Research Article

Epidemiology and Outcomes of Acute Kidney Injury in COVID-19 Patients with Acute Respiratory Distress Syndrome: A Multicenter Retrospective Study

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Abstract

Background: Acute kidney injury (AKI) is associated with increased mortality in patients with acute respiratory distress syndrome (ARDS). However, the epidemiological features and outcomes of AKI among COVID-19 patients with ARDS are unknown. ***Methods:*** We retrospectively recruited consecutive adult COVID-19 patients who were diagnosed with ARDS according to Berlin definition from 13 designated intensive care units in the city of Wuhan, China. Potential risk factors of AKI as well as the relation between AKI and in-hospital mortality were investigated. ***Results:*** A total of 275 COVID-19 patients with ARDS were included in the study, and 49.5% of them developed AKI during their hospital stay. In comparison with patients without AKI, patients who developed AKI were older, tended to have chronic kidney disease, had higher Sepsis-Related Organ Failure Assessment score on day 1, and were more likely to receive invasive ventilation and develop acute organ dysfunction. Multivariate analysis showed that age, history of chronic kidney disease, neutrophil-to-lymphocyte ratio, and albumin level were independently associated with the occurrence of AKI. Importantly, increasing AKI severity was associated with increased in-hospital mortality when adjusted for other potential variables: odds ratio of stage 1 = 5.374 (95% CI: 2.147–13.452; $p < 0.001$), stage 2 = 6.216 (95% CI: 2.011–19.210; $p = 0.002$), and stage 3 = 34.033 (95% CI: 9.723–119.129; $p < 0.001$). ***Conclusion:*** In this multicenter retrospective study, we found that

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nearly half of COVID-19 patients with ARDS experienced AKI during their hospital stay. The coexistence of AKI significantly increased the mortality of these patients.

Introduction

The rapid spread of COVID-19 has caused a global pandemic since it was firstly reported in Wuhan, China [1]. The total number of coronavirus cases across the world has reached 17,889,134, and over 686,145 deaths occurred as of 3 August 2020 [1]. Although most infected patients showed mild symptoms, around 5% of the patients required intensive cares based on initial studies [2, 3].

Acute respiratory distress syndrome (ARDS) is the principal feature of critically ill patients with COVID-19, which is associated with worse outcome in these patients [4–6]. However, initial studies reported that critically ill patients with COVID-19 often had multiple organ dysfunction besides ARDS [6–8]. Previous studies found that 20–40% of intensive care unit (ICU) patients with CO-VID-19 experienced acute kidney injury (AKI) [6, 9]. However, epidemiological features of AKI as well as its contribution to the risk of death in COVID-19 patients with ARDS are unknown yet. A better understanding of these is essential to facilitate early intervention to improve the outcome of patients with COVID-19, given that the occurrence of AKI may be associated with increased mortality in patients with ARDS [10]. In this multicenter retrospective study including patients from 13 ICUs in the city of Wuhan, we aimed to investigate the epidemiological features of AKI and its related in-hospital mortality in COVID-19 patients with ARDS.

Methods

Participants

This study included consecutive adult patients (aged ≥18 years) from 13 designated ICUs in the city of Wuhan. All patients were confirmed with SARS-CoV-2 infection by quantitative polymerase chain reaction test of throat swab samples or sputum samples according to the WHO guidance. The study periods and number of included patients in each center are listed in online suppl. Table 1; see www. karger.com/doi/10.1159/000512371 for all online suppl. material. These patients were transferred from floors or other hospitals due to worsened conditions that needed intensive care. This study was approved by the Shanghai East Hospital Ethics Committee.

Data Collection

The detailed clinical information of each patient was obtained by physicians using a standard questionnaire after they were ad-
mitted to the ICU. Clinical information including demographic data, medical history, comorbidities, symptoms, signs, laboratory findings, chest computed tomographic scans, and treatment of the patients received due to the virus infection were recorded. We also calculated each patient's Sepsis-Related Organ Failure Assessment (SOFA) score (which can range from 0 to 24, with higher scores indicating more severe illness) on day 1 of ICU admission to evaluate the severity of the diseases.

