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Vitamin D deficiency may increase the risk of acute kidney injury in patients with diabetes and predict a poorer outcome in patients with acute kidney injury

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Abstract

Background People with diabetes are much more likely to develop acute kidney injury (AKI) than people without diabetes. Low 25-hydroxy-vitamin D [25(OH)D] concentrations increased the risk of AKI in specific populations. Few studies have explored the relationship between the 25(OH)D level and AKI in patients with diabetes. We conducted this study to investigate the relationship between the plasma level of 25(OH)D and the risk of AKI in patients with diabetes, and to evaluate whether the 25(OH)D level could be a good prognostic marker for AKI progression.

Methods A total of 347 patients with diabetes were retrospectively reviewed. The primary endpoint was the first event of AKI. The secondary endpoint is need-of-dialysis. AKI patients were further followed up for 6 months with the composite endpoint of end-stage renal disease (ESRD) or all-cause death. Kaplan–Meier survival analysis and Cox proportional hazards models were used.

Results During a median follow-up of 12 weeks (12.3 ± 6.7), 105 incident AKI were identified. The middle and high tertiles of baseline 25(OH)D levels were associated with a significantly decreased risk of AKI and dialysis compared to the low tertile group (HR = 0.25, 95% CI 0.14–0.46; HR = 0.24, 95% CI 0.13–0.44, respectively, for AKI; HR = 0.15; 95% CI 0.05–0.46; HR = 0.12; 95% CI 0.03–0.42, respectively, for dialysis). Sensitivity analysis revealed similar trends after excluding participants without history of CKD. Furthermore, AKI patients with 25(OH)D deficiency were associated with a higher risk for ESRD or all-cause death (HR, 4.24; 95% CI, 1.80 to 9.97, $P < 0.001$).

Conclusion A low 25 (OH) vitamin D is associated with a higher risk of AKI and dialysis in patients with diabetes. AKI patients with 25(OH)D deficiency were associated with a higher risk for ESRD or all-cause death.

Keywords Acute kidney injury, Diabetes, Prognosis, Risk factor, Vitamin D

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Background

Diabetes mellitus (DM) is now a major concern for public health worldwide. According to the 10th edition of the International Diabetes Federation Atlas, 537 million individuals worldwide were estimated to have diabetes in 2021, and by 2045, that number is predicted to rise to 783 million [1]. Numerous studies have drawn similar conclusions: people with diabetes are much more likely to develop acute kidney injury (AKI) than people without diabetes [2]. Administrative data from the Centers for Disease Control and Prevention indicate that the number of AKI hospitalizations increased more than fourfold between 2000 and 2014, among which persons with diabetes accounted for about 40% of all AKI hospitalizations, with absolute increases in AKI hospitalizations being larger among persons with diabetes than among persons without diabetes [3]. Moreover, not only is AKI more common in persons with diabetes, but also, if a person with diabetes develops AKI, their prognosis is worse as well. In one study, rates of dialysis-requiring AKI were approximately five times higher among persons with diabetes than among persons without diabetes [4]. Aside from the risk of end-stage renal disease (ESRD) among persons with diabetes, AKI has also been shown to be associated with an increased risk of death [5]. Patients with diabetes are commonly affected by a variety of comorbidities that increase their risk of developing AKI. Obesity, heart failure, hypertension, prior AKI episodes, chronic kidney disease (CKD), and even certain antihypertensive and antidiabetic medications have all been linked to an increased risk of AKI [6, 7]. Thus, a better understanding of the main predictors of AKI will enable physicians to identify high-risk patients for early intensification and individualization of treatment to prevent AKI and its potential impact on long-term renal complications.

As a pleiotropic steroid hormone, vitamin D has been linked to a variety of biological activities; among them, the potential of vitamin D in the protection of diabetic nephropathy has attracted particular attention. Experimental evidence reported that it plays an important role in modulating cell proliferation, apoptosis, differentiation, inflammation response, immune function, and vascular and metabolic properties such as insulin secretion and sensitivity [8, 9]. 25-hydroxyvitamin D [25(OH)D] is synthesized by 25-hydroxylase catalyzing vitamin D, which is considered the best indicator of vitamin D status [10]. Studies have found that 25(OH)D deficiency increases the risk of T2DM development and the incidence of its complication [11]. Low 25 (OH) vitamin D levels in patients with CKD have been linked to an increased risk of all-cause mortality and faster progression of kidney disease [12]. The role of vitamin D in CKD has aroused our curiosity about its role in AKI. We noticed that observational studies have suggested a link between low 25(OH)D levels and a higher risk of AKI in critically ill, patients undergoing coronary angiography and the general population [13–15]. However, to date, no studies have explored the relationship between the 25(OH)D level and AKI in patients with diabetes mellitus, a population with a high rate of 25 (OH) vitamin D deficiency. To address these knowledge gaps, this study aims to test the hypothesis that 25 (OH) vitamin D deficiency is associated with AKI and is predictive of the need for renal replacement therapy in patients with diabetes mellitus. Moreover, we also examined the impact of 25(OH)D level on the progression of AKI with the composite endpoints of ESRD or mortality in AKI patients.

Materials and methods

Research subjects

A total of 347 patients with diabetes mellitus from January 2019 to December 2022 in The First Affiliated Hospital of Guangxi Medical University were retrospectively reviewed. DM was diagnosed according to the World Health Organization criteria. All the patients should have intact information on the baseline serum 25(OH)D level. Exclusion criteria were as follows: (1) malignancies; (2) women with pregnancy; (3) CKD stage 5 or renal replacement therapy (RRT); and (4) patients with new-onset diabetes after transplantation. This study was approved by the Ethics Committee of the First Affiliated Hospital of Guangxi Medical University [Approval number: 2019(KY-E028)]. As this was a retrospective analysis of anonymized clinically obtained data and all patient identifiers were removed, there was no need for patients to sign an informed consent form. We implemented strict protocols to ensure that all participant data was anonymized and securely stored. Access to identifiable information was restricted to authorized personnel only. This study was conducted in accordance with the tenets of the Declaration of Helsinki.

