Research Square

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Correlation Study of Chest CT Features of Severe/Critical type COVID-19 with Early Renal Damage and Clinical Prognosis

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Keywords: Coronavirus Disease 2019 (COVID-19), severe/critical type, estimated glomerular filtration rate (eGFR), crazy-paving pattern, clinical prognosis

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Abstract

Background: Among patients with confirmed severe/critical type COVID-19, we found that although the seurm creatinine (Cr) value is in normal range, patients might have occured early renal damage. For severe/critical type COVID-19 patients, whether some chest CT features can be used to predict the early renal damage or clinical prognosis.

Methods: 162 patients with severe/critical type COVID-19 were reviewed retrospectively in 13 medical centers from China. According to the level of eGFR, 162 patients were divided into three groups, group A (eGFR < 60 ml/min/1.73m^2), group B (60 ml/min/1.73m^2 ≤ eGFR < 90 ml/min/1.73m^2 group) and group C (eGFR ≥ 90 ml/min/1.73m^2). All patients' baseline clinical characteristics, laboratory data, CT features and clinical outcomes were collected and compared. The eGFR and CT features was assessed using univariate and multivariate Cox regression.

Results: Baseline clinical characteristics showed that there were significant differences in age, hypertension, cough and fatigue among groups A, B and C. Laboratory data analysis revealed significant differences between the three groups of leukocyte count, platelet count, C-reactive protein, aspartate aminotransferase, creatine kinase. Chest CT features analysis indicated that crazy-paving pattern has significant statistical difference in groups A and B compared with group C. The eGFR of patients with crazy-paving pattern was significant lower than those without crazy-paving pattern (76.73 ± 30.50 vs. 101.69 ± 18.24 ml/min/1.73m^2, p < 0.001), and eGFR (OR = 0.962, 95% CI = 0.940-0.985) was the independent risk factor of crazy-paving pattern. The eGFR (HR = 0.549, 95% CI = 0.331-0.909, p = 0.020) and crazy-paving pattern (HR = 2.996, 95% CI = 1.010-8.714, p = 0.048) were independent risk factors of mortality.

Conclusions: In patients with severe/critical type COVID-19, the presence of crazy-paving pattern on chest CT are more likely occured the decline of eGFR and poor clinical prognosis. The crazy-paving pattern appeared could be used as an early warning indicator of renal damage and to guide clinicians to use drugs reasonably.

Background

From December 2019, the first case unknown viral pneumonia was found in Wuhan, China. The World Health Organization (WHO) has officially named the unknown viral pneumonia called Coronavirus Disease 2019 (COVID-19) pneumonia on 11 February 2020. The International Committee on Taxonomy of Viruses (ICTV) declared the novel coronavirus named severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) [1]. To date, WHO reported 23752965 confirmed cases and 815038 cases deaths in the world [2]. The main symptoms of patients with COVID-19 could have fever, fatigue, dry cough, pharyngeal pain, nasal congestion, runny nose, diarrhea and myalgia [3]. Some severe type COVID-19 patients could rapidly progress to organ dysfunction, such as acute respiratory distress syndrome (ARDS), acute cardiac injury and acute kidney injury (AKI) and so on [2, 4].

According to the diagnosis and treatment program of COVID-19 (Trial Seventh Edition) issued by the National Health Commission of the People's Republic of China, the clinical classification of COVID-19 include mild, moderate, severe, and critical types [5]. Patients with severe type need meet any of the followings: (I) severe respiratory distress (respiratory rate (RR) ≥ 30 breaths/min); (II) SpO2 < 93% at rest; (III) PaO2/FiO2 ≤ 300 mmHg; and additional supple patients' pulmonary imaging that the lesions progressed more than 50% within 24 ~ 48 hours should be managed as severe type. Critical type, one of the following occurred: (I) respiratory failure requiring mechanical assistance; (II) shock; and (III) Complicated with extra pulmonary organ failure, requiring intensive care unit (ICU) care. Among patients with confirmed severe/critical type COVID-19, we found that although the seurm creatinine (Cr) value is in normal range, patients might have occured early renal damage (namely 60 ml/min/1.73 m^2 ≤ estimated glomerular filtration rate (eGFR) < 90 ml/min/1.73 m^2). According to the National Kidney Foundation (NKF) Kidney Disease Outcome Quality Initiative (K/DOQI) proposed that eGFR could be used to detect early renal damage [6].

Relevant research proved that severe/critical type COVID-19 have some chest CT features [7, 8]. For severe/critical type COVID-19 patients with an early decline in eGFR, while Cr value is in the normal range, whether some chest CT features appear can be used to indicate the possibility of kidney injury, so as to guide clinicians to further calculate eGFR and avoid the selection of COVID-19 drugs that aggravate kidney damage. In the present study, we explored the correlation between chest CT features and early renal damage, and the relationship between chest CT features and clinical prognosis.

Materials And Methods

Patient population

In this study, records for 162 patients (105 males and 57 females, median age 55.66 ± 14.75 years, range from 21 to 91 years, with severe/critical type COVID-19 patients were reviewed retrospectively for the period from 15 January 2020 to 20 February 2020 in 13 medical centers from China. According to the level of eGFR (6), 162 patients were divided into three groups, namely eGFR < 60 ml/min/1.73m^2 group (Group A), 60 ml/min/1.73m^2 ≤ eGFR < 90 ml/min/1.73m^2 group (Group B) and eGFR ≥ 90 ml/min/1.73m^2 group (Group C). All institutional review boards approved this study and waived written informed consents.

