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Association of perinephric fat stranding with CT severity scores and mortality in COVID-19 patients

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ABSTRACT

Aims: To investigate the relationship between the presence of perinephric fat stranding (PFS) on the first CTwith three consecutive chest CT severity scores (CT-SS), mortality and intensive care unit admission in COVID-19 patients.

Methods: This single-center retrospective study, included 457 (≥18 years) COVID-19 patients with positive RT-PCR tests.A radiologist calculated three consecutive CT-SS for COVID-19 pneumonia using a visual scoring system ranging from 0 to 25 points.Grades of PFS on initialCTs were defined as none, mild, moderate, or severe. Firstly,patients were divided into two groups, with and without PFS. The Association of PFS with demographic and laboratory data, CT-SS and mortality rates were analyzed. We divided patients into four subgroups based on PFS grading and investigated temporal changes of mean CT-SS of three consecutive CTs in each PFS subgroup using a paired-sample test and Wilcoxon signed-rank test.

Results: Patients with PFS were associated with older age($p<0.001$) and had higher CT-SS ($p=0.03$). We found a particularly strong association between PFS and mortality ($p<0.001$) and intensive care unit admission ($p=0.001$). Statistical associations were found between PFS and elevated serum BUN ($p=0.004$), creatinine ($p=0.007$), CRP ($p=0.02$) and ferritin ($p=0.005$). In multivariate logistic regression analysis, older age was associated with 1.067-fold ($p< 0.001$), PFS 1.964-fold ($p=0.007$), elevated serum creatinine 3.630-fold ($p=0.005$) higher risks of mortality.In PFS subgroups other than severe, there were significant increases between the first and second CT-SS($p<0.001$, $p<0.001$, $p=0.003$).

Conclusion: Perinephric fat stranding is an important CT finding that can alert cliniciansto the poor prognosis of COVID-19 patients in early periods.

Keywords: COVID-19, Coronavirus, CT, perinephric fat stranding

INTRODUCTION

Coronavirus disease 2019 (COVID-19) is a pandemic infection caused by the severe "severe acute respiratory syndrome coronavirus 2" (SARS-CoV-2). COVID-19 typically affects the pulmonary system. But in severe cases, it can affect many extra-pulmonary systems.[1]

SARS-CoV-2 potentially affects many organs such as the kidney, intestine, liver, gallbladder and testis.[2–4] Since the outbreak of COVID-19, acute kidney injury (AKI) associated with COVID-19 has been reported in studies.[5–7] Renal dysfunction due to COVID-19 manifests clinically with elevated serum creatinine (SCr) levels.[5–7] Its mechanism has not yet been clearly elucidated. In studies, cytokine storm, direct attack by SARS-CoV-2, immune system-related injury and hypercoagulation were listed among the causes of COVID-19-related renal dysfunction.[8–10]

The perinephric space is an important compartment of the retroperitoneum affected by various acute diseases. Perinephric fat stranding (PFS) is pathologically seen as a result of the thickening of the septa formed by fibrous lamellae.[11] On non-enhanced computed tomography (NECT) imaging, PFS is observed as increased soft tissue densities as streaks in the perinephric adipose tissue, thickening of the perirenal fascia and minimal fluid in the perinephric area. Although SCr values still have a very important role in indicating acute renal failure, since the changes of SCr only show functional changes in the kidney, they do not directly reflect renal parenchymal injury.[12] With progressive renal parenchyma injury, inflammation and fluid may spread into the perirenal fat area, resulting in streaking in the perinephric adipose tissue.COVID-19 patients with perinephric fat stranding (PFS) had higher SCr levels, possibly as a result of more severe parenchymal injury and

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inflammation.[13] PFS may also occur after urinary obstruction, spontaneous stone removal, renal infection, inflammation, renal vascular disease and renal trauma.[14] To evaluate the parenchymal damage due to COVID-19 only, we did not include patients with urinary stones or hydronephrosis, pyelonephritis and a history of chronic renal failure.

