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ORIGINAL RESEARCH

Impact of Diabetes on the Recurrence and Prognosis of Acute Kidney Injury in Older Male Patients: A 10-Year Retrospective Cohort Study

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ABSTRACT

Introduction: While patients with diabetes are at higher risk of developing acute kidney injury (AKI), there are few studies on the recurrence of AKI in older adult patients. This study therefore aimed to examine the impact of diabetes on AKI recurrence and long-term outcomes in older male patients.

Methods: This retrospective cohort study included older male patients who experienced AKI during hospitalization from July 2007 to August 2011. Medical records of all patients were followed up for 10 years. Patients with AKI were classified into groups with and without diabetes. We analyzed differences in common geriatric comorbidities, AKI recurrence frequency, and severity between the two groups, identified risk factors affecting recurrence frequency, and assessed outcomes.

Results: Of all 266 patients, 128 had diabetes and 138 did not. The AKI recurrence rate was significantly higher in the group with diabetes (80.5 vs. 66.7%; $P = 0.011$). There was a significantly higher proportion of AKI caused by infections in patients with diabetes (43.3 vs. 33.2%, $P = 0.006$). The proportion of patients with an AKI recurrence frequency ≥ 3 was significantly higher in the group with diabetes (44.7 vs. 29.4%, $P = 0.027$). Diabetes and coronary heart disease were independent risk factors for AKI recurrence ($P < 0.05$), diabetes control was associated with multiple AKI recurrences ($P = 0.016$), and no significant difference was found between the groups regarding the 10-year prognosis ($P = 0.522$). However, a subgroup analysis showed that patients with multiple AKI recurrences within 2 years had the worst survival outcome ($P = 0.004$).

Conclusions: Older male patients with diabetes are prone to AKI recurrence after initial onset of AKI. Diabetes is an independent risk factor for AKI recurrence, and active diabetes control (HbA1c < 7%) may thus reduce the recurrence of AKI and improve the very poor outcomes of patients with multiple recurrences of AKI within 2 years.

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Graphical abstract:

Impact of Diabetes on the Recurrence and Prognosis of Acute Kidney Injury in Older Male Patients: A 10-Year Retrospective Cohort Study

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Methods

Age≥65

With T2DM （n=128）

Without T2DM （n=138）

Analysed the differences in common geriatric comorbidities, acute kidney injury (AKI) recurrence frequency and severity between the two groups and identified risk factors affecting the recurrence frequency and assessed the outcome of AKI in older male patients.

Results

The proportion of patients with more than three AKI recurrences was significantly higher in the group with diabetes

Characteristic	Group with diabetes n=128	Group without diabetes n=138	P value
Recurrent AKI, n (%)	**n=128**	92 (66.7)	0.011*
Recurrent AKI frequency, n (%)			
1	32 (31.1)	40 (43.5)	0.073
2	25 (24.3)	25 (27.2)	0.064
≥3	46 (44.7)	27 (29.4)	0.027*

The proportion of patients with more than three AKI recurrences was significantly higher in the group with HbA1c level ≥7%

Characteristic	Group with HbA1c ≥7% n=39	Group with HbA1c <7% n=89	P value
HbA1c (%), mean±SD	7.6±0.5	6.4±0.4	0.000*
Recurrent AKI, n (%)	34 (87.2)	69 (77.5)	0.205
Recurrent AKI frequency, n (%)			
1	8 (23.5)	26 (37.7)	0.151
2	9 (26.5)	25 (36.2)	0.322
≥3	17 (50.0)	18 (26.1)	0.016*

Conclusions: Older male patients with diabetes were prone to AKI recurrence after initial onset of AKI. Diabetes was an independent risk factor for AKI recurrence. Active diabetes control may thus reduce the recurrence of AKI. The outcome of patients with multiple recurrences of AKI within 2 years was poor.

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Keywords: Diabetes; Older adult; Acute renal injury; Recurrence; Prognosis

Key Summary Points
Why carry out this study?
Patients with diabetes are at higher risk of developing acute kidney injury (AKI).
Studies of diabetes on the recurrence of AKI in older adult patients are scarce.
We examined the impact of diabetes on AKI recurrence and long-term outcomes in older male patients.
What was learned from the study?
Older male patients with diabetes were prone to AKI recurrence after initial onset of AKI, with diabetes as an independent risk factor.
Since outcomes after multiple recurrences within 2 years are poor, blood glucose needs to be closely monitored in older patients with AKI.
Geriatric AKI requires prompt diagnosis and management to prevent AKI recurrence and improve prognosis.

