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Original Article

The duration of acute kidney injury is an additional parameter to predict 1-year survival in very elderly patients

Qinglin Li[1,#], Yan Wang[2,#], Feihu Zhou[1,3,4,*]

[1] Department of Critical Care Medicine, The First Medical Center, Chinese PLA General Hospital, Beijing 100853, China
[2] Department of Cardiology, The Second Medical Center, Chinese PLA General Hospital, Beijing 100853, China
[3] Chinese PLA General Hospital National Clinical Research Center for Geriatric Diseases, Beijing 100853, China
[4] Medical Engineering Laboratory of Chinese PLA General Hospital, Beijing 100853, China

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ABSTRACT

Background: Acute kidney injury (AKI) is primarily defined and classified according to the magnitude of the elevation of serum creatinine (Scr). We aimed to determine whether the duration of AKI adds prognostic value in addition to that obtained from the magnitude of injury alone.

Methods: This retrospective study enrolled very elderly inpatients (≥75 years) in the Chinese PLA General Hospital from January 2007 to December 2018. AKI was stratified by magnitude according to KDIGO stage (1, 2, and 3) and duration (1–2 days, 3–4 days, 5–7 days, and >7 days). The primary outcome was the 1-year mortality after AKI. Multivariable Cox regression analysis was performed to identify covariates associated with the 1-year mortality. The probability of survival was estimated using the Kaplan–Meier method, and curves were compared using the log-rank test.

Results: In total, 688 patients were enrolled, with the median age was 88 (84–91) years, and the majority (652, 94.8%) were male. According to the KDIGO criteria, 317 patients (46.1%) had Stage 1 AKI, 169 (24.6%) had Stage 2 AKI, and 202 (29.3%) had Stage 3 AKI. Of the 688 study subjects, 61 (8.9%) with a duration of AKI lasted 1–2 days, 104 (15.1%) with a duration of AKI lasted 3–4 days, 140 (20.3%) with a duration of AKI lasted 5–7 days, and 383 (55.7%) with a duration of AKI lasted >7 days. Within each stage, a longer duration of AKI was slightly associated with a higher rate of 1-year mortality. However, within each of the duration categories, the stage of AKI was significantly associated with 1-year mortality. When considered separately in multivariate analyses, both the duration of AKI (3–4 days: HR=3.184; 95% CI: 1.733–5.853; P <0.001, 5–7 days: HR=1.915; 95% CI: 1.073–3.416; P=0.028; >7 days: HR=1.766; 95% CI: 1.017–3.065; P=0.043) and more advanced AKI stage (Stage 2: HR=3.063; 95% CI: 2.207–4.252; P <0.001; Stage 3: HR=7.333; 95% CI: 5.274–10.197; P <0.001) were independently associated with an increased risk of 1-year mortality.

Conclusions: In very elderly AKI patients, both a higher stage and duration were independently associated with an increased risk of 1-year mortality. Hence, the duration of AKI adds additional information to predict long-term mortality.

Introduction

Acute kidney injury (AKI) is a common complication in the elderly, and its etiology is more often multifactorial, characterized by a precipitous decline in the glomerular filtration rate (GFR) within a short time period (several hours to several days).[1] The syndrome encompasses the entire spectrum of disease from minimal asymptomatic elevations in serum creatinine (Scr) concentration to complete anuric renal failure; for decades, there has been a lack of a consensus definition.[2] Over the past 20 years, there have been three main classification systems used in clinical practice to assess AKI severity: the Risk-Injury-Failure-Loss-End-stage (RIFLE) criteria, the Acute Kidney Injury Network (AKIN) criteria, and the Kidney Disease: Improving Global Outcomes (KDIGO) criteria.[3] The three systems have considered the changes in Scr levels and urine output as the primary dimensions in grading the severity of AKI; for example, with the use of the KDIGO guidelines, AKI severity is classified

* Corresponding author: Feihu Zhou, Department of Critical Care Medicine, The First Medical Centre, Chinese PLA General Hospital, Beijing 100853, China.
E-mail address: feihuzhou301@126.com (F. Zhou).
# Qinglin Li and Yan Wang contributed equally to this work.

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into three stages on the basis of either the increase in Scr level or the duration and extent of oliguria.[4–6] However, none of the diagnostic and staging criteria take into account the duration of Scr elevation, which reflects the time to renal function recovery and could be an important potential dimension of AKI along with severity.[7,8] Some studies in different clinical settings have reported time as an independent prognostic marker or another dimension of AKI severity to predict long-term mortality, progression to chronic kidney disease (CKD), and cardiovascular outcomes.[9–12] In addition, persistent AKI (P-AKI) has also been viewed as a relevant endpoint for future studies, and it has been posited that we should target AKI duration for clinical management.[13,14] However, to our knowledge, few studies have specifically focused on duration in elderly populations with AKI.

Thus, we sought to explore the association between the duration of AKI based on Scr and 1-year mortality and to examine whether the duration of AKI offered any additional prognostic information over the magnitude of elevation in Scr.

Methods

Data sources and patients

This retrospective study was conducted at the Chinese People's Liberation Army (PLA) General Hospital National Clinical Research Center for Geriatric Diseases (Beijing, China). All very elderly patients (age ≥75 years) with normal renal function admitted from January 2007 to December 2018 were included. The study design was approved by the Clinical Ethics Committee of the Chinese PLA General Hospital (number: S2017-054-01). The requirement to obtain written informed consent from each patient was waived because this was an observational retrospective study. The patients' information was anonymous and deidentified. This study was conducted in accordance with the Declaration of Helsinki.

