Estimation of biochemical factors affecting survival in intensive care COVID-19 patients undergoing chest CT scoring
A retrospective cross-sectional study

Hakan Dal, MDa, Esra Sultan Karabulut Keklik, MDb, Hakan Yilmaz, MDb, Mücahit Avcil, MDc, Eda Yaman, MDe,*, Gökçe Dağtekin, MDf, Süleyman Diker, MDb, Sema Can, MDg

Abstract
Coronavirus disease 2019 (COVID-19) is a rapidly spreading deadly respiratory disease that emerged in the city of Wuhan in December 2019. As a result of its rapid and widespread transmission, the WHO declared a pandemic on March 11, 2020 and studies evaluating mortality and prognosis in COVID-19 gained importance. The aim of this study was to determine the factors affecting the survival of COVID-19 patients followed up in a tertiary intensive care unit (ICU) and undergoing chest computed tomography (CT) scoring. This retrospective cross-sectional study was conducted with the approval of Uşak University Medical Faculty Ethics Committee between July and September 2020. It included 187 symptomatic patients (67 females, 120 males) with suspected COVID-19 who underwent chest CT scans in the ICU. Demographics, acute physiology and chronic health evaluation (APACHE II), chest CT scores, COVID-19 real-time polymerase chain reaction (RT PCR) results, and laboratory parameters were recorded. SPSS 15.0 for Windows was used for the data analysis. The ages of the patients ranged from 18 to 94 and the mean age was 68.0 ± 13.9 years. The COVID-19 RT PCR test was positive in 86 (46.0%) patients and 110 patients (58.8%) died during the follow-up. ICU stay (P = .024) and total invasive mechanical ventilation time (P < .001) were longer and blood urea nitrogen (BUN) was higher (P < .001) in the nonsurvivors. Patients with an APACHE II score of 23 and above had a 1.12-fold higher mortality rate (95% CI 0.061-0.263). There was no significant difference in total chest CT score between the survivors and nonsurvivors (P = .210). Chest CT score was not significantly associated with mortality in COVID-19 patients. Our idea that COVID-19 will cause greater mortality in patients with severe chest CT findings has changed. More studies on COVID-19 are needed to reveal the markers that affect prognosis and mortality in this period when new variants are affecting the world.

Abbreviations: APACHE = acute physiology and chronic health evaluation, BUN = blood urea nitrogen, COVID-19 = coronavirus disease 2019, CT = computed tomography, ICU = intensive care unit, MV = mechanical ventilation, RT PCR = real-time polymerase chain reaction, SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2, WHO = World Health Organization.

Keywords: chest CT scoring, COVID-19, intensive care unit, pneumonia

1. Introduction
Coronavirus disease 2019 (COVID-19), caused by the new coronavirus severe acute respiratory syndrome coronavirus 2, is a highly contagious respiratory disease that has emerged, causing a large number of deaths and impairing quality of life.[1,2] COVID-19 first appeared in the city of Wuhan in China Hubei province in December 2019.[3] The World Health Organization (WHO) declared a public health emergency and a pandemic on March 11, 2020, after the disease spread rapidly around the world and the disease was seen in all continents and in more than 190 countries.[3]

COVID-19 is a disease with a very variable clinical course that may have a symptomless or mild course and may leave patients needing oxygen support for the rest of their lives and even lead to death. With this disease, the number of presentations to health centers dramatically increased and the capacities of hospitals and intensive care units (ICUs) were put under pressure. Therefore, the management of disease severity is important for prevention of earlier death due to COVID-19 and poor

No financial support is reported.

The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

Correspondence: Eda Yaman, Uşak Medical Faculty, Department of Emergency Medicine, Uşak, 64100, Turkey (e-mail: edayamancbu2017@hotmail.com).

Copyright © 2022 the Author(s). Published by Wolters Kluwer Health, Inc. This is an open-access article distributed under the terms of the Creative Commons Attribution-Non Commercial License 4.0 (CCBY-NC), where it is permissible to download, share, remix, transform, and buildup the work provided it is properly cited. The work cannot be used commercially without permission from the journal.

