Acute Kidney Injury in COVID-19: clinical outcomes and risk factors

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Abstract

Background:

Understanding of the incidence and effects of acute kidney injury (AKI) in patients diagnosed with COVID-19 is limited. The purpose of this study was to examine risk factors and related outcomes associated with AKI among patients diagnosed with COVID-19.

Method:

This is a retrospective cohort study of patients diagnosed with COVID-19 associated-pneumonia admitted to a tertiary hospital in Wuhan between January to February 2020. AKI was defined and staged according to the Kidney Disease: Improving Global Outcome (KDIGO) classification criteria. Cox's multivariate regression and logistic regression modelling were used to assess the effects of AKI on hospital mortality and risk factors associated with occurrence of AKI. Primary outcomes were risk-adjusted in-hospital mortality.

Results:

342 patients were finally enrolled in this study. AKI occurred in 13.4% (n = 46), among them 7.0% (n = 24) developed stage 1AKI, and 6.4% (n = 22) developed stage 2 - 3 AKI. Overall 26.9% (n = 92) died during hospitalization. Among them 19.3% (57/296) of the non-AKI patients died, 62.5%(15/24) of stage 1 AKI patients, and 90.9% (20/22) of stage 2 - 3 AKI patients died. AKI was strongly associated with mortality (HR 2.52; 95% CI, 1.59-3.96; p 0.001). Further analysis shows that progression to AKI stage 2 - 3 doubles the hazard ratio for death. Age, leukocytes number, fibrinogen concentration, C-reative protein level, and severity of pneumonia at admission were independent risk factors associated with the development of AKI.

Conclusion:

Acute kidney injury is common among hospitalized COVID-19 patients and strongly associated with increased mortality, early detection and prevention of the progression of AKI may be critical to reduce mortality of these patients.

Introduction

Coronavirus disease 2019 (COVID–19) has caused huge morbidity and mortality across the world since the beginning of this year, affecting more than 330,000 people, as of April 28, 2020). COVID–19 patient cases are often characterized by respiratory failure and progression to multi-organ dysfunction with reported hospital mortality ranging from 2.3% to 49%[1,2]. Acute kidney injury (AKI) is commonly observed in coronavirus infections according to previous experiences of SARS and MERS outbreaks. Reported AKI developed in approximate 6.7% SARS-Cov infected patients and 75% MERS-Cov infected patients respectively[3,4]. Several factors may contribute to the development of AKI among COVID–19

patients. Firstly, studies have shown that this novel severe acute respiratory syndrome coronavirus 2 (SARS-CoV–2) has a similar genome sequence with SARS-CoV with the kidney as one of the primary targets of the virus[5], [6]. Secondly, emerging evidence has shown that SARS-CoV–2 target angiotensin-converting enzyme 2 (ACE–2) receptor to enter affected cells, kidney tubular cells are packed with ACE–2 receptors which may worsen the incidence of AKI[7]. Finally, risk factors associated with the development of AKI such as hypoxemia, shock, inflammatory storm, use of nephrotoxic antibiotics, and fluid overload can all been observed in COVID–19 patients. These risk factors may actually increase the incidence and perhaps lead to worsening AKI outcomes.

Despite the risk factors associated with AKI in COVID–19 patient cases, only a few studies report the incidence and associated outcomes of AKI. In a retrospective observed study involving 59 COVID–19 cases, researchers found an high prevalence of renal abnormalities with 34% of patients developing massive albuminuria on the first day of admission, then 63% develop proteinuria during hospitalization[8]. In another study by Fei et al. AKI occurred in 28 of enrolled patients whereas 27 of patients with AKI finally died during hospitalization[9]. One recently published study that enrolled 701 COVID–19 patients reported 5.1% of enrolled patients developed AKI, with a more than 20% increase of mortality for patients with AKI compared to those without[8]. However, most of these studies either enrolled COVID–19 patients who had not been hospitalized or not were designed to assess the effects of AKI. Very few studies have provided quantitative evidence of AKI in terms of COVID–19 outcomes. The incidence of AKI, risk factors, and mortality associated with AKI have not been fully documented. The objectives of this study were to describe the incidence of AKI among COVID–19 cases, as well as describing the clinical characteristics and severity of AKI and the survival in relation to AKI.