All patients' medical history, laboratorial data and CT images were collected and reviewed by two radiologists with 15 and 10 years experience. The Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) creatinine equation was used to calculate the eGFR value [9]. All baseline data were collected on the first day in-hospital. The baseline clinical data include: age, sex, contact history (travel or residence history in Wuhan and the local community with confirmed patient), respiratory rate (RR), fever, cough, myalgia, fatigue, headache, nausea, diarrhoea, abdominal pain, dyspnea, comorbidities (cardiovascular disease, diabetes, hypertension, chronic obstructive pulmonary disease (COPD), chronic liver disease,

chronic kidney disease and malignancy). The baseline laboratorial data include: leukocyte, neutrophil, lymphocyte, haemoglobin, platelet, prothrombin time, activated partial thromboplastin time, creatinine (Cr), eGFR, C-reactive protein (CRP), albumin (ALB), alanine aminotransferase (ALT), aspartate aminotransferase (AST), creatine kinase (CK) and lactate dehydrogenase (LDH). The blood gas analyses include: SpO_2, PaO_2 and FiO_2. Chest CT changes: CT images rapid progression (> 50%) within 24 ~ 48 hours.

Inclusion and exclusion criteria

The inclusion criteria were as follows: (i) clinically confirmed COVID-19 (COVID-19 nucleic acid or gene sequence (+)); (ii) meet severe type COVID-19 confirmed condition (RR ≥ 30 breaths/min; SpO_2 < 93% at rest; PaO_2/FiO_2 ≤ 300 mmHg; and rapid progression (> 50%) on CT images within 24 ~ 48 hours)；(iii) meet critical type COVID-19 confirmed condition (respiratory failure, need mechanical assistance; shock; and extra pulmonary organ failure, intensive care unit (ICU) is needed); (iv) with eGFR calculation results; (v) underwent chest CT examination.

The exclusion criteria were as follows: (i) pregnant women or children; (ii) merely underwent chest radiography; (iii) larger CT artifacts on image.

CT images acquistion

All patients were supine position, held their breath, and scanned from the apex to the bottom of the lung. A Siemens Emotion 16 scanner CT (Siemens Healthineers; Erlangen, Germany) was applied to scan 18 patients from Yichang or Wuhan, China, using 5 mm slice thickness. A GE Discovery CT750 HD (GE Healthcare，Milwaukee, Wis, USA) was adopted to scan 60 patients from Wenzhou, Xiaogan or Haikou, China, using 5 mm slice thickness. A Siemens second generation 64-slice dual-source CT scanner (SOMATOM Definition Flash, Siemens Healthcare, Erlangen, Germany) was used to scan 40 patients from Urumqi, Huangshi or Wuhan, China, using 5 mm slice thickness. A Philips Ingenuity core 128 spiral CT scanner (Philips Medical Systems, Best, the Netherlands) was used to scan 17 patients from Xiangyang or Xuzhou, China, using 1.5 mm slice thickness. A Siemens Emotion 16 VC20B 16-slice spiral CT scanner (Siemens Healthcare GmbH, Erlangen, Germany) was used to scan 27 patients from Huanggang or Jingzhou, China, using 1.5 mm slice thickness. All scans were underwent without contrast agent.

CT characteristics evaliation at baseline

According to the peer-reviewed literature on COVID-19 and the Fleischner Society glossary of terms [4], we summarized the image characteristics as follows: (i) number of lesions (single or multiple); (ii) lesion-involved lung segment number (0 ≤ numbers ≤ 20); (iii) shape of lesions (round or irregular shape); (iv) density of lesions (ground glassopacity (GGO), consolidation, GGO with consolidation); (v) crazy-paving

pattern (GGO with superimposed interlobular and intralobular septal thickening); (vi) interstitial changes; and (vii) pleural effusion.

Statistical Analysis

Regarding measurement data: (I) those with a normal distribution are expressed as the mean ± SD; and (II) those with a non-normal distribution are expressed as the median

(interquartile range) [M (IQR)]. Qualitative data were expressed as the number of cases and the percentage [n (%)]. between groups were analyzed using Student's t-test. Qualitative data were analyzed using the chi-square (χ^2) or Fisher's exact test. Intergroup comparisons were determined with Bonferroni correction, $p < 0.05/3 = 0.0167$ was considered statistically significant. Logistic regression analysis was used to estimate the significant variables ($p < 0.05$). Receiver operating characteristic (ROC) curve analysis was performed to determine the cut-off value. Patient's outcome was assessed using Kaplan-Meier survival analysis, and the influence of eGFR and CT features on patient's outcomes was calculated using Cox proportional hazards modelMultivariate Cox analysis was used to determine the independent predictors of prognosis. The reported p values were two-sided, and a $p < 0.05$ was considered statistically significant. All the analyses were performed using SPSS software (version 25.0).

Results

We collected 1,177 patients confirmed with COVID-19 from 13 medical centers, exclude the mild type (n = 38) and moderate type (n = 977) of COVID-19 patients, and only retain the severe/critical type (n = 162) of COVID-19 patients, including group A (n = 26), group B (n = 37) and group C (n = 99). 162 patients who were confirmed as severe type COVID-19 from the First People's Hospital of Yichang, Yichang, China (n = 4); the General Hospital of the Yangtze River Shipping, Wuhan, China (n = 14); the Second Affiliated hospital of Wenzhou Medical University and the Sixth People's Hospital of Wenzhou, Wenzhou, China (n = 28); the Central Hospital of Xiaogan, Xiaogan, China (n = 27); the First Affiliated Hospital of Xinjiang Medical University, Urumqi, China (n = 5); the Xiangyang Central Hospital, Xiangyang, China (n = 13); the Affiliated Hospital of Xuzhou Medical University, Xuzhou, China (n = 4); the Huangshi Central Hospital, Huangshi, China (n = 28); the Hainan Provincial People's Hospital, Haikou, China (n = 5); the Huanggang Central Hospital, Huanggang, China (n = 3), the Hubei Taihe Hospital, Wuhan, China (n = 7) and the Jingzhou Central Hospital, Jingzhou, China (n = 24) between Jan 15, 2020 and Feb 20, 2020, and who were retrospectively enrolled in this study.

