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Mortality estimation using APACHE and CT scores with stepwise linear regression method in COVID-19 intensive care unit: A retrospective study

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ABSTRACT

Background: COVID-19 is a disease with high mortality worldwide, and which parameters that affect mortality in intensive care are still being investigated. This study aimed to show the factors affecting mortality in COVID-19 intensive care patients and write a model that can predict mortality.
Methods: The data of 229 patients in the COVID-19 intensive care unit were scanned. Laboratory tests, APACHE, SOFA, and GCS values were recorded. CT scores were calculated with chest CTs. The effects of these data on mortality were examined. The effects of the variables were modeled using the stepwise regression method.
Results: While the mean age of female (30.14%) patients was 69.1 ± 12.2, the mean age of male (69.86%) patients was 66.9 ± 11.5. The mortality rate was 69.86%. Age, CRP, D-dimer, creatinine, procalcitonin, APACHE, SOFA, GCS, and CT score were significantly different in the deceased patients than the survival group. When we attempted to create a model using stepwise linear regression analysis, the appropriate model was achieved at the fourth step. Age, CRP, APACHE, and CT score were included in the model, which has the power to predict mortality with 89.9% accuracy.
Conclusion: Although, when viewed individually, there is a significant difference in parameters such as creatinine, procalcitonin, D-dimer, GCS, and SOFA score, the probability of mortality can be estimated by knowing only the age, CRP, APACHE, and CT scores. These four simple parameters will help clinicians effectively use resources in treatment.

1. Introduction

COVID-19, which started in China, has spread worldwide in an unprecedented way. The spread of the disease turned into a pandemic, and thousands of individuals were infected. Some survived with mild symptoms, while others were treated with severe symptoms in intensive care units (ICU). While patients struggled to survive in intensive care, physicians were also struggling with this new unknown virus. Which scoring system would more accurately determine mortality or which laboratory parameters were more valuable for inpatient follow-up were investigated.[1]

Patients hospitalized in the ICU owing to the coronavirus are followed up with scoring systems to evaluate the severity of the disease. The Acute Physiology and Chronic Health Evaluation (APACHE) and Sequential Organ Failure Assessment (SOFA) scoring systems are frequently used in patient follow-up in the ICU.[2,3]

Computed tomography (CT) is frequently used to diagnose COVID-19 and to understand the extent and severity of the disease.[4] Significant CT findings (according to the international standard terminology defined by the Fleischner Society) can be counted as ground-glass opacity, cobblestone appearance, and consolidation in lung segments.[5] Some semi-quantitative scoring systems are used to quantify the pulmonary involvement of all these abnormalities, and one of them is the method in which five lung lobes are scored. Thus, the total CT score is found by adding the individual lobar scores, and it ranges from 0 (no involvement) to 25 (maximum involvement).[6]

In our study, we aimed to find a relationship between mortality rate and the APACHE, SOFA, Glasgow Coma Scale (GCS), CT score, and laboratory values of patients.

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2. Methods

2.1. Patient selection

After obtaining the permission of the local ethics committee, patients hospitalized in the COVID-19 ICU between October 1, 2020, and December 31, 2020, were retrospectively screened. The reason for choosing this period was that the general population in our country was not vaccinated, and the intensive care occupancy rates were high at the time.

2.2. Inclusion criteria

Being over 18, CT results, and laboratory values available, diagnosed with COVID-19 by polymerase chain reaction (PCR) test.

2.3. Exclusion criteria

Being younger than 18, CT images or laboratory values are not available.

During this period, 229 COVID-19 patients were followed up in the ICU. Among the laboratory values used in the follow-up of the patients, ferritin, d-dimer, C-reactive protein (CRP), procalcitonin, and creatinine values were recorded. GCS, APACHE, SOFA values used in intensive care follow-up were noted.

2.4. Image analysis

The same radiologist with 16 years of expertise in thoracic radiology performed image analysis utilizing the institutional digital database system (Akgun Picture Archiving and Communication System (PACS), version 6.1.0, Turkey). Each of the five lung lobes was scored from 0 to 5. A value of 0 indicates no involvement, 1 indicates less than 5% involvement, 2 indicates involvement of 5%–25%, 3 indicates involvement of 26%–49%, 4 indicates involvement of 50%–75%, and 5 indicates more than 75% involvement. The total CT score is the sum of the individual lobar scores. Thus, a patient's CT score ranges from 0 (no involvement) to 25 (maximum involvement).