Diagnostic criteria

AKI was defined referring to the diagnostic criteria of AKI in the Kidney Disease: Improving Global Outcomes guideline: Scr increased by ≥26.5 μmol/L within 48 h or increased by >50% of the baseline value within 7 days. The diagnostic criteria was programmed into the *AKI automated electronic alert system*, which has been incorporated into the HIS system, and the onsets of AKI were captured and recorded. The criteria of AKI stage: stage 1: Scr increase to 1.5–1.9 times of baseline value or increased≥0.3 mg/dL, stage 2: Scr increase to 2.0–2.9 times of base value, stage 3: Scr increase to 3 times or ≥4.0 mg/ dL or begin RRT [16]. Diagnosis of diabetes conforms to World Health Organization criteria as follows: (1) random blood glucose≥11.1 mmol/L, (2) fasting

blood glucose (FBG) ≥ 7.0 mmol/L, or (3) postprandial blood glucose (PBG) ≥ 11.1 mmol/L [17].

Clinical data collection

Demographic data and baseline clinical data were collected, including age, gender, body mass index (BMI), blood pressure, baseline levels of routine blood tests, liver function, renal function, electrolytes, 25-hydroxyvitamin D3 [25(OH)D3], blood glucose, glycosylated hemoglobin (HbA1c), N-Terminal Pro-Brain Natriuretic Peptide (NT-pro BNP) and diagnosed comorbidity. The baseline Scr was defined as a stable Scr within the last 3 months or longer if none was available within 3 months. Other laboratory indicators were the first-time values after hospitalization. The current medications of participants were also recorded, including SGLT2 inhibitor, RAS blockers, Vitamin D analogues. The serum 25(OH)D level was determined by chemiluminescence immunoassay (ARCHTECT i2000SR, USA).

Follow-up and outcome measures

The follow-up time was no less than 12 weeks. The primary outcome was the first event of AKI. The secondary outcome is need-of-dialysis. Furthermore, in order to explore the impact of 25(OH)D level on the progression of AKI, we followed up the AKI patients for 6 months with the composite endpoint of ESRD or all-cause death. ESRD was defined as the need for long-term dialysis or renal transplantation.

Statistical analysis

We divided the study population into tertiles according to baseline serum 25(OH)D level. Data were presented as mean ± SD, median and interquartile range, or percentage. As appropriate, comparisons between groups were performed using one-way analysis of variance (ANOVA), Kruskal–Wallis test, or χ^2 test. Kaplan–Meier analysis and the log-rank test were used to assess AKI-survival and dialysis-survival among groups. The covariates considered for adjustment included sex, age, BMI, Hb, ALB, blood pressure, HbA1c, drug use (SGLT2 inhibitor, RAS blocker, vitamin D analogue), previous AKI history, diagnosed comorbidity, estimated GFR (eGFR) calculated using the four-variable Modification of Diet in Renal Disease study equation (MDRD4). In addition, we followed up the patients with AKI for 6 months. Kaplan–Meier analysis and Cox proportional hazards regression models were performed to evaluate the effect of serum 25(OH)D level on composite outcomes of all-cause-death or ESRD in AKI patients. Univariate Cox regression was used to screen the risk factors affecting the prognosis, and the "forward LR" method was then.

used to screen the variables of $p<0.05$ that were included in the multivariate Cox proportional hazards regression model. A p-value of <0.05 was considered statistically significant. All statistics were done in IBM SPSS v.24.0 and Graphpad Prism 10.0.

Results

Baseline clinical characteristics according to tertiles of the serum 25(OH)D level

Among 418 diabetic patients with intact baseline serum 25(OH)D level information, 38 had stage 5 CKD or had regular RRT, 18 had incomplete baseline data (including BMI, NT-pro BNP and HbA1c data), and 15 were lost to follow-up. Finally, a total of 347 patients were included in this study, with an average age of 61.29 ± 14.4 years and a male-to-female ratio of 1.84:1. The serum 25(OH)D level was 22.33 ± 8.8ng/mL. Average level of the systolic BP, ALB, HbA1c, and baseline eGFR were 136.6mmHg, 33.0 g/L, 7.54%, and 67.17mL/min/1.73m^2, respectively. The clinical characteristics of the study population according to tertiles of the serum 25(OH)D levels are presented in Table 1. Compared to the patients in the high tertile, those in the low tertile tended to have higher levels of systolic blood pressure, diastolic blood pressure, white blood cell, and NT-pro BNP while lower level of albumin (ALB), calcium and hemoglobin (Hb) (all $P<0.05$). Kidney function was better when the serum 25(OH)D level was higher, wherein baseline eGFR was significantly increased in the highest tertile. In addition, patients in the middle and low tertiles were more likely to have CKD, chronic heart failure, previous AKI onsets, and infections at baseline (all $P<0.05$). There were no differences in age, gender, BMI, WBC, HbA1c, uric acid and use of SGLT2 inhibitor or RAS blocker between groups.

Baseline serum 25(OH)D and the risk for AKI

During a median follow-up time of 12 weeks (12.3 ± 6.7), 105 incident AKI were identified. AKI rate in the lowest tertile was the highest among groups ($P<0.001$), with 58 patients (50%) suffering from AKI. The causes of AKI were as follows: nephrotoxin (23 patients, 21.3%), infection (47 patients, 44.8%), ischemic acute tubular necrosis (24 patients, 22.2%), hepatorenal syndrome (3 patients, 2.8%) and obstructive uropathy (6 patients, 5.6%). There were no significant differences in enrollment 25(OH)D levels according to etiology of AKI (Supplementary Fig. 1). No significant differences were found in the distribution of 25(OH)D tertiles in different groups according to AKI etiology (shown in Fig. 1). Among the 105 incident AKI, 20 patients had stage 1 AKI, 43 patients had stage 2 AKI, and 42 patients had stage 3 AKI. The distribution of different stages of AKI among groups is shown in Fig. 2. Compared to the middle and high tertile, patients in the low tertile had the highest rate of stage 3 AKI ($P<0.05$). The predictive role of baseline 25(OH)D for the occurrence of AKI was examined in multivariate

Table 1 Clinical characteristics and laboratory findings of all enrolled patients according to tertiles of vitamin D level