Table 1 showed that all patients' baseline clinical characteristics, there were significant differences in age, hypertension, cough and fatigue among the groups (all $p < 0.05$). After intergroup comparisons, the results showed that the age was older in group A than group C (63.19 ± 17.04 vs. 53.12 ± 12.89, $p < 0.0167$), the incidence of hypertension was higher in group A than group C (65% vs. 33%, $p < 0.0167$), and the clinical manifestation of fatigue was more in group C than group B (47% vs. 14%, $p < 0.0167$).

Table 1
Baseline clinical characteristics of groups A, B and C

Variable	Group A (n = 26)	Group B (n = 37)	Group C (n = 99)
Demographics			
Age, mean ± SD, (yr)	63.19 ± 17.04*	56.76 ± 16.12	53.12 ± 12.89
Sex, No. (%)			
Male	20 (77)	22 (59)	63 (64)
Female	6 (23)	15 (41)	36 (36)
Contact history, No. (%)			
Yes	14 (54)	19 (51)	51 (52)
No	12 (46)	18 (49)	48 (48)
Underlying diseases			
Cardiovascular disease, No. (%)	7 (27)	5 (14)	18 (18)
Diabetes, No. (%)	7 (27)	5 (14)	17 (17)
Hypertension, No. (%)17	17 (65)*	18 (49)	33 (33)
COPD, No. (%)	2 (8)	3 (8)	4 (0)
Chronic liver disease, No. (%)	1 (4)	0 (0)	5 (5)
Chronic kidney disease, No. (%)	0 (0)	0 (0)	0 (0)
Malignancy, No. (%)	0 (0)	4 (11)	7 (7)
Signs and symptoms			
Fever, No. (%)	22 (85)	33 (89)	86 (87)
Cough, No. (%)	16 (62)	22 (59)	76 (77)
Myalgia, No. (%)	5 (19)	6 (16)	16 (16)
Fatigue, No. (%)	9 (35)	5 (14)*	47 (47)
Headache, No. (%)	2 (8)	5 (14)	13 (13)
Nausea, No. (%)	4 (16)	2 (5)	14 (14)
Diarrhoea, No. (%)	3 (12)	4 (11)	17 (17)
Abdominal pain, No. (%)	1 (4)	0 (0)	5 (5)
Dyspnea, No. (%)	13 (50)	13 (35)	43 (43)
*: $p < 0.0167$ vs. Group C			

Table 2 summarizes the laboratory findings, blood gas analyses and chest CT changes at baseline of the cohort. There were significant differences between group A, group B and group C in leukocyte count, platelet count, Cr, eGFR, C-reactive protein, AST, CK, RR ≥ 30 breaths/min and CT images rapid progression (> 50%) within 24 ~ 48 hours (all $p < 0.05$)..After intergroup comparisons, the results showed that the leukocyte count in group A was significantly different from that in group B (8.17 ± 4.06 vs. 5.28 ± 2.04, $p < 0.0167$). The C-reactive protein or CK in group A was significantly higher than group C (72.37 ± 79.04 vs. 39.01 ± 35.93, 629.84 ± 1081.93 vs. 184.39 ± 242.98, all $p < 0.0167$). The Cr in groups A and B were significantly different from that in group C (178.79 ± 103.34 vs. 59.42 ± 15.56, 86.06 ± 13.95 vs. 59.42 ± 15.56, all $p < 0.0167$), and group A was significantly higher than group B (178.79 ± 103.34 vs. 86.06 ± 13.95, $p < 0.0167$). The eGFR in groups A and B were significantly lower than group C (39.72 ± 14.56 vs. 107.24 ± 12.95, 77.78 ± 7.51 vs. 107.24 ± 12.95, all $p < 0.0167$), and group A was lower than group B (39.72 ± 14.56 vs.77.78 ± 7.51, $p < 0.0167$).

Table 2
Laboratory findings, blood gas analyses and chest CT changes (baseline) of groups A, B and C

Variable	Group A (n = 26)	Group B (n = 37)	Group C (n = 99)
Leukocyte count, $\times 10^9$/L	8.17 ± 4.06#	5.28 ± 2.04	6.61 ± 3.66
Neutrophil count, $\times 10^9$/L	7.19 ± 4.32	4.29 ± 2.39	6.21 ± 3.87
Lymphocyte count, $\times 10^9$/L	0.71 ± 0.29	0.89 ± 0.39	0.92 ± 1.17
Haemoglobin, g/L	119.44 ± 62.23	130.39 ± 30.88	130.17 ± 31.77
Platelet count, $\times 10^9$/L	146.86 ± 69.17	153.40 ± 65.24	187.35 ± 75.86
Prothrombin time, s	16.42 ± 12.17	14.75 ± 4.71	15.97 ± 11.48
Activated partial thromboplastin time, s	31.59 ± 9.93	31.68 ± 11.10	35.63 ± 43.36
Creatinine (Cr), μmol/L	178.79 ± 103.34*#	86.06 ± 13.95*	59.42 ± 15.56
eGFR, mL/min/1.73 m^2	39.72 ± 14.56*#	77.78 ± 7.51*	107.24 ± 12.95
C-reactive protein, mg/L	72.37 ± 79.04*	53.02 ± 51.13	39.01 ± 35.93
Albumin (ALB), g/L	38.6 ± 11.46	36.5 ± 5.25	37.04 ± 8.83
Alanine aminotransferase (ALT), U/L	36.39 ± 30.04	48.11 ± 35.65	42.02 ± 36.52
Aspartate aminotransferase (AST), U/L	81.2 ± 148.45	55.71 ± 33.27	39.35 ± 36.75
Creatine kinase (CK), U/L	629.84 ± 1081.93*	320.71 ± 496.98	184.39 ± 242.98
Lactate dehydrogenase (LDH), U/L	410.14 ± 215.55	355.62 ± 170.77	340.11 ± 157.82
PaO2/FiO2 ≤ 300 mmHg, No. (%)	21 (81)	28 (76)	78 (79)
RR ≥ 30 breaths/min, No. (%)	17 (65)	17 (46)	36 (36)
SpO2 < 93% at rest, No. (%)	19 (73)	26 (70)	72 (73)
CT images rapid progression (> 50%) within 24 ~ 48 h, No. (%)	9 (35)	5 (14)	13 (13)

*: $p < 0.0167$ vs. Group C, #: $p < 0.0167$ vs. Group B.