Method

This is a retrospective cohort study involving patients diagnosed with COVID–19, admitted to the People's Hospital of Wuhan University (central and eastern districts) between January 30, 2020 and March 17, 2020. This hospital was designated by the Chinese government to treat *only* COVID–19 patients during the initial outbreak period. Medical records and compiled data from inpatients and outpatients were obtained directly through the emergency department. Data around recent exposure histories, clinical signs, chest computed tomography (CT), and laboratory findings from the sample taken upon admission were extracted from the electronic medical records systems. All laboratory testing including RT-PCR was performed according to the needs of individual patients. Laboratory assessments consisted of complete blood count, blood chemical analysis, coagulation testing, liver assessments and renal functions, as well as measures of electrolytes, C-reactive protein, procalcitonin, and lactate dehydrogenase. The presence of radiologic abnormalities was determined on the basis of a description from physicians within the department of radiology and were reviewed through consultation with physicians in the department of respiratory medicine.

A confirmed COVID–19 case involved a risk assessment with diagnostic criteria which, at the time included: (1) recent exposure history, clinical signs (i.e., cough, fever, myalgia); (2) blood cell count

(normal or reduced white blood cell count/decreased lymphocyte count); (3) chest CT image abnormalities (i.e., small patches, infiltration shadows, interstitial lung changes, and multiple lung abrasion, either unilateral or bilateral), and; (4) positive results on high throughput sequencing or real-time reverse transcriptase–polymerase chainreaction (RT-PCR) assays of nasal and pharyngeal swab specimens. The severity of COVID–19 at admission was evaluated depending on the Chinese guideline for diagnosis and treatment of novel coronavirus disease, version 6[10].

The following exclusion criteria were applied: (1) Those less than 18 years of age; (2) previous chronic kidney disease or with elevated serum creatinine compared to the reference value (97umol/L) at first lab test; (3) diagnosis of malignant tumors; (4) death or discharge within 24 hours of admission. Degrees of severity of COVID–19 pneumonia were classified as mild and severe using definitions of the guidance of the National Health Commission of China. Please see Table 1 for further details.

AKI was identified according to the Kidney Disease Improving Global Outcomes criteria calculated during the first 7 days after admission. Precise urine output data were not available for most patients in this study, therefore serum creatinine criteria were used. Baseline creatinine was defined for all analyses, and moderate to severe AKI were defined as stage 2–3, as previously described[11]. Reference serum creatinine levels were taken as the lowest value recorded between hospitalization and the standard lab value (i.e., 97umol/L). The primary outcome was survival during hospital stay and data were compared between patients *with* and *without* suspected or diagnosed AKI, herein defined as the non-AKI group.

Statistical analysis

Statistical analyses were performed using Stata IC (version 15.1), with statistical significance set at p 0.05. Comparisons across groups were performed using chi-square test or Fiser's exact test for categorical variable and Mann-Whitney's U test or Student's t-test, as appropriate for continuous variables. Multivariate logistic regression model was used to identify independent risk factors associated with the development of AKI. Survival analysis between the AKI and non-AKI groups was compared using the Kaplan-Meier method with log-rank test. Cox's proportional hazards model was used to assess severity and age adjusted survival at 30 days after hospitalization.

Results

Baseline characteristics and exposures

A total of 379 patients diagnosed as COVID–19 were enrolled during the study period. Among them 11 had underlying kidney disease, 19 patients had elevated Scr upon admission, and 7 patients had a history of cancer. Data from the remaining 342 patients became the sample of this retrospective cohort study. The median age of enrolled patients was 56 years (IQR 39–68 years), 49.1% were male. More than half of the patients admitted had comobidities (60.2%, n = 206) with cardiac disease being the most common comorbidity (27%, n = 95). As all patients enrolled were SARS-CoV–2 RNA positive, antiviral treatment

was administered in all enrolled patients. In addition, antibiotics was also used among majority of patients (86.3%, n = 295). Corticosteroid and intravenous immunoglobin was administered in almost half of the enrolled patients. The estimated average onset time from the development of the first symptom to hospitalization was 9 days (IQR 6–12 days). Upon admission, 52.6% (n = 180) were assessed to be non-severe cases compared to 47.4% (n = 162) were considered cases with severe pneumonia according to the guidelines published by the Chinese Health Authorities (see table 2 for further details).

