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Research article

# COVID-19 associated kidney impairment in adult: Qualitative and quantitative analyses with non-enhanced CT on admission

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ABSTRACT

*Purpose:* To qualitatively and quantitatively assess kidney imapairment in adults with COVID-19 by analysing imaging features on non-enhanced CT (NECT) and possible correlation between renal parenchymal attenuation (RPA) and serum creatinine (SCr) levels on admission.

*Methods:* This study was approved by the local institutional ethics committee. A total of 82 patients with COVID-19 admitted from 10/1/2020~15/3/2020 were enrolled. RPA and perinephric fat stranding (PFS) were evaluated on NECT imaging. According to the presence of PFS, the patients were divided into two groups: Group A, 38 patients with PFS, and Group B, 44 patients without PFS. Clinical data, including age, gender, clinical classification, SCr levels, and RPA on NECT were analysed. The RPA and SCr of the two groups with COVID-19 were analysed to determine possible difference and correlation. Eighty subjects with no kidney diseases were randomly selected as control group to determine the RPA of normal kidney performed on the same CT scanner.

*Results:* Mean age, male to female ratio, number of severe and critical cases, and SCr of Group A were higher than those of Group B. Both mean RPA of Group A and Group B were lower than that of control. Mean RPA of Group A was even lower than that of Group B. A significant weak negative linear correlation between RPA on NECT and SCr in COVID-19 was indicated.

*Conclusions:* Decrease in RPA on NECT was observed in patients with COVID-19 and a weak linear negative correlation with SCr levels was found. The presence of PFS suggested more severe renal impairment in COVID-19. RPA measurements and PFS could be useful in quantitative and qualitative evaluation of COVID-19 associated renal impairment on admission.

## 1. Introduction

Coronavirus disease 2019 (COVID-19) is a pandemic infection caused by severe acute respiratory syndrome coronavirus 2 (SARSia [1–3]. Moreover, some studies suggested that the virus can also affect kidney, gastrointestine and eye [4–8]. According to some studies [9–11], angiotensin-converting enzyme 2 (ACE2) was the functional receptor for SARS-CoV-2 and the virus potentially involved many organs

*Abbreviations:* ACE2, Angiotensin-converting enzyme 2; COVID-19, Coronavirus disease 2019; CT, Computed tomography; HU, Hounsfield units; MERS, Middle East respiratory syndrome coronavirus; NECT, Non-enhanced computed tomography; PFS, Perinephric fat stranding; ROI, Region of interest; RPA, Renal parenchymal attenuation; RR, Relative Ratio; RT-PCR, Reverse transcription-polymerase chain reaction; SARS-CoV, Severe acute respiratory syndrome coronavirus; SARS-CoV-2, Severe acute respiratory syndrome coronavirus 2; SCr, Serum creatinine.

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including intestine, kidney, gallbladder, liver and testis, similar to severe acute respiratory syndrome coronavirus (SARS-CoV) and Middle East respiratory syndrome coronavirus (MERS-CoV). Recently, some studies have reported COVID-19 associated renal impairment, manifested as hematuria, proteinuria, and acute kidney injury [12–14].

Imaging is vital in detecting and monitoring lung impairment caused by COVID-19 infection. There have been many reports showing the importance of lung imaging for the disease [1,15–17]. However, to date, there are few studies on imaging findings of the kidney impairments, especially studies on quantitative radiological analyses. In one preprint study the preliminary outcomes showed that CT value of the renal parenchyma in COVID-19 decreased on non-enhanced CT (NECT) [18], indicating its potential qualitative value. As we reviewed the imaging of all adult patients with COVID-19 admitted to our hospital who performed chest NECT, we found that some patients showed perinephric fat stranding (PFS), indicating the thickening of perinephric bridging septa due to increased fluid collection [19]. In addition, after measuring the renal parenchyma attenuations (RPA) on CT images, we also found that the CT values may potentially be correlated to serum creatinine (SCr) levels. Therefore, in this study, we aimed to analyse the imaging features and determine the potential qualitative and quantitative value of NECT imaging on renal impairment in COVID-19, hence may highlight the radiological findings in clinical management and provide clues for further researches.