Chest CT showed abnormalities in all the 162 patients at baseline, 158 (97.5%) patients had multiple lesions, 150 (92.6%) patients had irregular shape of lesion, 94 (58%) patients had crazy-paving pattern, 132 (81%) patients had interstitial changes and 10 (6%) patients had pleural effusion (Fig. 1, 2). No significant differences in lesion-involved lung segment numbers among the three groups, and the average number of involved lung segments in each group was > 15 (Fig. 3). Compared with the group C, group A or B were more likely to appear crazy-paving pattern (24 [92%] vs. 42 [42%], 28 [76%] vs. 42 [42%], all $p < 0.0167$) (Table 3). And the eGFR value of patients with crazy-paving pattern was significant lower than those without crazy-paving pattern (76.73 ± 30.50 vs. 101.69 ± 18.24 ml/min/1.73 m^2, $p < 0.001$).

Table 3
Chest CT features (baseline) analysis of groups A, B and C

Features	Group A (n = 26)	Group B (n = 37)	Group C (n = 99)
Lesion numbers, No. (%)			
Single	0 (0)	1 (3)	3 (3)
Multiple	26 (100)	36 (97)	96 (97)
Lesion-involved lung segment number, No.	16.19 ± 6.24	16.43 ± 5.36	15.57 ± 6.08
Lesion shape, No. (%)			
Round	7 (27)	15 (41)	38 (38)
Irregular shape	23 (88)	36 (97)	91 (92)
Lesion density, No. (%)			
GGO	3 (12)	1 (3)	5 (5)
Consolidation	1 (4)	0 (0)	0 (0)
GGO with consolidation	22 (85)	36 (97)	92 (93)
Crazy-paving pattern, No. (%)	24 (92)*	28 (76)*	42 (42)
Interstitial changes, No. (%)	20 (77)	31 (84)	81 (82)
Pleural effusion, No. (%)	2 (8)	4 (11)	4 (4)
*: $p < 0.0167$ vs. Group C.			

Table 4 revealed that the risk factors related to crazy-paving pattern identified by logistic regression results. Univariate logistic regression analysis indicated that eGFR, platelet count, LDH were risk factors of crazy-paving pattern (all $p < 0.05$). The factors with $p < 0.10$ in univariate logistic regression analysis were selected to multivariate logistic regression analysis, which indicated that eGFR (OR = 0.962, 95% CI = 0.940–0.985, $p = 0.001$) was independent risk factor of crazy-paving pattern (Table 4). The cut-off level

of eGFR was determined as 85.74 ml/min/1.73 m^2 based on ROC curve analysis (Area Under Curve (AUC) = 0.763, 95% CI 0.689–0.838) (Fig. 4).

Table 4
Risk factors related to crazy-paving pattern identified by univariate and multivariate logistic regression analysis

	Univariate logistic regression		Multivariate logistic regression	
	OR (95%CI)	p value	OR (95%CI)	p value
eGFR	0.958 (0.942–0.974)	< 0.001	0.962 (0.940–0.985)	0.001
Age	1.022 (1.000-1.044)	0.051	0.997 (0.954–0.985)	0.881
Platelet count	0.991 (0.986–0.996)	0.001	0.994 (0.987-1.000)	0.060
CK	1.001 (1.000-1.002)	0.088	1.000 (0.999–1.001)	0.810
LDH	1.003 (1.000-1.005)	0.031	1.001 (0.998–1.004)	0.518
Lung segment involved numbers	1.049 (0.993–1.108)	0.085	0.962 (0.940–0.985)	0.332

Table 5 demonstrated that the clinical outcomes of groups A, B and C. In the incidence of mortality, enter ICU and adopt mechanical ventilation, group A or group B were significantly higher than group C (all $p < 0.0167$). Although there were no statistical difference between groups A and B in the incidence of mortality, group A seemed to have a higher mortality trend than group B. We believe that further expansion of the sample size will be statistically significant. Furthermore, univariate COX regression analysis indicated that age, eGFR, lymphocyte count and crazy-paving pattern were risk factors of mortality (all $p < 0.05$). The factors with $p < 0.10$ in univariate COX regression analysis were selected to multivariate COX regression analysis, which indicated that eGFR (HR = 0.549, 95% CI = 0.331–0.909, p = 0.020) and crazy-paving pattern (HR = 2.996, 95% CI = 1.010–8.714, p = 0.048) were independent risk factors of mortality (Table 6, Fig. 5).