Development of AKI

AKI at any stage was identified in 13.4% (n = 46) of the cases in this study by 7 days after admission. 7.0% (n = 24) were stage 1, and 6.43 % (n = 22) were assessed to be stage 2–3. Compared with patients without AKI (i.e., AKI-), age, percentage of being a male, comorbidity of cardiac disease, severity of pneumonia were significantly higher in patients with AKI (i.e., AKI+). The AKI+ group also had an higher leukocyte and lower lymphocyte counts, higher leverls of C-reactive protein, procalcitonin, and aspartate aminotransferase.

Elevated biomarkers of myocardial dysfunction such as B-type natriuretic peptide and cardiac troponin I were much higher in the AKI+ group. In addition, dysfunction of coagulation system was observed with significantly higher Fibrinogen and D-dimer in the AKI+ group. Bilateral penumonia was more commonly seen in the AKI+ group, and corticosteroids was more often used in AKI+ group. There was no significant difference in terms of antibiotic use and pre-hospitalization days between groups (see table 3 for details).

In bivariate logisitic analysis, the following factors were significantly associated with the development of AKI: age (p 0.001), male (p 0.001), history of cardiovascular disease (p 0.001), leukocytes count (p 0.001), C-reactive protein (p 0.001), albumin (p 0.001), cardiac troponin I (p 0.001), fibrinogen (p 0.001), D-dimer (p = 0.005), use of corticosteroids (p = 0.01), and severity of pneunonia at admission (p 0.001). In the multi-logistic regression model, several factors were independently associated with the development of AKI: age increase (OR = 1.12,95% CI:1.05–1.25); with a past medical history of cardiac disease (OR = 2.17, 95% CI:1.33–4.22); elevated leukocytes (OR = 1.36, 95%CI:1.11–1.66); higher levels of C-reactive protein (OR = 1.03, 95%CI:1.01–1.05), increased fibrinogen (OR = 1.08, 95%CI:1.02–1.13, p = 0.004), and severity of pneumonia on admission (OR = 2.65, 95%CI:1.11–3.88, p 0.001). The model was statistically significant x^2 = 76.4 and can explain 55.8% (R^2) of the variance in AKI development.

Mortality

Overall mortality was 26.9% (92/342) in this study. Mortality was significantly higher in those with AKI (AKI+ versus AKI-: 19.3% (57/298) compared to 76.1% (35/44). Through stratification, we found a mortality rate for stage 1 AKI patients of 62.5% (i.e., 15/24). This dramatically rose to 90.9% (i.e., 20/22) for stage 2 - 3 AKI patients. The median number of in-hospital survival days was significantly shorter for AKI+ group compared to AKI- group (AKI+ 21days vs. AKI- 18 days; p < 0.001). In the final model AKI was

significanlty assocaited with mortality (log-rank test, $x^2 = 80.1$, p 0.001). Please see Figure 1 for complete data.

Covariate-adjusted hazards analyses for death are shown in table 4, a diagnosis of AKI at any stage was associated with significantly higher hazard ratio (HR) of death during hospital stay (HR = 1.90, 95%CI:1.20–3.00, p = 0.006) compared to those without AKI. Furthermore, severity of AKI was also independently associated with a greater hazard ratio for death after covariate - adjustment (Stage 1 AKI vs. Non-AKI, HR = 1.4; 95%CI 0.77–2.55; p 0.001; Stage 2 - 3 AKI vs. no AKI HR = 2.56; 95%CI 1.50–4.39; p 0.001).

Discussion

The current study found that the incidence of AKI was common among COVID–19 patients with significantly increased hospital mortality even after adjusting for possible confounding variables. Additionally, those with stage 2 or 3 AKI encountered double the risk of death compared to patients without AKI. Another important finding was that age, history of cardiac disease, higher leukocytes count, C-reative protein, fibrinogen, and severity of pneumonia were identified as risk factors associated with the development of AKI. This finding has profound implications not only for the hospitalized population but for those at risk of contracting this virus.