How to cite this article: Dal H, Karabulut Keklik E-S, Yilmaz H, Avcil M, Yaman E, Dağtekin G, Diker S, Can S. Estimation of biochemical factors affecting survival in intensive care COVID-19 patients undergoing chest CT scoring: A retrospective cross-sectional study. Medicine 2022;101:40(e30407).

Received: 23 December 2021 / Received in final form: 13 July 2022 / Accepted: 26 July 2022
http://dx.doi.org/10.1097/MD.0000000000030407
prognosis in critical care patients. For this purpose, many studies have explored the factors affecting the course and mortality of the disease. There are studies showing that there is a relationship between advanced age, presence of comorbidity, high C-reactive protein, high D-dimer, lactate dehydrogenase level, procalcitonin level, lymphocyte count, need for mechanical ventilation (MV), chest computed tomography (CT) score, and the course of the disease.[4,5] The aim of our retrospective study was to determine the factors affecting the survival of COVID-19 patients followed up in a tertiary intensive care unit (ICU) and undergoing chest CT scoring.

2. Materials and methods

2.1. Ethical approval

This retrospective cross-sectional study was carried out in Uşak Research and Training Hospital. The study protocol was approved by Uşak University Medical Faculty Local Ethics Committee with the number/date 26.11.20/01.07.2020. The study was conducted in accordance with the Declaration of Helsinki. Written informed consent was waived due to the retrospective nature of the study.

2.2. Study design and population

This retrospective cross-sectional study was conducted with the approval of Uşak University Medical Faculty Ethics Committee between July and September 2020. The study included 187 symptomatic patients (67 females, 120 males) with suspected COVID-19 who underwent chest CT scans in the ICU.

The exclusion criteria were as follows:

1. Patients under the age of 18,
2. Pregnant and lactating women,
3. Those with a diagnosis of any malignancy,
4. Patients hospitalized in the ICU for <24 hours,
5. Patients transferred from Uşak University Faculty of Medicine Training and Research Hospital to an external center,
6. Patients with at least 1 value missing in the parameters to be evaluated in the study,
7. Patients who had not had a chest CT scan.

All patients who were older than 18 years of age and were followed up in the intensive care unit for at least 24 hours with the suspicion of symptomatic COVID-19 in the Uşak University Faculty of Medicine Training and Research Hospital between June and September 2020 and who did not meet the exclusion criteria were included.

Patients with symptoms of high fever and respiratory tract infection (cough, shortness of breath, use of accessory respiratory muscles); patients with oxygen saturation in room air below 90%; patients with a respiratory rate above 30; laboratory-tested COVID-19 patients with supporting findings (high C-reactive protein, lymphopenia, high procalcitonin, high D-dimer, etc); patients with bilateral lobular, peripheral localized patchy ground-glass opacities on thorax CT imaging; and patients with positive reverse transcriptase polymerase chain reaction (RT PCR) results and symptomatic COVID-19 were considered patients.[6,7]

2.3. Data collection

Demographics, COVID-19 RT PCR test results, comorbidities, survival, length of hospital stay, duration of MV, acute physiology and chronic health evaluation (APACHE II) score, chest CT score, the first and last routine blood tests including arterial blood gas analysis, complete blood count, electrolytes, renal-liver function tests, coagulation, and inflammatory parameters were evaluated. A low-dose chest CT device (Toshiba Aquilion 16 CT Scanner, Kyoto, Japan) for imaging COVID-19 patients was used for all assessments.

2.4. Statistical analysis

All statistical calculations were performed with SPSS 15.0 (SPSS for Windows, Chicago, IL, USA). The chi-square test, Student t-test, and multivariate logistic regression analysis were used for analysis of the data. The results were presented as mean ± standard deviation and median (minimum–maximum) for the quantitative data and as frequency (percentage) for the categorical data. In the analyses, P < .05 was accepted as statistically significant.