Table 5
The clinical outcomes of groups A, B and C

	Group A (n = 26)	Group B (n = 37)	Group C (n = 99)
Mortality, n (%)	14 (54)*	11 (30)*	7 (7)
Enter ICU, n (%)	12 (46)*	22 (59)*	15 (15)
Adopt mechanical ventilation, n (%)	13 (50)*	17 (46)*	15 (15)
**: $p < 0.0167$ vs. Group C			

Table 6
Risk factors related to mortality identified by univariate and multivariate COX regression analysis

	Univariate COX regression		Multivariate COX regression	
	HR (95%CI)	p value	HR (95%CI)	p value
Age	1.027 (1.001–1.053)	0.043	1.023 (0.995–1.053)	0.113
eGFR	0.379 (0.244–0.587)	< 0.001	0.549 (0.331–0.909)	0.020
Lymphocyte count	0.271 (0.076–0.969)	0.045	0.369 (0.098–1.384)	0.139
Lung segment involved numbers	1.075 (0.994–1.163)	0.072	1.069 (0.987–1.159)	0.102
Crazy-paving pattern	5.924 (2.259–15.534)	< 0.001	2.996 (1.010–8.714)	0.048

Discussion

Obtained from the latest data of World Health Organization (WHO), the confirmed COVID-19 cases has achieved 23788899 (until 24:00 of 26 August 2020) in the world already greatly exceeded the overall reported cases of SARS-CoV in 2003 (8422). The widespread spread of COVID-19 has seriously affected global public health. Relevant study reports COVID-19 could lead to kidney damage and recommend close monitoring the kidney functions [10, 11]. In the present study, we found that group A and group B were significantly different from group C in crazy-paving pattern and mortality. This means that in patients with severe/critical type COVID-19, when eGFR declined to < 90 ml/min/1.73 m^2, we should pay attention to the appearance of crazy-paving pattern on chest CT. When crazy-paving pattern appears, it indicates that patients will have more poorer clinical prognosis (include mortality, enter ICU and adopt mechanical ventilation). And we found that the lesion-involved lung segment numbers in severe/critical type COVID-19 were more than 15. At the same time, it also reminds that for severe/critical type COVID-19, when Cr value is at the upper limited in normal range, the crazy-paving pattern appear on the chest CT, we need to calculate eGFR value. According to the level of eGFR to detect early kidney damage, so as to guide clinicians to avoid using anti-COVID-19 drugs that affect kidney function.

In our study, we found 32% patients with severe/critical type COVID-19 occured eGFR < 90 mL/min/1.73 m^2, and these patients are more likely to appear crazy-paving pattern on chest CT. Moreover, by multivariate logistic regression analysis results, we proved that only eGFR was independent risk factor of crazy-paving pattern in severe/critical type COVID-19. And the presence of crazy-paving pattern means that patients with severe/critical type COVID-19 are more likely associated with eGFR

declined, especially in the patients with normal Cr value but occured the decline of eGFR. Moreover, by multivariate COX regression analysis, we found that eGFR and crazy-paving pattern were independent risk factors of mortality. In patients with severe/critical type COVID-19 were more likely mortality when they have decreased eGFR and occured crazy-paving pattern.

At present, the renal function evaluation of patients with COVID-19 usually adopt serum Cr test, and when the Cr value > 110 μmol/L, patients could be considered as renal insufficiency or renal failure [12, 13]. According to the CKD clinical practice guidelines, eGFR in 60 ~ 89 mL/min/1.73 m^2 was considered to have mild kidney damage [6]. Therefore, the eGFR conversion of Cr can early detect the kidney damage, especially for the severe/critical type COVID-19 patients. Due to the increasing number of confirmed patients, if eGFR calculation was required for each patient, which increases the workload of the doctor in the front line of anti-epidemic, especially for clinicians in all non-kidney fields. This study shows that for patients with severe/critical type COVID-19, even if the Cr is at a normal range or at the upper limited in normal range, when appeared crazy-paving pattern on chest CT, doctors should pay attention to the eGFR value in time, patients may have a early renal function impairment and poor clinical prognosis.

Furthermore, when severe/critical type COVID-19 patients appear crazy-paving pattern on chest CT, it strongly suggested that doctors to calculate the eGFR, once eGFR < 90 ml/min/1.73 m^2, doctors should avoid choosing the first-line drugs (Guidelines for the diagnosis and treatment of COVID-19 (Trial Seventh Edition) issued by the National Health Commission of the People's Republic of China) may aggravate kidney damage, such as chloroquine phosphate, ribavirin and so on. At the same time, in the guidelines regarding the recommendation to use the Chinese traditional medicine "Qingfei Paidu Decoction" in the treatment of COVID-19 [5]. However, the "Asarum" component in the decoction has been clearly classified as aristolochic acid in Chinese Pharmacopoeia [14], which is induced nephrotoxicity, so the dosage can be removed or reduced. Therefore, crazy-paving pattern could be used as an effective early warning indicator to guide medication.

Since 1972, Jelliffe first proposed that eGFR can be used to evaluate renal function, the index has been used up to now [15]. Based on Cr value to calculate eGFR is widely used to evaluate renal dysfunction in the early stage. At present, renal function can be categorized into five stages based on the level of eGFR [6]: stage 1, kidney damage with normal or raised eGFR (≥ 90 mL/min/1.73 m^2); stage 2, kidney damage with mild eGFR (60 ~ 89 mL/min/1.73 m^2); stage 3, kidney damage with moderate eGFR (30 ~ 59 mL/min/1.73 m^2); stage 4, kidney damage with severe eGFR (15 ~ 29 mL/min/1.73 m^2); and stage 5, kidney failure with eGFR (< 15 mL/min/1.73 m^2). As mentioned above, eGFR < 90 mL/min/1.73 m^2 could be used as the standard of renal function decline. The reason for the decline of eGFR in severe/critical COVID-19 patients still needs to be further explored. Relevant study reported that SARS-CoV-2 may directly attack the tubular cells by binding ACE2 (angiotensin converting enzyme II) receptor in the kidney, which may induce kidney injury and eGFR decline; In addition, the eGFR decline may also be secondary to inflammation, sepsis, shock or insufficient blood volume in the course of severe type COVID-19 [16, 17].