DIGITAL FEATURES

This article is published with digital features, including a graphical abstract, to facilitate understanding of the article. To view digital features for this article, go to https://doi.org/10.6084/m9.figshare.20405430.

INTRODUCTION

Diabetes is a global public health concern with high morbidity and mortality. In the past decade, there was a rapid increase in the incidence of diabetes in China. A national epidemiological survey in 2020 showed that the total standardized prevalence of diabetes among Chinese adult residents was 12.8% [1]. Given its core pathophysiological changes, such as increased blood glucose, metabolic disorder, and insulin resistance, diabetes can impair the functions of many organs, especially the kidneys.

The morbidity and mortality rate of acute kidney injury (AKI) has increased in recent years, which has attracted the attention of clinicians. Numerous studies have demonstrated that diabetes is an independent risk factor for AKI [2, 3]. A classic study reported that the risk of AKI in patients with diabetes was 2.46 times higher than that of patients without diabetes [4]. A retrospective cohort study conducted on patients with or without chronic kidney disease (CKD) reported that the risk of AKI was 2–5 times higher in patients with diabetes compared to patients without diabetes [5]. Previous studies have found that micro-inflammation is one of the important causes of diabetic target organ damage and mainly manifests as inflammatory cell infiltration and mild increase in adhesive molecules, chemokines, and inflammatory cytokines. Our previous research [6] found that injury of the renal tubular interstitium was the earliest renal lesion in diabetes; the increases in the renal glomerular volume, renal glomerular membrane proliferation, interstitial fibrosis, and vascular lesions appeared subsequently. The earliest renal lesions included the degeneration of tubular epithelial cells and local infiltration of inflammation cells in the rat model of type 2 diabetes, in which diabetes was induced using a high-fat, high-sugar diet and a small dose of streptomycin. Inflammatory cell infiltration and degenerative tubular necrosis occurred almost simultaneously in the kidneys of the diabetic rats. Compared with the control group, the main inflammatory cells were CD68-positive cells. Meanwhile, the expression of Toll-like receptor 4 (TLR4) on the surface of inflammatory cells increased significantly. Long-term hyperglycemia may lead to chronic low-level inflammatory states in patients with diabetes. It can thus be predicted that patients with diabetes and renal tubule interstitial damage

caused by microinflammation are more prone to develop AKI when they also have clinical risk factors such as hypovolemia, hypotension, and the use of nephrotoxic agents.

Our previous research also found that the incidence of AKI in the very elderly hospitalized patients is high, and that infection, hypovolemia, nephrotoxic drugs, and cardiovascular diseases are risk factors for AKI in clinical settings [7]. Older adult patients often have multiple comorbidities and are prone to AKI; AKI occurrence can repeatedly be induced in the presence of certain inducing factors. Repeated AKI can cause continuous deterioration of renal function, eventually leading to a poor prognosis. According to our clinical experience, older patients with diabetes are prone to AKI and to multiple relapses of AKI, which significantly affects their survival prognosis. However, studies on the impact of diabetes on AKI recurrence and overall prognoses in older adult patients are scarce. This study thus aimed to analyze the impact of diabetes on AKI recurrence and long-term outcomes in older adult patients with AKI.

METHODS

Study Population

Data of registered inpatients enrolled at the geriatric department of PLA General Hospital between July 2007 and August 2011 were collected from the hospital's electronic medical record system. A total of 2960 patients were hospitalized during this period, including 318 who met the AKI diagnostic criteria. We excluded another 35 patients who died within 1 week of the onset of AKI, five who received a kidney transplant, and 12 with incomplete information or who were lost to follow-up. Finally, 266 older male patients with AKI were included in our analyses (Fig. 1). This clinical retrospective study was approved by the Ethics Committee of PLA General Hospital (reference number S2021-424-01; approved July 29, 2021). Consent was waived due to the retrospective nature of the study and the inclusion of only anonymized data.

Clinical Data

The age of all patients and their underlying diseases, including hypertension, coronary heart disease, diabetes, tumor, stroke, and chronic obstructive pulmonary disease, were recorded. All patients were retrospectively followed for 10 years to record the occurrence of AKI and all related information, such as cause of AKI, stage of AKI severity, peak serum creatinine levels, frequency of AKI, and time of patient death.

As for the AKI diagnostic criteria, this study used changes in serum creatinine to determine if patients had developed AKI, since details on urine volume were incomplete in the retrospective data. AKI was defined according to the 2012 Kidney Disease Improving Global Outcomes (KDIGO) Clinical Practice Guideline for Acute Kidney Injury [8] as an increase in serum creatinine levels by more than 26.5 μmol/l within 48 h or an increase in serum creatinine levels of more than 1.5 times the baseline value within 7 days. AKI was then staged for severity using the serum creatinine changes outlined in the 2012 version of the KDIGO guidelines (Table 1). Peak serum creatinine was the highest value of serum creatinine detected during each AKI occurrence.