In the literature, PFS was observed in some COVID-19 patients on theirchest NECT images and they reported that PFS was associated with severe renal failure. The study results showthat CT findings can provide a sensitive and non-invasive assessment of renal failure in COVID-19 patients and alert clinicians at the early stage of the disease, especially at admission.[13]

Chest computed tomography severity score (CT-SS) is a scoring system calculated based on the percentage of COVID-19 parenchymal involvement and shows the severity of COVID-19 pneumonia. Therefore, it is a very important CT finding for the prognosis of the patient.

In our study, we aimed to investigate the prognosis of COVID-19 patients by using the relationship between the presence of perinephric fat stranding on the first non-contrast CT and consecutive CT-SS and mortality rates.

METHODS

Our study is a single-center retrospective study of 549 patients who applied to our hospital between October 2021 and March 2022. The study was initiated with the approval of the Amasya University Medical Faculty Clinical Researches Ethics Committee (Date: 06.10.2022; Decision No: 95). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki and Good Clinical Practice.

Study Population and Data Collection

Inclusion criteria: Patients over 18 years old and with laboratory-confirmed COVID-19 by a positive real-time reverse transcriptase–polymerase chain reaction (RT-PCR) test.

Exclusion criteria: Pediatric patients, pregnant women, patients with negative RT-PCR tests, those with image artifacts that prevent evaluation on NECT, incomplete clinical data and chest CT images, with urolithiasis and/or hydronephrosis, unilateral or bilateral atrophic kidney, chronic kidney disease (CKD) and acute pyelonephritis were excluded from the study.

We excluded a total of 92 patients according to our exclusion criteria. So finally, a total of 457 COVID-19 patients were included in the study. Detailed information about the number of excluded patients due to each exclusion criterion is given in **Figure 1**.

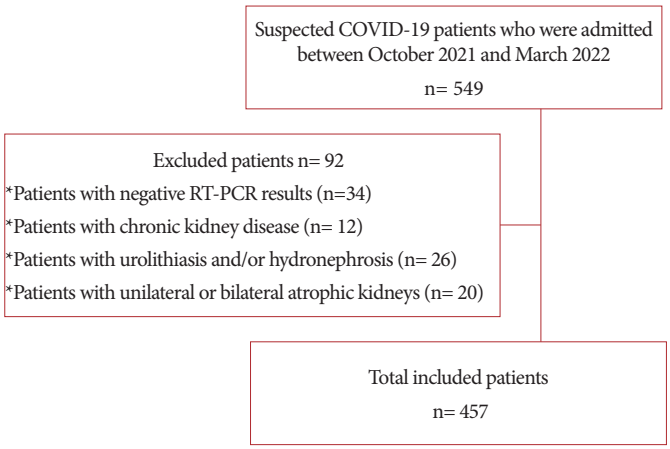


Figure 1. Flowchart for patient inclusion

Clinical and Laboratory Data

All patients' demographic information, comorbidities, the laboratory findingsobtained within 1 day from the initial chest CT data were reviewed from the electronic medical records of our hospital. In addition, admission to the hospital and/or ICU, length of stay and date of death were also screened.

Chest CT Image Acquisition

In all non-contrast chest CT scans, patients were instructed to hold their breath in the supine position. Axial images included areas from the beginning of the thorax to the upper abdomen(including the middle part of the kidneys).The lower pole of the kidneys was included in the evaluation in patients who had thorax CT and abdominal CT performed simultaneously.Control CTs of the patients were performed in cases such as respiratory distress, decreased oxygen saturation and worsening clinical and laboratory findings.

The multidetector CT (MDCT) scanner 128-slice GE Healthcare Revolution EVO CT (GE Medical Systems; Milwaukee, WI) was used to scan all patients. Chest CT scanning parameters were as follows: Tube current, 100–450 mA; tube voltage, 120 kV; beam collimation, 64 mm × 0.625 mm; beam pitch, 1.375; reconstruction kernel, standard; slice thickness and section overlap, 0.625 mm; and, 0.625 mm gantry rotation, 0.4 seconds; acquisition direction, craniocaudal.

Image Analysis

Chest CT images of the patients were retrospectively reviewed by a radiologist with 16 years of experience (B.A) on a standard clinical Picture Archiving and Communication Systems (PACS) workstation, blinded to the patient's clinical data and outcomes of the study.CT severity scores (CT-SS) for COVID-19 pneumonia were calculated using a visual scoring system in CT images previously used in the literatüre.[15] It was calculated as, 0 if there is no lung involvement; 1 if < 5% involvement; 2 if 5–25% involvement; 3 if 26–49%; 4 if 50-75% involvement; 5 if there is > 75% involvement. Total CT-SS is obtained by summing 5 lung lobe scores (score range: 0-25).