The crazy-paving pattern can be defined as diffuse or scattered ground-glass attenuation superimposed on a network of interlobular septal thickeding and intralobular lines [18]. In 1958, Rosen SH et al. first described crazy-paving appearance and proved that it can appear in pulmonary alveolar proteinosis (PAP) [19]. After that, crazy-paving pattern was also confirmed to be present in pneumocystis jirovecii pneumonia (PCP), cryptogenic organizing pneumonia (COP), sarcoidosis, bronchioloalveolar carcinoma, adult respiratory distress syndrome (ARDS), etc [20–22]. Frazier et al. found that crazy-paving pattern was likely associated with an interstitial inflammatory cellular infiltration or fibrosis [23]. Johkoh et al. proposed that crazy-paving pattern represents a slight increase in the severity of the pathologic process at the borders of unit structures [24]. In recent COVID-19 studies, we found that crazy-paving pattern can also appear in COVID-19 pneumonia. Li et al. reported that 25 patients with confirmed severe/critical type COVID-19, 56% (14/25) of patients had crazy-paving pattern on chest CT [7]. Feng et al. described that within 1 ~ 13 days of confirmed COVID-19, about 31% (19/62) patients appear crazy-paving pattern [25]. The study show that 58% (94/162) severe type COVID-19 patients appear crazy-paving pattern. The reason for the different percentages is due to the different experimental designs and patient numbers. Furthermore, through chest CT features analysis of groups A, B and C, we found lung segment involved numbers of three groups were all above 15, which further clarifies the accompanying conditions when the crazy-paving pattern appears.

There are several limitations to our investigation. First, the sample size of this study is relatively small, and the conclusions of this research need to be further studied in a larger data set. Second, due to this study adopted patients' baseline laboratory results, there is still a lack of timeline about eGFR results for patients after onset of illness. Finally, it is uncertain whether the eGFR decline of patients with severe/critical COVID-19 is caused by CKD or AKI. These problems will be further demonstrated in future study.

Conclusion

In patients with severe/critical type COVID-19, eGFR declined has some correlation with chest CT feature (crazy-paving pattern), the presence of crazy-paving pattern are more likely occured the decline of eGFR and poor clinical prognosis. The crazy-paving pattern could be used as an early warning indicator of renal damage in severe/critical type COVID-19 and helps to guide clinicians to avoid using anti-COVID-19 drugs that affect kidney function.

Declarations

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Authors' contributions

G.L. and Y.C.G.: Project development, data collection and management, data analysis, and manuscript writing. G.M.L., Z.Y.S. and S.L.: Project development and data collection. L.J.Z., C.S.Z. and F.Z.: Project development and manuscript editing. J.D., Z.Q.C., W.W., X.Z. and C.S.Z.: Data analysis, supervision and manuscript editing.

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Availability of data and materials

The data supporting the conclusions of this article are included within the article.

Ethics approval and consent to participate

This study was approved by the Ethics Committee of Jinling Hospital, Medical School of Nanjing University. Due to the urgent exploration for this disease, written informed consent was waived.

Consent for publication

The manuscript is approved by all authors for publication. This article does not contain any individual person's data in any form.

Competing interests

The authors have no potential conflicts of interest to disclose.

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Figures

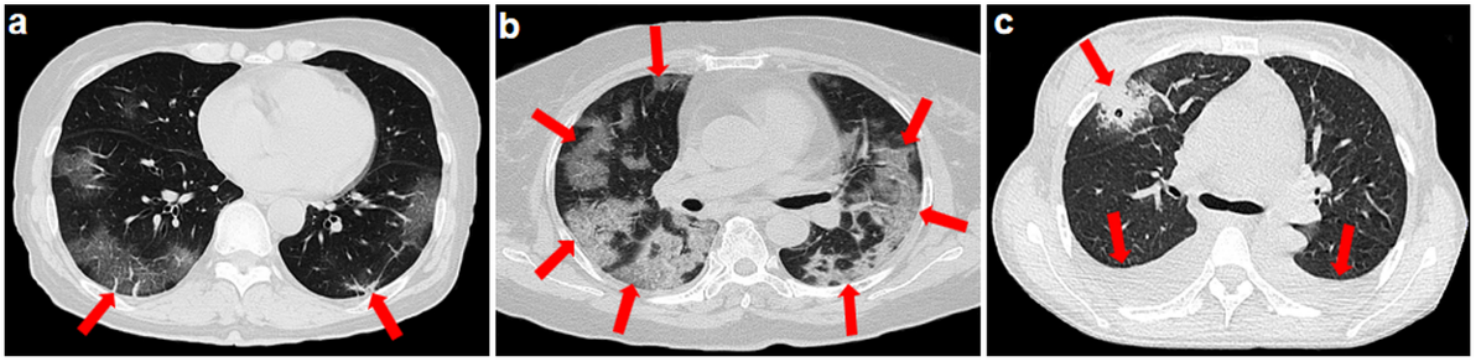

Figure 1

Relevant CT manifestations of COVID-19 A: Chest CT images showed crazy-paving pattern with interstitial change (arrows). B: Chest CT images showed crazy-paving pattern with multiple and irregular shape (arrows). C: Chest CT images showed GGO with consolidation and pleural effusion (arrows).