## 2. Materials and methods

### *2.1. Study population*

This study was approved by our Institutional Ethics Committee. The requirement for informed consent was waived since the study had no risk and would not adversely affect the subjects' rights or welfare.

One hundred and three patients with COVID-19 confirmed by reverse transcription-polymerase chain reaction (RT-RCR) via sputum test, admitted to our hospital from 10/1/2020~15/3/2020, were retrospectively reviewed. The medical records of the patients, including gender, age, clinical classification, SCr, NECT images of chest and upper renal poles within the scanning range, were collected. The exclusion criteria were as follows: (1) Patients with other renal diseases or diseases that may potentially involve kidney, including glomerulonephritis, urolithiasis, renal tumors, history of renal surgery, diabetes, multiple organ failure; (2) Patients whose CT imaging showed obvious respiratory artifacts that affected the measurement of renal density, or without enough images ($\leq$ 3 slices of each kidney on 5-mm-thick axial reformation imaging within the chest CT scanning range) to measure the attenuation.

Finally a total of 82 patients with COVID-19 were enrolled, including 51 males and 31 females aged 24 years~90 years (mean $52.86 \pm 14.53$ years). Among them, 38 patients with PFS on NECT images were all enrolled into Group A, and 44 patients without PFS were all enrolled into Group B.

To determine the RPA values of normal kidneys performed with the same CT scanner, 80 cases (40 males and 40 females) aged between 18 and 82 years (mean $50.61 \pm 15.14$ years) who visited for annual preventive health physical examination and underwent chest NECT from 1/11/2019~31/12/2019 using the same CT scanner were randomly selected as control group (Group C). The exclusion criteria were the same as those for Group A and Group B.

### *2.2. Clinical classification*

All patients were divided into four categories: mild type, common type, severe type and critical type, according to the Guidelines for Diagnosis and Treatment of COVID-19 issued by National Health Commission (7th edition) (in Chinese) [20]. (1) Mild type: presenting with mild clinical symptoms and without pulmonary changes on imaging; (2) common type: presenting with fever, respiratory or other symptoms with pneumonia on imaging; (3) severe type: presenting with any item of the following: respiratory distress, respiratory rate $\geq$ 30 times/min; oxygen saturation $\leq$ 93 % in resting state; PaO2/FiO2$\leq$ mmHg (1 mmHg = 0.133 kPa); (4) critical type: presenting with any item of the following: respiratory failure requiring mechanical ventilation; shock; requiring ICU monitoring and treatment due to multiple organ failure.

### *2.3. Scanning protocol*

CT scans were performed on a 64-slice spiral CT (Revolution EVO, General Electric Medical Systems). Patients were scanned in supine position, ranging from the apex to the base of the lung. This scanning range usually included upper poles of both kidneys and a proportion of middle part of left kidney. Both the left and right renal upper poles of each enrolled case were observed for this study.

The scanning parameters were as follows: tube voltage 120 kV, tube current 120 mA with mA modulation, $64 \times 0.625$-mm collimation and 1.375 pitch. All axial images were reconstructed at 5.0-mm slice thickness and 5.0-mm interval.