In addition,the radiologist evaluated the perirenal areas included in the first chest NECT for the presence or absence of PFS and classified the grades of PFS that were used in previous studies.[16,17] Since the drugs used during the treatment of COVID patients can potentially lead to renal failure, the evaluation for PFS was only made on the first CT scans of the patients at admission. Follow-up CTs were evaluated only for CT-SS, which indicates the severity of parenchymal involvement. The PFS was defined on CT as thin or thick streaks of soft tissue attenuation and/or any associated perirenal fluid extending radially or parallel to the renal capsule, which could be short or long.[17] First, we divided patients into two groups, with and without PFS and the association of PFS with demographic and laboratory data, CT-SS and mortality rates was analyzed. Then, we divided patients into four subgroups according to the grading of PFS. Grades of PFS on NECT are defined as follows: None: Normal perinephric area; Mild: few thin streaks extending to kidney capsule; Moderate: multiple thin streaks extending into the renal capsule; Severe: many thick and long streaks extending to the renal capsuleand/or presence of perinephric fluid.[16,17] We investigated the temporal changes of the mean CT-SS of three consecutive CTs in each PFS subgroup.

Statistical Analysis

SPSS Statistics for Windows, Version 22.0 (IBM Corp. Released 2017. Armonk, NY) was used for statistical analysis. The Kolmogorov-Smirnov test was used to examine the conformity of the variables to the normal distribution. In descriptive analyses, normal distribution data were shown as mean and standard deviation (mean±SD).Student's t-test was used in the comparison of continuous variables according to the presence of PFS, which were normally distributed. Chi-square or Fisher tests were used instead of comparing categorical variables according to the presence of PFS (The Fisher test was used when the values displayed in the cells did not meet the assumptions of the Chi-Square test). Statistically significant variables, obtained from univariate analysis were analyzed by multivariate logistic regression analysis to determine independent predictors of patients' mortality. The Hosmer-Lemeshow test was used for model fit. Paired samples test was used to evaluate the temporal changes of mean CT-SS values in three consecutive CTs in each PFS subgroup. Wilcoxon signed-rank test was used when the number of cases was less than 30 and parametric assumptions could not be provided. A $p<0.05$ value was considered a statistically significant result.

RESULTS

Demographic Features

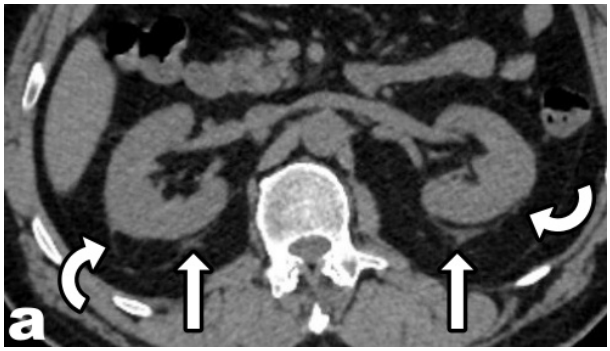
The study population included 457 patients with a mean age of 63.86 ±14.06 years.A total of 181/457 (39.61%) patients had PFS. The mean age of the PFS group was 67.76 ±11.45. A total of 258/457 (56.46%) were male. In the PFS group, 73.26% (137/187) of the patients were male. PFS was statistically associated with older age ($p<0.001$) andmale gender ($p<0.001$). Of the study population, 8.32% were outpatients, 118/457 (25.82%) were treated in the intensive care unit (ICU) and 127/457 (27.79%) died.In the group of patients with PFS, 62/181(34.25%) were treated in the ICU and 70/181 (38.67%) died. We found a particularly strong association between the presence of PFS with mortality rates ($p<0.001$) and the need for ICU treatment ($p=0.001$).The most common comorbidities of the study population were cardiovascular disease (260/457; 56.9%) and diabetes mellitus (DM) (140/457;30.6%) (**Table 1**).