Variables	25(OH)Vitamin D			
	low tertile (*n* = 116)	middle tertile (*n* = 116)	high tertile (*n* = 115)	*P* value
Age(year)	62.1.9 ± 12.7	60.1 ± 16.3	61.3 ± 14.5	0.33
BMI((kg/m^2)	24.0 ± 4.0	23.9.3 ± 3.8	23.9 ± 4.0	0.64
Male, n(%)	74(63.8%)	75(64.7%)	78(67.8%)	0.80
Systolic BP(mmHg)	142.1 ± 25.7**	135.0 ± 24.5	132.5 ± 21.5	0.003
Diastolic BP(mmHg)	80.3 ± 19.4	73.8 ± 13.0$^{\#}$	76.8 ± 15.0	0.001
WBC(×10^9 /L)	14.3 ± 9.0	11.9 ± 7.2	11.9 ± 5.8	0.06
Hb(g/L)	95.3 ± 21.6	103.5 ± 22.7$^{*\#}$	98.5 ± 21.5	0.02
ALB(g/L)	29.3 ± 5.9***	35.8 ± 6.2$^{\#}$	34.0 ± 5.0	<0.001
25(OH)vitamin D(ng/mL)	12.8 ± 3.3***	22.5 ± 2.3$^{***\#}$	31.8 ± 6.1	<0.001
Calcium(mmol/L)	2.0 ± 0.1***	2.09 ± 0.11$^{\#}$	2.11 ± 0.11	<0.001
NT-pro BNP(pg/mL)	5265.0 ± 3333.7***	3527.1 ± 1099.1$^{\#}$	3753.5 ± 1486.3	<0.001
HbA1c(%)	7.4 ± 1.6	7.7 ± 1.7	7.5 ± 1.7	0.241
Baseline eGFR(ml/min/1.73m^2)	64.1 ± 39.5*	62.8 ± 32.1*	74.6 ± 33.3	0.03
Uric acid(μmol/L)	407.6 ± 197.0	426.3 ± 207.3	401.8 ± 173.3	0.44
Diagnosed comorbidity				
infection, n(%)	64(55.2%)	59(50.9%)	45(39.1%)	0.041
CKD, n(%)	102(87.9%)	95(81.9%)	84(73.0%)	0.015
CHF, n(%)	50(43.1%)	40(34.5%)	31(27.0%)	0.036
Previous AKI	32(27.6%)	26(22.4%)	11(9.6%)	0.002
Drug usage, n(%)				
SGLT2 inhibitor	32(27.6%)	24(20.7%)	34(29.6%)	0.27
RAS blockers	32(27.6%)	46(39.7%)	42(36.5%)	0.13
Vitamin D analogues	77(66.4%)	36(31.0%)	34(29.6%)	<0.001

BMI: body mass index; BP: blood pressure; WBC: white blood cell; Hb: hemoglobin; ALB: albumin; NT-pro BNP: N-Terminal Pro-Brain Natriuretic Peptide; HbA1c: glycosylated hemoglobin; eGFR: estimated glomerular filtration rate; CHF: chronic heart failure; SGLT2: sodium-glucose co-transporter 2; RAS: renin-angiotensin system

$^{*}P < 0.05$ compared to the high tertile group

$^{**}P < 0.005$ compared to the high tertile group

$^{***}P < 0.001$ compared to the high tertile group

$^{\#}P < 0.05$ compared to the low tertile group

Cox regression models. After adjustment for age, gender, BMI, NT-pro BNP, blood pressure, ALB, baseline eGFR, and history of AKI, baseline 25(OH) D (1 ng/mL) as a continuous variable was an independent predictor of AKI (HR = 0.96; 95% CI 0.93– 0.98).

When patients were tertiled by baseline serum 25(OH) D, Kaplan–Meier analysis showed that time-to-AKI was significantly shorter for patients in the low tertile compared to patients in the middle and the high tertile group ($p < 0.001$, Fig. 3a). The difference in risk between middle and high tertile groups did not reach statistical significance. In addition, baseline 25(OH)D as a categorical variable was used in multivariate Cox regression models. The adjusted model included baseline eGFR, Hb, previous AKI, CKD complication. As shown in Table 2, the middle and high tertiles of baseline 25(OH)D levels were associated with a significantly decreased risk of AKI compared to the low tertile group (HR = 0.25, 95% CI 0.14–0.46; HR = 0.24, 95% CI 0.13–0.44, respectively). Age, sex, BMI, ALB, HbA1c, blood pressure, treatment with SGLT2 inhibitor, RAS blocker and vitamin D analogues were removed as non-confounders. Considering CKD comorbidities significantly influence prognostic outcomes, we made a sensitivity analysis excluding 66 cases without history of CKD. Similar trends were found after excluding participants without CKD complication (Supplemental Table 1).

Baseline serum 25(OH)D and the risk for dialysis

During follow-up, 32 patients achieved the dialysis endpoint. The Kaplan-Meier survival curves for the secondary endpoint are shown in Fig. 3b. The cumulative incidence of dialysis significantly decreased across increasing tertiles of serum 25(OH)D ($P < 0.001$), which suggested that patients with a lower serum 25(OH)D level had a worse kidney outcome. More specifically, in pairwise comparison using the Log-rank test, the *P*-value was 0.001 (the lowest vs. middle tertile), and < 0.001 (the lowest vs. highest tertile), respectively. The difference in risk between middle and high tertile groups did not reach statistical significance. The association between the 25(OH)D level and risks for secondary outcome was