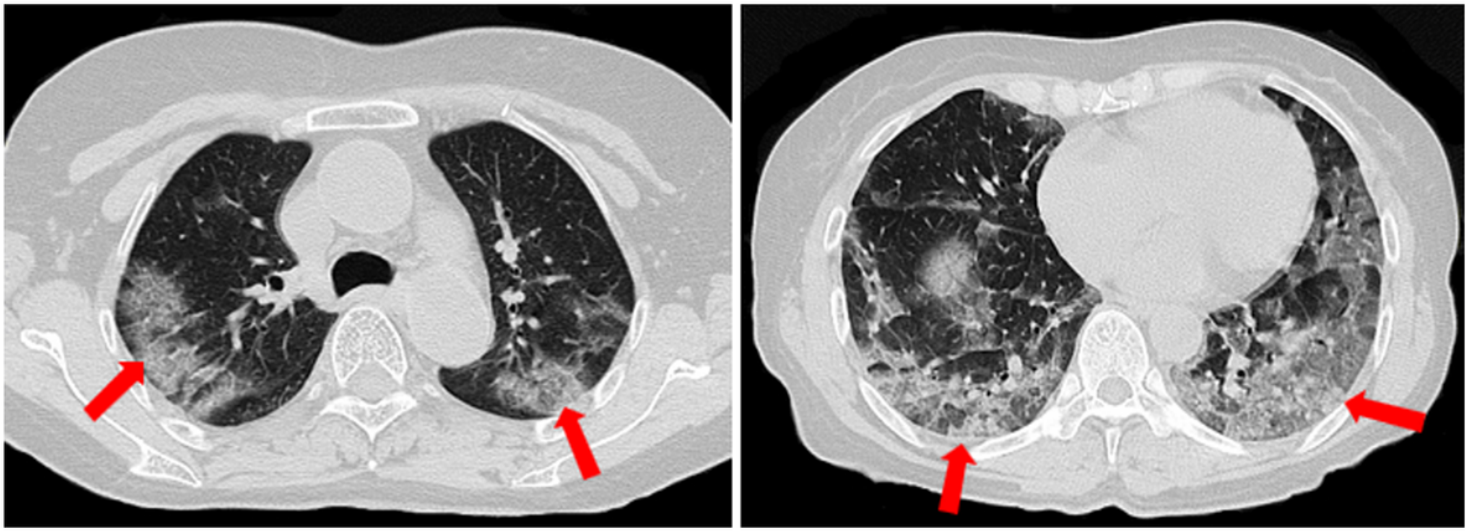

Figure 2

Chest CT feature of COVID-19 crazy-paving pattern A 56-old-year man presenting with fever, cough, and myalgia with Wuhan exposure history. SARS-CoV-2 nucleic acid test (+). The CT showed typical crazy-paving pattern (arrow).

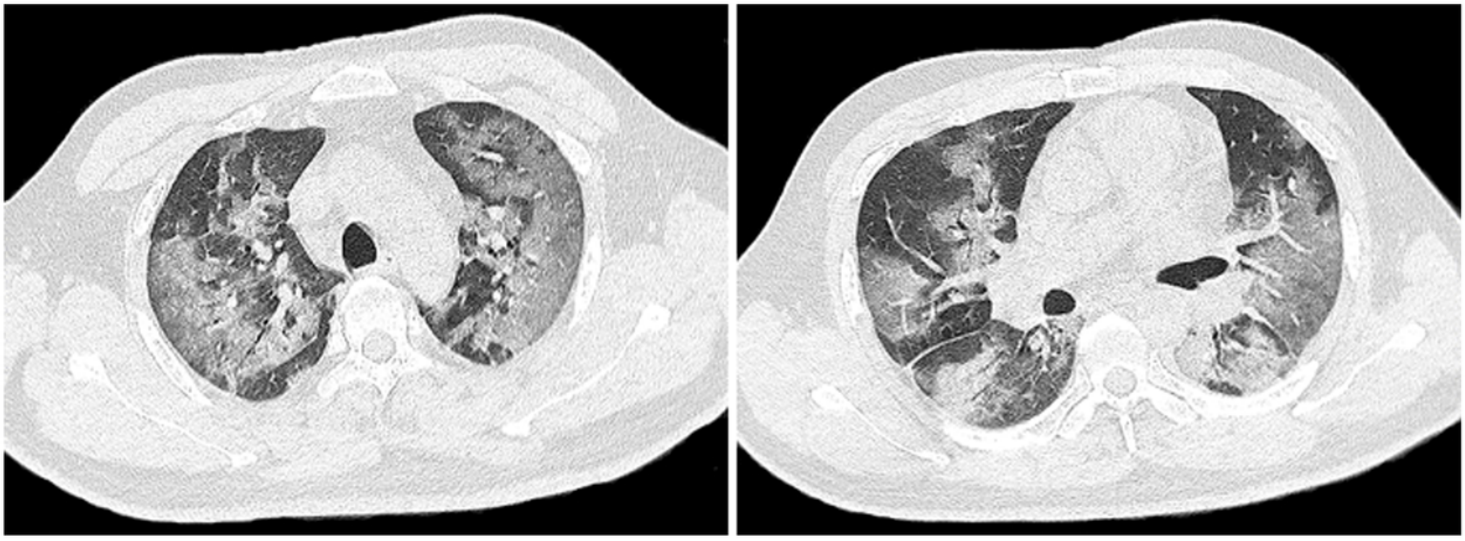

Figure 3

Chest CT feature of COVID-19 multiple lung segments involved A 44 year man presenting with cough, fatigue, headache, and nausea with Wuhan exposure history. SARS-CoV-2 nucleic acid test (+). The CT showed multiple lung segments involved.

