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The role of ANDC early warning score in predicting prolonged hospitalization in SARS-Cov-2 infected patients

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Abstract

Aim: To evaluate the ability of the age, neutrophil-to-lymphocyte ratio, D-dimer, C-reactive protein (ANDC) score to predict prolonged hospitalization in SARS-CoV-2-infected patients.

Material and methods: This is a prospective and observational study conducted with patients hospitalized due to SARS-CoV-2 infection. The patients were divided into expected and prolonged hospitalization groups according to their length of hospital stay, and those who were hospitalized for seven days or longer were included in the prolonged hospitalization group. The receiver operating characteristic analysis was performed and the DeLong equality test was applied to compare the area under the curve values of the investigated parameters. Their odds ratios were also calculated.

Results: The study included a total of 397 patients. The median length of hospital stay was 8 days (25th-75th percentiles: 5-13). The univariant analysis revealed significant differences in the ANDC scores between the expected and prolonged hospitalization groups (101 (80.1-127) versus 114 (94.3-141), p<0.001, Mann-Whitney U test). The area under the curve value of the ANDC score in the prediction of prolonged hospitalization was 0.609 (75.91% sensitivity, 42.94% specificity, 62.3% positive predictive value, and 58.9% negative predictive value at a cut-off value of 93.5), and the odds ratio was 2.6.

Conclusion: Our results suggest that ANDC score is a predictor of prolonged hospitalization in SARS-CoV-2-infected patients. However, multicenter studies are needed to confirm our findings in larger samples.

Key words: ANDC score, COVID-19, SARS-CoV-2, length of stay, prolonged hospitalization

Introduction

In December 2019, pneumonia cases of unknown cause were detected in Wuhan, China. The sequence analyses performed on the lower respiratory tract samples taken from these cases revealed a new coronavirus called severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), and the disease caused by this virus was named coronavirus disease 2019 (COVID-19). With the rapid spread of the disease, a pandemic was declared on March 11, 2020. The pandemic has placed an extra burden on the healthcare system worldwide [1], with the patient load exceeding the current bed and staff capacity, especially during peak periods. Early warning systems have been discussed in the literature in order to determine high-priority cases and use the available beds and health capacity effectively [2].

Researchers have investigated many early warning scores (EWSs) as a predictor of poor outcome. Scoring systems, such as CURB-65, CURB, and pneumonia severity index have been shown to predict the severity of pneumonia [3,4]. Laboratory parameters have been used to predict severe disease and need for supportive care. Hematological parameters and their combinations were primarily investigated for this purpose, as they are

easily accessible and inexpensive. Higher D-dimer, C-reactive protein (CRP), and neutrophil-to-lymphocyte ratio (NLR) values are well-known predictors of mortality [5]. Weng et al. [6] developed a new mortality predictor by adding age to these laboratory parameters and named this newly developed EWS as the age, NLR, D-dimer, CRP (ANDC) score. Other researchers [7,8] have discussed the ability of the ANDC score to predict mortality in different patient groups such as geriatrics or pediatrics. In this study, we aimed to test the ability of the ANDC score to predict prolonged hospitalization in SARS-CoV-2-infected patients.

Material and methods

Study design

This study was carried out as a prospective and observational study at a tertiary hospital with 685 beds, of which 152 were allocated to intensive care. During the peak periods of the pandemic, all the beds of the center where the study was conducted were reserved for patients with SARS-CoV-2.

Study population

Patients who applied to the hospital's emergency department with SARS-CoV-2 symptoms and findings between December 15, 2021, and March 15, 2022, and were hospitalized with positive rt-PCR results were included in the study. Patients who were admitted directly to the intensive care unit directly from emergency department or those who died at emergency department were excluded from the study because of the possible short length of stay despite the severity of the disease. Patients who were transferred to another hospital during their stay were also excluded. The total duration of stay in the wards and intensive care units was considered as the total length of hospital stay.