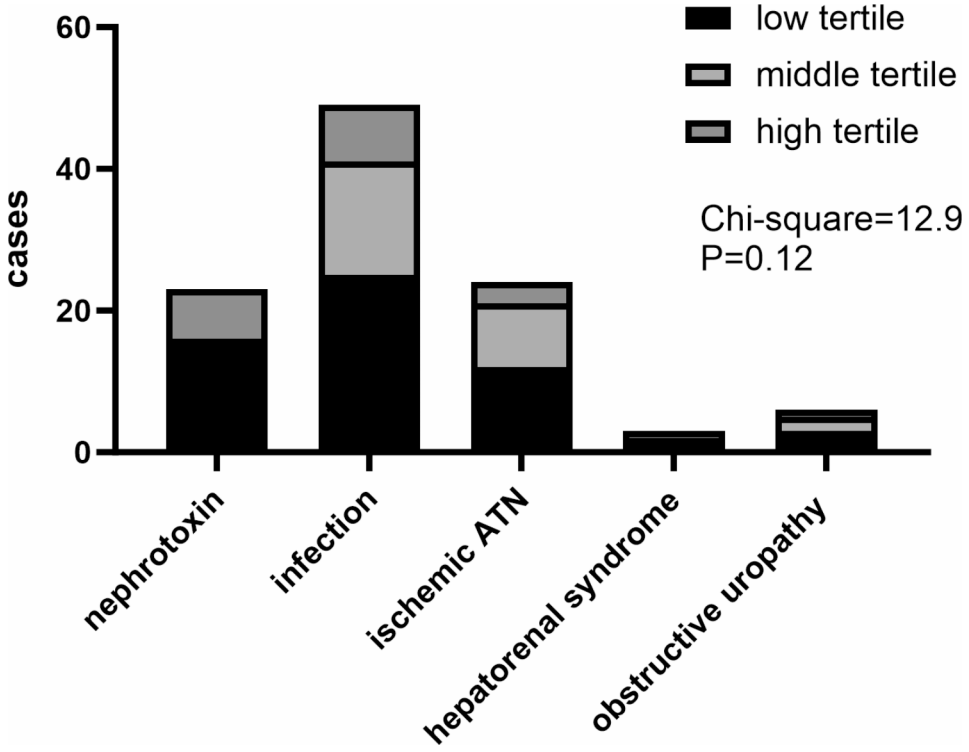

Fig. 1 The distribution of 25(OH)D tertiles in different groups according to AKI etiology. No significant differences were found

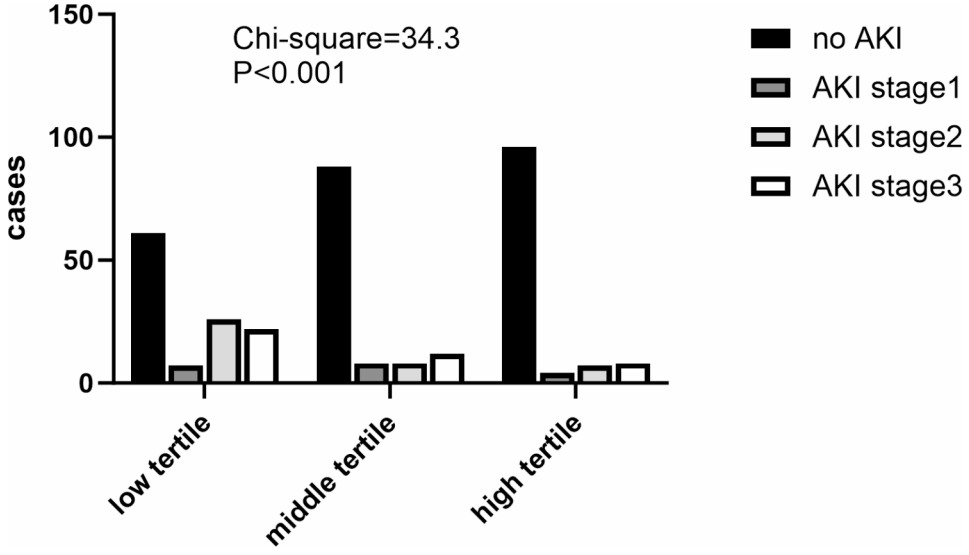

Fig. 2 The distribution of different stages of AKI among groups. Compared to the middle and high tertile, patients in the low tertile had the highest rate of stage 3 AKI (22 cases in the low tertile group, 12 and 8 cases in the middle and high tertile group, respectively; $P < 0.001$)

further determined by the Cox proportional hazards regression model (Table 2). After adjustment of baseline eGFR, Hb, blood pressure, previous AKI, CKD complication, treatment with SGLT2 inhibitor, RAS blocker and vitamin D analogues, we observed a significantly decreased risk of dialysis in the middle and high tertile of the serum 25(OH)D level (HR = 0.15; 95% CI 0.05–0.46; HR = 0.12; 95% CI 0.03–0.42, respectively) compared with the low tertile of the serum 25(OH)D level. Similar trends were found after excluding participants without history of chronic kidney disease (Supplemental Table 1).

The associations between baseline 25(OH)D level and clinical outcomes of ESRD or mortality in AKI patients

To further evaluate the potential impact of serum 25(OH)D on long-term renal complications and survival

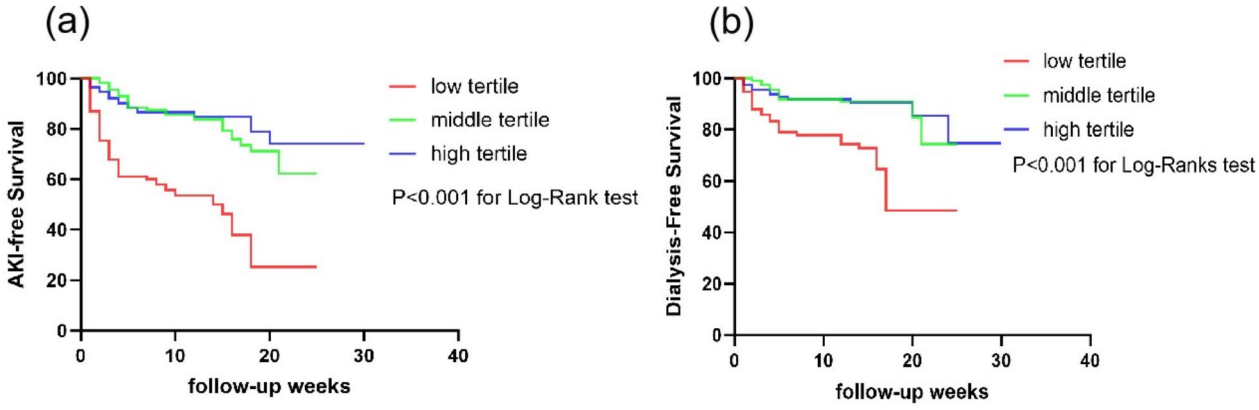

Fig. 3 The risk for AKI and dialysis in strata of tertiles of the serum 25(OH)D levels. (**a**) Kaplan–Meier analysis showed that time-to-AKI was significantly shorter for patients in the low tertile compared to patients in the middle and the high tertile group ($p < 0.001$). (**b**) The cumulative incidence of dialysis significantly decreased in the middle and the high tertile group ($P < 0.001$)