AKI recurrence was defined as AKI reappearing after more than 30 days of the last AKI

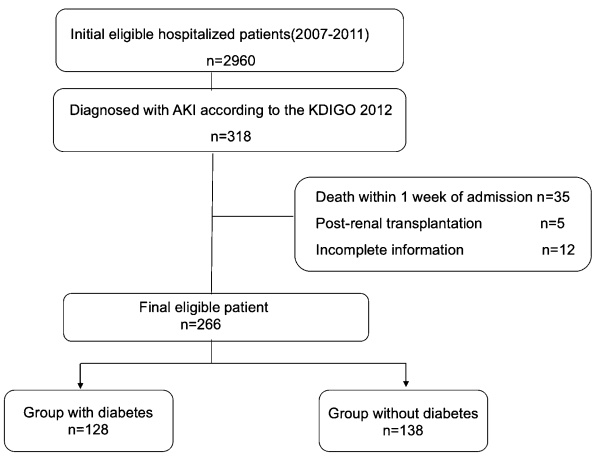

Fig. 1 Flow diagram of cohort creation, with exclusion and inclusion criteria

Table 1 Classification schemes for AKI

Stage	Serum creatinine
1	1.5–1.9 times baseline or $\geq$ 0.3 mg/dl ($\geq$ 26.5 μmol/l) increase
2	2.0–2.9 times baseline
3	3 times baseline or $\geq$ 4.0 mg/dl ($\geq$ 353.6 μmol/l) increase or initiation of RRT or in patients < 18 years of age a decrease in estimated GFR < 35 ml/min/1.73 m^2

RRT renal replacement therapy

occurrence, while multiple recurrences were defined as AKI occurring more than three times in the same patient.

For the definition of comorbidities, we referred to the Diabetes Medical Diagnostic Standards issued by the American Diabetes Association (ADA) in 2021 [9] to define type 2 diabetes, which was diagnosed if the patient had at least two different fasting blood glucose levels above 7.0 mmol/l. The definition of acute cardiovascular and cerebrovascular events (ACCE) was based on the International Classification on Diseases 11th revision published by the World Health Organization in 2018 and included acute myocardial infarction (BA41), sudden cardiac death (no independent encoding), and stroke (8B0, 8B11, 8B20, 8B0) [10]. Coronary heart disease (CHD) was defined based on the 2019 ESC guideline for the diagnosis and management of chronic coronary syndromes and included chronic and acute coronary syndromes [11]. The duration of diabetes was defined as the time from the diagnosis of diabetes to the first recurrence of AKI. The definition of diabetic kidney disease (DKD) was defined based on the consensus reached by the US Food and Drug Administration (FDA) and National Kidney Foundation (NKF) in 2014, that is, glomerular filtration rate (GFR) below 60 ml/(min·1.73m^2) or urine albumin/creatinine above 30 mg/g for more than 3 months [12].

All patients were followed up for 10 years from the time of their first hospitalization. The endpoint of the study was patient death or survival within a decade. Survival was recorded if patients were hospitalized or still alive (confirmed through a telephone call) at the follow-up endpoint. Death was confirmed through follow-up via telephone or other means or recorded if the patient had a definite time of death in the electronic medical record system.

Statistical Analysis

Statistical analysis was performed using SPSS version 26.0 (SPSS, Inc., Chicago, IL, USA). Normally distributed measurement data were expressed as means ± standard deviations (SDs), and *t* tests were used for between-group comparisons. Non-normally distributed measurement data were expressed as medians (quartiles) [M (Q1, Q3)], and between-group comparisons were made using the Mann–Whitney *U* test. Categorical data were expressed as frequencies and percentages. We used Pearson's chi-squared test and binary logistic regression (both two-sided) to analyze independent risk factors for AKI recurrence. A Kaplan–Meier survival analysis was conducted to analyze the patients' 2-year and 10-year prognoses. $P < 0.05$ was considered to reflect statistical significance.

RESULTS

Baseline Characteristics of Patients with Acute Kidney Injury

The 266 patients were divided into a group with diabetes (n = 128) and a group without diabetes (n = 138). The mean age of patients in both groups was 86.6 ± 5.0 and 86.5 ± 6.2 years, respectively; there was no significant difference in age between the two groups (P = 0.882). The group with diabetes had a significantly higher proportion of individuals with hypertension (86.7% vs. 72.5%; P = 0.004) (Table 2). There was no significant difference in the proportions of individuals with other comorbidities, such as coronary heart disease, tumor, or stroke between the two groups.