Some recent studies report varied incidence of AKI from 2.5% to 45% among COVID–19 patients. In a very early study of COVID–19 from China, Guan et al. reported an incidence of AKI in 2.5% of patients diagnosed with COVID–19 and a mortality rate of 1.4% for all patients[12]. In another study by Cheng et al AKI occurred in 5.1% of all patients with a mortality rate of 16.1% for patients without AKI; however, this mortality increased to 33% when AKI occurred[8]. In contrast to these studies, our study observed an higher incidence of AKI which may be explained because there are several factors which differentiate our study from previous studies. For example, the median age in this study was 56 years which older than the population in Guan et al's study which was 47 years. Also, more than 70% of the patients in our study presented with bilateral CT anomalies and nearly half were assess to be severely ill upon admission which is much higher than previous studies.

The findings from this study appear to confirm Cheng et al's findings around risk factors associated with the development of AKI. Higher levels of C-reative protein and leukocytes count suggests that cytopathic effects may play an important role in the development of AKI. Another important risk factor of AKI is a past medical history of cardiac disease as an independent risk factor of AKI in our model. This finding may be explained through recent evidence that SARS-CoV–2 can bind to angiotensin-converting enzyme 2 (ACE2) receptor of human cells which are highly expressed in both the heart and kidney[13–15]. Futher more, higher fibrinogen was identified as independent risk factors associate with AKI in our study, a consistent finding with other researchers who reported coagulopathy as one of common complication in COVID–19 patients[16–18]. This suggests that SARS-CoV–2 may causes organ dysfunction through the activation of coagulation although more research is needed to further understand this dynamic.

Nevertheless, there was a pronounced trend (if not statistically different) when we consider the number of prehospital days and the development of AKI. One possible reason for this may be the difficulty in early identification for AKI. The rise of Scr is often delayed and do not meet KDIGO creatinine criteria for AKI. In our previous study we found that monitoring only Scr criteria may actually delay the detection of AKI[11]. Another report from Cheng et al, also reported 44% of COVID–19 patients have underlying renal impairment at admission that may not fully meet the currently used KDIGO criteria to make a final diagnosis of AKI[8]. These findings suggest there is likely to be a substantial underestimation for the incidence of AKI in COVID–19 patients when using *only* the KDIGO Scr criteria.

Our study further addressed AKI as an independent risk factor which was strongly associated with increased mortality. Importantly, in this study the mortality rate was more than 90% for those whom had been diagnosed as stage 2–3 AKI during hospitalization. This mortality was much higher than those reported by Cheng et al[8], but similar to Tao et al's study[18]. In Tao et al's study, 28 out of 29 patients with AKI died. Several factors may be related to the high mortality of AKI observed in this study. First, the dataset of this study was collected in the very early period of this COVID–19 pandemic when medical resources had not been redirected. The lack of early diagnostics and condition management techniques for such patients is likely to have contribute to the higher mortality observed. Second, according to the Chinese COVID–19 guidelines[10], there was a median pre-hospitalization period of 9 days with almost half of all patients being critically ill upon admission. Lung-kidney interactions have been reported by researchers and studies have shown that lung injury is associated with increased AKI[19]. But this is of course bi-directional having AKI also increases the occurrence of lung injury[20]. Therefore, this lung-kidney interaction is likely to have increased mortality in this study.

Despite the high mortality associated with stage 2 and 3 AKI, only 3 out of 22 stage 2 and 3 patients received renal replacement therapy (RRT). The treatment of stage 2 and 3 AKI is mainly limited to supportive care with no specific therapies, and life-threatening complications such as acidosis, fluid overload, and electrolytes disorders may all be associated with increased mortality. Although the initial use of RRT remains controversial, delayed use of such treatment may contribute to increased mortality[21,22]. Two factors may contribute to the restricted use of RRT. Firstly, a shortage of RRT machines at the very early stages of this viral outbreak is likely to have impacted this study sample. Secondly, the optimal start time for RRT was unknown. Even though several large randomized trials have failed to highight benefit for early RRT[23,24] a delay is likely to impact on those suffering. Such an high mortality rate further highlights the importance of early detection of AKI for patients with COVID–19. Progression to AKI stage 2 and 3 appears to double the risk of death. These findings further suggest that attempting to prevent progression of AKI to stage 2–3 is crucial in reducing mortality because less than 10% survive when AKI has developed to stage 2–3.