### *2.4. Qualitative analysis*

The images of all enrolled patients were reviewed by two radiologists (R.Z. and R.Y., more than 6 years of experience in abdominal imaging) who were unware of patients' clinical data. All images were evaluated at a soft tissue setting with window width of 300 Hounsfield units (HU) and window level of 20 HU [21]. PFS was defined as thin or thick soft tissue attenuation strands extending radially or parallelly to renal capsule which can be short or long, and/or any coalescent perirenal fluid [22]. For some severe patients, the stranding may extend to perirenal fascia/Gerota's fascia and lead to focal or diffuse thickening of the fascia. However, solely thickened Gerota's fascia with absence of soft tissue strands within perirenal space was not considered as PFS. When the two radiologists (R.Z. and R.Y.) differed on the presence of PFS, they firstly reviewed some other cases of same age visiting for annual preventive health physical examination with the same exclusion criteria above, then compared the imaging to determine whether it was normal. If the fat stranding in COVID-19 was more obvious than normal subjects of same age, then the case was enrolled into PFS group. With a consensus reached by the two radiologists, the presence or absence of PFS in each

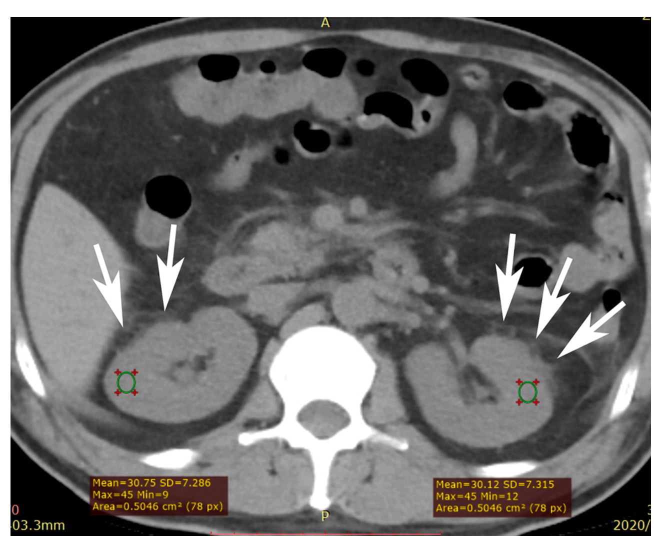


**Fig. 1.** Axial non-enhanced CT scan obtained at upper portion of kidneys. Each ROI had a similar area of approximately 0.5 $cm^2$. Note bilateral perinephric fat stranding (white arrow). (Right kidney; 30.75 HU vs. Left kidney; 30.12 HU).

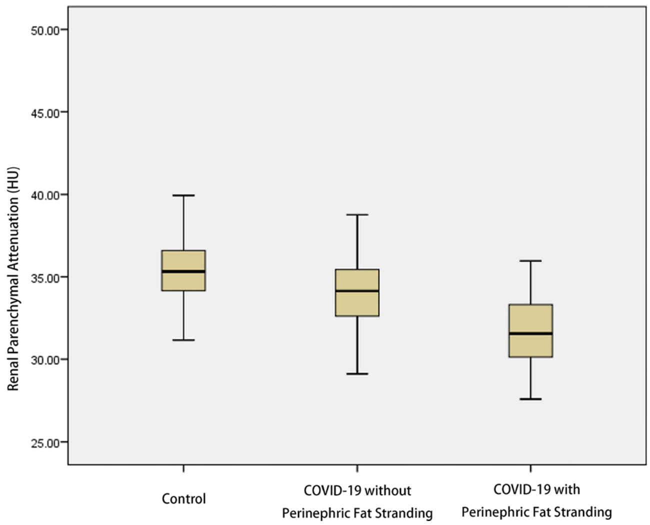


**Fig. 2.** The mean renal parenchyma attenuation (RPA) of each group. Boxplots showing differences in mean RPA between groups. (35.72 ± 2.78 HU in control group, 34.11 ± 2.23 HU in COVID-19 without perinephric fat stranding, and 31.68 ± 2.16 HU in COVID-19 with perinephric fat stranding respectively).

patient was determined (Fig. 1). The difference of SCr between Group A (COVID-19 subjects with PFS) and Group B (COVID-19 subjects without PFS) was analysed.