Table 2 Baseline characteristics between the groups with and without diabetes

Characteristic	Group with diabetes $n = 128$	Group without diabetes $n = 138$	*P* value
Age (years) mean ± SD	86.6 ± 5.0	86.5 ± 6.3	0.882
Age (years), *n* (%)			
65–70	2 (1.6)	4 (2.9)	0.463
70–75	3 (2.3)	7 (5.1)	0.242
75–80	9 (7.0)	10 (7.4)	0.946
≥ 80	114 (89.1)	117 (84.8)	0.302
Comorbidity			
Hypertension, *n* (%)	111 (86.7)	100 (72.5)	0.004*
CHD, *n* (%)	112 (87.6)	109 (79.0)	0.064
Tumor, *n* (%)	76 (59.4)	84 (60.9)	0.804
COPD, *n* (%)	82 (64.1)	87 (63.0)	0.863
Stroke, *n* (%)	72 (56.3)	68 (49.3)	0.255
AKI frequency, *n* (%)	402	310	
AKI stage, *n* (%)			
1	373 (92.8)	269 (86.8)	0.035*
2	29 (7.2)	36 (11.6)	0.038*
3	5 (1.2)	5 (1.6)	0.664
Etiologies of AKI, *n* (%)			
Infections	174 (43.3)	103 (33.2)	0.006*
Pulmonary infection	145 (83.3)	70 (68.0)	0.003*
Skin and soft tissue infection	12 (6.9)	9 (8.7)	0.576
Gastrointestinal infection	4 (2.3)	7 (6.8)	0.064
Urinary infection	9 (5.2)	10 (9.7)	0.149
Others	4 (2.3)	7 (6.8)	0.064
Hypovolemia, *n* (%)	86 (21.4)	75 (24.2)	0.376
Medications, *n* (%)	42 (10.5)	46 (14.9)	0.078
Antibiotic	36 (85.7)	30 (65.2)	0.046*
NSAID	3 (7.1)	7 (15.2)	0.233
Diuretic	2 (4.8)	5 (10.9)	0.290
Others	1 (2.4)	4 (8.7)	0.201
ACCE, *n* (%)	34 (8.5)	27 (8.7)	0.905
Others, *n* (%)	34 (16.4)	34 (19.0)	0.259

Table 2 continued

Characteristic	Group with diabetes $n = 128$	Group without diabetes $n = 138$	*P* value
Recurrent AKI, *n* (%)	103 (80.5)	92 (66.7)	0.011*
Recurrent AKI frequency, *n* (%)			
1	32 (31.1)	40 (43.5)	0.073
2	25 (24.3)	25 (27.2)	0.064
≥ 3	46 (44.7)	27 (29.4)	0.027*

Data presented are *n* (%) or means ± SD

*$P < 0.05$, statistical significance

CHD coronary heart disease, *ACCE* acute cardiovascular and cerebrovascular events, *COPD* chronic obstructive pulmonary disease, *NSAID* nonsteroidal anti-inflammatory drugs

The descriptive analysis revealed that the top four causes of AKI in the group with and that without diabetes were infections (43.3 vs. 33.2%; $P = 0.006$), hypovolemia (21.4 vs. 24.2%; $P = 0.0376$), medications (10.5 vs. 14.9%; $P = 0.078$), and acute cardiovascular and cerebrovascular events (8.5 vs. 8.7%; $P = 0.905$). Pulmonary infections were more common in the group with diabetes (83.3 vs. 68.0%; $P = 0.003$), and antibiotics were the most common cause of AKI overall (85.7 vs. 65.2%; $P = 0.046$) (Table 2).

A total of 712 AKI events occurred in all patients during the follow-up period, 402 events in the group with diabetes, and 310 events in the group without diabetes. The proportion of patients that developed either stage 1 or 2 AKI was significantly higher in the group with diabetes ($P = 0.035$, $P = 0.038$); however, there was no significant difference between the two groups in the proportion of patients that developed stage 3 AKI ($P = 0.664$) (Table 2).

During the follow-up period, 103 (80.5%) and 92 (66.7%) patients in the groups with and without diabetes, respectively, had recurrent AKI, with the group with diabetes having a significantly higher recurrence rate ($P = 0.011$). In the group with diabetes, 32 (31.1%) patients experienced AKI recurrence once, 25 (24.3%) experienced it twice, and 46 (44.7%) experienced recurrence three times or more. Meanwhile, in the group without diabetes, 40 (43.5%) patients experienced AKI recurrence once, 25 (27.2%) experienced it twice, and 27 (29.4%) experienced recurrence more than three times. The proportion of patients with more than three AKI recurrences was significantly higher in the group with diabetes compared to the group without ($P = 0.027$).