This study has several limitations. First, this retrospective study was based on only a small inpatient population in Wuhan. This is not only a small sample which lacks strength for generalizations but also (as has been mentioned), while COVID–19 is not a mosaic virus, it is mutation high. This means that this virus may be becoming more efficient at transmitting from person-to-person. This may mean that any

recommendations are time sensitive which reuires further research. Additionally, all data included here were from a single center and treatments may have been limited by the availability of continuous renal replacement apparatus. Given this restriction and the time period in which these data were recorded our findings may not be generalizable to other COVID–19 patients. Second, only serum creatinine levels were available for this study, which may have led to an underestimation of the incidence of AKI within this sample and may therefore have created some definition bias. Third, our results apply only to hospitalized patients and not for COVID–19 cases who are in the general public. However, there are ramifications for those at risk of kidney infection which requires further research.

Conclusion

Acute kidney injury is common among hospitalized COVID-19 cases, and strongly associates with inhospital mortality. Close monitoring and early intervention to prevent progression of AKI may be important to reduce mortality in COVID-19 patients.

Declarations

Authors of this paper here declare that our research proposal was fully agreed by the ethical committee of The First Affiliated Hospital of USTC (University of Science and Technology of China) and because this is a retrospective study with no medical intervention, no written consent was required from the patients.

Tables

Table 1. Severity of Pneumonia	
Mild pneumonia	no signs of clinical syptoms, no CT findings
	Fever and respiratory symptoms but with out he signs of the following
Severe pneumonia	1. respiratory rate ≥ 30/min
	2. SpO2 ≤93% at rest and breath room air
	3. Arterial blood gas show PaO2/FiO2≤300 mmHg
	4. respiratory failure requiring mechanical ventilation
	5. Shock
	6. multiple organ failures

Table 2. Baseline characteristics and laboratory and CT findings of 342 patients with COVID-19				
	All=342	**AKI-**	**AKI+**	**P**
Characteristic		**n=298**	**n=46**	
Age (yrs)	56(39,68)	54(37,65)	74(66,80)	0.001
male n(%)	168(49.1)	137(46.0)	31(70.5)	0.03
Smoking status	12(3.5)	12(4)	0(0)	>0.99
Chief complaint at admission				
Fever	270(79.0)	235(78.9)	35(79.6)	0.917
Cough	37(10.8)	35(11.7)	2(4.6)	0.197
Dyspnea	3(0.9)	1(0.3)	2(4.6)	0.051
Myalgia	1(0.3)	1(0.3)	1(2.3)	0.971
Pharyngitis	7(2.1)	6(2)	2(4.6)	>0.99
Chest pain	7(2.1)	5(1.7)	0(0)	0.224
Diarrhoea	4(1.2)	4(1.3)	0(0)	>0.99
Vomit	2(0.6)	2(0.7)	0(0)	>0.99
Fatigue	11(3.2)	9(3)	2(4.6)	0.639
Comorbid conditions				
Cardiac disease	95(27.8)	67(22.5)	28(63.6)	0.001
Pulmonary disease	25(7.31)	19(6.4)	6(13.6)	0.106
Endocrine disease	41(12)	32(10.7)	9(20.5)	0.064
Gastrointestinal disease	31(9.1)	27(9.1)	4(9.1)	0.995
Neuro disease	14(4.09)	10(3.4)	4(9.1)	0.073
Laboratory findings at admission Median(IQR)				
RBC × 10^6/μL	4.2(3.8,4.6)	4.2(3.8,4.6)	4.2(3.7,4.6)	0.119
Platelets×10^3/μL	192(149,250)	192(149,250)	188(115,240.5)	0.04
Hemoglobin,g/dL	129(117,140)	128(117,140)	130.5(119,143)	0.491
Leukocytes/μL	5.5(4.1,7.3)	3.37(2.42,4.89)	8.34(4.11,11.47)	