The exclusion criteria were CKD of any stage, kidney transplantation, hospitalization for <2 days, missing data for at least two Scr measurements during hospitalization, and missing or incomplete medical history. The hospitalization records of all potential study participants were collected. If one patient met the AKI criteria, the following information was recorded: age, sex, body mass index (BMI), inpatient ward, previous medical history, laboratory test results, baseline Scr, estimated GFR (eGFR) at baseline, Scr at diagnosis of AKI, peak Scr, blood urea nitrogen (BUN), peak BUN, uric acid, serum prealbumin, albumin, blood glucose, electrolytes, C-reactive protein (CRP), hemoglobin, the primary cause of AKI (sepsis, hypovolemia, cardiovascular events, nephrotoxic drugs, surgery, etc.), oliguria status, renal replacement therapy (RRT) status, mechanical ventilation status, systolic blood pressure, diastolic blood pressure, mean arterial pressure, and patient prognosis on year 1 after AKI.

Definitions

The Scr criteria in the KDIGO guidelines were used for screening because retrospectively collected urine data can be inaccurate. AKI stage was determined using the peak Scr level after AKI onset: Stage 1, an increase ≥26.5 μmol/L, or an increase ≥1.5- to <2.0-fold above the baseline value; Stage 2, an increase to ≥2.0- to <3.0-fold above the baseline value; and Stage 3, an increase to ≥3.0-fold above the baseline value, an increase to ≥353.6 μmol/L, or the initiation of RRT. We used the equation of the Chronic Kidney Disease Epidemiology Collaboration to calculate the eGFR from the baseline Scr level.[15] The baseline Scr level was defined as the most recent measurement in the previous 3 months.[16] The peak Scr level was the highest Scr level reached during the episode. The peak BUN level was the highest BUN level reached during the episode. We defined transient AKI (T-AKI) as the return of the Scr level to the baseline value within 48 h after AKI and P-AKI as the continuance of elevation of Scr beyond 48 h from AKI onset.[17] We also classified P-AKI into three categories based on duration: (1) AKI that resolved in 3–4 days, (2) AKI that resolved in 5–7 days, and (3) AKI lasting >7 days. The primary outcome was 1-year all-cause mortality.

Statistical analysis

Continuous parametric variables are presented as the means ± standard deviations, and continuous non-parametric variables are presented as medians with interquartile ranges (25th and 75th percentiles). Categorical variables are presented as numbers (*n*) or percentages (%). Group comparisons were conducted using one-way ANOVA or the Kruskal–Wallis *H* test for continuous variables and Pearson's chi-square or Fisher's exact test for categorical variables. Multivariable Cox regression analysis was performed to identify covariates associated with the 1-year mortality. The probability of survival was estimated using the Kaplan–Meier method, and curves were compared using the log-rank test. *P*-values <0.05 were considered to indicate statistical significance. Statistical analyses were performed using SPSS version 21.0 for Windows (SPSS, Inc., Chicago, IL, USA).

Results

Study population

During the study period, 760 of 3861 very elderly patients developed AKI during hospitalization. Of these patients, 10 were excluded due to the length of hospital stay <48 h, and 3 were excluded because of missing required data; a total of 747 AKI patients were eligible for analysis, including 685 (91.7%) patients with P-AKI and 62 (8.3%) with T-AKI. Of the 747 patients, we additionally excluded 54 who died within 48 h post-AKI because we could not determine the duration of AKI, resulting in 693 AKI patients who were eligible for the final analyses.

AKI

During the study period, 5 patients were lost to follow-up, and 688 AKI patients were included in the analysis. The study flowchart is presented in Figure 1. The median age of the 688 participants was 88 (84–91) years, and the majority (652, 94.8%) were male. According to the KDIGO criteria, 317 patients (46.1%) had Stage 1 AKI, 169 (24.6%) had Stage 2 AKI, and 202 (29.3%) had Stage 3 AKI. Of the 688 study subjects, we stratified patients by duration of AKI: 1–2 days (61; 8.9%), 3–4 days (104; 15.1%), 5–7 days (140; 20.3%), and >7 days (383; 55.7%). The overall 1-year mortality was 48.3% (332/688), and RRT was required in only 0.6% (4/688) of patients. The baseline