Subgroup Analysis Based on the Recurrence of Acute Kidney Injury

We further analyzed all patients in subgroups formed on the basis of AKI recurrence; there were 195 patients in the recurrent AKI group, of whom 103 (52.8%) had diabetes and 169 (86.7%) had coronary heart disease, and 71 patients in the non-recurrent AKI group, of whom 25 (35.2%) had diabetes and 52 (73.2%) had coronary heart disease. The mean duration of diabetes mellitus in the recurrent AKI group and the non-recurrent AKI group was 9.0 ± 10.4 years and 6.0 ± 9.5 years, respectively. As shown in Table 3, the proportions of patients with diabetes or coronary heart disease and the mean duration of diabetes mellitus were significantly higher/longer in the recurrent than in the non-recurrent subgroup group ($P = 0.011$, $P = 0.010$, $P = 0.039$). There were no significant differences in age or other comorbidities such as hypertension, tumors, or DKD between the recurrent and non-recurrent AKI groups ($P > 0.05$). The identified differences were introduced into the multivariate logistic regression equation using the rewind method

Table 3 Subgroup analysis based on the recurrence of AKI

Characteristic	Group with recurrent AKI (n = 195)	Group with non-recurrent AKI (n = 71)	P value
Age (years) mean ± SD	86.8 ± 5.4	86.0 ± 6.4	0.336
Age (years), n (%)			
65–70	1 (0.5)	1 (1.4)	0.454
70–75	6 (3.1)	6 (8.5)	0.078
75–80	12 (6.2)	3 (4.2)	0.720
≥ 80	177 (90.8)	61 (85.9)	0.254
Hypertension, n (%)	155 (79.5)	56 (78.9)	0.913
CHD, n (%)	169 (86.7)	52 (73.2)	0.010*
Diabetes mellitus, n (%)	103 (52.8)	25 (35.2)	0.011*
Tumor, n (%)	84 (43.1)	33 (46.5)	0.721
Stroke, n (%)	99 (50.8)	41 (57.8)	0.313
COPD, n (%)	120 (61.5)	49 (69.0)	0.263
Duration of DM (years) mean ± SD	9.0 ± 10.4	6.0 ± 9.5	0.039*
DKD	18 (9.23)	5 (7.04)	0.574

Data presented are n (%) or means ± SD

*$P < 0.05$, statistical significance

CHD coronary heart disease, *ACCE* acute cardiovascular and cerebrovascular events, *COPD* chronic obstructive pulmonary disease, *DM* diabetes mellitus, *DKD* diabetic kidney disease

for variable screening. The regression analysis revealed that diabetes (odds ratio [OR] = 1.862, 95% confidence interval [CI]: 1.039–3.335) and coronary heart disease (OR = 2.074, 95% CI: 1.036–4.153) were independent risk factors for AKI recurrence. The results are shown in Table 4.

Subgroup Analysis of Acute Kidney Injury Recurrence Based on the HbA1c

Based on the above results, we further performed a subgroup analysis of AKI recurrence with regard to diabetes control. The 128 patients in the group with diabetes were divided into a group with a HbA1c level ≥ 7% and a group with a HbA1c level < 7%. There were 34 (87.2%) and 69 (77.5%) patients in these groups, respectively, who had recurrent AKI. In the group with a HbA1c ≥ 7%, eight (23.5%) patients experienced AKI recurrence once, nine (26.5%) experienced it, and 17 (50%) experienced recurrence three times or more. Meanwhile, in the group with a HbA1c < 7%, 26 (37.7%) patients experienced AKI recurrence once, 25 (36.2%) experienced it twice, and 18 (26.1%) experienced recurrence more than three times. The proportion of patients with more than three AKI recurrences was significantly higher in the group with HbA1c level ≥ 7% compared to the group HbA1c level < 7% (P = 0.016). The results are shown in Table 5.

Clinical Outcome Analysis

The 10-year mortality rate in the groups with and without diabetes was 91.4% (11 survivors) and 89.9% (14 survivors), respectively. The Kaplan–Meier survival analysis revealed no significant difference in the 10-year survival between patients in the groups with and without diabetes (P = 0.522) (Fig. 2a). However, the subgroup analysis of the 2-year prognosis based on the occurrence of diabetes and multiple AKI recurrences revealed that the patients in the group with diabetes and multiple AKI recurrences within 2 years had the worst survival prognosis (P = 0.004). The results are shown in Fig. 2b, c.

