Declined eGFR Associated with Poor Prognosis in COVID-19 Patients in Wuhan, China: A Retrospective Cohort Study

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Research

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Abstract

Background: Increasing evidence revealed that kidney was one of the targets of SARS-CoV-2. However, the incidences of kidney abnormalities were significantly different, from 0.5 to 75.4% in coronavirus disease 2019 (COVID-19) patients. The association of kidney injury with prognosis remain controversial.

Methods: In this retrospective cohort study, laboratory confirmed COVID-19 inpatients with severe type were enrolled. Demographic, clinical and laboratory data were collected. Association of estimated glomerular filtration rate (eGFR) with 28-days mortality was analyzed.

Results: The total 28-days mortality of hospitalization was 22.3% (79/354). Non-survivors had a significantly declined eGFR levels than survivors (75.95 [IQR: 47.22, 92.84] ml/min/1.73m² vs. 96.43 [IQR: 84.11, 108.47] ml/min/1.73m², $P < 0.001$). The 28-days mortality in declined eGFR group (< 90 ml/min/1.73m²) was significantly higher than that in normal eGFR group (38.5% vs. 10.7%, $P < 0.001$). Multivariate logistic regression revealed that the independent risk factors of 28-days outcome included lower eGFR (OR: 3.97, 95%CI: 1.42-11.11), elevated WBC (OR: 7.08, 95%CI: 3.15-15.90), lymphopenia (OR: 2.58, 95%CI: 1.21-5.49) and IL-6 (OR: 7.90, 95%CI: 2.19-28.49). Kaplan-Meier analysis indicated the survival disadvantage in patients with declined eGFR. ROC curve showed the eGFR cut-off value for predicting 28-days death was 82.2 μ mol/L, with the sensitivity of 76.7% and speciality of 66.3%.

Conclusion: Declined eGFR was associated with poor prognosis and could be used an independent risk factor of 28-days mortality in COVID-19 patients. Early detection and surveillance for eGFR may benefit to identify patients with high-risk of progression.

Background

Coronavirus disease 2019 (COVID-19) has resulted in considerable morbidity and mortality worldwide since December 2019, with at least 20% of COVID-19 patients have severe disease. Recent reports showed the mortality of COVID-19 patients with severe form or critical illness as high as 28.3% [1]. Although lungs were the main targets of SARS-CoV-2, increasing evidence revealed that SARS-CoV-2 infection could also be found out of lung, such as digestive system, cardiovascular system and kidney [2]. Disorder of coagulation and injury of cardiovascular system have been proved associated with in-hospital mortality in COVID-19 patients.

However, the association of kidney injury with prognosis remain controversial. The incidences of kidney abnormalities were significantly different. Some studies revealed acute kidney injury (AKI) occurred in 2.9–23% of ICU patients [3–5]. A recent report indicated 75.4% patients had abnormal urine dipstick tests or AKI [6]. A recent study showed that kidney diseases was associated with in-hospital death of patients with COVID-19 [3]. However, another report indicated that COVID-19 did not result in acute kidney injury (AKI) [6]. This might be due to the different methods of kidney injury evaluation and definition. Although serum creatinine remains the most widely used biomarker to evaluate renal function, it is a delayed renal functional marker when it is generally increased after sever kidney damage [8].

The estimated glomerular filtration rate (eGFR) is widely accepted as the total index to evaluate renal function for acute or chronic kidney disease [9–12]. However, the relationship of eGFR and prognosis of COVID-19 patients was unclear. So, aim of this study was to estimate the potential association of kidney function (using eGFR) with 28-days mortality of COVID-19 patients, which would help for the early identification of patients with progression risk.

Methods

Subjects and methods

In this retrospective single-centre cohort study, we enrolled 354 laboratory confirmed COVID-19 inpatients who were admitted to Wuhan Tongji Hospital from February 10 to March 29, 2020. Diagnosis and disease severity of all patients were determined according to the Chinese management guideline for COVID-19 (version 7.0). This study was approved by the institutional review boards at the First Affiliated Hospital of Soochow University and Wuhan Tongji Hospital. As COVID-19 is an emerging infectious disease, the written informed consent was exempted.

Baseline demographic data and clinical features were recorded. The eGFR was estimated using the Modification of Diet in Renal Disease Study equation [12]. Patients were followed-up to 28 days after admission. The primary outcome was 28-days mortality in hospital. The criteria for discharge were defined as all of the following: absence of fever for at least 3 days; clinical remission of respiratory symptoms; substantial improvement in both lungs in chest CT; and two throat-swab samples with SARS-CoV-2 RNA negative obtained at least 24 hours apart.