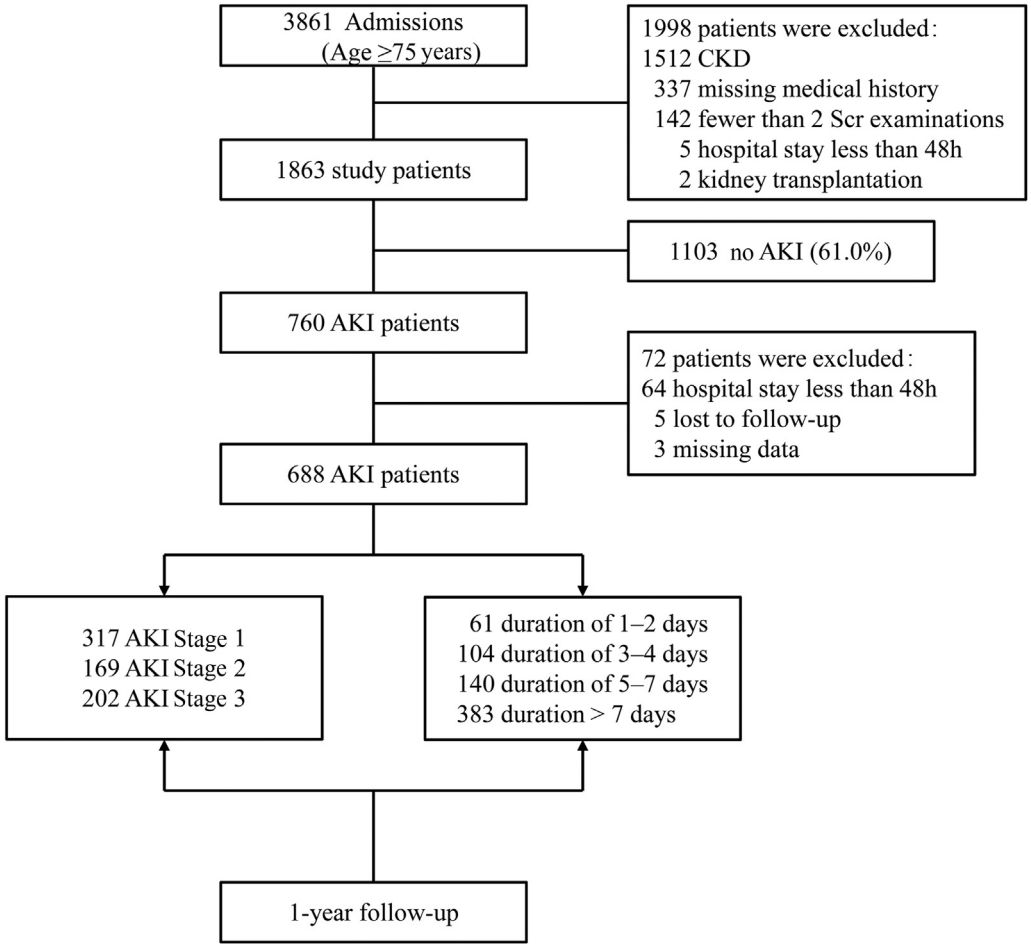

Figure 1. Flowchart of the patient inclusion and exclusion process. AKI: acute kidney injury; CKD: chronic kidney disease.

characteristics by strata of KDIGO and AKI duration are shown in Table 1.

AKI and KDIGO stage

A comparison of patients with different stages of AKI indicated no significant differences in sex, the presence of comorbidities (such as hypertension, chronic obstructive pulmonary disease, and diabetes mellitus), AKI etiology (such as hypovolemia and surgery), or electrolyte imbalance (such as calcium, phosphonium, and magnesium). Patients with AKI Stage 1 or Stage 2 were significantly more likely to have cardiovascular events (P=0.028) and nephrotoxicity (P=0.020), but sepsis (P <0.001) was more common in patients with more advanced AKI. Compared with patients with Stage 1 and 2 AKI, patients with Stage 3 AKI had significantly lower baseline Scr levels (P <0.001), were more frequently treated with mechanical ventilation (P <0.001), more frequently needed RRT (P=0.007), and more frequently suffered from low mean arterial pressure (P <0.001) and oliguria (P <0.001). In addition, patients with more advanced AKI were older (P <0.001) and had significantly lower BMI (P=0.021), higher baseline eGFR (P <0.001), higher Scr and peak Scr levels (both P <0.001), higher BUN and peak BUN levels (both P <0.001), higher uric acid levels (P <0.001), higher blood glucose levels (P <0.001), higher serum potassium levels (P <0.001), higher serum sodium levels (P <0.001), higher CRP levels (P <0.001), lower albumin levels (P <0.001), lower prealbumin levels (P <0.001), and lower hemoglobin levels (P <0.001) at the time of AKI diagnosis. Accordingly, the proportion of patients referred to nephrologists increased with increasing degrees of AKI (P <0.001). The 1-year mortality increased significantly with the AKI stage (20.5% for Stage 1, 58.0% for Stage 2, and 83.7% for Stage 3; P <0.001).

AKI and its duration

The groups of patients with different durations of AKI had similar distributions of sex and BMI, as well as the presence of comorbidities (such as hypertension, chronic obstructive pulmonary disease, and diabetes mellitus), AKI etiology (such as hypovolemia, nephrotoxicity, and surgery), mean arterial pressure, oliguria, blood glucose, electrolyte imbalance (such as calcium and phosphonium), CRP, albumin, and prealbumin on the day of AKI development. Compared to patients with T-AKI, patients with P-AKI were older (P=0.001), had significantly higher baseline Scr levels (P=0.002), had lower baseline eGFR (P <0.001), were less likely to have coronary disease (P=0.013) and cardiovascular events (P=0.002), but more likely to suffered from sepsis (P=0.043) and needed mechanical ventilation (P <0.001). In addition, patients with P-AKI had significantly higher Scr and peak Scr levels (both P <0.001), higher BUN and peak BUN levels (both P <0.001), higher uric acid lev-

Table 1
Characteristics of patients according to AKI stage and AKI duration.