Each measurement of serum creatinine (SCr) and use of renal replacement therapy during their hospital stay (including non-ICU stay) was recorded to determine whether and when AKI occurred in these patients. The medical record of the patients, including the blood gas test, oxygen saturation and fraction of inspired oxygen, and respiratory supports, was independently reviewed by 2 physicians to determine the diagnosis and timing of ARDS.

AKI and ARDS Definition

AKI was determined by the increase of SCr according to the Kidney Disease Improving Global Outcomes (KDIGO) 2012 guidelines [11]. Briefly, AKI was diagnosed if an absolute increase in SCr of ≥0.3 mg/dL (≥26.5 μmol/L) within 48 h or a 50% increase in SCr from baseline within 7 days occurred, by significantly decreased urine output [11]. AKI was further classified to 3 stages based on KDIGO criteria.

The lowest level of in-hospital SCr rather than prehospital creatinine was used as reference creatinine in this study due to several reasons. First, prehospital creatinine was often unavailable or uncollected by medical stuff due to the heavy burden of this disease during outbreak [9]. Second, many patients were already severely ill before they were admitted to the ICU due to lack of medical resources. Therefore, some patients' kidney function was already damaged before admission, which may affect the accurate identification of the occurrence of AKI [11]. Modification of Diet in Renal Disease (MDRD) formula was not used to back-calculate baseline creatinine because this method overestimates the prevalence of AKI [12]. Therefore, we only included patients who had at least 2 creatinine measurements during their hospital stay. Patients who were on regular dialysis due to chronic renal failure were excluded as it would obscure the real change of creatinine. ARDS was defined according to the Berlin definition [13].

Statistical Analysis

Continuous variables were presented as median and interquartile range (IQR), and categorical variables were expressed as percentages. Baseline characteristics between AKI and non-AKI groups were compared with the unpaired Student's t test or Mann-Whitney test for continuous variables and the χ^2 or Fisher's exact tests for categorical variables. Univariate logistic regression analyses were performed to examine the association between each of the indicators and in-hospital mortality separately. We also conducted multivariate logistic regression to determine the variables that independently associated with AKI or in-hospital mortality. A criterion of $p < 0.05$ for entry and a $p \geq 0.10$ for removal was imposed in this procedure. Odds ratios (ORs) for continuous variables were described using standardized ORs, which were associated with a 1 standard deviation change in the variable. A two-sided p value of <0.05 was considered to indicate statistical significance. All analyses were performed with SPSS 25.0 software (SPSS Inc., Chicago, IL, USA).

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Table 1. Clinical features, laboratory findings on admission, and outcomes of the COVID-19 patients with acute respiratory distress syndrome