Table 2 Multivariate Cox regression for predicting the primary endpoint (AKI) and secondary endpoint (need-of dialysis)

variables	Primary endpoint		Secondary endpoint	
	HR(95%CI)	*P*	HR(95%CI)	*P*
Tertile of 25(OH)D				
Low(reference)	1.00		1.00	
Middle	0.25(0.14–0.46)	< 0.001	0.15(0.05–0.46)	< 0.001
High	0.24(0.13–0.44)	< 0.001	0.12(0.03–0.42)	< 0.001
Baseline eGFR	0.98(0.95–1.01)	< 0.001	0.99(0.95–1.03)	0.11
Hb	0.99(0.97–1.08)	0.33	0.97(0.95–0.99)	0.009
Previous AKI	5.08(2.72–9.51)	< 0.001	3.83(1.19–12.36)	0.03
CKD complication	22.54(5.45–93.28)	< 0.001	5.36(1.13–25.45)	0.04

eGFR was estimated using the MDRD equation. The covariates considered for adjustment included sex, age, BMI, blood pressure, ALB, baseline eGFR, Hb, HbA1c, previous AKI history, CKD complication, treatment with SGLT2 inhibitor, RAS blocker and vitamin D analogues

in AKI patients, we followed up the 105 AKI patients for 6 months and dichotomized them based on their baseline serum concentration of 25(OH)D, into two groups: levels of 25(OH)D < 15 ng/ml vs. 15 ng/ml or greater, which is the thresholds for 25(OH)D deficiency. During a median follow-up time of 25 weeks, 8 patients had renal function recovered and stopped dialysis. The composite endpoint of ESRD or all-cause death was reached by 20 patients with 25(OH)D deficiency (46.5%) and 17 patients without (27.4%). The causes of death were as follows: severe infection (two patients), gastrointestinal bleeding (one patient), heart failure (one patient), and myocardial infarction (one patient). Kaplan-Meier survival curves for the composite endpoint are shown in Fig. 4. Significantly higher composite endpoint survival was observed in patients with 25(OH)D ≥ 15ng/mL($P = 0.015$). Figure 5 shows the results of the Cox regression analysis. Hazard ratios were adjusted for age, gender, baseline eGFR, systolic blood pressure, use of insulin, infection, chronic heart failure, and previous AKI history. The results showed that patients with 25(OH)D deficiency were associated with a higher risk for ESRD or all-cause death (HR, 4.24; 95% CI, 1.80 to 9.97, $P < 0.001$).

Discussion

In this study, we mainly analyzed the relationship between the 25(OH)D level and the risk of AKI in patients with diabetes mellitus, as well as the impact of 25(OH)D level on the progression of AKI. We identified that low 25 (OH) vitamin D is associated with a higher risk of AKI and need-of dialysis in patients with diabetes mellitus. Furthermore, AKI patients with 25(OH)D deficiency had a higher risk for ESRD or all-cause death.

Vitamin D deficiency and insufficiency is a global health issue that afflicts more than one billion children and adults worldwide [18]. It is worth noting that vitamin D deficiency is one of the factors accelerating insulin resistance formation and has been linked to the onset of diabetes [19]. Vitamin D deficiency or insufficiency is highly prevalent among patients with diabetes [20]. The Endocrine Society recommends that vitamin D level be maintained at least above 75 nmol/L (30 ng/mL), and preferably between 100 and 150 nmol/L (40–60 ng/mL) [21]. In our study, the average level of 25(OH)D is 22.33 ± 8.8ng/mL, which is significantly lower than the recommended level. Cumulative evidence suggests an association of a low 25(OH)D level with clinical

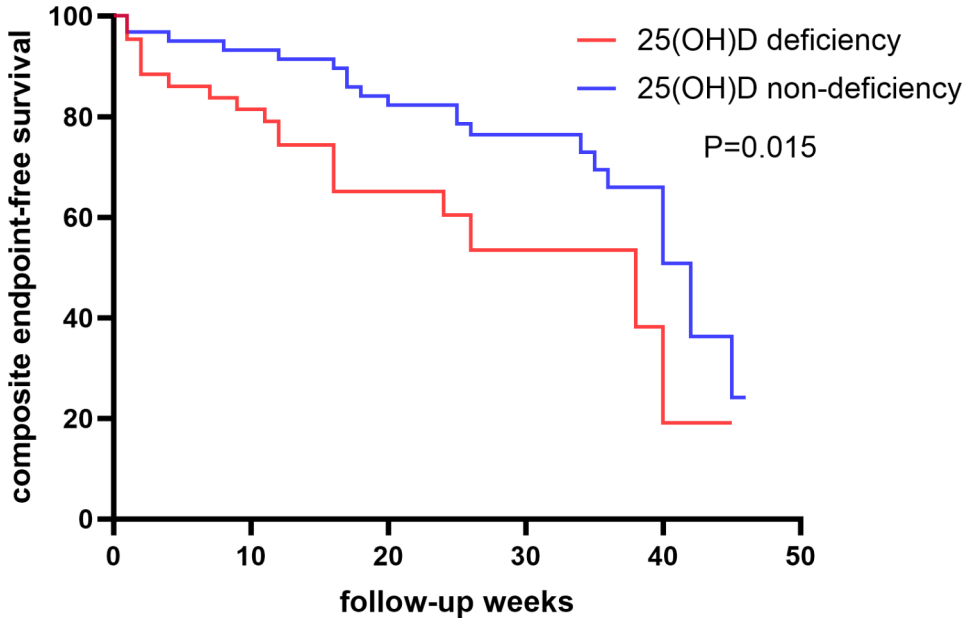

Fig. 4 Kaplan Meier survival curves for the composite end point (ESRD or all-cause death) comparing AKI patients with 25(OH) vitamin D deficiency (< 15 ng/ml) to those with 25(OH) vitamin D levels ≥ 15 ng/ml. Significantly higher composite endpoint survival was observed in patients with 25(OH) D ≥ 15ng/mL(*P* = 0.015)