### 2.5. *Quantitative analysis*

One radiologist (R.Z.) who was blinded to clinical data measured the CT values in random slices of the upper pole of each kidney. Three regions of interest (ROIs) in each kidney were randomly selected with only renal parenchyma included. Each ROI had a similar area of approximately 0.5 $cm^2$ (Fig. 1), and the average of the three ROIs was used as the mean value of each kidney. The average value of both kidneys was used as the mean RPA value for each subject. The RPA change (ΔRPA) of each subject was calculated as the mean RPA value of the subject minus the mean RPA value of the control group (Group C).

As known, the absolute attenuations of organs detected in different CT scanner may show some variations, therefore Relative Ratio (RR) of the attenuation change may be a more reliable indicator [23]. The RR of ΔRPA in each subject was calculated as the ΔRPA of the subject divided by the mean RPA value of Group C.

Finally, the correlation between RPA and SCr of all patients with COVID-19 was analysed.

### 2.6. *Statistical analysis*

Statistical data was conducted with the SPSS 24.0 software package. The age differences was made by one-way ANOVA and the gender comparison was made by Pearson Chi-square test. The suitability of the data to the normal distribution was tested with the Shapiro Wilk test. Continuous variables (RPA, ΔRPA, RR of ΔRPA and SCr) were reported as mean ± standard deviation if they followed a normal distribution. One-way ANOVA followed by Least Significant Difference (LSD) test was used to make pairwise comparison between groups. The predictive performance of RPA in differentiating renal impairment was evaluated with a receiver operating characteristic (ROC) curve analysis. The optimal cut-off value from the ROC curve analysis was extracted. The sensitivity and specificity corresponding to the cut-off values were then calculated. The correlation between RPA and SCr was made by Spearman correlation analyses. $P < 0.05$ was considered statistically significant.

## 3. Results

### 3.1. *Clinical data*

Symptoms of COVID-19 patients on admission included fever (63/82, 76.8 %), cough (61/82, 74.4 %), fatigue (42/82, 51.2 %), headache (25/82, 30.5 %), dyspnea (11/82, 13.4 %), and diarrhoea (3/82, 3.7 %). Three cases (3/82, 3.7 %) were asyptomatic.

Among 82 patients with COVID-19, PFS was present in 38 cases (Group A), and absent in 44 cases (Group B). The relevant clinical characteristics are shown in Table 1. The age, number of male cases and mean SCr of Group A were significantly higher than those of Group B ($p < 0.01$).

The number of cases with elevated SCr levels and number of overall severe/critical cases were also higher in Group A (25, 36, respectively) than those in Group B (1, 22, respectively), $p < 0.01$.

### 3.2. *NECT imaging findings of kidneys in COVID-19*

Among 82 COVID-19 patients, about 46.3 % (38/82, Group A) showed PFS on NECT images (Fig. 1).

There was no significant RPA difference between left renal upper pole and right renal upper pole in each group. The mean RPA of each group was shown in Fig. 2. Mean RPA of overall COVID-19 patients was 32.99 ± 2.19 HU. The RPA of Group A (31.68 ± 2.16 HU) was significantly lower than that of Group B (34.11 ± 2.23 HU). The RPAs of both Group A and Group B were significantly lower than that of Group C (35.72 ± 2.78 HU), the control group (Fig. 3).

ROC curve analysis showed that the RPA difference had moderate accuracy (Fig. 4. Area under the curve 0.784, 95 % confidence interval 0.710–0.858, $p < 0.01$). The optimal cutoff value was 33.75 HU, with a sensitivity of 84.7 %, specificity of 61.0 %.