Characteristic	AKI patients (*n*=688)	KDIGO stage				AKI duration				
		AKI Stage 1 (*n*=317, 46.1%)	AKI Stage 2 (*n*=169, 24.6%)	AKI Stage 3 (*n*=202, 29.3%)	*P*-value	1–2 days (*n*=61, 8.9%)	3–4 days (*n*=104, 15.1%)	5–7 days (*n*=140, 20.3%)	>7 days (*n*=383, 55.7%)	*P*-value
Age (years)	88 (84–91)	87 (83–90)	90 (85–92)	89 (84–92)	<0.001	87 (84–91)	86 (83–89)	88 (84–91)	88 (84–92)	0.001
Male sex	652 (94.8)	299 (94.3)	163 (96.4)	190 (94.1)	0.523	57 (93.4)	99 (95.2)	131 (93.6)	365 (95.3)	0.839
BMI (kg/m^2)	23.0 ± 3.1	23.4 ± 3.2	22.7 ± 3.1	22.8 ± 3.1	0.021	22.6 ± 4.1	23.4 ± 3.3	23.1 ± 3.0	23.0 ± 3.0	0.415
Comorbidity										
Coronary disease	525 (76.3)	253 (79.8)	117 (69.2)	155 (76.7)	0.032	50 (82.0)	67 (64.4)	113 (80.7)	295 (77.0)	0.013
Hypertension	502 (73.0)	243 (76.7)	116 (68.6)	143 (70.8)	0.118	51 (83.6)	74 (71.2)	100 (71.4)	277 (72.3)	0.270
COPD	474 (68.9)	217 (68.5)	117 (69.2)	140 (69.3)	0.974	42 (68.9)	63 (60.6)	100 (71.4)	269 (70.2)	0.251
Diabetes	265 (38.5)	113 (35.6)	62 (36.7)	90 (44.6)	0.108	25 (41.0)	42 (40.4)	47 (33.6)	151 (39.4)	0.596
Baseline Scr (μmol/L)	72.0 (60.0–83.0)	80.0 (73.0–88.0)	67.0 (56.0–74.0)	62.0 (52.0–72.0)	<0.001	70.0 (61.0–81.0)	71.0 (62.0–80.0)	70.0 (57.0–80.0)	74.0 (62.0–85.0)	0.002
Baseline eGFR (mL/min/1.73 m^2)	78.4 (71.7–84.9)	74.2 (68.0–79.0)	81.3 (75.9–87.2)	83.3 (77.6–89.4)	<0.001	80.1 (74.4–85.6)	79.7 (75.4–86.0)	79.9 (75.5–86.6)	76.9 (69.7–83.8)	<0.001
Etiology of AKI										
Sepsis	285 (41.4)	99 (31.2)	71 (42.0)	115 (56.9)	<0.001	19 (31.1)	40 (38.5)	71 (50.7)	155 (40.5)	0.043
Hypovolemia	142 (20.6)	75 (23.7)	34 (20.1)	33 (16.3)	0.130	12 (19.7)	17 (16.3)	32 (22.9)	81 (21.1)	0.640
Cardiovascular events	105 (15.3)	60 (18.9)	24 (14.2)	21 (10.4)	0.028	14 (23.0)	24 (23.1)	10 (7.1)	57 (14.9)	0.002
Nephrotoxicity	88 (12.8)	50 (15.8)	23 (13.6)	15 (7.4)	0.020	4 (6.6)	11 (10.6)	16 (11.4)	57 (14.9)	0.229
Surgery	45 (6.5)	22 (6.9)	11 (6.5)	12 (5.9)	0.904	9 (14.8)	7 (6.7)	6 (4.3)	23 (6.0)	0.086
Others	23 (3.3)	11 (3.5)	6 (3.6)	6 (3.0)	0.939	3 (4.9)	5 (4.8)	5 (3.6)	10 (2.6)	0.631
Clinical conditions										
MAP (mmHg)	79±14	82±13	78±14	75±13	<0.001	81±14	78±14	78±14	80±13	0.272
Oliguria	35 (5.1)	5 (1.6)	8 (4.7)	22 (10.9)	<0.001	2 (3.3)	3 (2.9)	8 (5.7)	22 (5.7)	0.544
Mechanical ventilation	259 (37.6)	45 (14.2)	83 (49.1)	131 (64.9)	<0.001	8 (13.1)	34 (32.7)	54 (38.6)	163 (42.6)	<0.001
Laboratory parameters										
Scr (μmol/L)	128.0 (115.0–143.6)	123.8 (114.4–135.9)	129.4. (111.6–146.5)	139.9 (120.2–160.6)	<0.001	116.3 (108.1–135.3)	123.0 (111.1–137.9)	124.4. (109.0–138.0)	132.0 (120.0–148.0)	<0.001
Peak Scr (μmol/L)	142.2 (123.1–205.0)	126.0 (115.8–138.0)	149.8 (127.6–176.0)	290.0 (218.1–393.5)	<0.001	118.0 (110.5–136.5)	124.9 (113.1–146.0)	137.9 (118.6–181.0)	156.0 (134.8–249.0)	<0.001
BUN (mmol/L)	12.4 (8.8–20.1)	9.4 (7.1–12.3)	15.0 (10.3–21.0)	20.2 (12.9–28.9)	<0.001	9.3 (7.2–13.0)	11.1 (7.6–17.3)	14.0 (9.5–22.3)	12.9 (9.2–20.8)	<0.001
Peak BUN (mmol/L)	17.0 (10.5–32.4)	10.7 (8.1–15.0)	20.0 (13.6–26.6)	39.6 (27.5–54.7)	<0.001	10.8 (8.0–15.0)	13.1 (9.1–23.6)	18.1 (11.5–32.6)	20.8 (11.2–36.4)	<0.001
Uric acid (mmol/L)	363.2 (285.6–461.0)	344.2 (275.0–422.2)	381.0 (302.3–499.6)	388.0 (312.5–520.6)	<0.001	333.5 (267.8–416.5)	343.6 (270.8–433.9)	361.0 (297.8–470.2)	372.0 (293.7–471.0)	0.026
Blood glucose (mmol/L)	7.3 (5.8–10.0)	6.7 (5.5–9.0)	7.6 (6.0–10.2)	8.0 (6.1–11.2)	<0.001	7.6 (6.2–9.9)	7.4 (6.0–9.8)	7.6 (6.1–10.0)	7.0 (5.4–10.3)	0.185
Serum potassium (mmol/L)	4.1 (3.8–4.6)	4.1 (3.8–4.4)	4.1 (3.9–4.7)	4.3 (3.9–4.9)	<0.001	4.1 (3.8–4.3)	4.0 (3.8–4.5)	4.3 (3.9–4.9)	4.1 (3.8–4.7)	0.028
Serum sodium (mmol/L)	140.0 (136.0–146.0)	139 (135.0–143.0)	142.0 (137.0–149.0)	143.0 (136.0–149.0)	<0.001	138.0 (132.0–142.0)	139 (133.0–145.0)	140.0 (136.0–148.0)	141.0 (137.0–147.0)	0.001
Serum calcium (mmol/L)	2.2 (2.1–2.4)	2.2 (2.1–2.3)	2.2 (2.1–2.4)	2.2 (2.1–2.3)	0.980	2.2 (2.0–2.3)	2.2 (2.1–2.4)	2.2 (2.1–2.4)	2.2 (2.1–2.4)	0.431
Serum phosphonium (mmol/L)	1.2 (0.9–1.4)	1.2 (1.0–1.4)	1.1 (0.9–1.4)	1.2 (0.9–1.5)	0.335	1.1 (0.9–1.5)	1.1 (0.9–1.3)	1.1 (0.9–1.4)	1.2 (1.0–1.4)	0.321
Serum magnesium (mmol/L)	0.9 (0.8–1.0)	0.9 (0.8–1.0)	0.9 (0.8–1.0)	0.9 (0.7–1.0)	0.479	0.9 (0.7–1.0)	0.9 (0.8–1.0)	0.9 (0.8–1.0)	0.9 (0.8–1.0)	0.032
CRP (mmol/L)	3.7 (1.8–9.1)	2.4 (1.5–5.6)	5.0 (2.2–10.5)	6.6 (3.0–12.2)	<0.001	3.5 (1.6–8.7)	4.2 (1.9–9.9)	4.7 (1.8–10.1)	3.5 (1.8–8.5)	0.487
Albumin (g/L)	34.5 ± 5.5	36.5 ± 4.8	33.7 ± 5.7	31.9 ± 5.0	<0.001	36.0 ± 5.2	34.6 ± 6.0	34.5 ± 5.8	34.2 ± 5.2	0.103
Prealbumin (g/L)	179 (138–230)	207 (164–258)	165 (129–223)	150 (113–192)	<0.001	186 (142–234)	174 (137–217)	175 (135–230)	180 (140–239)	0.603
Hemoglobin (g/L)	112 ± 22	120 ± 19	109 ± 23	103 ± 22	<0.001	119 ± 20	118 ± 21	114 ± 22	109 ± 22	<0.001
Nephrology consultation	180 (26.2)	39 (12.3)	45 (26.6)	96 (47.5)	<0.001	7 (11.5)	16 (15.4)	27 (19.3)	130 (33.9)	<0.001
RRT	4 (0.6)	0	0	4 (2.0)	0.007	0	0	0	4 (1.0)	0.195
1-year mortality	332 (48.3)	65 (20.5)	98 (58.0)	169 (83.7)	<0.001	14 (23.0)	44 (42.3)	70 (50.0)	204 (53.3)	<0.001