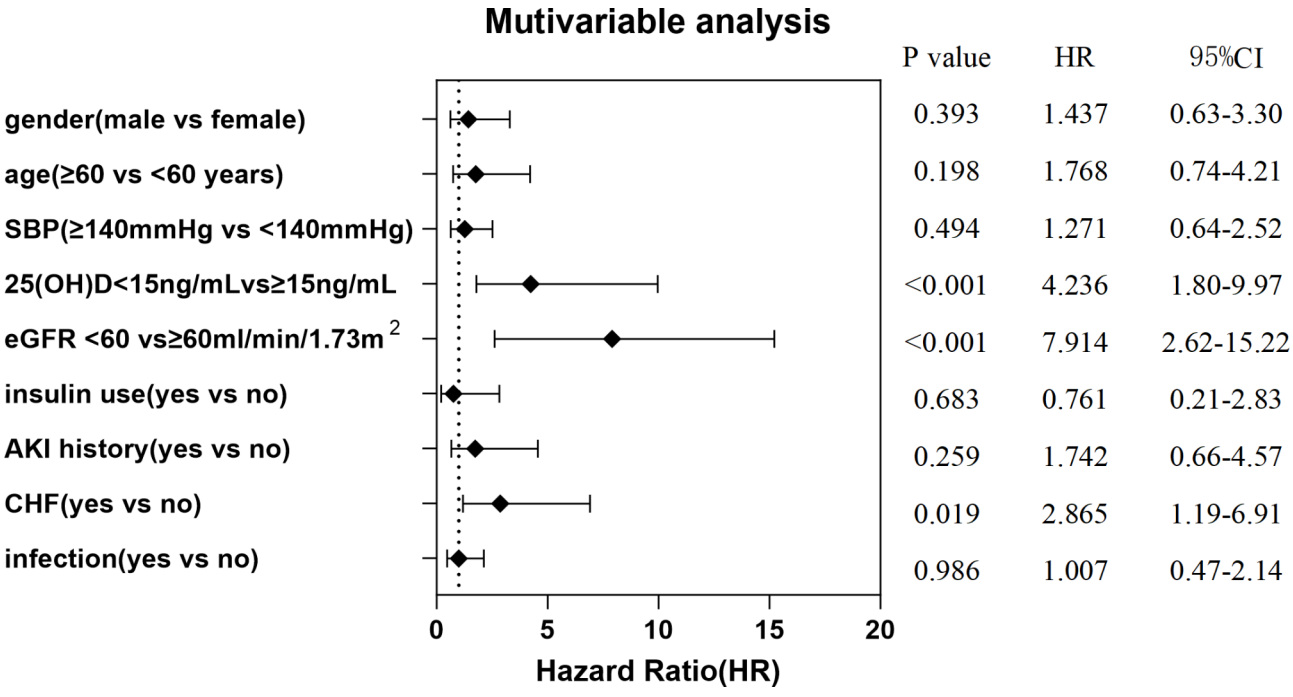

Fig. 5 Association of the serum 25(OH)D levels with HR of composite end point (ESRD or all-cause death). Cox regression analysis showed that patients with 25(OH)D deficiency were associated with a higher risk for ESRD or all-cause death after adjusting for age, gender, baseline eGFR, systolic blood pressure, use of insulin, infection, chronic heart failure, and previous AKI history. eGFR, estimated glomerular filtration rate; SBP, systolic blood pressure; CHF, chronic heart failure

parameters related to kidney damage. For example, Ravani et al. found that the baseline level of 25(OH)D was directly and significantly correlated with eGFR [12]. Furthermore, vitamin D deficiency was linked to vascular calcification, vascular endothelial function, cardiovascular events, and cardiovascular mortality [22, 23]. The large NHANES (National Health and Nutrition Examination Survey) III cross-sectional study revealed an inverse

relationship between 25(OH)D levels and blood pressure after adjusting for common confounders [24]. Moreover, in observational studies, lower 25(OH)D concentrations were associated with infectious disease. For example, Mehmet et al. found that vitamin D deficiency may increase the risk of COVID-19 infection and the likelihood of severe disease [25]. Our observations at baseline revealed that patients with low 25(OH)D level tended to have higher blood pressure, higher NT-pro BNP, lower eGFR, and were more likely to have infection and chronic heart failure at baseline, which are consistent with these previous reports. Given that cardiovascular disease and infections are highly prevalent and account for the major reasons of death among patients of diabetes, we advocate future studies evaluating the association of 25(OH)D level with the primary endpoint of cardiovascular diseases or infections in this population.

Despite the intensive research efforts of recent years, there are no effective treatments specifically for AKI beyond supportive care. This inertia has prompted the well-known International Society of Nephrology's 0 by 25 initiative, which aims to zero preventable deaths from AKI by 2025 [26]. The initiative stresses the delineation of AKI under the "5 Rs," i.e., risk assessment, recognition, response, renal support, and rehabilitation. For the risk assessment, several risk factors such as age, higher BMI, pre-existing CKD, hypertension, higher HbA1c, using angiotensin-converting enzyme inhibitors or angiotensin II receptor blockers (ACEIs/ARBs) or other comorbid conditions were demonstrated to be associated with the occurrence of AKI in DM. In our study, we identified that 25 (OH) vitamin D deficiency is an independent risk factor of AKI and is predictive of the need for dialysis in patients with diabetes mellitus. Sensitivity analysis excluding the patients without CKD showed similar trends. Similarly, Andrea et al. found deficiency of 25-hydroxyvitamin D prior to hospital admission is a significant predictor of acute kidney injury and mortality in a critically ill patient population [13]. Moreover, a large-scale, prospective study including 413,169 UK adults showed serum 25(OH)D concentrations was inversely associated with new-onset AKI, independent of genetic risks for kidney diseases [27]. A meta-analysis [28] suggested that serum $1,25(OH)_2D$ levels, rather than 25(OH)D, is significantly lower in AKI patients than in those without AKI, which is inconsistent with our study. However, 1,25(OH)2D is less often measured in the clinical practice due to its short half-life, so as in our center. We think 25(OH)D is more acceptable for clinical reference. Furthermore, the population included in our study are the patients with diabetics, while the population included in the meta-analysis are diverse. This may partially explain the inconsistence of the results. To the best of our knowledge, this is the first study evaluating this issue in the diabetes population. Since vitamin D deficiency is easily modifiable and nutritional vitamin D is cost-effective, our conclusions, if validated, would facilitate the economic management of diabetes to some extent.