In laboratory findings, statistical associations were found between the presence of PFS with elevated serum blood urea nitrogen (BUN) ($p=0.004$),serum creatinine (SCr) ($p=0.007$), C-reactive protein (CRP) ($p=0.02$), ferritin ($p=0.005$) and other abnormal laboratory findings shown in **Table 2**. In our study population, 89/457 (19.5%) patients had increased SCr levels (SCr>1.2 mg/dl) and 52.8% of these patients had PFS.

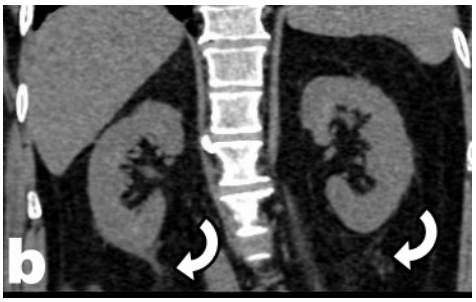
Of all inpatients, the mean length of stay at the hospital was 15.57±12 days and the mean length of stay at the ICU was 14.19±12.7 days. While there was a significant relationship between the presence of PFS and the longer length of stay in the hospital ($p=0.003$), there was no significant difference between the length of stay in the ICU ($p=0.323$) (**Table 2**).

Comparison of the Presence of PFS with First, Second and Third CT-SS

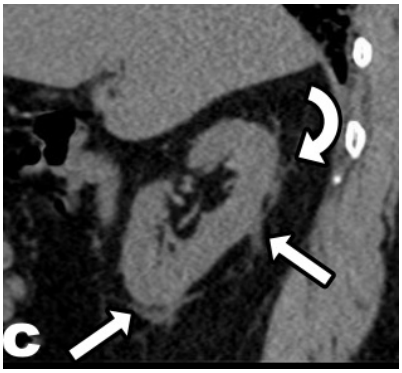
In the total study population, 250 patients had a second follow-up chest CT and 106 had a third follow-up chest CT. The mean first CT-SS of total patients was 10.39±7.81. The mean value of initial CT-SS was 11.72±7.93 in the group with PFS. There was a statistical association between the presence of PFS on the first CT with the high first, second and third CT-SS ($p=0.003$,$p<0.001$, $p=0.009$) (**Figure 2, 3**) (**Table 2**).



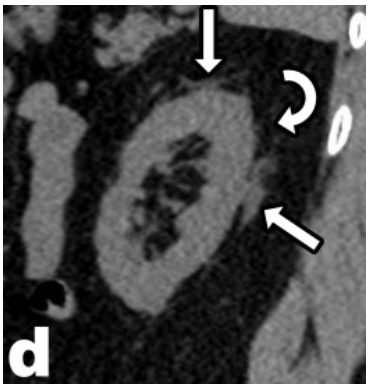
(a) Axial image of initial non-contrast CT shows bilateral perinephric fat stranding (curved arrows) and minimal perinephric fluid (straight arrows). Compatible with severe grade PFS



(b) Coronal image of initial non-contrast CT shows bilateral perinephric fat stranding (curved arrows)

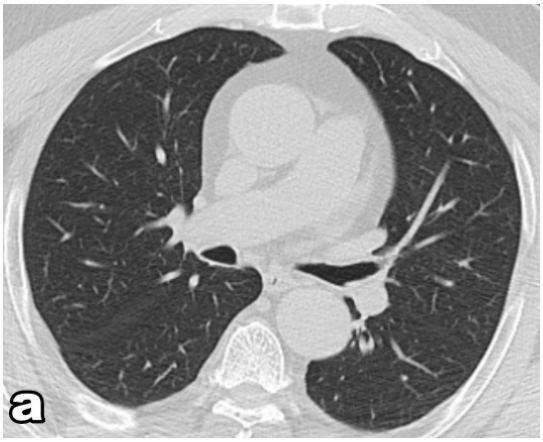


(c) Sagittal image of initial non-contrast CT showsperinephric fat stranding (curved arrows) and minimal perinephric fluid (straight arrows) (right kidney)