				0.001
Lymphocytes/μL	1.1(0.7,1.5)	1.13(0.81,1.55)	0.69(0.46,1.20)	0.001
C-reactive protein,mg/dL	23.6(5,72.4)	16(5,58.9)	92(60.5,188.4)	0.001
Procalcitonin, ng/mL	0.06(0.03,0.12)	0.05(0.03,0.094)	0.184(0.06,0.952)	0.001
Alanine aminotransferase, U/L	26(17,42)	25(17,41)	27(21.5,55)	0.252
Aspartate aminotransferase, U/L	29(21,43)	27(20,41)	43(31.5,61.5)	0.001
Albumin, g/L	37.7(33.6,41.2)	38.2(34.7,41.6)	33.2(31.3,37.1)	0.001
Serum creatinine	59(50,76)	59(50,73)	66.5(57,81.5)	0.001
Usea nitrogen	4.6(3.7,6.3)	4.3(3.61,5.74)	8.47(5.43,17.25)	0.001
B-type natriuretic peptide,pg/mL	169.4(40.0,169.4)	130.6(35,468.7)	758.1(282.5,2637)	0.001
cardiac troponin I, ug/L	0.006(0.006,0.022)	0.006(0.006,0.011)	0.048(0.011,0.315)	0.001
Activated partial thromboplastin time, s	26.6(14.1,29.6)	26.9(22.8,29.8)	14.8(12.7,29.1)	0.151
Prothrombin time,s	11.5(6.9,12.4)	11.55(10.7,12.4)	11.2(5.12,14)	0.909
Fibrinogen	4.6(3.2,23.6)	4.21(3.16,6.78)	25.4(6.03,29.3)	0.001
D-Dimer	0.71(0.35,2.42)	0.59(0.31,1.54)	3.72(0.72,17.14)	0.001
Chest CT bilateral pneumonia	263(76.9)	229(87.1)	44(100)	0.008
Severe pneumonia	162(47.4)	123(41.3)	39(88.6)	0.001
mehcanical ventilation	19(5.6)	8(2.8)	11(24.4)	0.001
Prehospital time,days	9(6,12)	9(6,12)	10(7,13)	0.19
Antibiotic use	295(86.3)	254(85.2)	41(93.2)	0.153
Corticosteroids use	146(42.7)	118(39.6)	28(63.6)	0.003
Intravenous	169(49.4)	146(49)	23(52.3)	0.685

immunoglobin				
survival time, days	20(16,25)	21(16,26)	18(15,21)	0.013
data are presented as No.(%) or median (1st-3rd quartiles)				

Table 3. Multilogistic regression model for risk factors of AKI

Factor	Univariable model		Multivariable model	
	Odds ratio (95%CI)	P value	Odds ratio (95%CI)	P value
Age	1.08(1.05-1.11)	<0.001	1.12 (1.05-1.25)	<0.001
Male	2.80(1.41-5.57)	<0.001	2.57 (0.68-9.74)	0.165
Cariovascular disease	6.03(3.08-11.8)	<0.001	1.17 (0.33-4.22)	0.805
Leukocytes/μL	1.27(1.16-1.39)	<0.001	1.36 (1.11-1.66)	0.003
Platelets×10^3/μL	1.0(0.99-1.00)	0.301	1 (0.99-1.01)	0.803
C-reactive protein,mg/dL	1.02(1.01-1.02)	<0.001	1.01 (1-1.02)	0.044
Albumin, g/L	1.06(1.03-1.10)	<0.001	0.99 (0.82-1.19)	0.898
Cardiac troponin I, ug/L	3.7(1.60-8.58)	<0.001	1.51 (0.68-3.35)	0.31
Procalcitonin, ng/mL	1.35(0.87-2.10)	0.054	1.1 (0.83-1.46)	0.517
Fibrinogen	1.05(1.02-1.08)	<0.001	1.08 (1.02-1.13)	0.004
D-Dimer	1.02(1.01-1.03)	0.005	0.97 (0.94-1.01)	0.115
Prehospital time	1.28(0.67-2.43)	0.224	0.7(0.17-2.81)	0.614
Severity of Pneumonia	11.1(4.25-20.9)	<0.001	2.65 (1.11-3.88)	<0.001

Table 4. Multivariate Cox Regression Analysis on the Mortality associated with AKI		
Factor	**Hazard ratio (95%CI)**	**P value**
No AKI	Reference	
AKI at any stage	1.90(1.20-3.00)	0.006
Stage1 AKI	1.40(0.77-2.55)	0.003
Stage2-3 AKI	2.56(1.50-4.39)	0.001
Age≥65	2.51(1.48-4.23)	0.001
Severe pneumonia	11.73(4.56-30.14)	0.001