2.5. Statistical method

Since the dependent variable (mortality) was discrete (0: no death, 1: death) in the study, analysis was performed with a linear probability model. In this multivariate model, where the dependent and independent variables are differentiated, logistic regression was performed since the dependent variable is a nominal scale variable. In regression models where the dependent variable is two-state (such as whether the patient dies or not), these variables can be explained as dummy variables. The SPSS 20 program was used to build the model in the study. Chi-square was used for the existence of the relationship between the explanatory variables in the estimated model and the dependent variable, and Cox-Snell and Nagelkerke statistics were used to measure the model's explanatory power. Finally, the model coefficients were reported, and the estimated model was expressed as a function. The reference value was taken as $P \leq 0.05$ to test the statistical significance.

3. Results

Two hundred and twenty-nine patients were included in the study. While the average age of 69 female (30.14%) patients was 69.17, the average age of 160 (69.86%) male patients was 66.9. The average age of all patients was 67.59 (min: 25, max: 96).

The average of the GCS, APACHE, SOFA and CT score values calculated during the examination of patients and laboratory values are shown in Table 1.

160 (69.86%) patients died. Of these, 111 (69.37%) were male, and 49 (30.63%) were female. No correlation was found between death and gender with the Chi-square test. The *t*-test showed that the following factors were correlated with mortality: Age, APACHE, SOFA, GCS, CT score, CRP, D-dimer, procalcitonin, and creatinine values (Table 2).

Table 1
Descriptive statistics of patients.

	Descriptive statistics				
	N	Minimum	Maximum	Mean	Std. deviation
GCS	229	3	15	12,45	3,722
APACHE	229	2	47	17,95	9,985
SOFA	229	2	17	11,68	3,62
CT score	229	0	25	13,11	7,447
Ferritin	229	12,61	2000	810,48	554,83
Creatinine	229	0,44	8,17	1,35	1,15
D-Dimer	229	110	34,600	3622,58	6177,31
Procalcitonin	229	0,025	100	3,75	14,27
CRP	229	1,40	493,64	106,10	91,23
Age	229	25	96	67,59	11,95

The above-mentioned factors were used in the model to predict mortality. For this purpose, the forward stepwise regression technique was used. In step 4, the appropriate model was reached. The descriptive statistics of the model are presented below. As shown in Table 3, the Chi-square statistical value of the model was found to be 96.506, and it was statistically significant. Therefore, we concluded that the model coefficients were significant, and there was a relationship between the dependent and independent variables.

The classification table is another indicator of model fit. Table 4 shows that the model correctly predicts survival by 65.2% and mortality by 89.9%. In general, the model has an accurate classification rate of 82.4%.

Table 5 shows that the model explains 34.6% of the change in the dependent variable according to Cox-Snell and 49% according to Nagelkerke. The explanatory power of the model is high.

APACHE, CT Score, CRP, and age were the variables included in the model. According to the model, a high APACHE value increases the probability of dying 1.081 times, CT Score value 1.076 times, CRP value 1.019 times, and age 1.035 times (Table 6).

The equation of the model is as follows:

$$L = \mathrm{Ln}\left(\frac{P}{1-P}\right) = Z$$

$$= -5,073 + 0,078\mathrm{APACHE} + 0,073\mathrm{BTScore} + 0,019\mathrm{CRP} + 0,034\mathrm{Age}$$

$$P(Y) = \frac{e^{z}}{1+e^{z}} = \frac{1}{1+e^{-z}}$$

Based on the model, it will be possible to make a successful prediction about an intensive care patient's survival rate utilizing the above statistics. Here, P(Y) gives us the probability of event Y. Y stands for the dependent variable. Event Y is the death of the patient in our study. e is a

Table 2
Clinical and demographic characteristics related to mortality of the patients.

		Survival (n: 69) (30.14%)	Ex (n: 160) (69.86%)	Total (n: 229)	P
Gender	Female	20	49	69	0.87
	Male	49	111	160	
Age		62.50	69.78	67.59	0.00
APACHE		12.53	20.28	17.95	0.001
SOFA		12.17	11.46	11.68	0.00
GKS		13.94	11.80	12.45	0.00
CT score		10.65	14.16	13.11	0.023
CRP		44.60	132.62	106,10	0.00
Ferritin		708.22	855.13	810,48	0.055
D-dimer		2365.34	4164.75	3622,58	0.009
Procalcitonin		1.13	4.88	3,75	0.002
Creatinine		1.01	1.50	1,35	0.00

Table 3
Omnibus tests of model coefficients.