Data collection

Patients' demographics and comorbidities were recorded in the study form. The length of hospital stays and laboratory parameters were obtained from the hospital computer-based data recording system. Comorbidities were recorded as chronic obstructive pulmonary disease, hypertension, diabetes mellitus, coronary artery disease, congestive heart failure, asthma, history of malignancy, chronic kidney disease, and hyperlipidemia. As laboratory parameters, white blood cell count, neutrophil count, lymphocyte count, platelet count, hemoglobin count, hematocrit count, mean platelet volume, mean corpuscular volume, sodium, potassium, glucose, blood urea nitrogen, creatinine, albumin, alanine aminotransferase, aspartate aminotransferase, D-dimer, troponin ferritin, and CRP were recorded. NLR, platelet-to-lymphocyte ratio (PLR), and ANDC score were calculated. The ANDC score was calculated using the formula (1.14 x Age (years) - 20) + 1.63 x NLR + 5.00 x D-dimer (mg/L) + 0.14 x CRP (mg/L). Patients were divided into two groups as expected hospitalization and prolonged hospitalization according to their length of hospital stay. Patients who were hospitalized for seven days or longer were included in the prolonged hospitalization group. In-hospital mortality data were obtained from the hospital computer-based data recording system.

Statistical analysis

Jamovi software (The Jamovi Project, Version 1.6.21.0; 2020) was used for statistical analyses. The conformity of the parameters to the normal distribution was evaluated with the Shapiro-Wilk test. Categorical data were shown using number and percentages, and continuous data with median and 25th-75th percentile values. The chi-square test was used for the intergroup comparison of categorical data, and the Mann-Whitney U test for the intergroup comparison of continuous data. The receiver operating characteristic (ROC) analysis was performed to measure the ability of the parameters to predict prolonged hospitalization. The optimum cut-off levels for the parameters were found using Youden's index with the formula, sensitivity + (1 - specificity). The results of the ROC analysis were shown using the area under the curve (AUC), accuracy, positive predictive value, negative predictive value, 95% confidence interval, and cut-off value. The odds ratios were used to determine and compare the predictive ability of the parameters. P values below 0.05 were accepted as statistically significant.

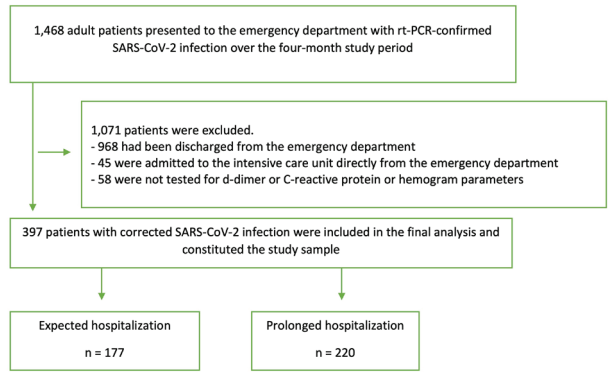
Ethics

Ethical approval for the study was obtained from the Republic of Turkey Ministry of Health Ümraniye Hospital Clinical Researches Ethical Committee (approval number: B.10.1.TKH.4.34.H.GP.0.01/320). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki. Consent to participate in the study was obtained from the patients with sufficient consciousness and from the relatives of those with impaired consciousness.

Results

A total of 1,468 patients presented to the emergency department with confirmed SARS-CoV-2 infection during the period from December 15, 2021 to March 15, 2022. Of those patients, 968 were excluded because they had been discharged from the emergency department, 45 because they were admitted to the intensive care unit directly from the emergency department, and 58 because they were not tested for D-dimer or CRP or hemogram parameters. The remaining 397 patients constituted the study sample, and their data were included in the final analysis (Figure 1).

Figure 1 - Flowchart of the study



Of the 397 patients in the sample, 209 (52.6%) were female. The median age was 74 years (25th-75th percentiles: 63-82), and their median length of hospital stay was 8 days (25th-75th percentiles: 5-13). The in-hospital mortality rate was 16.6% (66 patients).