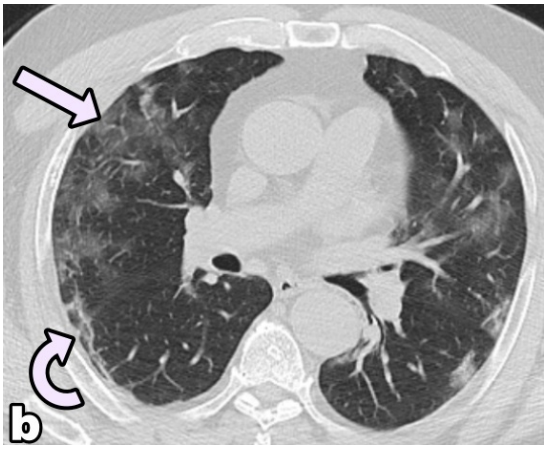


(d) Sagittal image of initial non-contrast CT shows perinephric fat stranding (curved arrows) and minimal perinephric fluid (straight arrows) (left kidney)

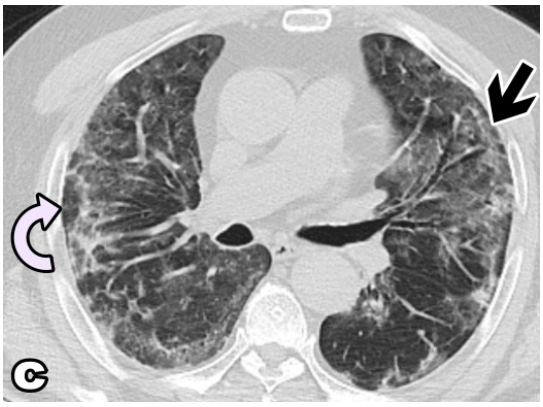
Figure 2 a, b, c, d. A 62-year-old man with a positive RT-PCR test. He was hospitalized after the second CT and treated in the intensive care unit. He was discharged after 24 days of treatment.



(a) Axial lung window of non-contrast first chest CT shows no pathological findings. CT severity score= 0



(b) Axial lung window of non-contrast second chest CT shows bilateral ground glass. opacities (straight white arrow) and subpleural lines (curved arrow). CT severity score=15



(c) Axial lung window of non-contrast second chest CT shows bilateral subpleural lines (curved arrow) and crazy-paving pattern (straight black arrow). CT severity score=23

Figure 3 a, b, c. Axial lung window of non-contrast first (a), second (b), and third (c) chest CT images of the patient in Fig 2.

Comparison of the Grading of PFS with First, Second and Third CT-SS

In the current study,276 (60.4%) patients had no PFS, 129 (28.2%) patients had mild stage PFS, 47 (10.3%) patients had moderate stage PFS, 5 (1.1%) patients had severe stage PFS in their initial non-contrast CT. Among the patients with three consecutive CTs, the mean values of the first, second and third CT-SS in each PFS subgroupare as in **Figure 4**. In the mild,and moderate subgroups, there were significant increases between the first and second CT-SS (p<0.001, p=0.003) (**Table 3**). Since only one patient in the severe group had three CTs, statistical analysis could not be determined between PFS subgroups with a third CT-SS.

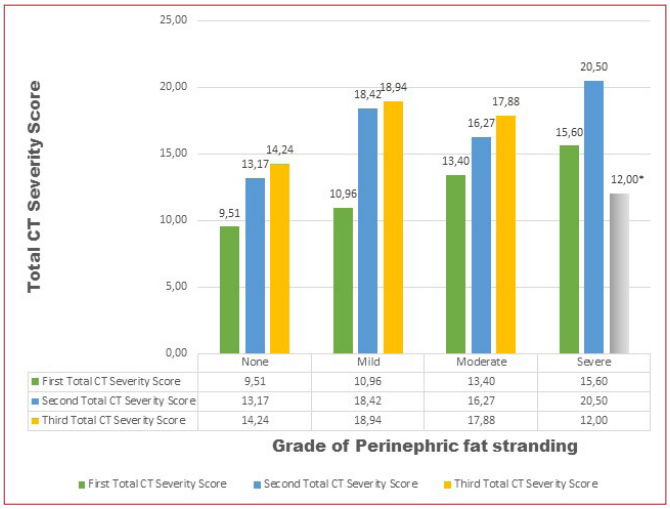


Figure 4. The statistical graphic shows the mean values of three consecutive CT severity scores in each PFS subgroup. * Since there was only one patient in the severe group with three CTs, statistical analysis could not be determined between PFS subgroups with a third CT-SS.