	All (n = 275)	No AKI (n = 139)	AKI (n = 136)	p value
Age	69 (62–77)	68 (58–74)	70 (64–78)	0.007
Sex				
Male	161 (58.4)	80 (57.6)	81 (59.6)	0.736
Female	114 (41.5)	59 (42.4)	55 (40.4)	
Comorbidities, n (%)				
Hypertension	150 (54.5)	79 (56.8)	71 (52.2)	0.441
Diabetes	62 (22.5)	32 (23.0)	30 (22.1)	0.849
Coronary artery disease	35 (12.7)	16 (11.5)	19 (14.0)	0.541
Chronic obstructive lung disease	37 (13.5)	23 (16.5)	14 (10.3)	0.129
Chronic kidney disease	16 (5.8)	1 (0.7)	15 (11.0)	<0.001
Laboratory findings at admission				
White blood cell count, ×10^9/L	9.20 (6.50–12.56)	8.90 (6.21–11.20)	9.72 (6.71–14.17)	0.003
Neutrophil count, ×10^9/L	7.68 (5.16–11.36)	7.32 (4.95–9.79)	8.64 (5.41–12.88)	0.001
Lymphocyte count, ×10^9/L	0.71 (0.47–0.96)	0.78 (0.57–0.98)	0.62 (0.38–0.86)	0.110
NLR	11.62 (6.60–21.64)	9.22 (6.05–14.60)	15.50 (8.25–26.24)	<0.001
Monocytes, count, ×10^9/L	0.45 (0.29–0.64)	0.47 (0.31–0.65)	0.43 (0.27–0.64)	0.979
Platelet count, ×10^9/L	201 (130–285)	246 (156–321)	165 (102–230)	<0.001
C-reactive protein, mg/L	57.65 (23.40–141.91)	41.76 (19.65–111.93)	90.11 (34.34–168.75)	0.003
Procalcitonin, ng/mL	0.30 (0.12–0.96)	0.23 (0.09–0.44)	0.44 (0.16–1.57)	0.589
ALT, U/L	32.0 (19.8–48.0)	33.0 (21.5–47.0)	30.2 (17.1–54.1)	0.046
AST, U/L	35.0 (23.2–52.0)	33.8 (23.2–45.0)	38.0 (23.2–58.0)	0.055
Total bilirubin, μmol/L	13.80 (9.78–19.20)	13.87 (9.93–17.65)	13.80 (9.59–20.92)	0.612
Direct bilirubin, μmol/L	7.40 (4.28–12.53)	9.40 (4.40–13.58)	6.53 (3.89–11.00)	0.375
Albumin, g/L	30.95 (27.78–34.02)	33.00 (29.15–37.00)	29.85 (26.83–31.90)	<0.001
D-dimer, μg/mL	1.83 (0.56–7.48)	0.72 (0.33–4.30)	3.43 (1.68–17.34)	0.001
Glucose, mmol/L	7.90 (5.82–10.48)	8.10 (5.84–10.21)	7.65 (5.80–11.17)	0.220
SOFA score on day 1	5 (3–7)	5 (2–6)	5 (4–8)	0.002
Mechanical ventilation, n (%)				
None	52 (18.9)	35 (25.2)	17 (12.5)	<0.001
Noninvasive	130 (47.3)	85 (61.2)	45 (33.1)	
Invasive	93 (33.8)	19 (13.7)	74 (54.4)	
Reference SCr, μmol/L	59.3 (43.0–74.0)	59.2 (42.6–67.8)	59.3 (43.9–81.5)	0.025
Creatinine measurement, times	6 (3–10)	3 (2–6)	7 (4–11)	<0.001
CRRT, n (%)	37 (13.5)	0 (0.0)	37 (27.2)	<0.001
ECMO, n (%)	7 (2.5)	1 (0.7)	6 (4.4)	0.064
SCr$_{discharge}$/SCr$_{Reference}$*	1.30 (1.20–1.66)	1.23 (1.16–1.30)	1.75 (1.65–2.38)	0.12
Mortality, n (%)	142 (51.6)	33 (23.7)	109 (80.1)	<0.001

AKI, acute kidney injury; NLR, neutrophil-to-lymphocyte ratio; ALT, alanine aminotransferase; AST, aspartate aminotransferase; eGFR, estimated glomerular filtration rate; SOFA, Sepsis-Related Organ Failure Assessment; ARDS, acute respiratory distress syndrome; SCr, serum creatinine; CRRT, continuous renal replacement therapy; ECMO, extracorporeal membrane oxygenation. * Calculated in survivors.

Results

Baseline Characteristics

During the study periods, a total of 275 COVID-19 patients from 13 ICUs who were diagnosed with ARDS according to Berlin criteria were included in the study (online suppl. Table 1). Baseline clinical characteristics of these patients are shown in Table 1. The median age was 69 (IQR: 62–77) years and 58.4% were male. Of those patients, 136 (49.5%) developed AKI based on KDIGO criteria: 46 patients (33.8%) developed stage I AKI, 30 patients (22.1%) developed stage II AKI, and 60 patients (44.1%) developed stage III AKI. A total of 142 (51.6%) patients died during their hospital stay.

Table 2. Risk factors associated with acute kidney injury

Variables	Univariate analysis			Multivariate analysis		
	odds ratio	95% CI	*p* value	odds ratio	95% CI	*p* value
Age	1.027	1.007–1.048	0.008	1.026	1.003–1.050	0.029
Sex (female)	0.921	0.570–1.488	0.736	0.996	0.565–1.756	0.988
Comorbidities						
Hypertension	0.830	0.516–1.334	0.441			
Diabetes	0.946	0.537–1.667	0.849			
Coronary artery disease	1.248	0.613–2.543	0.541			
Chronic obstructive lung disease	0.579	0.284–1.179	0.132			
Chronic kidney disease	17.107	2.227–131.423	0.006	13.019	1.624–104.361	0.016
NLR	1.044	1.022–1.065	<0.001	1.037	1.013–1.061	0.002
Albumin	0.864	0.815–0.917	<0.001	0.895	0.841–0.953	0.001
SOFA score	1.147	1.048–1.254	0.003	1.058	0.955–1.172	0.278