AKI episodes are linked to a cumulative risk of developing advanced CKD and increased mortality in DM, independent of other major risk factors of CKD progression. Our previous study including 916 AKI in DM patients, showed that 66.8% did not recover kidney function at 90 days [29]. Some studies found that vitamin D deficiency can exacerbate pre-existing AKI by deteriorating the renal vascular condition, and it can accelerate the AKI-to-CKD progression via both an increased TGF-β1 signaling and a decreased VDR and Klotho [30]. Braun et al. found that 25(OH)D can act as an independent prognostic biomarker of 30-day mortality [13]. Similarly, Zapatero et al. showed that lower levels of serum 25(OH)D were more common in non-survivor AKI patients, indicating serum 25(OH)D acted as a prognostic biomarker of mortality (best cutoff value = 10.9 ng/ml) [31]. In our study, we identified that patients in the low tertile of 25(OH)D had the highest rate of stage 3 AKI. 25(OH)D deficiency is associated with a higher risk for the composite clinical endpoint of all-cause death or ESRD in patients with AKI. This predictability is not only independent of other important risk factors relevant to renal progression but is also unaffected by infection, chronic heart failure, and previous AKI history. There is plenty of evidence that supports the idea that vitamin D supplementation can help improve the prognosis of patients with CKD [32]. However, we still have limited information on how vitamin D supplementation can affect the clinical outcomes of patients with AKI. Xu et al. studied the effect of pre-treatment with VitD on liposaccharide (LPS)-induced AKI mice and found that it can attenuate AKI through an anti-oxidative mechanism via increasing glutathione (GSH), superoxide dismutase (SOD)-1, and SOD-2 and via decreasing nitric oxide synthase (iNOS), p47phox, and gp91phox (subunits of renal NADPH oxidase) and an anti-apoptotic mechanism [33]. Although VitD seems to ameliorate AKI, its administration should be performed with extreme caution. Hypervitaminosis D can significantly afflict kidney function by inducing hypercalcemia and hyperphosphatemia. Therefore, we urge researchers to conduct future studies that focus on determining the therapeutic protocols of vitamin D as a treatment for AKI and its potential adverse effects.

Limitations of the current study need to be mentioned. First, our study is an retrospective observational study. We may have less control over variables compared to prospective studies, thus impacting the validity of conclusions, and causality cannot be inferred. The patients included in our study were hospitalized patients, and quite a number of them were complicated with infection

and heart failure (two of the main causes of hospitalization for diabetics), thus, selection bias may be present. The conclusions may not be applicable to broader DM populations due to specific sample characteristics. Second, despite adjustment for multiple potential confounders, residual confounding of unmeasured variables might lead to observed differences in outcomes. Specifically, vitamin D deficiency may simply be a reflection of the overall poor condition of the patient, for which we cannot fully adjust. Third, serum 25(OH)D was only assessed at baseline. More frequent measurements of 25(OH)D concentrations would have allowed a more accurate assessment of its long-term effects. A well-designed prospective study should be conducted to evaluate the time-weighted average (TWA) of the serum 25(OH)D level to reinforce the findings. Finally, our study did not address the vitamin D treatment effect, thus an adequately powered randomized controlled trial should be designed to determine whether 25(OH) vitamin D therapy is able to reduce the risk of AKI and improve the long-term outcomes in patients with DM.

Conclusion

Our data suggested that low 25 (OH) vitamin D is associated with a higher risk of AKI and is predictive need for dialysis in patients with diabetes mellitus. AKI patients with 25(OH)D deficiency were associated with a higher risk for ESRD or all-cause death. We call for further prospective studies and trials to: (1) determine the relation between 25 (OH) vitamin D and cardiovascular disease and infection in patients with diabetes, (2) find the best cutoff points with the most significant statistic importance, and (3) determine the therapeutic protocols of vitamin D as treatment of AKI and its potential adverse effects.

Abbreviations

25(OH)D	25-hydroxy-vitamin D
AKI	Acute kidney injury
ALB	Albumin
BMI	Body mass index
BP	Blood pressure
CHF	Chronic heart failure
DM	Diabetes mellitus
eGFR	Estimated glomerular filtration rate
ESRD	End-stage renal disease
FBG	Fasting blood glucose
Hb	Hemoglobin
HbA1c	Glycosylated hemoglobin
NT-pro	BNP N-Terminal Pro-Brain Natriuretic Peptide
PBG	Postprandial blood glucose
RAS	Renin-angiotensin system
RRT	Renal replacement therapy
SGLT2	Sodium-glucose co-transporter 2
WBC	White blood cell

Supplementary Information

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Supplementary Material 1

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Author contributions

LXH and LYZ are the first authors who were involved in the study design, analysis and interpretation of the data and in the writing of the report. MMQ and GTY acquired the data and participated in the interpretation of the data. YZH, PL are the corresponding authors who revised the article critically for important intellectual content. All authors reviewed the manuscript.

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Data availability

The datasets analyzed in the current study are not publicly available to ensure privacy of research participants and comply with regulations of the ethics approval. The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate

This study was approved by the Ethics Committee of the First Affiliated Hospital of Guangxi Medical University [Approval number: 2019(KY-E028)].

Consent for publication

Not applicable.

Competing interests

The authors declare no competing interests.

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References

1. Sun H, Saeedi P, Karuranga S, Pinkepank M, Ogurtsova K, Duncan BB, Stein C, Basit A, Chan JCN, Mbanya JC, et al. IDF diabetes atlas: global, regional and country-level diabetes prevalence estimates for 2021 and projections for 2045. Diabetes Res Clin Pract. 2022;183:109119.
2. Hertzberg D, Sartipy U, Holzmann MJ. Type 1 and type 2 diabetes mellitus and risk of acute kidney injury after coronary artery bypass grafting. Am Heart J. 2015;170(5):895–902.
3. Pavkov ME, Harding JL, Burrows NR. Trends in hospitalizations for acute kidney injury - United States, 2000–2014. MMWR Morb Mortal Wkly Rep. 2018;67(10):289–93.
4. Harding JL, Li Y, Burrows NR, Bullard KM, Pavkov ME. US trends in hospitalizations for dialysis-requiring acute kidney injury in people with versus without diabetes. Am J Kidney Dis. 2020;75(6):897–907.
5. Monseu M, Gand E, Saulnier PJ, Ragot S, Piguel X, Zaoui P, Rigalleau V, Marechaud R, Roussel R, Hadjadj S, et al. Acute kidney injury predicts major adverse outcomes in diabetes: synergic impact with low glomerular filtration rate and albuminuria. Diabetes Care. 2015;38(12):2333–40.
6. Shi N, Liu K, Fan Y, Yang L, Zhang S, Li X, Wu H, Li M, Mao H, Xu X, et al. The association between obesity and risk of acute kidney injury after cardiac surgery. Front Endocrinol (Lausanne). 2020;11:534294.
7. Hertzberg D, Sartipy U, Lund LH, Rydén L, Pickering JW, Holzmann MJ. Heart failure and the risk of acute kidney injury in relation to ejection fraction in patients undergoing coronary artery bypass grafting. Int J Cardiol. 2019;274:66–70.