Statistical analysis

Continuous data with normal distribution were presented as mean $\pm$ standard deviation. Continuous data with skewed distribution were presented as median [interquartile range (IQR)]. Frequency data were expressed as proportions. Comparisons of continuous variables were made with Student's *t* test or the Mann-Whitney *U* test when appropriate. Categorical variables were assessed using the χ^2 test or Fisher's exact test as appropriate. Multivariate logistic regression models were used to determine the independent risk factors for 28-days mortality after hospitalization. Kaplan-Meier analysis was used for survival curves by the log-rank test. Data were analyzed using SPSS 19.0. A two-tailed *P* value < 0.05 was considered statistically significant.

Results

The baseline characteristics of survivors and non-survivors

Total of 354 adult inpatients were included. The median age was 63 years old (IQR: 51,71), 56.8% (201/354) were male, and 22.3%(79/354) died during the first 28 days of hospitalization. The most

common symptoms were fever (78.8%) and cough (75.8%). The most popular comorbidities was hypertension (29.9%).

Survivors were younger (60ys vs. 71ys, $P < 0.001$), have a higher levels of lymphocyte count ($1.29 [0.93, 1.79] \times 10^9 /L$ vs. $0.59 [0.43, 0.87] \times 10^9 /L$, $P < 0.001$) and platelet count ($236 [185, 311] \times 10^9 /L$ vs. $145 [97, 224] \times 10^9 /L$, $P < 0.001$), a lower levels of WBC count ($5.96 [4.65, 7.62] \times 10^9 /L$ vs. $9.01 [5.80, 13.36] \times 10^9 /L$, $P < 0.001$), hs-CRP ($8.1 [1.6, 46.6] \text{ mg/L}$ vs. $105.6 [64.6, 146.6] \text{ mg/L}$, $P < 0.001$), IL-6 ($4.19 [1.71, 16.91] \text{ pg/mL}$ vs. $54.88 [27.89, 166.05] \text{ pg/mL}$, $P < 0.001$) and creatinine ($66 [56, 77] \mu\text{mol/L}$ vs. $85 [68, 117] \mu\text{mol/L}$, $P < 0.001$) than that in non-survivors. Non-survivors had a significantly higher eGFR levels than survivors ($96.43 [84.11, 108.47] \text{ ml/min/1.73m}^2$ vs. $75.95 [47.22, 92.84] \text{ ml/min/1.73m}^2$, $P < 0.001$). Non-survivors received higher ratio of mechanical ventilation (77.2% vs. 3.6%) treatment.

Clinical features of patients with or without declined eGFR levels

Patients with declined eGFR level ($< 90 \text{ ml/min/1.73m}^2$) were older (73yrs vs. 56yrs, $P < 0.001$), have a higher levels of WBC count ($7.08 [4.80, 9.71] \times 10^9 /L$ vs. $6.08 [4.84, 7.63] \times 10^9 /L$, $P = 0.005$), IL-6 ($29.32 [5.26, 65.07] \text{ pg/mL}$ vs. $4.09 [1.63, 15.23] \text{ pg/mL}$, $P < 0.001$) and creatinine ($87 [73, 108] \mu\text{mol/L}$ vs. $60 [52, 69] \mu\text{mol/L}$, $P < 0.001$), a lower levels of lymphocyte count ($0.88 [0.50, 1.16] \times 10^9 /L$ vs. $1.30 [0.93, 1.81] \times 10^9 /L$, $P < 0.001$) and platelet count ($188 [126, 288] \times 10^9 /L$ vs. $233 [191, 303] \times 10^9 /L$, $P < 0.001$) as compared with patients with normal eGFR levels.

Decline Egfr Associated With Short-term Prognosis In Covid-19 Patients

As shown in Table 2, the 28-days mortality in decline eGFR group was significantly higher than that in normal eGFR group (38.5% vs. 10.7%, $P < 0.001$). Multivariate logistic regression analysis (Table 3) revealed that the independent risk factors of 28-days outcome included lower eGFR (OR: 3.97, 95%CI: 1.42–11.11), elevated WBC (OR: 7.08, 95%CI: 3.15–15.90), lymphopenia (OR: 2.58, 95%CI: 1.21–5.49) and IL-6 (OR: 7.90, 95%CI: 2.19–28.49).