The median of D-dimer, neutrophil count, lymphocyte count, NLR, and CRP values were found to be 830 (500-1930) mg/dL, 5.67 (3.93-7.75) 103/µL, 1 (0.66-1.38) 103/µL, 5.64 (3.37-9.38), and 74 (32.6-139) mg/dL, respectively. The most frequent comorbidity was hypertension (230 patients, 57.9%). The baseline characteristics and laboratory parameters of the enrolled patients are presented in Table 1.

Table 1 Baseline characteristics and laboratory parameters of the enrolled patients and their comparison between the expected and prolonged hospitalization groups

Variables	Total n = 397	Expected hospitalization n = 171 (41.3%)	Prolonged hospitalization n = 226 (56.9%)	P
	n (%)/median (25th-75th percentiles)	n (%)/median (25th-75th percentiles)	n (%)/median (25th-75th percentiles)	
Age	74 (63 - 82)	73 (59 - 81)	76 (67 - 83)	**0.014**
<65 years	105 (26.4%)	58 (33.9%)	47 (20.8%)	**0.003**
≥65 years	292 (73.6%)	113 (66.1%)	179 (79.2%)	
Gender				
Female	209 (52.6%)	96 (56.1%)	113 (50.0%)	0.225
Male	188 (47.4%)	75 (43.9%)	113 (50.0%)	
Symptoms				
Cough	141 (35.5%)	61 (35.7%)	80 (35.4%)	0.955
Shortness of breath	171 (43.1%)	64 (37.4%)	107 (47.3%)	**0.048**
Comorbidities				
Chronic obstructive pulmonary disease	51 (12.8%)	18 (10.5%)	33 (14.6%)	0.229
Hypertension	230 (57.9%)	92 (53.8%)	138 (61.1%)	0.147
Diabetes mellitus	140 (35.3%)	64 (37.4%)	76 (33.6%)	0.433
Coronary artery disease	90 (22.7%)	31 (18.1%)	59 (26.1%)	0.060
Congestive heart failure	43 (10.8%)	13 (7.6%)	30 (13.3%)	0.072
History of malignancy	47 (11.8%)	20 (11.7%)	27 (11.9%)	0.939
Hyperlipidemia	27 (6.8%)	7 (4.1%)	20 (8.8%)	0.062
Chronic kidney disease	40 (10.1%)	11 (6.4%)	29 (12.8%)	**0.036**
Vital parameters				
Systolic blood pressure	125.0 (112.0 - 142.0)	121.0 (110.0 - 140.0)	128.0 (115.0 - 144.0)	**0.014**
Diastolic blood pressure	72.0 (64.0 - 80.0)	70.0 (60.0 - 80.0)	73.0 (64.0 - 80.0)	0.122
Pulse pressure	85.0 (77.0 - 95.0)	85.0 (78.0 - 95.0)	84.0 (75.0 - 95.0)	0.147
Oxygen saturation	95.0 (93.0 - 97.0)	96.0 (94.0 - 97.0)	95.0 (92.0 - 97.0)	**0.002**
Laboratory parameters				
White blood cell count (103/μL)	7.21 (5.60 - 9.86)	7.09 (5.27 - 9.22)	7.43 (5.63 - 10.44)	0.203
Neutrophil count (103/μL)	5.67 (3.93 - 7.75)	5.30 (3.71 - 7.03)	5.92 (4.17 - 8.45)	0.071