2.5. Chest CT scoring

Chest CT scoring of the patients was performed in the form of semiquantitative CT severity scoring recommended by Pan et al and Francone et al.[7,8] The bilateral lungs were divided into 5 regions according to the anatomical structure: left upper lobe, left lower lobe, right upper lobe, right middle lobe, and right lower lobe. The score was calculated according to the severity of each lobe involvement as follows: 0: No involvement, 1: <5% involvement, 2: 5% to 25% involvement, 3: 26% to 50% involvement, 4: 51% to 75% involvement, 5: 75% to 100% involvement. The total chest CT score was calculated by summing the separately calculated scores for the 5 lobes. Accordingly, the lowest score was 0 and the highest score was 25.

| Parameters                        | n (%)         |
|-----------------------------------|---------------|
| Gender                            |               |
| Male                              | 120 (64.2)    |
| Female                            | 67 (35.8)     |
| Age, y                            | 68.0 ± 13.9   |
| BMI                               |               |
| <30.0                             | 149 (79.7)    |
| ≥30.0                             | 38 (20.3)     |
| Total chest CT scoring            |               |
| Mean ± SD                         | 14.89 ± 6.59  |
| W/IG therapy                      |               |
| (+)                               | 72 (38.5)     |
| (−)                               | 115 (61.5)    |
| Tocilizumab treatment             |               |
| (+)                               | 67 (35.8)     |
| (−)                               | 120 (64.2)    |
| Hemofiltration                    |               |
| (+)                               | 27 (14.4)     |
| (−)                               | 160 (85.6)    |
| Plasma treatment                  |               |
| (+)                               | 57 (30.5)     |
| (−)                               | 130 (69.5)    |
| COVID-19 RT PCR test results      |               |
| Negative                          | 101 (54.0)    |
| Positive                          | 86 (46.0)     |
| Comorbidities                     |               |
| Hypertension                      | 99 (52.9)     |
| Coronary artery disease           | 60 (32.1)     |
| Congestive heart failure          | 37 (19.8)     |
| Chronic obstructive pulmonary disease | 68 (36.4)   |
| Diabetic mellitus                 | 65 (34.8)     |
| Chronic renal failure             | 9 (4.8)       |
| APACHE score                      | Mean ± SD     |
| 21.79 ± 8.62                     |

APACHE = Acute Physiology and Chronic Health Evaluation, BMI = body mass index, W/IG = intravenous immunoglobulin, RT PCR = reverse transcriptase polymerase chain reaction.
3. Results

While 64.2% (n = 120) of the patients were male, 35.8% (n = 67) were female, and the ages of the patients ranged from 18 to 94, with a mean age of 68.0 ± 13.9 years. The distribution of the study group according to demographics and clinical characteristics is given in Table 1.

The COVID-19 PCR test was positive in 86 patients (46.0%) in the study group, and 110 of the patients (58.8%) died in the ICU follow-up. The mean age of the patients who died during intensive care follow-up was significantly higher than the age of those who survived (P = .002). The total chest CT score was 14.89 ± 6.585 points on average. There was no significant difference in total chest CT scores between living and deceased patients (P > .210).

The length of stay in the ICU of the patients who died during the intensive care follow-up was significantly longer than that of the surviving patients (P = .024). The duration of treatment with a mechanical ventilator in patients who died during intensive care follow-up was significantly longer than that of the patients who survived (P < .001). The distribution of the survivors and nonsurvivors according to clinical parameters is given in Table 2.

Blood urea nitrogen (BUN) was significantly higher in the nonsurvivor group (P < .001). The comparison of the patients in the study group according to their laboratory results is given in Table 3.

Multivariate logistic regression analysis was performed with age, gender, COVID-19 RT PCR results, presence of comorbidity, and APACHE II scores thought to be related to mortality in the study group. Mortality was 1.12 times higher in patients with an APACHE II score of 23 and above compared to patients with an APACHE II score of 22 and below (95% CI 0.061–0.263). The results of the multivariate logistic regression analysis with variables related to mortality in the study group are shown in Table 4.