Data are expressed as *n* (%), mean ± SD, or median (inter-quartile range).
AKI: acute kidney injury; BMI: body mass index; COPD: chronic obstructive pulmonary disease; eGFR: estimated glomerular filtration rate; KDIGO: Kidney Disease: Improving Global Outcomes; MAP: mean arterial pressure; Scr: serum creatinine; BUN: blood urea nitrogen; CRP: C-reactive protein; RRT: Renal replacement therapy.

els (P=0.026), higher serum potassium levels (P=0.028), higher serum sodium levels (P=0.001), higher serum magnesium levels (P=0.032), and lower hemoglobin levels (P <0.001) on the day of AKI development. Accordingly, the proportion of patients who received a nephrology consultation increased with the duration of AKI (P <0.001). The 1-year mortality increased significantly with the duration of AKI (23.0% for durations of 1–2 days, 42.3% for durations of 3–4 days, 50.0% for durations of 5–7 days; 53.3% for durations of >7 days; P <0.001).

1-year survival

The Kaplan–Meier survival plot demonstrates that 1-year survival was significantly different according to both the KDIGO stage (Figure 2A; log-rank test: P <0.001) and duration of AKI (Figure 2B; log-rank test: P <0.001). To better understand the prognostic role of AKI duration, we examined subgroups of AKI, first by each stage of KDIGO stratified by duration of AKI and then by AKI duration stratified by KDIGO stage. As the duration of AKI increased within each strata of AKI severity as defined by the KDIGO criteria (magnitude), 1-year survival decreased, but no significant differences were found for patients with Stage 1 and Stage 2 AKI (Stage 1, P=0.526; Stage 2, P=0.818; Stage 3, P=0.016, Table 2). However, survival significantly changed within each strata of AKI classified by duration (Table 2). Notably, the 1-year mortality was greater for those with a duration of 3–4 days, a duration of 5–7 days, and a duration of >7 days of AKI. Interestingly, for patients with P-AKI, the 1-year mortality for those with severe AKI (Stages 2 and 3) and a duration >7 days was similar to that of those with the most severe AKI (Stages 2 and 3) and with a duration of 3–4 days or a duration of 5–7 days of AKI (Table 2). These relationships were confirmed when we examined the stratified survival plots. When patients were stratified by the stage of AKI, patients with increasing duration of AKI had significantly worse 1-year survival in the group with AKI Stage 3 (Figure 3C; log-rank test: P <0.001), but no differences were found in the group with Stage 1 (Figure 3A; log-rank test: P=0.559) or Stage 2 (Figure 3B; log-rank test: P=0.740). By contrast, when patients were stratified by the duration of AKI, the magnitude of Scr increase as classified by KDIGO was significantly associated with 1-year mortality (Figure 4A; log-rank test: P=0.011 and Figure 4B; log-rank test: P <0.001 and Figure 4C; log-rank test: P <0.001 and Figure 4D; log-rank test: P <0.001).

Table 2
Mortality rate by acute kidney injury (AKI) stage stratified by duration of AKI.