Lymphocyte count (103/μL)	1.00 (.66 - 1.38)	1.06 (0.71 - 1.41)	0.96 (0.60 - 1.38)	0.178
Hemoglobin (g/dL)	12.2 (10.8 - 13.8)	12.4 (10.8 - 13.7)	12.1 (10.8 - 13.8)	0.934
Hematocrit (%)	37.1 (33.0 - 41.1)	37.1 (33.1 - 41.1)	37.1 (32.9 - 41.6)	0.875
Mean corpuscular volume (fL)	86.9 (82.9 - 91.0)	85.6 (82.9 - 90.9)	87.8 (82.8 - 91.2)	0.234
Platelet count (103/μL)	198.0 (156.0 - 256.0)	208.0 (164.0 - 270.0)	194.0 (146.0 - 241.0)	0.071
Mean platelet volume (fL)	9.8 (8.9 - 10.5)	9.6 (8.8 - 10.3)	10.0 (9.1 - 10.6)	**0.016**
Blood urea nitrogen (mg/dL)	43.6 (30.0 - 63.1)	38.4 (25.2 - 58.0)	46.7 (32.7 - 67.5)	**<0.001**
Creatinine (mg/dL)	.97 (.76 - 1.30)	0.88 (0.67 - 1.17)	1.04 (0.81 - 1.37)	**<0.001**
Sodium (mEq/L)	137.0 (134.5 - 139.5)	137.0 (134.5 - 139.0)	137.0 (134.5 - 140.0)	0.479
Potassium (mmol/L)	4.33 (3.99 - 4.68)	4.28 (3.99 - 4.66)	4.35 (4.00 - 4.69)	0.333
Albumin (g/dL)	36.00 (33.00 - 39.00)	36.01 (33.54 - 40.00)	35.86 (32.73 - 39.00)	0.060
Ferritin (mg/dL)	299.80 (144.90 - 589.35)	248.20 (127.00 - 492.70)	356.45 (181.30 - 700.20)	**0.013**
D-dimer (mg/dL)	830 (500 - 1930)	770 (470 - 1350)	895 (540 - 2060)	**0.008**
Troponin (cTnI) (ng/mL)	20.62 (9.74 - 38.84)	17.18 (7.72 - 26.97)	24.67 (11.42 - 56.03)	**<0.001**
Aspartate aminotransferase (IU/L)	19 (12 - 30)	18 (12 - 27)	19 (13 - 32)	0.183
Alanine aminotransferase (IU/L)	28 (21- 40)	26 (18 - 36)	30 (23 - 43)	**<0.001**
C-reactive protein. (mg/dL)	74.03 (32.59 - 138.70)	69.87 (27.55 - 120.39)	77.03 (40.89 - 149.38)	**0.024**
Glucose (mg/dL)	121 (101 - 163)	122.0 (102 - 155)	118.0 (100 - 167)	0.965
Neutrophil-to-lymphocyte ratio	5.64 (3.36 - 9.38)	4.89 (3.13 - 9.06)	6.17 (3.56 - 10.04)	**0.048**
Platelet-to-lymphocyte ratio	197.060 (130.682 - 310.170)	197.753 (133.047 - 296.610)	196.102 (127.273 - 336.000)	0.729
C-reactive protein-to-albumin ratio	2.09 (.86 - 3.92)	1.80 (0.70 - 3.24)	2.25 (1.05 - 4.25)	**0.014**
Blood urea nitrogen-to-/albumin ratio	1.24 (.81 - 1.80)	1.07 (0.70 - 1.59)	1.33 (0.90 - 1.99)	**<0.001**
Length of hospital stay (days)	7.6 (4.9 - 12.0)	4.6 (3.0 - 5.7)	11.1 (8.3 - 16.0)	**<0.001**
In-hospital mortality	66 (16.6%)	13 (7.6%)	53 (23.5%)	**<0.001**
ANDC	108.205 (87.649 - 136.891)	100.723 (78.983 - 129.253)	113.114 (94.495 - 140.546)	**<0.001**