4. Discussion

In the present study, we examined the variables affecting mortality in patients who were followed up in the ICU due to COVID-19 and whose chest CT score was calculated. Most of the patients followed up in the ICU were men and the mean age was over 68 years. The most common comorbid disease in patients was hypertension. In the literature, it was seen that patients with COVID-19 were mostly advanced age males, and the most common accompanying comorbidity was hypertension.9–11

| Table 2 | Clinical parameters of the survivors and nonsurvivors. |
|---------|------------------------------------------------------|
| Variables | Nonsurvivors | Survivors | Total | Test value; P |
| Gender | | | | |
| Female | 40 (36.4) | 27 (35.1) | 67 (35.8) | 0.033; 855 |
| Male | 70 (58.3) | 50 (64.9) | 120 (64.2) | |
| Age, y | | | | |
| Mean ± SD | 70.5 ± 13.3 | 64.3 ± 13.9 | 68.0 ± 13.9 | 3.091; 0.002 |
| BMI | | | | |
| <30 | 90 (81.8) | 59 (76.6) | 149 (79.7) | 0.468; 494 |
| ≥30 | 20 (18.2) | 18 (23.4) | 38 (20.3) | |
| Total chest CT score | | | | |
| Mean ± SD | 14.38 ± 6.86 | 15.61 ± 6.14 | 14.89 ± 6.585 | −1.229; 0.210 |
| COVID-19 RT PCR | | | | |
| Negative | 54 (49.1) | 47 (61.0) | 101 (54.0) | 2.603; 107 |
| Positive | 56 (50.9) | 30 (39.0) | 86 (46.0) | |
| Length of stay in ICU | | | | |
| Mean ± SD | 8.65 ± 4.60 | 7.08 ± 4.75 | 8.01 ± 4.71 | 2.276; 024 |
| Total MV duration | | | | |
| Mean ± SD | 8.20 ± 4.99 | 4.29 ± 3.88 | 6.59 ± 4.95 | 5.765; <.001 |

CT = computed tomography, ICU = intensive care unit, MV = mechanical ventilation, RT PCR = real-time polymerase chain reaction.

| Table 3 | Comparison of the laboratory findings of the nonsurvivors and survivors. |
|---------|------------------------------------------------------|
| Variables | Nonsurvivors (mean ± SD) | Survivors (mean ± SD) | Total (mean ± SD) | Test value; P |
| Hemoglobin | 12.06 ± 2.34 | 12.28 ± 2.13 | 12.15 ± 2.25 | −0.662; 509 |
| White blood cell | 11.89 ± 13.60 | 9.85 ± 5.37 | 11.05 ± 11.01 | 1.225; 222 |
| Platelet | 232.18 ± 114.41 | 240.44 ± 110.73 | 235.61 ± 112.66 | −0.485; 628 |
| pH | 9.06 ± 14.30 | 8.13 ± 4.40 | 8.67 ± 11.28 | 0.541; 589 |
| Lymphocyte | 4.78 ± 30.93 | 8.03 ± 42.97 | 6.13 ± 36.36 | −0.591; 555 |
| C-reactive protein | 144.64 ± 82.68 | 142.43 ± 90.39 | 143.73 ± 85.54 | 0.132; 895 |
| D-dimer | 2070.24 ± 1460.48 | 1989.19 ± 1461.26 | 1996.83 ± 1458.41 | 0.713; 477 |
| Fibrinogen | 536.45 ± 153.91 | 548.29 ± 158.44 | 541.21 ± 155.15 | −0.395; 694 |
| Activated partial thromboplastin time | 16.61 ± 1.78 | 51.70 ± 6.90 | 31.77 ± 34.61 | −0.530; 597 |
| Prothrombin time | 86.57 ± 27.94 | 90.71 ± 21.45 | 88.16 ± 25.61 | −0.945; 346 |
| Calcium | 8.07 ± 0.74 | 8.24 ± 0.64 | 8.14 ± 0.70 | −1.035; 104 |
| Potassium | 4.29 ± 0.89 | 4.27 ± 0.71 | 4.28 ± 0.82 | 0.138; 891 |
| Sodium | 138.35 ± 14.12 | 139.58 ± 4.68 | 138.87 ± 11.12 | −0.739; 461 |
| Creatinine | 1.61 ± 1.19 | 2.43 ± 5.85 | 1.96 ± 3.93 | −1.396; 164 |
| BUN | 46.76 ± 33.30 | 30.99 ± 20.62 | 40.14 ± 29.65 | 3.652; <.001 |