Group	Number of subjects	Number of deaths	Incidence (%)
AKI Stage 1			
1–2 (days)	39	5	12.8
3–4 (days)	65	16	24.6
5–7 (days)	58	11	19.0
>7 (days)	155	33	21.3
AKI Stage 2			
1–2 (days)	17	8	47.1
3–4 (days)	22	13	59.1
5–7 (days)	42	25	59.5
>7 (days)	88	52	59.1
AKI Stage 3			
1–2 (days)	5	1	20.0
3–4 (days)	17	15	88.2
5–7 (days)	40	34	85.0
>7 (days)	140	119	85.0

According to the multivariate regression analysis, both AKI duration (3–4 days: HR=3.184; 95% CI: 1.733–5.853; P <0.001, 5–7 days: HR=1.915; 95% CI: 1.073–3.416; P=0.028; >7 days: HR=1.766; 95% CI: 1.017–3.065; P=0.043) and more advanced AKI stage (Stage 2: HR=3.063; 95% CI: 2.207–4.252; P <0.001; Stage 3: HR=7.333; 95% CI: 5.274–10.197; P <0.001) were independently associated with 1-year mortality. The other independent risk factors for 1-year mortality included high serum sodium level (HR=1.019; 95% CI: 1.008–1.030; P=0.001), BMI (HR=0.913; 95% CI: 0.879–0.948; P <0.001), low mean arterial pressure (HR=0.992; 95% CI: 0.985–1.000; P=0.043), low albumin (HR=0.951; 95% CI: 0.928–0.974; P <0.001), and low prealbumin level (HR=0.959; 95% CI: 0.937–0.980; P <0.001) (Table 3).

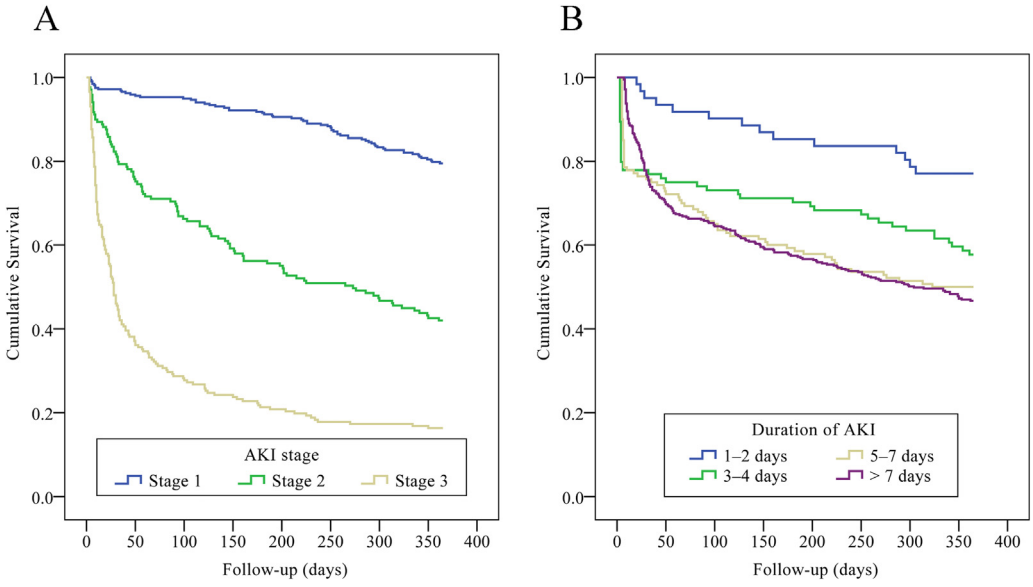

Figure 2. Kaplan–Meier survival plots according to AKI stage and duration (A: AKI stage, log-rank test: P <0.001; B: duration of AKI, log-rank test: P <0.001). AKI: acute kidney injury.

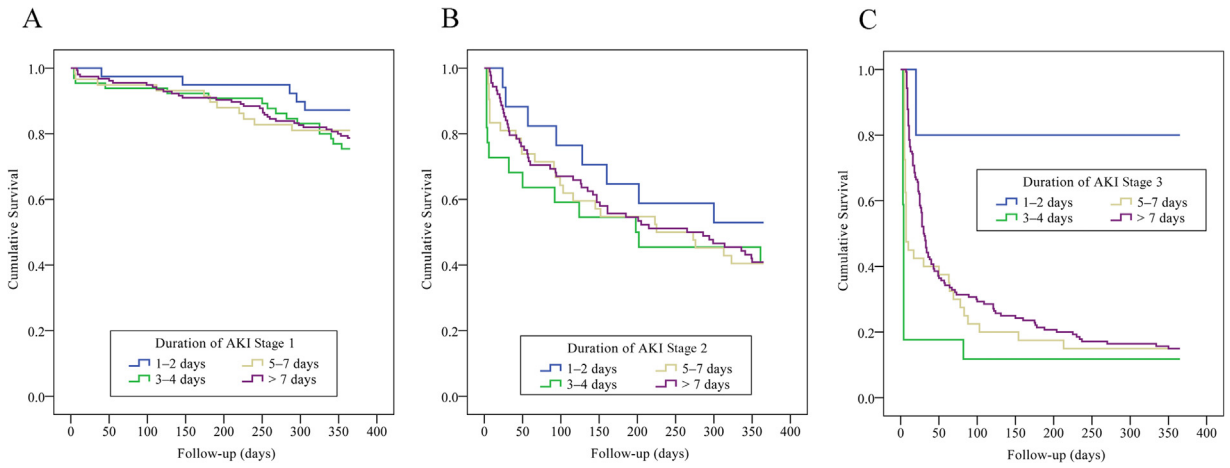

Figure 3. Kaplan–Meier survival plots according to AKI stage stratified by duration (A: Stage 1, log-rank test: *P*=0.559; B: Stage 2, log-rank test: *P*=0.740; and C: Stage 3, log-rank test: *P* <0.001).
AKI: acute kidney injury.

