinical and laboratory parameters for progressive disease

According to univariate Cox regression analysis, Day 1 values of D-dimer (HR = 1.2 with CI 95% 1.02-1.40), LDH (HR = 1,003

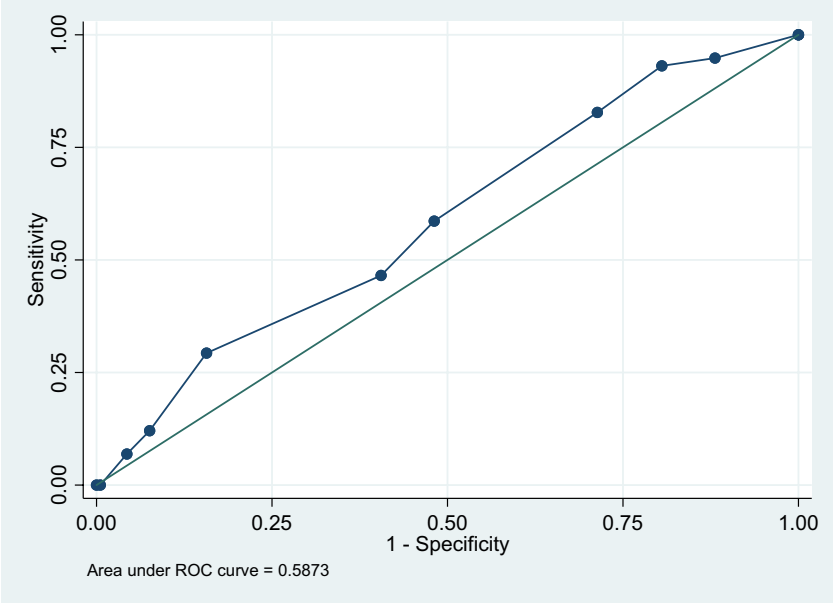

FIGURE 1 ROC curve of CALL score for prediction of progressive disease

TABLE 2 Performance of CALL score for progressive disease prediction

Variable	Patients N = 256
AUROC	0.5873 (0.50568-0.66897)
Cut-off value (95% CI)	**6**
Sensitivity, %	93.1 (83.3-98.1)
Specificity, %	19.5 (14-25.9)
Positive predictive value, %	26.6 (20.7-33.2)
Negative predictive value, %	90.0 (76.3-97.2)
Positive likelihood ratio	1.16 (1.05-1.28)
Negative likelihood ratio	0.354 (0.132-0.954)
Cutoff value (95% CI)	**9**
Sensitivity, %	46.6 (33.3-60.1)
Specificity, %	59.5 (52.0-66.6)
Positive predictive value, %	26.5 (18.2-36.1)
Negative predictive value, %	78 (70.3-84.5)
Positive likelihood ratio	1.15 (0.829-1.59)
Negative likelihood ratio	0.899 (0.688-1.18)

with CI 95% 1.000-1.006) and ferritin (HR = 1.001 with CI 95% 1.000-1.002) were statistically significant risk factors for progressive disease ($P < .05$ for all). Nevertheless, these parameters were not suitable for clinical use or predictive model development. The patients with LDH value ranging 250 to 500 had a HR of 2.011 (95% CI 1.137-3.556) relative to the patients with LDH value less than 250. However, this significantly increased risk was not observed in patients with LDH levels higher than 500 because of relatively low number of patients in this stratum. Also, we could not establish a multivariate model better than the CALL score (Table 3).

4 | DISCUSSION

In this study, we compared the clinical and laboratory characteristics of progressive and stable COVID-19 patients and evaluated the performance of the CALL score in our hospital settings. Then we tried to find additional parameters for improving CALL score performance. The performance of CALL score in our study population was lower compared with the original score. In the following paragraphs, we discussed the possible reasons behind this result, and possible solutions to adapt and improve this score for our clinical settings.