In our study, the relative RPA changes in patients with COVID-19 compared with normal kidney in control group were calculated as RR of ΔRPA, which were - 11.8 % ± 9.4 % ( - 4.04 ± 0.51HU) for Group A and - 4.4 % ± 9.9 % ( - 1.61 ± 0.49HU) for Group B respectively. The

**Table 1**
Clinical and radiological characteristics of patient with COVID-19.

| Characteristics | COVID-19 with PFS(n = 38) | COVID-19 without PFS(n = 44) | p value |
|---|---|---|---|
| Age (years) | 60.92 ± 10.93 | 45.91 ± 13.71 | 0.000 |
| Gender (Male/female) | 34/4 | 17/27 | 0.000 |
| Severe and Critical Cases (n) | 36 (94.7 %) | 22(50.0 %) | 0.000 |
| SCr (μmol/L) | 88.53 ± 26.96 | 68.61 ± 14.71 | 0.000 |
| Cases with elevated SCr (n) | 25(65.8 %) | 1 (2.3 %) | 0.000 |
| RPA (HU) | 31.68 ± 2.16 | 34.11 ± 2.23 | 0.000 |
| ΔRPA (HU) | - 4.04 ± 0.51 | - 1.61 ± 0.49 | 0.000 |
| RR of ΔRPA (%) | - 11.8 ± 9.4 | - 4.4 %± 9.9 | 0.001 |

The data of age, SCr, RPA, ΔRPA and RR of ΔRPA are shown as mean ± standard deviation. $P < 0.05$ was considered statistically significant.
COVID-19, Coronavirus disease 2019; PFS, Perinephric fat stranding; SCr, Serum creatinine; RPA, Renal parenchymal attenuation; ΔRPA, Renal parenchymal attenuation change; RR, Relative Ratio.

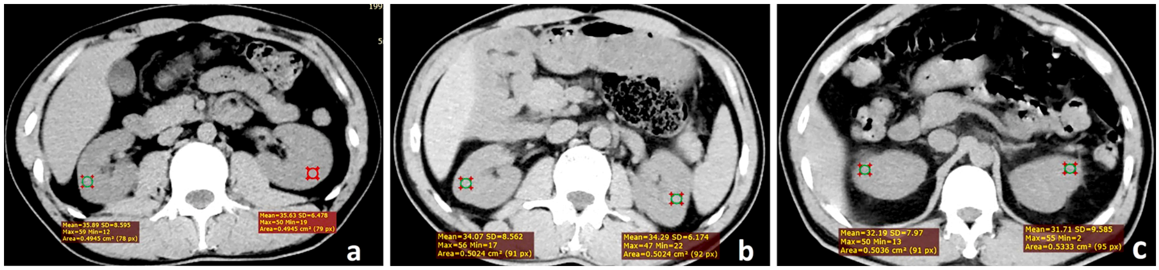


**Fig. 3.** Axial non-enhanced CT of cases in three groups.
CT images showing typical case in each group. (a, control. b, COVID-19 without perinephric fat stranding. c, COVID-19 with perinephric fat stranding). Note the renal parenchyma attenuation differences.

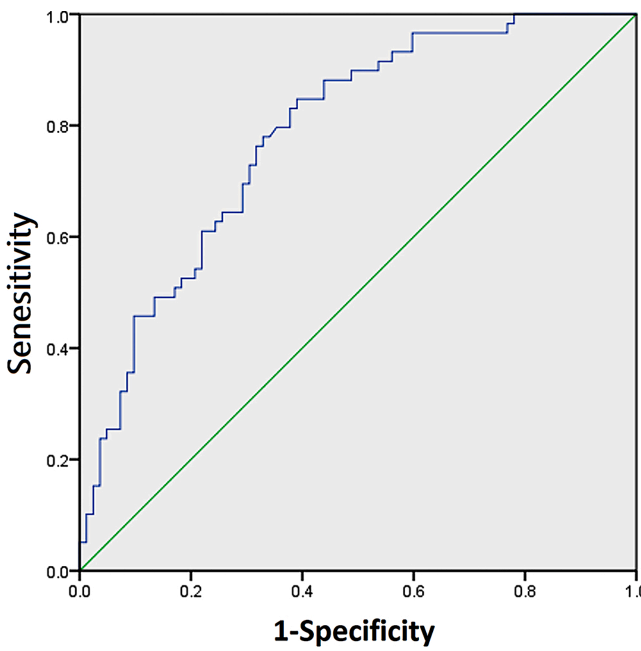


**Fig. 4.** Receiver operating characteristic curve.
Curve showing the RPA difference had moderate accuracy with area under the curve as 0.784 and 95 % confidence interval as 0.710–0.858, $p < 0.01$.