BUN = blood urea nitrogen.
The COVID-19 RT PCR result was positive in 86 of the patients in the study, and 56 of these patients died. The mortality rate was significantly higher in elderly patients (>70.5), those who stayed longer in the ICU, and those who had longer MV. In many studies, advanced age has been found to be a risk factor that increases mortality in COVID-19. In the study by Alhart et al., the mortality rate was high in patients with advanced age and long ICU stay. However, no correlation was found between the duration of MV and mortality. In the study by Bayrak et al., no significant relationship was found between the length of stay in the ICU and the mortality rate in patients with COVID-19, but mortality was significantly higher in patients with long intubation and MV times.

In our study, the mortality rate was significantly higher in patients with high BUN levels, which is one of the laboratory parameters. Except for BUN, no significant correlation was found between biochemistry, hemogram, blood gas, and coagulation parameters and mortality. In many studies in the literature, high BUN has been found to be associated with increased mortality in COVID-19 patients and this supports our study.

The APACHE II score is a frequently used system to predict the mortality rate of patients treated in the ICU. In our study, the mortality rate of patients with an APACHE II score of 23 and above was significantly higher. In many studies in the literature, APACHE II score has been found to be associated with an increased mortality rate.

Since the start of the COVID-19 pandemic, many patients have presented to our tertiary health care center. We were the only pandemic hospital in our city center. During this time, we realized that the mortality of patients with severe chest CT findings was not as high as we expected, and so we designed the present study. When we reviewed the literature, in some studies, a significant relationship was found between chest CT scoring and the prognosis and mortality of COVID-19 patients. However, in our study, the chest CT score was not significantly associated with mortality.

Our study has some limitations. We performed a retrospective analysis with data from a limited number of patients for a period of 3 months. During the current pandemic, it was predicted that a prospective study involving a larger number of patients would take longer and be more complex to complete. Patients with clinical symptoms and laboratory findings or chest CT findings compatible with COVID-19 and whose clinical conditions could not be explained by any other diagnosis were included in the study as symptomatic COVID-19 patients. The inclusion of patients with negative RT PCR results but clinical symptoms and laboratory or chest CT imaging compatible with COVID-19 is also a limitation.

| Variables                  | OR     | 95% CI     | P   |
|----------------------------|--------|------------|-----|
| Age Reference: <65 age     | 0.680  | 0.332–1.396| .294|
| Gender                     | 1.156  | 0.577–2.317| .682|
| Reference: female          |        |            |     |
| COVID-19 RT PCR            | 0.507  | 0.256–1.001| .050|
| Reference: negative        |        |            |     |
| Comorbidities              | 1.209  | 0.509–2.874| .667|
| Reference: (–)             |        |            |     |
| APACHE II Score            | 1.127  | 0.061–0.263| <.001|
| Reference: <22             |        |            |     |
| Constant                   | 6.983  | <.001      |     |

APACHE = acute physiology and chronic health evaluation, COVID-19 = coronavirus disease, RT PCR = real-time polymerase chain reaction.