Our COVID-19 patients were younger compared with some previous studies.[8] In addition, more than half of our patients were women, and 61% of them had one or more comorbidity. These patient characteristics indicated that our patient population tends to show less severe clinical course compared with previous studies on hospitalised patients.[9] As a result, progression and mortality were observed in 23% and 2% of patients, respectively. Nevertheless, the male gender, a low lymphocyte count, higher ferritin, CRP and fibrinogen levels at day 1 showed significant differences in the progressive group showed significant differences among our patient groups. These results were consistent with previous literature.[10-12]

The AUC value of the CALL score for the prediction of progressive disease was relatively low in our study compared with the original study describing the CALL score.[6] A low level of progressive disease can partially explain this result in our patient population. Also, at the beginning of the pandemic period, we hospitalised milder and younger patients without comorbidity because of a lack of information on the natural course of the disease. Finally, both COVID-19 strains and patient genetics may show diversity among countries and hospitals.[13] These factors may explain a relatively low performance of CALL score in our patient population.

According to our univariate COX regression models, day 1 D-dimer, LDH and ferritin levels showed a statistically significant

TABLE 3 Univariate Cox regression analysis for progressive COVID-19 disease

Variable	HR	95% CI	*P*
Univariate analysis			
Age	1.001	0.983-1.020	.892
Age >60	1.115	0.657-1.893	.686
Gender (male)	1.450	0.849-2.475	.173
Comorbidity	1.040	0.595-1.819	
Comorbidity (2 or more)	1.310	0.754-2.277	.338
Lymphocyte count (Day 1)	1.000	0.999-1.001	
Lymphocyte count <1000	1.305	0.772-2.207	
Lymphocyte count <800	1.103	0.625-1.947	.735
D-dimer (Day 1)	1.198	1.021-1.407	
D-dimer >0.55	1.392	0.804-2.409	.237
LDH (Day 1)	1.003	1.000-1.006	.025
LDH (250-500)	2.011	1.137-3.556	**.016**
LDH (>500)	3.056	0.886-10.549	.077
Ferritin (Day 1)	1.001	1.000-1.002	**.013**
CRP (Day 1)	1.005	0.998-1.012	.153
Fibrinogen (Day 1)	1.002	0.999-1.005	.083

P <.05 considered significant (in bold).

effect on progression. However, among these three variables, only D-dimer showed clinically significant effect on progression. Increased D-dimer, ferritin and LDH levels are related to proinflammatory conditions associated to cytokine storm, dysfunctional immune system, endothelial damage and hypercoagulability lead to progressive disease.[14] However, we could not establish a better multivariate model to improve CALL score, probably because of the relatively low number of patients with disease progression. Nevertheless, these findings may guide future studies to develop new scoring systems and algorithms, including D-dimer for predicting progressive disease.

There are several limitations to the study. The number of patients with the progressive disease was limited. The clinical settings and hospitalisation criteria for our patients showed essential differences from the original CALL score study. Further prospective studies are needed in different regions and countries. Other infectious agents, which may cause COVID-19 like clinical presentations (eg, Influenza), were not ruled with laboratory methods.

5 | CONCLUSION

Prediction of progressive disease is vital for healthcare professionals for better management of COVID-19 patients. Because of the relatively low performance of CALL score in our patient population, we recommend using of D-dimer as a component of future predictive scoring systems for severe COVID-19 disease.

DISCLOSURE

All authors declare that they have no conflicts of interest.

AUTHORS' CONTRIBUTIONS

Buket Erturk Sengel: acquisition of data, drafting the article, Elif Tukenmez Tigen: acquisition of data, participate in drafting the article, Can Ilgin: analysis and interpretation of data, drafting the article, Tugce Basari, Merve Bedir: acquisition of data, Zekaver Odabasi: revising it critically for intellectual content, Volkan Korten: conception and design of the study, revising it critically for intellectual content, final approval of the version. All authors have read and approved the final manuscript.

ETHICAL APPROVAL

The study protocol was approved by the local ethics committee of Marmara University School of Medicine (Reference number: 09.2020.723).

DATA AVAILABILITY STATEMENT

Data openly available in a public repository that issues datasets with DOIs.

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How to cite this article: Erturk Sengel B, Tukenmez Tigen E, Ilgin C, et al. Application of CALL score for prediction of progression risk in patients with COVID-19 at university hospital in Turkey. *Int J Clin Pract*. 2021;75:e14642. https://doi.org/10.1111/ijcp.14642