DISCUSSION

AKI is currently associated with high morbidity and mortality in hospitals. In a previous study, we found an overall incidence of AKI in very elderly patients of 14.8% [7]. Older individuals

Table 4 Multivariate logistic regression analysis of recurrent AKI

Characteristic	β value	SE value	Wald χ^2/value	*P* value	OR value	95% CI
CHD	0.729	0.354	4.241	0.039	2.074	1.036–4.153
Diabetes mellitus	0.621	0.298	4.362	0.037	1.862	1.039–3.335

CHD coronary heart disease, *CI* confidence interval

Table 5 Subgroup analysis of recurrence of AKI based on the HbA1c

Characteristic	Group with HbA1c ≥ 7% *n* = 39	Group with HbA1c < 7% *n* = 89	*P* value
HbA1c (%), mean ± SD	7.6 ± 0.5	6.4 ± 0.4	0.000*
Recurrent AKI, *n* (%)	34 (87.2)	69 (77.5)	0.205
Recurrent AKI frequency, *n* (%)			
1	8 (23.5)	26 (37.7)	0.151
2	9 (26.5)	25 (36.2)	0.322
≥ 3	17 (50.0)	18 (26.1)	0.016*

HbA1c hemoglobin A1c
*$P < 0.05$, statistical significance

are more likely to experience AKI, with morbidity increasing with age [13]. The kidneys of older individuals are affected by structural and functional changes caused by factors such as aging, comorbidities, and multiple medications; therefore, they have a higher incidence of AKI with a poor prognosis and a higher mortality risk than the general population [14]. The incidence of AKI among older individuals aged > 75 years amounts to 3.5 times the incidence of AKI among younger individuals; moreover, the mortality rate of AKI among older individuals is as high as 50% [15]. Additionally, Formica [16] reported that the prevalence of AKI among individuals aged > 65 years is 25 times that among those aged < 65 years. As many as one-third of the hospitalized older adult patients with AKI are re-hospitalized within 12 months due to AKI recurrence [17]. In China, the mortality of patients with AKI aged 65–80 years is approximately 10.3%, and the mortality of those aged over 80 years is as high as 19.6% [18]. Diabetes has been considered a risk factor for AKI; a meta-analysis showed that the hazard ratios for AKI are higher in patients with diabetes compared with those without diabetes at any level of an estimated GFR [3]. At present, most studies examining the prognosis of geriatric AKI are short-term studies, and reports on the impact of diabetes on the long-term prognosis of geriatric AKI are scarce. Therefore, we analyzed the data of older male patients who had experienced AKI during hospitalization at our hospital, retrospectively followed up their case data for 10 years, and explored the impact of diabetes on AKI recurrence and patient outcomes.

Our study found that the incidence of AKI recurrence was significantly higher in patients with diabetes than in patients without diabetes, and that a recurrence frequency of ≥ 3 was more common in patients with diabetes. Multiple AKI recurrences often suggested a poor prognosis. These results are consistent with recent reports. Holmes [19] reported that the 30-day mortality rate was significantly higher in patients with multiple onsets of AKI than in patients with a single onset. Moreover, the