Table 1
Baseline characteristics of 354 COVID-19 patients with different outcomes.

Characteristics	Total	Survivor	Non-survivor	P value
N	354	275	79	
Age, y	63(51,71)	60(47,69)	71(63,79)	< 0.001
Male sex	201(56.8%)	146(53.1%)	55(69.6%)	0.009
Symptoms				
Fever	205(78.8%)	146(78.1%)	59(80.8%)	0.626
Cough	197(75.8%)	141(75.4%)	56(76.7%)	0.825
Sputum	122(46.9%)	93(49.7%)	29(39.7%)	0.146
Dyspnea	112(43.1%)	68(36.4%)	44(60.3%)	< 0.001
Fatigue	124(47.7%)	87(46.5%)	37(50.7%)	0.546
Nausea and vomiting	42(16.2%)	36(19.3%)	6(8.2%)	0.030
Comorbidity				
Hypertension	106(29.9%)	79(28.7%)	27(34.2%)	0.351
Diabetes	52(14.7%)	42(15.3%)	10(12.7%)	0.563
Cardiac disease ^a	37(10.5%)	23(8.4%)	14(17.7%)	0.017
Chronic lung disease	21(5.9%)	16(5.8%)	5(6.3%)	0.792
Chronic kidney disease	2(0.6%)	0(0%)	2(2.5%)	0.049
Laboratory finding				
WBC count, $\times 10^9$ /L	6.39(4.84,8.27)	5.96(4.65,7.62)	9.01(5.80,13.36)	< 0.001
Lymphocyte, $\times 10^9$ /L	1.11(0.73,1.62)	1.29(0.93,1.79)	0.59(0.43,0.87)	< 0.001

Continuous variables are expressed as median values (interquartile ranges), and categorical variables are presented as number of patients (percentages).

WBC, white blood cell; hs-CRP, high-sensitive C-reactive protein; IL-6, interleukin-6. IMV: invasive mechanical ventilation; NIPPV: noninvasive positive pressure ventilation.

^a Includes congestive heart disease and coronary atherosclerotic heart disease.

Characteristics	Total	Survivor	Non-survivor	P value
Platelet count, ×10 ⁹ /L	222(161,300)	236 (185,311)	145(97,224)	< 0.001
Creatinine, μmol/L	69(57,83)	66(56,77)	85(68,117)	< 0.001
eGFR, ml/min/1.73m ²	92.82(75.92,105.42)	96.43(84.11,108.47)	75.95(47.22,92.84)	< 0.001
IL-6, pg/mL	7.31(2.27,35.50)	4.19(1.71,16.91)	54.88(27.89,166.05)	< 0.001
Treatment or complication				
ICU admission	38(10.7%)	7(2.5%)	31(39.2%)	< 0.001
Septic shock	13(3.7%)	2(0.7%)	11(13.9%)	< 0.001
IMV	35(9.9%)	5(1.8%)	30(38.0%)	< 0.001
NIPPV	36(10.2%)	5(1.8%)	31(39.2%)	< 0.001
Continuous variables are expressed as median values (interquartile ranges), and categorical variables are presented as number of patients (percentages).				
WBC, white blood cell; hs-CRP, high-sensitive C-reactive protein; IL-6, interleukin-6. IMV: invasive mechanical ventilation; NIPPV: noninvasive positive pressure ventilation.				
^a Includes congestive heart disease and coronary atherosclerotic heart disease.				

Table 2
Characteristics of 354 COVID-19 patients with different eGFR levels.

Characteristics	Total	Normal eGFR (≥ 90 ml/min/1.73m ²)	Declined eGFR (< 90 ml/min/1.73m ²)	P value
N	354	206	148	
Age, y	63(51,71)	56(43,63)	73(66,79)	< 0.001
Male sex	201(56.8%)	110(53.4%)	91(61.5%)	0.130
Comorbidity				
Hypertension	106(29.9%)	48(23.3%)	58(39.2%)	0.001
Diabetes	52(14.7%)	28(13.6%)	24(16.2%)	0.492
Cardiac disease ^a	37(10.5%)	14(6.8%)	23(15.5%)	0.008
Chronic lung disease	21(5.9%)	11(5.3%)	10(6.8%)	0.578
Chronic kidney disease	2(0.6%)	0(0%)	2(1.4%)	0.174
Laboratory finding				
WBC count, $\times 10^9$ /L	6.39(4.84,8.27)	6.08(4.84,7.63)	7.08(4.80,9.71)	0.005
Lymphocyte, $\times 10^9$ /L	1.11(0.73,1.62)	1.30(0.93,1.81)	0.88(0.50,1.16)	< 0.001
Platelet count, $\times 10^9$ /L	222(161,300)	233(191,303)	188(126,288)	< 0.001
Creatinine, μ mol/L	69(57,83)	60(52,69)	87(73,108)	< 0.001
eGFR, ml/min/1.73m ²	92.82(75.92,105.42)	102.80(95.36,112.58)	73.47(56.00,82.26)	< 0.001
IL-6, pg/mL	7.31(2.27,35.50)	4.09(1.63,15.23)	29.32(5.26,65.07)	< 0.001
Outcome				