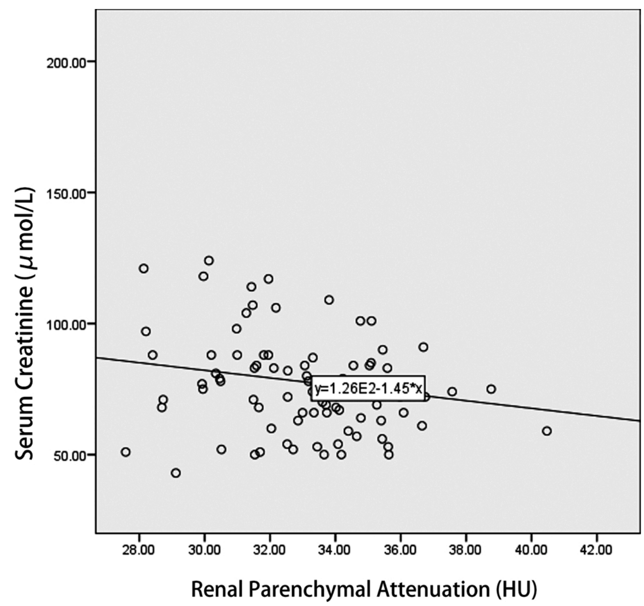


**Fig. 5.** Correlation between RPA on NECT imaging and SCr in COVID-19.
A significant ($p = 0.02$) weak negative linear correlation ($r$= - 0.256) was indicated.
RPA, Renal parenchymal attenuation; NECT, non-enhanced CT; SCr, Serum creatinine.

differences above were all statistically significant ($p < 0.01$) (Table 1).

### 3.3. Correlation between RPA and SCr in COVID-19

25 cases (25/38, 65.8 %) in Group A had elevated SCr, significantly higher than that in Group B (1/44, 2.3 %). The mean SCr of Group A was 88.53 ± 26.96 μmol/L, which was also significantly higher than that of Group B (68.61 ± 14.71 μmol/L). A significant ($p = 0.02$) weak negative linear correlation ($r$= - 0.256) between RPA on NECT imaging and SCr in patients with COVID-19 was found (Fig. 5).

## 4. Discussion

Coronaviruses, such as MERS-CoV, could cause renal impairment, manifested as elevated SCr clinically. Since the outbreak of COVID-19, some reports have shown that the disease can involve kidney and cause renal dysfunction [12–14]. The mechanism has not been elucidated clearly yet. Currently, it is speculated that the impairment may be related to direct attack by SARS-CoV-2, immune-mediated injury, cytokine storm and hypercoagulation [4–6].

Previous reports have shown the value of NECT on assessment of various renal diseases, especially pyelonephritis, obstruction [21,24]. This study further highlighted the NECT imaging value on assessment for renal impairment associated with COVID-19, featuring as PFS and decreased renal parenchymal density.