Variables included in multivariate analysis were age, sex, chronic kidney disease, NLR, albumin, and SOFA score. NLR, neutrophil-to-lymphocyte ratio; SOFA, Sepsis-Related Organ Failure Assessment.
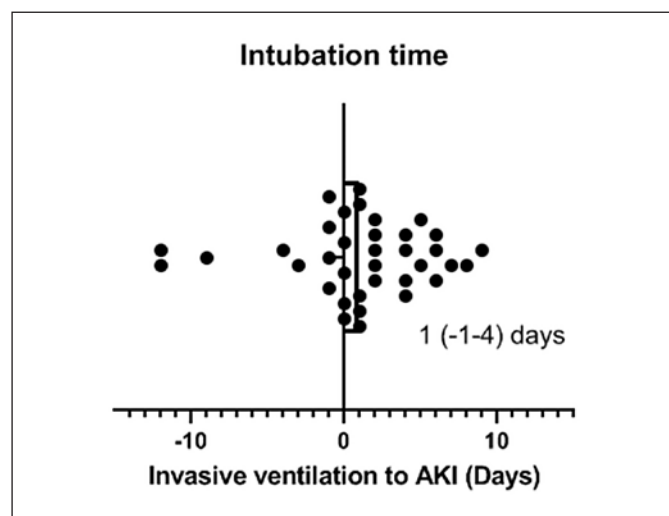

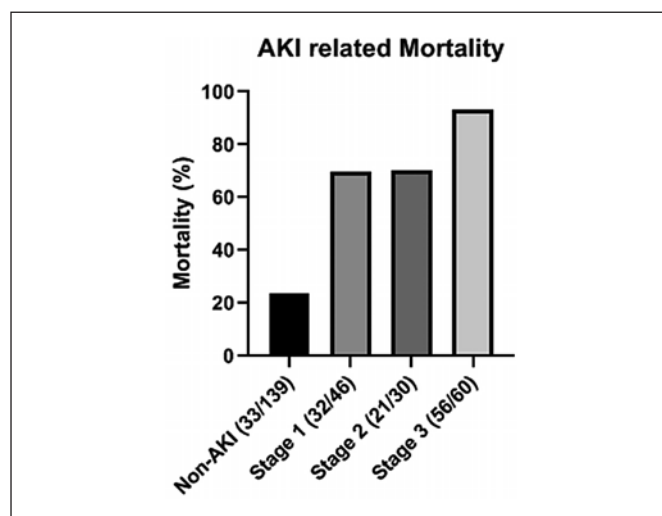**Fig. 1.** Timing of the occurrence of AKI and intubation. AKI, acute kidney injury.

Fig. 2. Mortality among patients with different stages of AKI. AKI, acute kidney injury.

Risk Factors Associated with the Development of AKI

Compared with patients without AKI, patients who developed with AKI were older, tended to have chronic kidney disease and worse kidney function at baseline, had higher SOFA score on day 1, and were more likely to receive invasive ventilation (Table 1). Among laboratory parameters on day 1 after ICU admission, AKI patients had higher white cell count, neutrophil count, neutrophil-to-lymphocyte ratio (NLR), C-reactive protein level, and D-dimer. Moreover, patients with AKI had lower platelet count and albumin level and had more organ dys-

function indicated by different laboratory parameters than patients without AKI (Table 1). After adjustment for sex, comorbidity, and SOFA score, age, a history of chronic kidney disease, NLR, and albumin level were independently associated with the occurrence of AKI (Table 2).