Results of Multivariate Analysis of Risk Factors for Mortality

In multivariate analysis, older age was associated with 1.067-fold (95% CI:1.041-1.094, p< 0.001), presence of PFS 1.964-fold (95% CI: 1.199-3.217, p=0.007), elevated SCr levels 3.630-fold (95% CI 1.471-8.953, p=0.005) higher risks of mortality (**Table 4**).

DISCUSSION

In our retrospective analysis, we investigated the relationship between the presence of perinephric fat stranding (PFS) with CT-SS, ICU admission and mortality rates of COVID-19 patients. We found that the presence of PFS on the first CT was associated with increased CT severity scores in three consecutive chest CTs, ICU admission and mortalityrates in COVID-19 patients. In multivariate logistic regression analysis, older age, PFS and elevated serum creatinine levels were associated with higher mortality risks.We also evaluated the temporal changes of three consecutive CT-SS values in each PFS subgroup based on PFS grading.In the subgroups other than severe, there were significant increases between the first and second CT-SS, but no significant increase was found between the second and third CT-SS.

Chest CT-SS can be calculated using software that describes the percentage of lung volumes affected or can be calculated by visually assessing the percentage of involvement in each lobe.[18-20] We used the 25-point CT severity scoring system in our study that was used in the past.[15] Since CT-SS shows the severity of COVID-19 pneumonia, it is a very important CT finding for the prognosis of patients. Zhou et al.[21] reported that the total CT-SS in COVID-19 patients who died was significantly higher than those who recovered. Francone et al.[22] reported that CT-SS was significantly higher in critical and severe patients than in the mild stage. They reported that COVID-19 patients with a CT-SS greater than 18 predicted a high patient mortality rate. Therefore, in our study, we evaluated the effect of the presence and grade of PFS on

the serial chest CT-SS of the patients. We found a statistical association between the presence of PFS with the high first, second and third CT-SS. Based on these results, we can say that the presence of PFS adversely affects the prognosis of COVID-19 patients. In addition, in our multivariate logistic regression analysis, we found that the presence of PFS 1.964 times increased mortality.

Besides SARS-COV-2 primarily affecting the respiratory tract, the kidney may be among the important target organs. Regardless of underlying kidney diseases, acute kidney injury (AKI) is a common complication of COVID-19.The pathogenesis of COVID-19-related AKI is multifactorial. The causes of AKI in COVID-19 include inflammation and sepsis, critical hypoxia, acute cardiorenal syndrome, hemodynamic abnormalities, cytokine storm, rhabdomyolysis, mitochondrial damage, endothelial dysfunction, microembolism, renal infarction and use of nephrotoxic drugs.[23,24] Prerenal factors cause acute kidney injury more frequently than renal factors in COVID-19. Acute tubular necrosis was found to predominate in the histological evaluation of acute kidney injury in COVID-19 patients.[24]

In the literature, the incidence of AKI in hospitalized COVID-19 patients has reached 9%, while it has been reported to be as high as 68% in critically ill patients admitted to the ICU.[25] A meta-analysis of 20 studies conducted in the United States and Europe showed that the incidence of AKI in hospitalized COVID-19 patients was 28.6%.[26] AKI is associated with a worse clinical course, higher mortality and morbidity.[27,28] Patients with kidney failure at any stage are at high risk for susceptibility to COVID-19 infection, hospitalization and mortality.[28–30] Silver et al.[31] reported a meta-analysis of 54 studies in 30,657 patients with COVID-19, the incidence of acute kidney injury was 28%, compared to 46% in ICU patients. Chan et al.[25] reported that the mortality rate of hospitalized COVID-19 patients was 50% in patients with AKI and 8% in patients without AKI. In our study, in accordance with the literature, advanced age, presence of PFS and high serum creatinine levels were associated with higher mortality risks in multivariate logistic regression analysis.