PFS pathologically suggests thickening of perinephric bridging septa, which are fibrous lamellae that divide the perinephric space into multiple compartments and limit the distribution of fluid, such as urine, pus, blood [25]. On CT imaging, PFS features as increased density of perinephric fat, soft tissue stands, thickening of perirenal fascia and possible presence of fluid in perinephric space. In our study, a group of 38 COVID-19 subjects (38/82, 46.3 %) showed PFS with only 25 subjects showing elevated SCr levels, whereas the mean SCr level of the group was higher than that of the group without PFS. Though SCr still has a crucial role in assessing acute kidney injury, it does not incorporate parameters that directly indicate renal parenchymal damage, since changes in SCr merely reflect functional changes [26]. Our findings suggested that PFS was related to a relatively higher SCr level even though it may be within normal range. PFS was a visual radiologic manifestation clinically indicating the underlying renal damage. In other words, PFS on NECT could be used as a qualitative indicator for detecting renal damage associated with COVID-19, which was more intuitively than serum renal function tests and could promptly alert clinicians to provide more necessary and timely treatment on admission.

Moreover, RPA in COVID-19 patients decreased compared to control group. Patients with PFS showed a greater attenuation decrease with a percentage of - 11.8 % ± 9.4 %, while patients without PFS presented a smaller decrease with a percentage of - 4.4 % ± 9.9 %. Furthermore, the overall mean RPA values in COVID-19 showed a weak negative linear correlation with the SCr values ($r$= - 0.256). These findings suggested that measurement of RPA may be used as a potential quantitative method for renal impairment associated with COVID-19. Pathologically, the RPA decrease in COVID-19 may be the results of complex multi-factorial pathophysiology, including proximal acute tubule injury, acute pyelonephritis, endothelial cell swelling [4]. With injury progressing in renal parenchyma, inflammation and fluid may extend beyond kidney and into the perirenal fat space, resulting in PFS. The greater RPA decrease and higher SCr level in COVID-19 with PFS were probably due to more severe parenchyma injury and inflammation.

The above results indicated that NECT imaging findings of the kidneys could be useful in qualitative and quantitative evaluation on renal impairment associated with COVID-19, and could provide beneficial references for clinical practice, especially on admission.

However, there were several limitations in this study. First, limited by the scanning range of chest NECT, observation and measurement of the kidneys in all patients were only conducted on the renal upper poles, and some statistical deviation may have occurred. Hence, though the impairment in kidney with COVID-19 may be diffuse and the attenuation change may be homogeneous, studies based on whole kidney are expected. Second, our hospital is one of the province-designated hospitals for the treatment of COVID-19 adults, especially for severe and critical cases. Therefore, the severe cases may account for a relatively higher percentage than that in other hospitals. Further studies on more mild cases and children are required. Third, the number of cases was relatively small in this study, and studies with larger number are needed for further assessment of the correlation between the imaging findings and serum biomarkers of renal function.

In conclusion, our study for the first time reported the value of PFS on qualitative assessment for renal impairment in COVID-19, the presence of which on NECT were more common in elderly, male and severe cases, and indicated more severe renal impairment in COVID-19. This study also confirmed the quantitative correlation between RPA on NECT and SCr, the currently important serum biomarker for renal function. The results above suggested that NECT findings could provide sensitive and noninvasive evaluation on renal impairment in COVID-19, which will be timely clues for clinical practice, especially on admission. In addition, we call for more researches on the pathophysiological mechanism of renal impairment in COVID-19 to guide clinical managements more precisely as well as to understand imaging features more clearly.

## Ethics approval and consent to participate

This retrospective, single-center study was approved by our Institutional Ethics Committee, and a waiver of informed consent was obtained.

## CRediT authorship contribution statement

**Qiang Huang:** Data curation, Writing - original draft. **Jian Li:** Data curation, Methodology. **Shuangzhi Lyu:** Conceptualization, Investigation. **Wenjie Liang:** Methodology, Writing - review & editing. **Rong Yang:** Data curation. **Rui Zhang:** Data curation. **Wenbo Xiao:** Methodology, Investigation. **Jinpeng Liu:** Data curation, Methodology. **Senxiang Yan:** Methodology, Supervision. **Liangrong Zheng:** Methodology, Supervision. **Feng Chen:** Methodology, Supervision.

## Declaration of Competing Interest

The authors report no declarations of interest.

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