Association between AKI and Invasive Ventilation

As patients with AKI had more invasive ventilation (54.4 vs. 13.7%) which itself is a risk factor of the development of AKI [10], we analyzed the clinical course of AKI related to intubation time. Among patients with both AKI

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Table 3. Association between acute kidney injury and in-hospital mortality

Variables	Univariate analysis			Multivariate analysis		
	odds ratio	95% CI	p value	odds ratio	95% CI	p value
Age	1.032	1.012–1.053	0.002	1.029	0.999–1.061	0.056
Sex (female)	0.623	0.384–1.009	0.055	0.454	0.217–0.950	0.036
Comorbidities						
Hypertension	0.816	0.507–1.313	0.403			
Diabetes	1.086	0.616–1.913	0.776			
Coronary artery disease	2.256	1.058–4.810	0.035			
Chronic obstructive lung disease	0.677	0.337–1.362	0.274	2.002	0.632–6.343	0.238
Chronic kidney disease	4.367	1.216–15.687	0.024	0.340	0.070–1.656	0.182
NLR	1.065	1.039–1.092	<0.001	1.052	1.020–1.086	0.001
Albumin	0.812	0.760–0.869	<0.001	0.886	0.820–0.958	0.002
AKI						
Non-AKI	Reference			Reference		
Stage 1	7.342	3.504–15.383	<0.001	5.374	2.147–13.452	<0.001
Stage 2	7.495	3.130–17.946	<0.001	6.216	2.011–19.210	0.002
Stage 3	44.970	15.165–133.354	<0.001	34.033	9.723–119.129	<0.001
SOFA score	1.273	1.153–1.406	<0.001	1.361	1.164–1.591	<0.001

Variables included in multivariate analysis were age, sex, chronic obstructive lung disease, chronic kidney disease, NLR, albumin, AKI, and SOFA score. NLR, neutrophil-to-lymphocyte ratio; AKI, acute kidney injury; SOFA, Sepsis-Related Organ Failure Assessment.

and invasive ventilation, 75% patients developed AKI after intubation and 25% patients experienced AKI ahead of intubation. Median time from intubation to the occurrence of AKI was 1 (IQR: −1 to 4) day (Fig. 1).

In-Hospital Mortality Related to AKI

A total of 37 (27.2%) patients with AKI ended up with continuous renal replacement therapy. Those who developed AKI during their hospital stay and survived had more increase in SCr from baseline to discharge than those without AKI development (Table 1), indicating a persistent kidney injury existed. Importantly, the mortality of patients with AKI was significantly higher than those without (80.1 vs. 23.7%, $p < 0.001$) despite slight difference in the severity of disease indicated by SOFA score between 2 groups (Table 1; Fig. 2). In terms of the KDIGO classification, there were 32 deaths (69.6%) among patients in the stage 1 category, 21 (70.0%) among those in the stage 2 category, and 56 (93.3%) among those in stage 3 category (Fig. 2).

There was a stepwise increase in mortality with increasing AKI severity (KDIGO stage 1: OR: 7.342, 95% CI: 3.504–15.383; KDIGO stage 2: OR: 7.495, 95% CI: 3.130–17.946; and KDIGO stage 3: OR: 44.970, 95% CI: 15.165–133.354). After adjusting for age, sex, underlying medical conditions, NLR, albumin, and SOFA score,

KDIGO stage 1 (OR: 5.374; 95% CI: 2.147–13.452; $p < 0.001$), KDIGO stage 2 (OR: 6.216; 95% CI: 2.011–19.210; $p = 0.002$), and KDIGO stage 3 (OR: 34.033; 95% CI: 9.723–119.129; $p < 0.001$) were still associated with increased in-hospital mortality (Table 3).

Discussion

In this multicenter study, we found that AKI is a common comorbidity among COVID-19 patients with ARDS. The risk factors associated with AKI included older age, a history of chronic kidney disease, increased NLR, and decreased albumin level. Importantly, the occurrence of AKI significantly increased the mortality of these patients. To the best of our knowledge, this is the first large-scale study that investigated the epidemiological features of AKI and its related death in COVID-19 patients with acute respiratory distress syndrome.