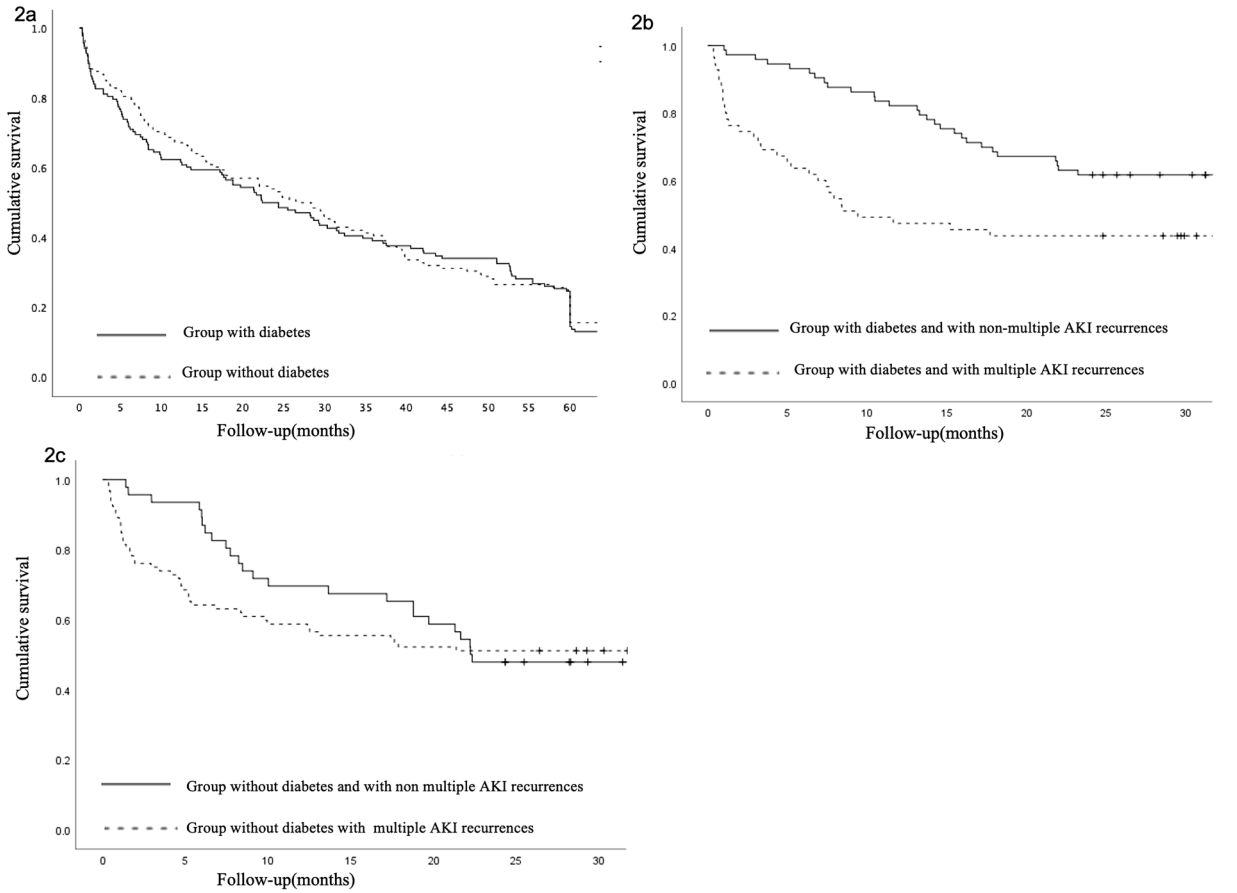

Fig. 2 **a** Kaplan–Meier survival curve for 10-year mortality between diabetic group and non-diabetic group ($P = 0.522$). **b** Kaplan–Meier survival curve for 2-year mortality between diabetic group with multiple AKI recurrences or non- multiple AKI recurrences($P = 0.004$). **c** Kaplan–Meier survival curve for 2-year mortality between non-diabetic group with multiple AKI recurrences or non- multiple AKI ($P = 0.632$)

possibility of subsequent AKI onsets increases with each onset of AKI. Additionally, Liu [20] reported that diabetes and acute heart failure are predictors of AKI recurrence and are correlated with mortality. Rodriguez [21] reported that patients with multiple onsets of AKI had a higher 4-year mortality than patients with a single onset of AKI. Our findings demonstrate that diabetes is an independent risk factor for AKI recurrence. Repeated onsets of AKI can cause renal interstitial fibrosis and decreased renal function. A recent study suggested that AKI is not a benign, self-limiting, and reversible disease, but that AKI occurrence increases the mortality risk with each onset of AKI [22]. Patients with diabetes are susceptible to the onset and recurrence of severe AKI. Li [23] reported that stage 2 and stage 3 AKI are independent risk factors for short-term mortality in older adult patients with AKI. We observed that the proportion of patients developing stage 1 and 2 AKI was significantly higher in the patients with diabetes than in the patients without diabetes; however, there was no difference between the two groups in the proportion of patients developing stage 3 AKI. This may be related to the relatively small sample size of patients with stage 3 AKI in our study.

AKI in older adult patients often has multiple etiologies. In our study, the top four etiologies in both patients with and those without diabetes were infections, hypovolemia, acute