References

[1] Drosten C, Gunther S, Preiser W, et al. Identification of a novel coronavirus in patients with severe acute respiratory syndrome. N Engl J Med. 2003;348:1967–76.
[2] Zaki AM, van Boheemen S, Bestebroer TM, et al. Isolation of a novel coronavirus from a man with pneumonia in Saudi Arabia. N Engl J Med. 2012;367:1814–20.
[3] Yaman F, Demirel B, Yilmaz A, et al. Retrospective evaluation of laboratory findings of suspected paediatric COVID-19 patients with positive and negative RT-PCR. Disas Emerg Med J. 2021;6:1–7.
[4] Hajahmadi S, Shayanfar A, Janghorbani M, et al. Chest computed tomography severity score to predict adverse outcomes of patients with COVID-19. Infect Chemother. 2021;53:308–18.
[5] Zhou F, Yu T, Du R, et al. Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study [published correction appears in Lancet. 2020 Mar 28;395(10221):1038]. Lancet. 2020;395:1054–62.
[6] Republic of Turkey Ministry of Health General Directorate of Public Health. Guide to COVID-19 (SARS-CoV2) Infection. 23 March 2020. Page 9. Available at https://www.ekmud.org.tr/files/uploads/files/Saglik-Bakanligi-COVID-19-rehberi-23032020.pdf. [Access date July 2, 2022].
[7] Pan F, Ye T, Sun P, et al. Time course of lung changes at chest CT during recovery from coronavirus disease 2019 (COVID-19). Radiology. 2020;295:715–21.
[8] Francone M, Iafrete F, Masgi GM, et al. Chest CT score in COVID-19 patients: correlation with disease severity and short-term prognosis. Eur Radiol. 2020;30:6808–17.
[9] Alamdari NM, Afagh S, Rahimi FS, et al. Mortality risk factors among hospitalized COVID-19 patients in a major referral center in Iran. Tohoku J Exp Med. 2020;252:73–84.
[10] Zhou S, Chen C, Hu Y, et al. Chest CT imaging features and severity scores as biomarkers for prognostic prediction in patients with COVID-19. Ann Transl Med. 2020;8:1449.
[11] Arement M, Yim E, Klaff L, et al. Characteristics and outcomes of 21 critically ill patients with COVID-19 in Washington State. JAMA. 2020;323:1612–4.
[12] Wang Y, Lu X, Li Y, et al. Clinical course and outcomes of 344 intensive care patients with COVID-19. Am J Respir Crit Care Med. 2020;201:1430–4.
[13] Wu Z, McGoogan JM. Characteristics of and important lessons from the coronavirus disease 2019 (COVID-19) outbreak in China: summary of a report of 72,314 cases from the Chinese Center for Disease Control and Prevention. JAMA. 2020;323:1239–42.

[14] Alharthy A, Aletreby W, Faqhi F, et al. Clinical characteristics and predictors of 28-day mortality in 352 critically ill patients with COVID-19: a retrospective study. J Epidemiol Glob Health. 2021;11:98–104.

[15] Bayrak V, Şentürk Durukan N, Demirer Aydemir F, et al. Risk factors associated with mortality in intensive care COVID-19 patients: the importance of chest CT score and intubation timing as risk factors. Turk J Med Sci. 2021;51:1665–74.

[16] Küçükceran K, Ayrancı MK, Girişgin AS, et al. The role of the BUN/albumin ratio in predicting mortality in COVID-19 patients in the emergency department. Am J Emerg Med. 2021;48:33–7.

[17] Cheng A, Hu L, Wang Y, et al. Diagnostic performance of initial blood urea nitrogen combined with D-dimer levels for predicting in-hospital mortality in COVID-19 patients. Int J Antimicrob Agents. 2020;56:106110.

[18] Wernly B, Lichtenauer M, Vellinga NAR, et al. Blood urea nitrogen (BUN) independently predicts mortality in critically ill patients admitted to ICU: A multicenter study. Clin Hemorheol Microcirc. 2018;69:123–31.

[19] Karthick D, Divahar M, Masoodu KSM, et al. Apache II score as a predictor of hospital mortality in COVID-19 patients. Int J Surg Res. 2020;9:9–16.

[20] Kocayiğit H, Özmen Süner K, Tomak Y, et al. Characteristics and outcomes of critically ill patients with covid-19 in Sakarya, Turkey: a single centre cohort study. Turk J Med Sci. 2021;510:440–7.

[21] Colombi D, Bodini FC, Petrini M, et al. Well-aerated lung on admitting chest CT to predict adverse outcome in COVID-19 pneumonia. Radiology. 2020;296:E86–96.

[22] Salaffi F, Carotti M, Tardella M, et al. The role of a chest computed tomography severity score in coronavirus disease 2019 pneumonia. Medicine (Baltim). 2020;99:e22433.