		Chi-square	df	Sig.
Step 4	Step	4,597	1	0,032
	Block	96,506	4	0,001
	Model	96,506	4	0,001

Table 4
Classification table.[a]

			Predicted		Percentage correct
			Survive	Ex	
Step 4	Observed	Survive	45	24	65,2
		Ex	16	142	89,9
	Overall percentage				82,4

[a] The cut value is 0,500.

Table 5
Explanatory power of the model.

Step	-2 log likelihood	Cox-Snell R square	Nagelkerke R square
4	182,334[a]	0,346	0,490

[a] Estimation terminated at iteration number 6 because parameter estimates changed by less than 0,001.

Table 6
Results of the model.

		Variables in the equation					
		B	S.E.	Wald	df	Sig.	Exp(B)
Step 4	APACHE[b]	0,078	0,025	9,671	1	0,002	1,081
	BT score[c]	0,073	0,026	8,161	1	0,004	1,076
	CRP[a]	0,019	0,003	28,724	1	0,001	1,019
	Age[d]	0,034	0,016	4,383	1	0,036	1,035
	Constant	−5,073	1,210	17,586	1	0,001	0,006

[a] Variable(s) included in step 1: CRP.
[b] Variable(s) included in step 2: APACHE.
[c] Variable(s) included in step 3: BT Score.
[d] Variable(s) included in step 4: Age.

fixed 23-digit value (base e = 2.718…). When death is taken as the dependent variable, the probability of the event increases as the statistical probability of P(Y) approaches 1. As the probability of P(Y) gets closer to 0, the probability of dying decreases. Thus, the calculated Z value is evaluated as the probability value that shows us the probability of the Y event by transformation.

For example, the predicted model value of an intensive care patient with a CT value of 20, an Apache value of 18, a CRP of 130, and an age of 71 is 0.852. Since P(Y) ≥ 0.50, Y is taken as 1. In other words, the survival probability of a patient with these values is very low.

$$L = \mathrm{Ln}\left(\frac{P}{1-P}\right) = Z$$
$$= -5,073 + 0,078*18 + 0,073*20 + 0,019*130 + 0,034*71 = 1,752$$

$$P(Y) = \frac{e^z}{1+e^z} = \frac{1}{1+e^{-z}} = \frac{1}{1+e^{-1752}} = 0,852$$

For another example, let us take an intensive care patient with a CT value of 19, an Apache value of 8, a CRP of 4.34, and age 59. The P(Y) value for a patient with these data would be 0.274. Since P(Y) ≤ 0.50, Y is taken as 0. In other words, the survival probability of a patient with these values is very high.

$$L = \mathrm{Ln}\left(\frac{P}{1-P}\right) = Z$$
$$= -5,073 + 0,078*8 + 0,073*19 + 0,019*4,34 + 0,034*59$$
$$= -0,97354$$

$$P(Y) = \frac{e^z}{1+e^z} = \frac{1}{1+e^{-z}} = \frac{1}{1+e^{0,97354}} = 0,274$$

These two examples show that those four variables are the most critical parameters indicating the probability of survival. Therefore, they should be carefully followed for every COVID-19 patient.

4. Discussion

Our study found that APACHE, SOFA, GKS, CT scores, and laboratory values such as CRP, D-dimer, and procalcitonin were associated with mortality in ICU patients with a diagnosis of COVID-19 followed. We wanted to create a model for estimating mortality by using these variables. We created the model using stepwise regression, and only APACHE, CT score, CRP, and age variables were included in the model.