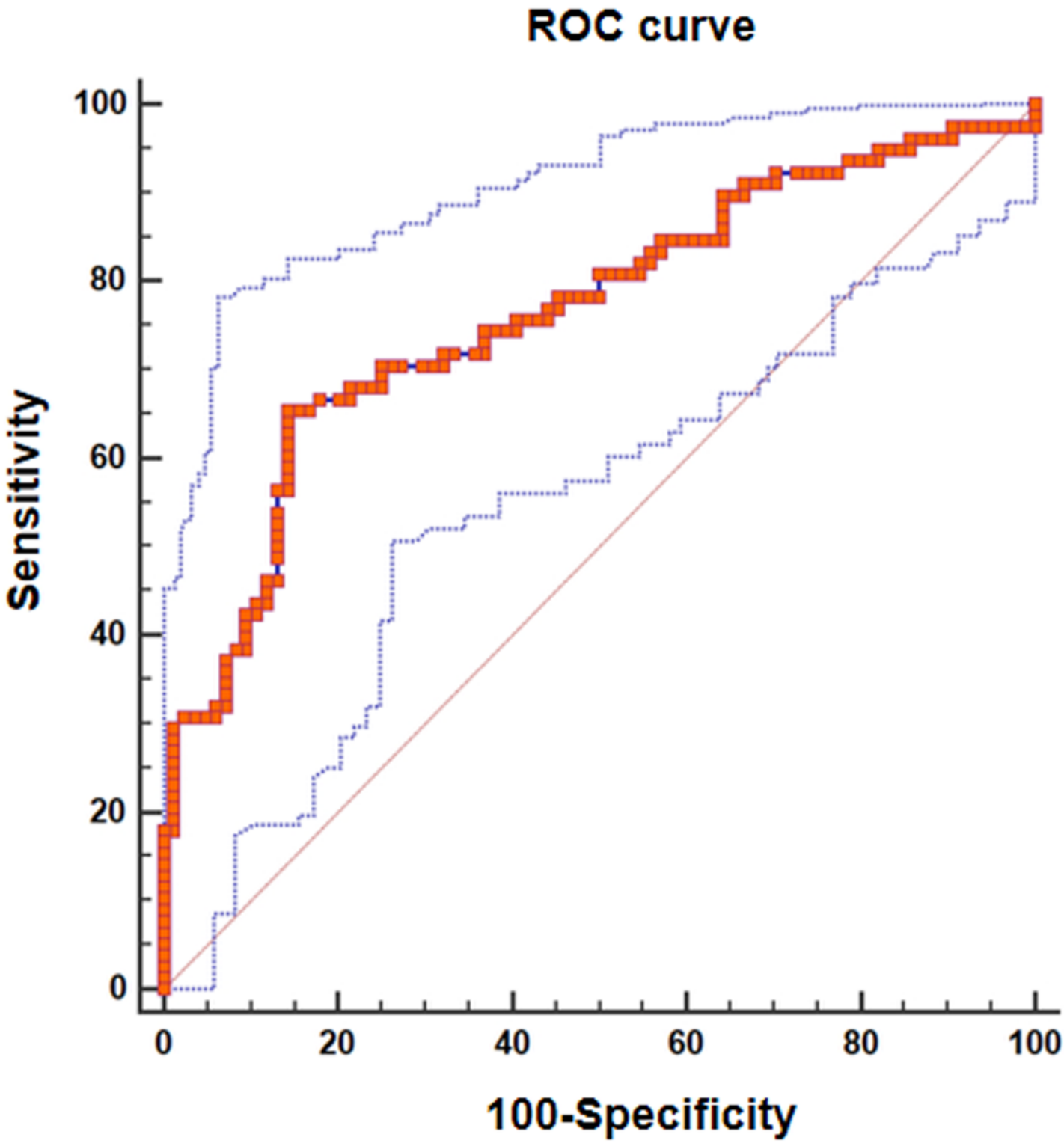

Figure 4

The relationship between eGFR and crazy-paving pattern analyzed by ROC curve

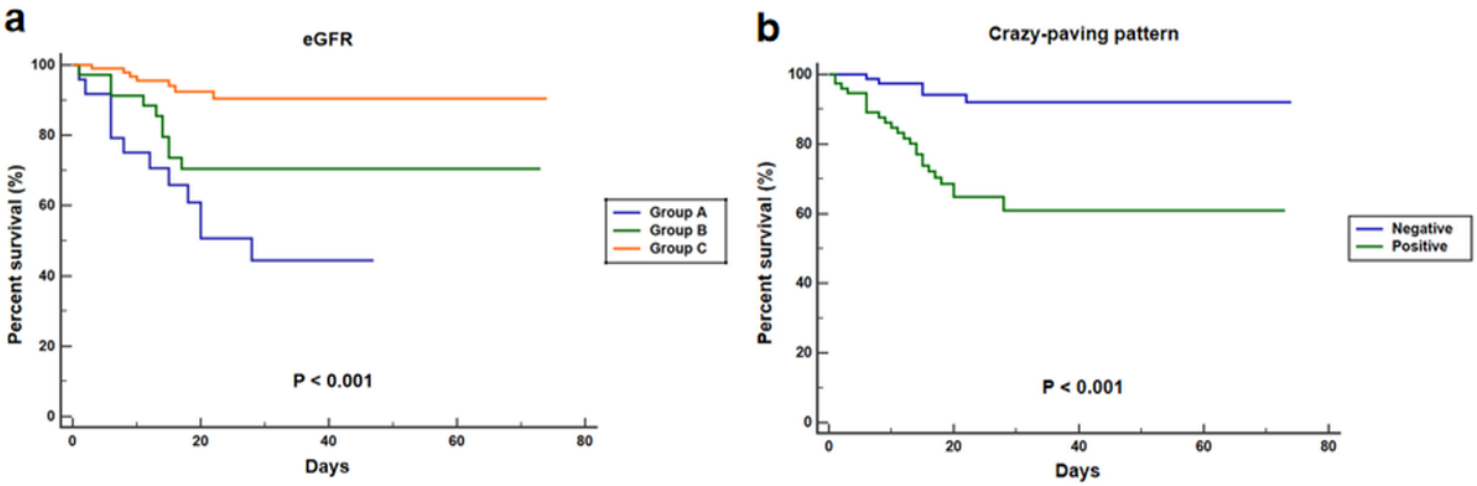

Figure 5

Kaplan-Meier curves for in-hospital mortality of patients with severe/critical type COVID-19 A. Subgroup by eGFR. B. Chest CT feature with or without crazy-paving pattern.