Continuous variables are expressed as median values (interquartile ranges), and categorical variables are presented as number of patients (percentages).

WBC, white blood cell; hs-CRP, high-sensitive C-reactive protein; IL-6, interleukin-6. IMV: invasive mechanical ventilation; NIPPV: noninvasive positive pressure ventilation.

^a Includes congestive heart disease and coronary atherosclerotic heart disease.

Characteristics	Total	Normal eGFR (≥ 90 ml/min/1.73m ²)	Declined eGFR (< 90 ml/min/1.73m ²)	P value
28-days death	79(22.3%)	22(10.7%)	57(38.5%)	< 0.001
Continuous variables are expressed as median values (interquartile ranges), and categorical variables are presented as number of patients (percentages).				
WBC, white blood cell; hs-CRP, high-sensitive C-reactive protein; IL-6, interleukin-6. IMV: invasive mechanical ventilation; NIPPV: noninvasive positive pressure ventilation.				
^a Includes congestive heart disease and coronary atherosclerotic heart disease.				

Table 3

Multivariate logistic regression analysis of risk factors for 28-days mortality in severe COVID-19 patients.

Variables	Multivariate	
	OR (95% CI)	P value
Age > 65 ys	2.08 (0.92–4.70)	0.079
WBC $> \times 10^9$ /L	7.08 (3.15–15.90)	< 0.001
Lymphocyte $< 0.8 \times 10^9$ /L	2.58 (1.21–5.49)	0.014
SCr > 70 μ mol/L	1.28 (0.54–3.01)	0.581
eGFR < 90 ml/min/1.73m ²	3.97 (1.42–11.11)	0.009
IL-6 > 7 pg/mL	7.90 (2.19–28.49)	0.002
WBC: white blood cells; SCr: serum creatinine; IL-6: interleukin-6; eGFR: estimated glomerular filtration rate; OR: odds ratio.		

Kaplan-Meier analysis (Fig. 1A) indicated that patients with declined eGFR levels had a significant survival disadvantage (log-rank $P < 0.01$) as compared to patients with normal eGFR levels. The ROC curve (Fig. 1B) showed that the area under curve (AUC) was 0.772. The cut-off value of eGFR for prognosis prediction was 82.2 μ mol/L, with the sensitivity of 76.7% and speciality of 66.3%.

Discussion

In this retrospective study, we identified the association of lower eGFR with 28-days mortality in COVID-19 patients. The cut-off value of eGFR for predicting the 28-days mortality was 82.2 μ mol/L, with the sensitivity of 76.7% and speciality of 66.3%. This cut-off value was slightly lower than the normal range (at least 90 ml/min/1.73m²), which suggesting that potential kidney injury might represented a higher

risk of diseases progression. It is essential of early detection and precaution to improve the prognosis of COVID-19.

Although the respiratory and immune systems are the major targets of COVID-19, kidney injury is a major complication. Some patients with COVID-19 also present with kidney injury, and autopsy findings of patients who died from the illness sometimes show renal damage. AKI occurred in 2.9–23% of ICU patients [3–5]. But another report indicated that 68.5% patients experienced remission of proteinuria, 45.7% experienced complete recovery of kidney function [6]. Update, it is remain controversial how to evaluated renal function or AKI precisely in COVID-19. SCr remains widely used as biomarker for renal function evaluation, but it is a delayed marker when it is generally increased after sever kidney damage. Although it is inconvenient to measure GFR directly, eGFR is widely accepted as the total index to evaluate renal function for acute or chronic kidney disease [9–11]. So, we used eGFR for the assessment of kidney injury in COVID-19 patients in this study. The median eGFR levels of total patients was 92.82 ml/min/1.73m². The median eGFR levels of non-survivors was significantly lower than survivor. In a recent study, eGFR < 60 ml/min per 1.73 m² was reported in 13.1% of COVID-19 patients [3]. In our study, the ratio was 16% (46/275), which was similar to previous report.