Many parameters are recommended in the intensive care follow-up of a COVID-19 patient. CRP is one of them. One study used a linear regression model to analyze the relationship between CRP levels and the severity of COVID-19 pneumonia. According to CT images, COVID-19 patients were classified as mild, moderate, and severe. This was the first study to find that the CRP level was significantly higher in moderate and severe patients compared to mild patients.[7] According to CT progress in another study, the disease course was categorized into four stages: Initial, progression, peak, and recovery. CRP levels in the severe group were greater in the initial and progression stages than in the mild group. CT severity scores were positively correlated with CRP, erythrocyte sedimentation rate, and granulocyte/lymphocyte ratio according to the correlation analysis. CRP levels in COVID-19 patients with severe disease increased considerably before CT findings. CRP, which was correlated with the development of this disease, predicted early severe COVID-19.[8] In a study from China, CRP and erythrocyte sedimentation rate (ESR) levels were significantly greater in elderly patients. Severe incidents in elderly COVID-19 patients were substantially associated with CRP levels in this study, which used multivariate logistic regression.[9] In another study from China, CRP and Serum Amyloid A (SAA) values were stated as increasing parameters as the severity of the disease increased.[10] Among the parameters examined in our study, CRP was the only laboratory value associated with mortality that could be included in our model, and an increase in CRP value increased mortality 1.019 times.

Ferritin is another acute-phase reactant used in disease follow-up. Many studies have evaluated the relationship between ferritin and disease severity. One study determined that the ferritin level was significantly higher in patients with moderate or high disease severity due to SARS-CoV2.[11] In a study conducted in China, ferritin in the critical group was considerably higher than in the moderate and severe groups. The median ferritin concentration in the death group was approximately three times higher than that of the survival group. Other inflammatory cytokines, such as CRP, were positively associated with ferritin levels. Ferritin was an independent predictor of in-hospital mortality in the logistic regression analysis. The high-ferritin group, in particular, was associated with a greater mortality rate.[12]

In a study comparing COVID-19 and Non-COVID-19 patients, the involvement of iron metabolism in infection appeared to be direct. On the other hand, iron changes appeared to be self-limited in the acute inflammation of patients who would go under surgery, as well as in other typical phlogistic processes.[13] Ferritin levels were also above normal in the patients in our study. When the effect status alone was examined, it was seen that it did not create a significant difference. For this reason, we thought that this variable should not be included in the

model.

Procalcitonin is an acute-phase reactant that increases, especially in bacterial infections. There are publications examining the relationship between the course of COVID-19 infection and procalcitonin. Krause et al examined 93 COVID-19 cases and reported that cases with procalcitonin (PCT) level >0.1 ng/mL required longer ventilation time, and all cases with PCT level >0.5 ng/mL were intubated.[14] In other studies, it was reported that the ventilation requirement was higher and more deaths occurred in the high PCT group.[15,16] Zhang et al examined 221 COVID-19 patients and found that high PCT levels showed a worse prognosis, and a high PCT level was associated with the severity of the disease.[17] While there are meta-analyses showing that higher PCT levels are associated with the severity of the disease,[18,19] there are also publications reporting the opposite.[20] In our study, PCT level, which was associated with mortality, was not included in the model. Although this valuable indicator shows the association of a bacterial infection and could be used to determine the antibiotic treatment, it was not a sufficient parameter on its own to predict mortality due to COVID-19.

The relationship between D-dimer and COVID-19 has also been investigated. A study conducted on 343 patients emphasized that the D-dimer value, which was four times higher than normal at first admission, significantly increased in-hospital mortality. It has been claimed that it can be an early and helpful marker to be used in the follow-up of the disease.[21] A study in which the researchers examined "D-dimer trend analysis" found that for each 1 μg/mL increase in administering D-dimer level, the risk of intubation increased by 8%. This retrospective study of 1065 inpatients with COVID-19 also found that the higher the intake of D-dimer, the greater the risk of mortality, the need for mechanical ventilation (intubation), and venous thromboembolism (VTE).[22] Researchers from Wuhan have also stated that procalcitonin, ferritin, and D-dimer values effectively predicted mortality in adult patients, whereas creatinine did not.[23] In our study, D-dimer values were significantly higher in the patients who died. However, D-dimer was eliminated from the estimation model, which shows that it has no explanatory power on its own.

We also investigated the effect of Glasgow, APACHE, and SOFA scoring systems frequently used in intensive care patient follow-up to estimate mortality rates. Only APACHE was statistically significant in predicting mortality among these three scoring systems in our study. There are publications emphasizing that a high SOFA score is useful in predicting mortality in patients with COVID-19.[23,24] There are also publications stating that these systems do not have superiority over each other.[25] However, there are more studies emphasizing that APACHE is a more reliable predictor of mortality.[26] A study comparing scoring systems in COVID-19 patients found that APACHE-II made more accurate predictions than Simplified Acute Physiology Score-II (SAPS-II), SOFA, and qSOFA.[27] In a study in which 249 COVID-19 patients in intensive care were examined, the researchers evaluated the SAPS-II, APACHE II, and SOFA scores. According to the study, APACHE II had the best mortality discrimination in ICU patients. The mortality risk increased by 1.155 for every point increase in the APACHE II.[28] In our study, mortality increased 1.078 times with the increase in the APACHE score.