The univariant analysis was performed to determine the differences in the investigated parameters between the study groups. Significant differences were found between the expected and prolong hospitalization groups in terms of the ANDC score (101 (80.1-127) versus 114 (94.3-141), $p < 0.001$), age (73 (59-81) versus 76 (67-83) years, $p = 0.014$), D-dimer (770 (480-1310) versus 895 (555-2075) mg/dL, $p = 0.008$), NLR (4.89 (3.13 - 9.06) versus 6.17 (3.56 - 10.04), $p = 0.048$), and CRP (69.87 (27.55-120.39) versus 77.03 (40.89-149.38) mg/L, $p = 0.024$). Table 1 shows the comparison of all the parameters between the two groups.

Table 2 Ability of the investigated parameters in to predict prolonged hospitalization in patients with SARS-CoV-2 infection

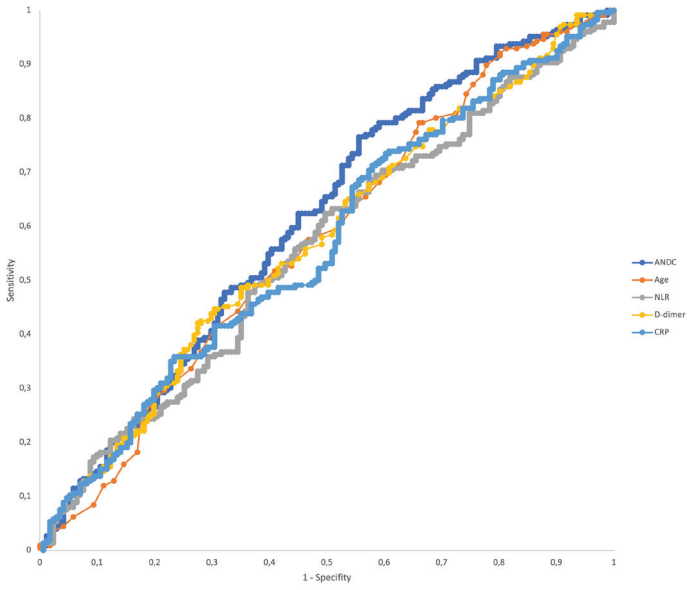
Variables	AUC	Cut-off value	95% CI	Accuracy	Sensitivity	Specificity	PPV	NPV	PLR	NLR	p value
ANDC	0.609	94.12	0.552-0.665	0.627	76.55%	44.44%	64.55%	58.91%	1.38	0.53	<0.001
Age	0.572	65	0.515-0.630	0.597	79.20%	33.93%	61.29%	55.21%	1.20	0.61	0.013
D-dimer	0.573	1190	0.516-0.630	0.552	42.04%	72.51%	66.90%	48.63%	1.53	0.80	0.012
Neutrophil-to-lymphocyte ratio	0.557	4.94	0.500-0.615	0.572	62.39%	50.29%	62.39%	50.29%	1.26	0.75	0.05
C-reactive protein	0.566	46.8	0.509-0.623	0.587	71.2%	42.09%	62.04%	52.62%	1.23	0.68	0.023

Table 3 Comparison of the area under the curve values of the investigated parameters according to the DeLong equality test

Variables		Age	D-dimer	Neutrophil-to-lymphocyte ratio	C-reactive protein
ANDC	AUC	0.609-0.572	0.609-0.573	0.609-0.557	0.609-0.566
	p value	0.206	0.284	0.08	0.025
Age	AUC		0.572-0.573	0.572-0.557	0.572-0.566
	p value		0.989	0.688	0.876
D-dimer	AUC			0.573-0.557	0.573-0.566
	p value			0.670	0.859
Neutrophil-to-lymphocyte ratio	AUC				0.557-0.566
	p value				0.796

The ROC analysis was performed to show the predictive power of the ANDC score and the parameters of ANDC in prolonged hospitalization. The AUC value of the ANDC score was found to be 0.609 and 75.91% sensitivity, 42.94% specificity, 62.3% positive predictive value, and 58.9% negative predictive value at a cut-off value of 93.5. The complete results of the ROC analysis are presented in Table 2 and Figure 2. The statistical differences in the AUC values according to the DeLong equality test are presented in Table 3.

Figure 2 - Receiver operating characteristic curve of the parameters for predicting prolonged hospitalization



The odds ratios of the investigated parameters were also calculated to compare their predictive ability in prolonged hospitalization. The odds ratios of the ANDC score, age, D-dimer, NLR, and CRP were calculated as 2.6, 1.9, 1.9, 1.6, and 1.8 respectively. The details of this analysis are presented in Table 4.