Respiratory system is the primary target organ of SARS-CoV-2, and the development of ARDS is the principal feature of critically ill patients with COVID-19 [7, 8, 14]. However, respiratory supports such as extracorporeal membrane oxygenation or ventilation treatment resulted in unsatisfied outcomes in these patients [15]. This observation indicates that other or-

gan dysfunctions besides ARDS might be also critical to determine the outcome of these patients. AKI is the most frequent extra-pulmonary organ dysfunction in patients with ARDS, which associated with a higher mortality in these patients [10]. The current study found COVID-19 patients with ARDS who were of older age or had a history of chronic kidney disease were more likely to develop AKI. Moreover, increased NLR and decreased albumin level were also independently associated with the development of AKI. Indeed, recent studies found NLR was the independent risk factor of poor outcomes in COVID-19 patients [16, 17]. Consistently, a study found that hypoalbuminemia is a significant predictor of AKI and the death following AKI development [18]. Thus, our study provided useful information for early recognition of AKI in COVID-19 patients with ARDS in clinical practice.

While the pathogenic features of SARS-CoV-2 have not been fully understood, the virus infection induced cytokine storm was considered playing an important role in the development of organ dysfunction [19]. These uncontrolled inflammatory responses to SARS-CoV-2 infection not only target the respiratory system to cause ARDS but also attack other organs such as kidney to induce multiple organ dysfunction [19]. Moreover, increased intrathoracic pressure induced by mechanical ventilation and gas exchange abnormalities due to respiratory failure can affect renal vascular resistance to reduce kidney perfusion to induce AKI [20, 21]. Another hypothesis is that SARS-CoV-2 can directly attack the kidney. This is evidenced by that the angiotensin-converting enzyme 2, which is the entry receptor for SARS-CoV-2, is expressed not only in the lung but also in the kidney [22]. Therefore, there has been a rising concern that SARS-CoV-2 can directly target the kidney by recognizing its receptor angiotensin-converting enzyme 2 to cause kidney injury. Further studies need to be conducted to investigate the underlying mechanisms of the development of AKI in patients with COVID-19.

Our study found the development of AKI significantly increased the mortality in COVID-19 patients with ARDS in a stepwise mode. Studies showed that the development of AKI could in turn reduce the clearance of cytokines and increase the fluid overload, both of which could deteriorate ARDS [23–25]. For instance, proinflammatory cytokines IL-6 and IL-8 are increased after the occurrence of AKI, which promote lung injury by facilitating neutrophil accumulation [23–26]. Therefore, the acute loss of lung and kidney functions could lead to a vicious circle. Our findings indicated that the early recognition and treatment of AKI are essential to improve the outcome of patients with COVID-19.

Several limitations of this study should be mentioned. First, the assessment of AKI and ARDS was not pre-planned due to the retrospective nature of the study. Although we conducted intense evaluation of SCr (medium 3 times in non-AKI patients and 7 times in AKI patients) and continuous respiratory monitoring during hospitalization, there is still a possibility that we may underestimate the incidence of AKI and ARDS in these patients. Second, we used the lowest level of in-hospital SCr instead of prehospital SCr as the reference creatinine due to the heavy burden of this disease during outbreak. A very recent study reported that only 15% of patients with COVID-19 had available prehospital creatinine level in the city of New York [9]. This may affect the accuracy of detecting AKI. However, there is no consensus recommendation for choosing reference creatinine [27]. Some studies found that using lowest inpatient SCr as reference creatinine is reasonable and it may even more accurately reflect kidney function, especially in patients with sepsis or prolonged critical illness [28, 29]. Third, urine output was not used as a parameter because it was not very accurately recorded in the heavy burden of COVID-19 during the outbreak in Wuhan, which may also cause an underestimate of the incidence of AKI in these patients.

Conclusion

In this study, we found that nearly half of COVID-19 patients with ARDS developed AKI. The mortality rate was significantly higher in AKI patients than those without. Moreover, the mortality rate in AKI patients increases in a stepwise mode with AKI stages.

Acknowledgments

Statement of Ethics

This study was approved by the Shanghai East Hospital Ethics Committee (2020-009) and carried out in accordance with the Declaration of Helsinki. Written informed consent was waived by the Ethics Committee due to the retrospective nature of this study and rapid emergence of this infectious disease.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

Funding Sources

Author Contributions

F.W. conceived and designed the study, analyzed the data, and wrote the paper. L.R., C.Q., J.H., Z.L., M.D., X.Z., W.G., S.G., and W.G. contributed to data acquisition and analysis. C.R., Q.L., Z.L., and C.L. interpreted the data and put expert insights in this study.

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