Another study evaluated the course of patients followed for COVID-19 with intermittent CT images. This research aimed to see how chest CT results changed from the time a patient was diagnosed with COVID-19 pneumonia to when they recovered. In the lung sections consisting of 5 lobes, the severity of the involvement was scored visually, giving a score between 1 and 5. Thus, while the minimum value a patient can receive is 0, the maximum value is 25. By looking at the total scores on intermittent CTs, they divided the course of the disease into four stages. Stage 1 (early stage) occurs 0–4 days after the initial symptom onset, and CT score is 2 ± 2. Stage-2 (progressive stage) appears 5–8 days after onset of the initial symptom and increases CT score to (6 ± 4). Stage-3 (peak stage) is seen 9–13 days after the initial symptom onset, and CT score rises to (7 ± 4). Stage-4 (absorption stage) is seen ≥14 days after onset of the initial symptom, and CT score decreases to (6 ± 4). The overall CT score increased until around ten days following the onset of symptoms in most patients (18 out of 21) and then gradually decreased. Ten days following the onset of acute symptoms, the total CT score peaked. The absorption stage lasted longer than 26 days (last day of follow-up) after the beginning of initial symptoms.[6]

In another study, researchers examined COVID-19 patients by scoring CT images. The images of the left lung consisting of 8 segments and the right lung consisting of 10 segments were scored between 0 and 2. In this way, the development of CT findings was divided into four stages in patients who could get a minimum score of 0 and a maximum score of 36. Early-stage (first five days); peak stage (six to ten days); absorption stage (eleven to fifteen days); and recovery stage (after 15 days). The highest average total CT score for all cases was 6.9 ± 4.3. In this study, patients with severe respiratory distress (respiratory rate ≥30 breaths/min), oxygen saturation ≤93.0% at a rest state, and PaO2/FiO2 = 300 mm Hg were excluded.[29] However, in our study, the patients were admitted to the ICU due to respiratory distress. Therefore, we think the mean CT scores were high in our study.

In an intensive care study, patients were divided into two groups, living and non-living, and a total of 86 patients were examined. In intensive care patients whose CT images were scored the same way as in our study, the average CT score was 12.8 ± 4.7. This mean value was also quite similar in our study (13.11 ± 7.4). ICU mortality was correlated with age > 60, CT score > 15, APACHE II score ≥ 15, having dementia, treatment without favipiravir, base excess in blood gas analysis ≤ −2.0, WBC > 10,000/mm^3, D-dimer > 1.6 μg/mL, troponin > 24 ng/L, and Na ≥ 145 mmol/L. Patients with a CT score ≥ 15 had 2.4 times higher mortality risk than those with a CT score < 15 points. The mortality risk increased by 5% for every one-point increase in APACHE II score.[30] As in previous studies, we found that this value was associated with mortality when we scored CT images.

This study's principal limitation was that it was a retrospective one. For this reason, only the tests previously requested by the doctor could be evaluated, and other factors could not be evaluated. There is a need for new studies that use other laboratory data that may be important in estimating mortality in COVID-19 patients and examining them with a stepwise regression model.

Our research found that scoring systems such as APACHE, SOFA, GCS, CT score, and laboratory values such as CRP, D-dimer, procalcitonin are associated with mortality, which correlates with previous studies. However, more importantly, we found that some of these variables are more valuable as predictors of mortality, and can be used to calculate the probability of mortality. In other words, if we know the CT score, APACHE score, CRP value, and age of patients in the intensive care follow-up, we can predict their chances of survival. Although an intensive care doctor experienced in inpatient follow-up can sometimes predict this on their own, they will be able to see the accuracy of their prediction thanks to this model. We think that such foresight, which will increase the prediction power of the doctor, is valuable in the COVID-19 era since the burnout of doctors is increasing. In this respect, we think that being the first anesthesia publication that uses only CT, APACHE, CRP, and age values in a model to estimate the mortality of a COVID-19 patient will be a valuable guide for our colleagues.

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Declaration of competing interest

The authors of this study declare that they have no competing interests.

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