cardiovascular events, and medications, with patients with diabetes showing a significantly higher proportion of infection-related AKI. Pulmonary infections were more common in the group with diabetes and antibiotics were the most common cause of AKI overall. Similarly, our previous study on the short-term prognosis of elderly patients with AKI found that infection, hypovolemia, use of nephrotoxic drugs, and cardiovascular events are common causes of AKI in elderly patients [24]. Currently, diabetes is considered a non-specific immune disease, with hyperglycemia being the main symptom, which involves chronic micro-inflammation mediated by inflammatory cytokines [25]. This micro-inflammatory environment is common in patients with diabetes and is considered an important etiology of damage to the target organs [26]. Muroya [27] reported that older rats with diabetes are more vulnerable to renal ischemia–reperfusion injury, which is associated with ICAM-1, inflammatory cell infiltration, and longer durations of renal medulla ischemia. Inflammation promotes diabetes development by increasing insulin resistance. Owing to hyperglycemia, insulin resistance may cause some complications, including AKI and diabetic nephropathy [28]. Given the persistent micro-inflammatory state in patients with diabetes coupled with the weak immunity and poor renal function reserve in older individuals, the appearance of inducing factors, including infections, hypovolemia, and acute cardiovascular events, greatly increases the recurrence rate of AKI. Infections can stimulate the body to release inflammatory mediators (e.g., interleukin-1, interleukin-6, and tumor necrosis factor), which cause an abnormal increase in platelets and microvascular thrombus formation. Additionally, inflammation induces platelets to activate neutrophils, which aggravates the inflammatory response. In cases where the infection cannot be promptly controlled, multiple organ failure or even death can occur.

Our findings show that coronary heart disease and arrhythmia are risk factors for AKI recurrence. Malhotra et al. [29] reported coronary heart disease as an independent predictor for AKI in intensive care unit inpatients. In a study including 190 patients undergoing cardiac surgery, Guan et al. [30] reported coronary heart disease and arrhythmia as risk factors for AKI related to cardiac surgery, which is consistent with our findings. Older individuals have a high incidence of medication-related AKI. Combinations of multiple nephrotoxic drugs, excessively long durations of medication, excessively high doses of drugs, and polypharmacy are more common in older adults [31], and NSAIDs (non-steroidal anti-inflammatory drugs), ACEIs (angiotensin-converting enzyme inhibitor), and ARBs (angiotensin receptor blocker), which are commonly used in older adults, can affect renal blood flow perfusion and are associated with AKI [32].

Diabetes and AKI are important factors affecting the survival and prognosis of older adult patients. A retrospective study on older individuals (age > 90 years) with a 10-year follow-up period reported an incidence rate of AKI of 45%. Moreover, patients with AKI had a significantly higher mortality rate than those without AKI (66.8 vs. 23.8%; $P < 0.001$) [33]. AKI occurrence in the presence of diabetes further affects the survival prognosis among older individuals. In our study, the overall mortality rate was 90.2%, with the group with diabetes showing a higher mortality rate than the group without diabetes. There was no between-group difference in the 10-year survival analysis, which was associated with the relatively old baseline ages (most patients were aged between 80 and 99 years). Notably, our population had numerous underlying diseases and geriatric comorbidities. Most of the patients included in our study died of pulmonary infections. Further, our findings suggest that patients with diabetes who showed multiple AKI recurrences within 2 years had a poor survival prognosis.

In our study, we found that the worse the diabetes control, the greater the possibility of multiple AKI recurrences in patients, suggesting that active diabetes control may reduce the recurrence of AKI. Research found that higher HbA1c categories were associated with a higher AKI risk [34], and HbA1c was found to be a predictive factor of AKI in patients with undergoing partial nephrectomy [35]. The 2020 American Diabetes Association guidelines recommend less stringent HbA1c goals (such as < 8% [64 mmol/l]) for patients with extensive comorbid conditions or older adults with coexisting chronic illnesses [34].

Most patients in our study fell into the oldest age range (≥ 75); these patients were followed up at our hospital for a long time, and the case data were relatively complete and comprehensive. There are currently very few related research reports on this topic. However, our study has certain limitations. First, this single-center retrospective cohort study had a relatively small sample size. Therefore, there is a need for multi-center prospective studies to further explore the mechanism underlying the effects of diabetes on AKI in older individuals. Second, this study was conducted only in male patients. Finally, given the numerous underlying diseases and comorbidities in older patients, AKI in older individuals often involves multiple complex etiologies and synergistic causes; therefore, the diagnosis of AKI in our study may have partly been based on subjective factors.

CONCLUSIONS

Our findings demonstrate that patients with diabetes are more likely to experience AKI recurrence than patients without diabetes. Our sample included multiple and complicated cases of AKI in older adult patients, with a relatively large proportion of patients with diabetes presenting with infection-induced AKI. Diabetes and coronary heart disease were found to be independent risk factors for AKI recurrence, and diabetes control was associated with multiple AKI recurrence; active diabetes control (HbA1c < 7%) may thus reduce the recurrence of AKI. Moreover, the patients with diabetes who experienced repeated recurrence of AKI within 2 years had a poor survival prognosis. These findings emphasize the need to closely monitor blood glucose levels in older patients with AKI in the clinical practice, as geriatric AKI requires prompt diagnosis and management to prevent recurrence and improve prognoses.

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

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