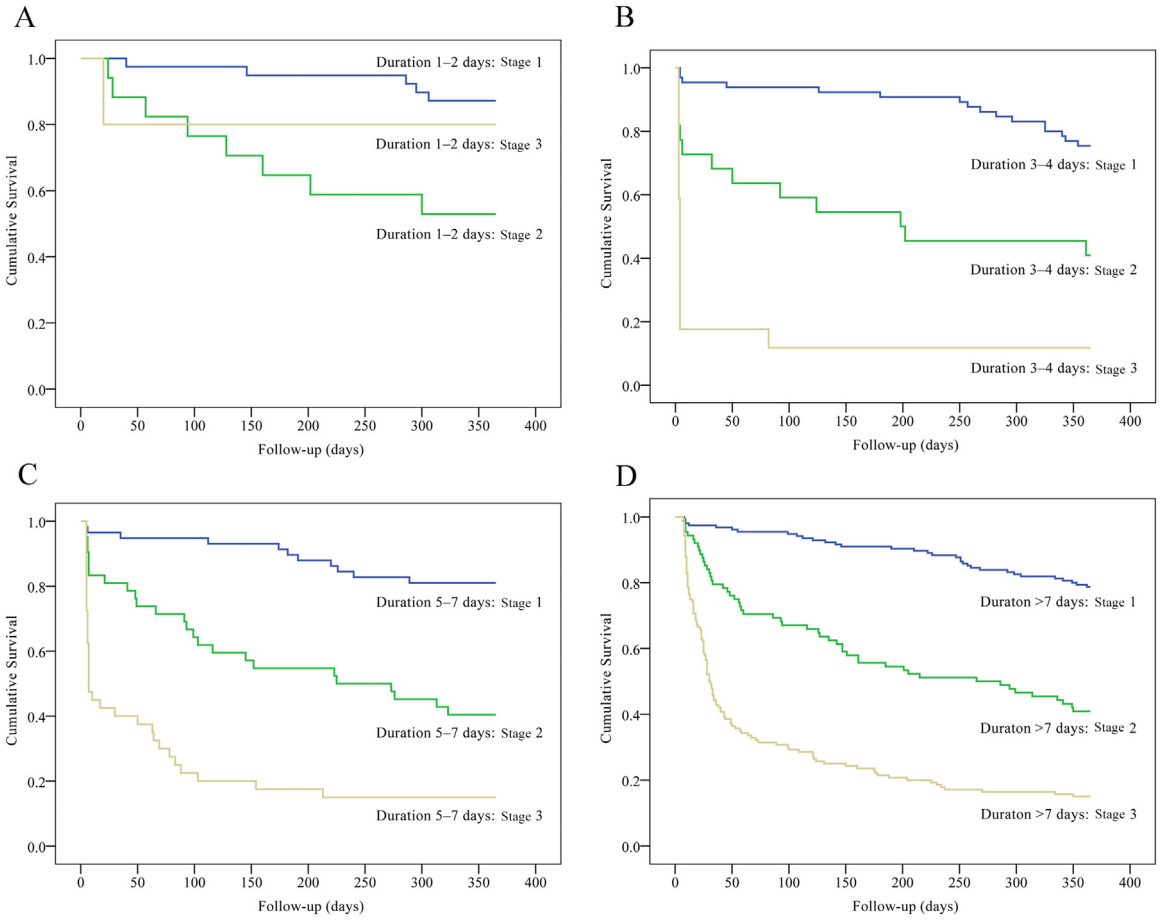

Figure 4. Kaplan–Meier survival plots according to AKI duration stratified by AKI stage (A: 1–2 days, log-rank test: *P*=0.011; B: 3–4 days, log-rank test: *P* <0.001; C: 5–7 days, log-rank test: *P* <0.001 and D: >7 days, log-rank test: *P* <0.001).
AKI: acute kidney injury.

Discussion

In this retrospective single-center study, we assessed the epidemiology of AKI duration and stage according to KDIGO staging criteria and their associations with 1-year outcomes in very elderly patients. We found that the duration of AKI was independently associated with 1-year mortality. Furthermore, the KDIGO stages of AKI were associated with 1-year survival once the duration of AKI was controlled. By contrast, when we controlled for the magnitude of increase in Scr, the duration of AKI within each strata of the KDIGO stage provided little additional prognostic information. The most impressive finding was that the mortality rate for those with severe AKI (KDIGO Stages 2 and 3) and short duration (1–2 days) was approximate 25% of

Table 3
Multivariate Cox proportional hazard model analysis of risk factors for 1-year mortality.

Risk factor	HR	95% CI	*P*
BMI	0.913	0.879–0.948	<0.001
MAP	0.992	0.985–1.000	0.043
Albumin	0.951	0.928–0.974	<0.001
Prealbumin	0.959	0.937–0.980	<0.001
Serum sodium	1.019	1.008–1.030	0.001
Duration of AKI (days)			0.001
1–2	–	–	–
3–4	3.184	1.733–5.853	<0.001
5–7	1.915	1.073–3.416	0.028
>7	1.766	1.017–3.065	0.043
AKI stage			<0.001
Stage 1	–	–	–
Stage 2	3.063	2.207–4.252	<0.001
Stage 3	7.333	5.274–10.197	<0.001

AKI, acute kidney injury; BMI, body mass index; MAP, mean arterial pressure; HR, hazard ratio.

those with the same stage of AKI (KDIGO Stages 2 and 3) with a long duration (3–4 days, 5–7 days, and >7 days) of AKI. This finding, although potentially intuitive, is novel in the AKI literature and demonstrates the limitations of the current AKI classification systems.