In declined eGFR group, the median serum creatinine level was 87.00 (IQR: 73,108) µmol/L, which remained in normal range. A recent study demonstrated that among patients with baseline SCr ≥ 0.7 mg/dl (61.9µmol/l) those who experienced a 0.3mg/dl increase in SCr within 48 h had clinically meaningful differences in outcomes (including length of hospital stay and mortality) when comparing with those who experienced a 50% increase in SCr from baseline within 7 days [8]. It indicated the advantage of eGFR in sensitivity for early-stage kidney injury evaluation as compared with SCr. Moreover, the cut-off value of eGFR for predicting the 28-days mortality was 82.2µmol/L, which was slightly lower than the normal range (at least 90 ml/min/1.73m²). It reveals that potential kidney impairment might occur before eGFR decreased significantly in early stage of SARS-CoV-2 infection. It is important of early detection and precaution to improve the prognosis of COVID-19.

A recent study showed that kidney diseases was associated with early in-hospital death of patients with COVID-19 [6]. However, another report indicated that COVID-19 did not result in acute kidney injury [7]. In previous study of patients with H1N1 virus infection, only those cases in the AKI III category were independently associated with mortality [13]. In this study, we identified that declined eGFR associated with poor short-term prognosis in COVID-19 patients. Previous studies have demonstrated that lower eGFR was risk factor for all-cause and cardiovascular mortality in high-risk populations, independent of each other and of cardiovascular risk factors [9–11]. In this study, we showed lower eGFR as an independent risk factor of 28-days mortality. This was in consistent with previous study. Previous reports have identified the direct cytopathic effects of SARS-CoV-2 on kidney tissue, the up-regulation of ACE2 in patients with COVID-19 and the SARS-CoV nucleoprotein antibody in tubules [14–15]. These provide direct evidence of the invasion of SARSCoV-2 into kidney tissue. About 5–10% of hospitalized patients and up to 60% of patients admitted to the intensive care unit had experienced acute kidney injure [16]. Early improvement in kidney injure may lead to a significant survival in severe sepsis [17]. This study and

previous reports demonstrated the association of kidney impairment with short-term mortality, which indicated the necessity of early detection and early interference of kidney injury in COVID-19 patients. However, there was no evidence for the impact of early kidney improvement on survival in COVID-19 patients. A prospective randomized controlled clinical trial could provide convincing evidence.

There are some limitations. First of all, this study only represented a part of COVID-19 patients in Wuhan as it is a single-center retrospective study. A large scale and multiple-center study might be more persuasive. Secondly, the role of different treatments might result in bias, including antiretrovirals and immunologic antibody therapy. We do not have statistical power to determine if these antiviral treatments had an effect on mortality, because of the lack of standardized antiviral therapies for the COVID-19 patients.

Conclusion

Lower eGFR was associated with poor prognosis and could be used an independent risk factor of 28-days mortality in COVID-19 patients. The eGFR cut-off value for predicting the 28-days mortality was 82.2 μ mol/L, with the sensitivity of 76.7% and speciality of 66.3%. Early detection and surveillance for eGFR may benefit to identify patients with high-risk of progression.

Abbreviations

COVID-19: coronavirus disease 2019; eGFR: estimated glomerular filtration rate; AKI: acute kidney injury; IQR: interquartile range; AUC: area under curve; WBC: white blood cell; hs-CRP: high-sensitive C-reactive protein; IL-6: interleukin-6; IMV: invasive mechanical ventilation; NIPPV: noninvasive positive pressure ventilation; SCr: serum creatinine; OR: odds ratio.

Declarations

Ethics approval and consent to participate

Not applicable

Consent for publication

Not applicable

Availability of data and materials

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

Competing interests

The authors declare that they have no competing interests.

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Author contributions

Chang-guo Wang and Si-jing Zhou collected and analyzed the data, wrote the manuscript. Wei-yun Zhang and Ying-ying Liu collected and analyzed the data. Jun-hong Jiang, Ran Wang and Da-xiong Zeng designed the study, analyzed the data, corrected the manuscript.

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Figures

Figure 1

Kaplan-Meier analysis and ROC curve.(A) Kaplan-Meier analysis of the 28-days mortality among COVID-19 patients with different eKaplan-Meier analysisGFR levels. (B) The ROC curve of eGFR for predicting prognosis of severe COVID-19 patients.