The perinephric bridging septa are composed of multiple fibrous lamellae that extend from the renal capsule through the perinephric fat to the renal fascia and other areas on the posterolateral surface of the capsule.[11] The presence of perinephric fat stranding septa localizes the spread of disease processes into the perinephric space, while the thickening of the fibrous septa is a nonspecific imaging finding.[32] In NECT, PFS is observed as linear density changes in perirenal adipose tissue.[33,34] PFS may occur in urinary obstruction, after the spontaneous passage of a stone, renal infection, inflammation, renal vascular disease and renal trauma.[14] Therefore, we excluded patients with urinary stones or hydronephrosis and underlying renal failure and pyelonephritis in our study. In Huang et al.'s[13] study, the rate of patients with PFS was reported to be 46.3% in COVID-19 patientsand SCr levels were elevated in 65.8% of patients with PFS. In the current study, the rate of patients with PFS was 39.6%. In our study population, 19.5% of patients had increased SCr levels and 52.8% of these patients had PFS. So in our study, statistical associations were found between PFS with elevated SCr values. Studies in the literature have reported that the incidence of PFS increases significantly with advanced age and male gender.[34,35] Huang et al.[13] reported that the age, number of male cases and mean SCr values of patients with PFS were significantly higher than those without PFS. In the current study, PFS was statistically associated with older age, male gender, elevated serum BUN and creatinine levels. Although serum Cr values are very important in assessing AKI, they do not include parameters that directly indicate renal parenchymal damage. Serum Cr values only reflect functional changes in the kidney.[12] Perinephric fat stranding on non-contrast CT can be used as a qualitative indicator to detect COVID-19-related kidney injury more intuitively than SCr values and can keep clinicians on alert to provide more appropriate and timely treatment to patients at admission.[13] Our results showed that the presence of PFS in NECT imaging can be useful in the qualitative and quantitative assessment of COVID-19-related kidney injury and can provide useful information for planning of the patient's treatment at admission. Huang et al.[13] showed that the presence of PFS was statistically associated with severe and critical COVID-19 cases. While their study compared the clinical staging of the patients with PFS, we investigated the relationship between PFS with COVID-19 pneumonia CT-SS and mortality and the need for ICU treatment. Susmitha et al.[36] found a statistically significant relationship between SCr and PFS. Also, in our study, a statistical relationship was found between the presence of PFS and high SCr values. But no significant association was found between the presence of PFS and CT-SS in their study.[36]

Differently, we found an association between the presence of PFS on the initial CT and high 3 consecutive CT-SS values. To our knowledge, our study is the first to evaluate the relationship between the presence of PFS with three consecutive CT-SS, mortality and the need for treatment in the ICU with a large sample size.We found a particularly strong association between PFS with high chest CT-SS, mortality rates and the need for ICU treatment. In addition, unlike other studies, we evaluated the temporal change of the CT-SS of three consecutive chest CTs in each PFS severity subgroup.

Study Limitations

The current study has several limitations. First, our study was a single-center retrospective analysis. Therefore, a multicenter prospective study is needed for more validation. Second, the evaluation of chest CTs was made by a single radiologist. It may be more beneficial to make the evaluation by more than one radiologist and to make an inter-rater comparison. Third, the upper pole and middle parts of the kidneys were included in the images, as the patients' non-contrast chest CTs were usually evaluated.Only, the lower pole was included in the evaluation in patients who had thorax CT and abdominal CT performed simultaneously.It was more appropriate for the entire kidney to be included in the evaluation area. But in our study, chest CTs of COVID-19 patients were scanned retrospectively.

CONCLUSION

The presence of perinephric fat stranding on the first NECT has important implications for the severity of pneumonia and increased ICU admission and mortality in COVID-19 patients. Therefore, when evaluating chest CT scans of COVID-19 patients, the investigation in terms of perinephric fat stranding may give useful information about COVID-19-related kidney injury and the prognosis of the patients.

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was initiated with the approval of the Amasya University Medical Faculty Clinical Researches Ethics Committee (Date: 06.10.2022, Decision No: 95).

Informed Consent: Because the study was designed retrospectively, no written informed consent form was obtained from patients.

Referee Evaluation Process: Externally peer-reviewed.

Conflict of Interest Statement: The authors have no conflicts of interest to declare.

Financial Disclosure: The authors declared that this study has received no financial support.

Author Contributions: All of the authors declare that they have all participated in the design, execution and analysis of the paper and that they have approved the final version.

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