Table 4 Odds ratio results obtained according to the optimum cut-off values

Variables	Odds ratio	95% confidence interval
ANDC	2.611	1.697-4.018
Age	1.955	1.245-3.069
D-dimer	1.913	1.248-2.933
Neutrophil-to-lymphocyte ratio	1.678	1.122-2.511
C-reactive protein	1.801	1.185-2.737

Discussion

In this study, we investigated to ability of the ANDC score and the parameters used in its calculation to predict prolonged hospitalization in SARS-CoV-2-infected patients. According to the results, there was a statistically significant difference between the prolonged and expected hospitalization groups in terms of all the investigated parameters. The odds ratio of the ANDC score was greater than the odds ratios of each of the parameters used to calculate this score. To the best of our knowledge, this study is the first to investigate whether the ANDC score could predict prolonged hospitalization in SARS-CoV-2-infected patients.

With the increased burden on the health system due to the pandemic, scoring systems such as ANDC, the Pandemic Respiratory Infection Emergency System Triage (PRIEST) Severity Score and the COVID-19 Community Mortality Risk Prediction tool (CoCoMoRP) have been developed using methods such as machine learning to assess the severity of COVID-19 cases. These scoring studies are based on vital parameters, laboratory parameters, and supportive treatment [6, 9, 10]. In a study conducted with patients with COVID-19 in the early period of the pandemic, Weng et al. [11] used the least absolute shrinkage and selection operator (LASSO) regression analysis and identified independent variables as age, D-dimer, NLR, and CRP. The authors named the new model they created with the LASSO method as the ANDC score. The primary outcome in the study of Weng et al. was all-cause death. They performed the ROC analysis to test the ability of the ANDC score to predict this outcome. They reported the AUC value as 0.921 [6], which is close to an ideal predictor [12]. To test the model, they validated the score with patients from another

hospital and reported the model as successful. In another study, Bilge et al. [13] tested the ability of the ANDC score to predict mortality in patients with malignancy hospitalized due to SARS-CoV-2-associated pneumonia. They reported the AUC value as 0.69 (95% confidence interval: 0.54 - 0.84), and the sensitivity and specificity as 80% and 46%, respectively at the cut-off value of 100.

In the current study, first, we performed a univariant analysis to reveal the relationship between the ANDC score and prolonged hospitalization. We found that the group with prolonged hospitalization had a higher ANDC score. We performed the ROC analysis to assess the ability of the score to predict prolonged hospitalization. We determined that the ANDC score had a relatively low AUC in predicting prolonged hospitalization. In addition, we compared the AUC values of the ANDC score with those of the parameters constituting this score. In our analysis using the DeLong equality test, there was no statistically significant difference between the AUC values of the ANDC score and age and D-dimer. According to the results of this analysis, it can be concluded that the ANDC score is not better than age and D-dimer in predicting prolongation of hospital stay. Finally, we dichotomized the parameters according to the cut-off values obtained by the ROC analysis and calculated the odds ratios. We determined that the ANDC score had an odds ratio above the odds ratios of the parameters that made up this score.

The most important shortcoming of our study was the relatively limited sample size and single-center design, limiting the generalizability of the findings. Another important limitation is that SARS-CoV-2 subtypes were not studied. However, our study included patients infected with SARS-CoV-2 in the fourth peak period of the pandemic, during which the delta variant was dominant in the Northern hemisphere.

Conclusion

The present study was done to test the ability of the ANDC score, which is known to predict mortality in SARS-CoV-2 infected patients, to predict prolonged hospitalization in SARS-CoV-2 infected patients. Based on all the observations from the present study, it was concluded that the ANDC score is a predictor of prolonged hospitalization in SARS-CoV-2 infected hospitalized patients.

Besides, compared to using the age, D-dimer, NLR, and C-reactive protein values alone, ANDC was found to be more valuable in predicting prolonged hospitalization in SARS-CoV-2 infected hospitalized patients. On the other hand, we recommend confirming the results of our study with larger samples and multicenter studies.

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