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Figures

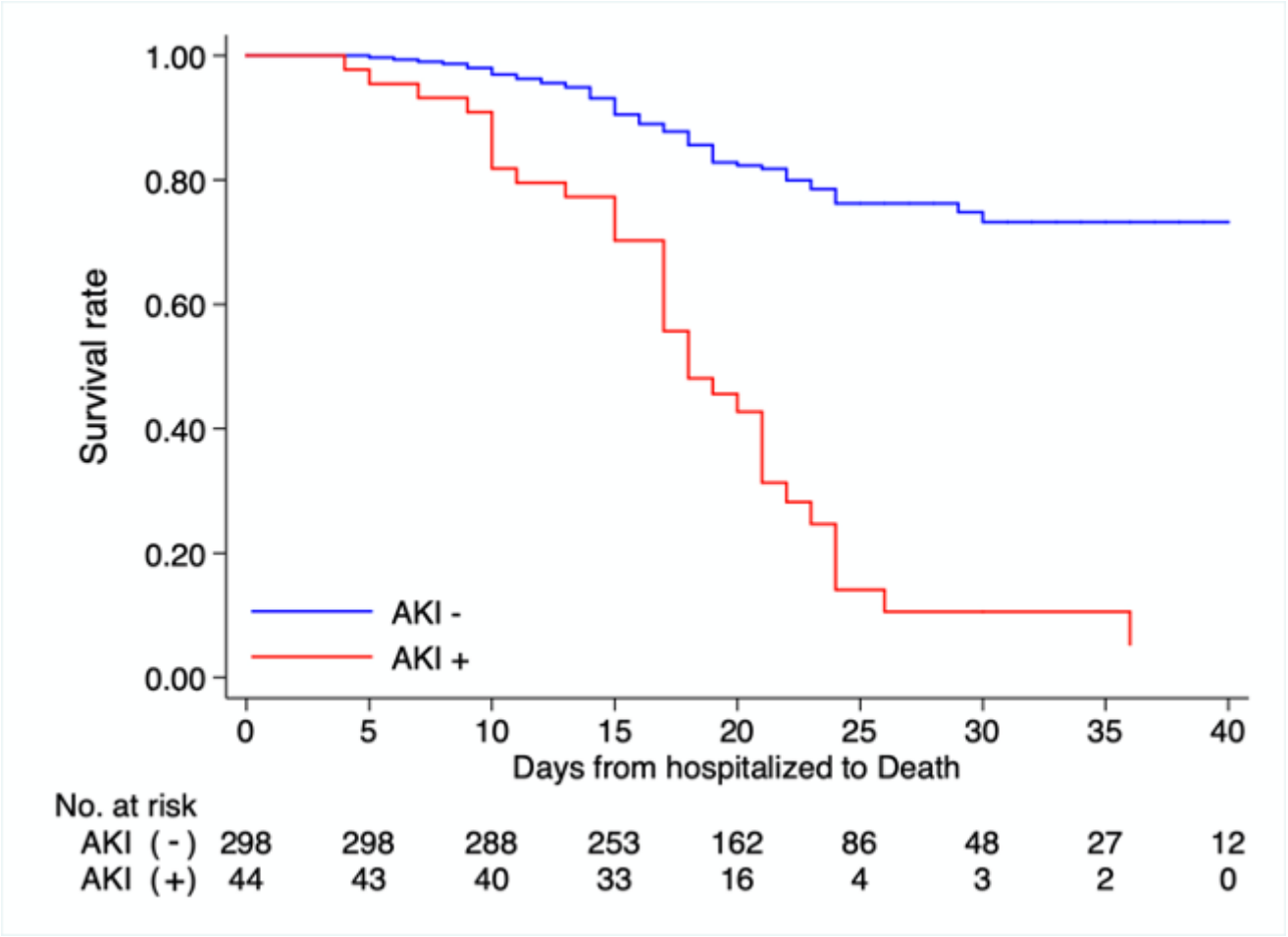

Figure 1

In-hospital survival of patients with and without AKI