Recently, the Acute Dialysis Quality Initiative 16 workgroup defined P-AKI as the continuance of AKI diagnosed by the Scr level or urine output criteria for >48 h after AKI onset. However, there is no further definition or distinction for different AKI durations. Several studies have separated AKI duration into several groups and used different diagnostic criteria including short duration of AKI (≤2 days), medium duration (3–6 days), and long duration (≥7 days or RRT requirement) by AKI Network (AKIN) definition;[3,9] short duration (≤2 days), medium duration (3–5 days), and long duration (≥6 days) by KDIGO definition;[12] T-AKI (≤3 days) and P-AKI (>3 days) by AKIN definition;[18] and short duration (≤2 days), medium duration (3–7 days), and long duration (>7 days) by KDIGO definition;[19] however, these analyses were not as detailed as ours, nor were the interactions between various degrees of AKI magnitude and duration and recovery examined as thoroughly as in this study. Herein, we demonstrated that the duration of AKI still provided prognostic information over the KDIGO stage alone and can provide additive risk information for 1-year mortality risks for very elderly patients, especially when AKI duration is longer than 48 h.

Most, if not all, previous studies of AKI and outcomes have focused solely on characterizing the severity of AKI by the magnitude of the increase in Scr or the need for RRT. Thus, it is highly likely that there was imperfect characterization of risk associated with AKI in all previous studies solely using the existing magnitude-based criteria for AKI. Our findings provide prognostic value for the field of AKI and represent an assessment of another dimension of AKI. The current consensus definition for AKI does not include any duration information, as proposed by the recent KDIGO guidelines. However, given that we found that the granularity of the risk associated with AKI with regard to 1-year mortality is increased by examining not only the magnitude of Scr increase but also the duration of the increase, future investigations of AKI should use at least this two-dimensional approach (magnitude of increase in Scr and time of elevation) to assess outcomes of AKI. Although the magnitude and duration of AKI were highly associated with each other, the addition of another dimension to the classification of AKI should be sought after and embraced. It is clear from clinical practice and from our study results that a patient who developed KDIGO Stage 2 or 3 AKI but rapid reversibility in Scr is phenotypically very different from a patient who experienced a sustained increase in Scr of Stage 2 or 3 AKI. In addition, if AKI staging is not carried out in one patient, then the duration of AKI can be used as a replacement to predict outcomes.

The classification of AKI by duration may discriminate between patients with T-AKI (pre-renal) or hemodynamic AKI that do not involve any true injury to the renal tubular cells and those with true intrinsic AKI (that is, structural kidney injury). Furthermore, the duration of AKI may be a surrogate of the renal recovery potential of the injured kidney or continued ongoing insults. It has been demonstrated that in elderly patients, renal recovery may be prolonged and frequently incomplete. Additionally, the duration of AKI may likely denote the overall illness severity of the patient, as those who are more severely ill and have continued extrarenal organ dysfunction will take longer to recover. By contrast, the magnitude of Scr increase depends on Scr generation, volume status, and renal elimination and may not always be reflective of true tubular injury or the extent of injury. In addition, because of the renal reserve, even in the elderly population, up to 50% of renal function may be lost before Scr begins to increase. These changes may lead to a significant delay in AKI diagnosis and the underestimation of the severity of AKI and increase the time required to identify a 50% relative increase in Scr. Therefore, the KDIGO diagnosis and staging of AKI with Scr may not be suitable for the elderly population.

The high rate of mortality and lack of specific treatment reinforce the need for effective prevention of AKI in the elderly population. In clinical practice, preventing the progression of T-AKI to P-AKI requires a timely diagnosis and early nephrological care of T-AKI. However, in China, a large Asian country with 20% of the world population, only 21–44% of patients receive a timely diagnosis of AKI, and the rate of missed diagnosis is up to three-quarters.[20–22] Multiple studies have observed low rates of nephrology follow-up care after an episode of AKI across different settings and countries. Delayed and absent nephrology referrals have been associated with a higher mortality rate, dialysis dependence, and longer duration of hospital stay.[23,24] In this study, only 180 (26.2%) of the AKI patients saw a nephrologist during the follow-up period. Even in patients with Stage 3 disease, the rate of nephrology consultation was lower than 50%; when patients experienced a long duration of AKI for more than 7 days, only one-third of the patients were referred to nephrologists. Thus, increasing the rates of timely diagnosis and nephrology consultation in all cases of AKI is a challenge.[20]

Limitations

However, this study had the following limitations. First, the results may lack generalizability. The elderly population in this center was mainly composed of retired people and was predominantly male. Whether the same findings apply to other hospitalized elderly patients and to females is unknown. Second, we lacked data on elderly patients without AKI. However, it would have been better to compare the elderly patients with AKI with a group of elderly patients without AKI.

Third, this study is retrospective research, and only 1-year mortality was analyzed. Long-term renal function data are lacking.

Conclusions

In conclusion, the duration of AKI in geriatric patients is independently associated with 1-year mortality and may provide prognostic information in addition to that provided by the magnitude of Scr alone. These data need to be validated in other settings of AKI, and if found to be valid, the duration of AKI should be incorporated into the consensus definitions of AKI and used in clinical studies of AKI in the future.

Ethical Statement

This study has been approved by the Ethics Committee of the Chinese PLA General Hospital (number: S2017-054-01). The requirement for written informed consent was waived by the ethics committee of the designated hospital because this was an observational retrospective study.

Availability of Data and Materials

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

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Conflict of Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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