8. Bouillon R, Marcocci C, Carmeliet G, Bikle D, White JH, Dawson-Hughes B, Lips P, Munns CF, Lazaretti-Castro M, Giustina A, et al. Skeletal and extraskeletal actions of vitamin D: current evidence and outstanding questions. Endocr Rev. 2019;40(4):1109–51.
9. Grammatiki M, Rapti E, Karras S, Ajjan RA, Kotsa K. Vitamin D and diabetes mellitus: causal or casual association? Rev Endocr Metab Disord. 2017;18(2):227–41.
10. Graidis S, Papavramidis TS, Papaioannou M. Vitamin D and acute kidney injury: a two-way causality relation and a predictive, prognostic, and therapeutic role of vitamin D. Front Nutr. 2020;7:630951.
11. Wimalawansa SJ. Associations of vitamin D with insulin resistance, obesity, type 2 diabetes, and metabolic syndrome. J Steroid Biochem Mol Biol. 2018;175:177–89.
12. Ravani P, Malberti F, Tripepi G, Pecchini P, Cutrupi S, Pizzini P, Mallamaci F, Zoccali C. Vitamin D levels and patient outcome in chronic kidney disease. Kidney Int. 2009;75(1):88–95.
13. Braun AB, Litonjua AA, Moromizato T, Gibbons FK, Giovannucci E, Christopher KB. Association of low serum 25-hydroxyvitamin D levels and acute kidney injury in the critically ill. Crit Care Med. 2012;40(12):3170–9.
14. Sahin I, Gungor B, Can MM, Avci II, Guler GB, Okuyan E, Biter H, Yildiz SS, Ayca B, Satilmis S, et al. Lower blood vitamin D levels are associated with an increased incidence of contrast-induced nephropathy in patients undergoing coronary angiography. Can J Cardiol. 2014;30(4):428–33.
15. Ishigami J, Grams ME, Michos ED, Lutsey PL, Matsushita K. 25-hydroxyvitamin D, fibroblast growth factor 23, and risk of acute kidney injury over 20 years of follow-up. Kidney Int Rep. 2021;6(5):1299–308.
16. Stevens PE, Levin A. Evaluation and management of chronic kidney disease: synopsis of the kidney disease: improving global outcomes 2012 clinical practice guideline. Ann Intern Med. 2013;158(11):825–30.
17. Alberti KG, Zimmet PZ. Definition, diagnosis and classification of diabetes mellitus and its complications. Part 1: diagnosis and classification of diabetes mellitus provisional report of a WHO consultation. Diabet Med. 1998;15(7):539–53.
18. Holick MF. The vitamin D deficiency pandemic: approaches for diagnosis, treatment and prevention. Rev Endocr Metab Disord. 2017;18(2):153–65.
19. Vondra K, Hampl R. Vitamin D and new insights into pathophysiology of type 2 diabetes. Horm Mol Biol Clin Investig. 2021;42(2):203–8.
20. Nasr MH, Hassan BAR, Othman N, Karuppannan M, Abdulaziz NB, Mohammed AH, Alsarani MA, Eskembaji MH, Aman AM, Othman G. Prevalence of vitamin D deficiency between type 2 diabetes mellitus patients and non-diabetics in the Arab Gulf. Diabetes Metab Syndr Obes. 2022;15:647–57.
21. Holick MF, Binkley NC, Bischoff-Ferrari HA, Gordon CM, Hanley DA, Heaney RP, Murad MH, Weaver CM. Evaluation, treatment, and prevention of vitamin D deficiency: an endocrine society clinical practice guideline. J Clin Endocrinol Metab. 2011;96(7):1911–30.
22. Wang AY, Lam CW, Sanderson JE, Wang M, Chan IH, Lui SF, Sea MM, Woo J. Serum 25-hydroxyvitamin D status and cardiovascular outcomes in chronic peritoneal dialysis patients: a 3-y prospective cohort study. Am J Clin Nutr. 2008;87(6):1631–8.
23. Wolf M, Shah A, Gutierrez O, Ankers E, Monroy M, Tamez H, Steele D, Chang Y, Camargo CA Jr., Tonelli M, et al. Vitamin D levels and early mortality among incident hemodialysis patients. Kidney Int. 2007;72(8):1004–13.
24. Scragg R, Sowers M, Bell C. Serum 25-hydroxyvitamin D, ethnicity, and blood pressure in the Third National Health and Nutrition Examination Survey. Am J Hypertens. 2007;20(7):713–9.
25. Kaya MO, Pamukçu E, Yakar B. The role of vitamin D deficiency on COVID-19: a systematic review and meta-analysis of observational studies. Epidemiol Health. 2021;43:e2021074.
26. Mehta RL, Cerdá J, Burdmann EA, Tonelli M, García-García G, Jha V, Susantitaphong P, Rocco M, Vanholder R, Sever MS, et al. International Society of Nephrology's 0by25 initiative for acute kidney injury (zero preventable deaths by 2025): a human rights case for nephrology. Lancet. 2015;385(9987):2616–43.
27. Zhou C, Ye Z, Yang S, Gan X, Zhang Y, Liu M, He P, Zhang Y, Wu Q, Nie J, et al. Associations between serum 25-hydroxyvitamin D, sun exposure time, dietary vitamin D intake, and new-onset acute kidney injury among 413,169 UK adults. J Nutr. 2023;153(3):713–22.
28. Zhang H, Jiang Y, Shi N, Lu YQ. Serum vitamin D levels and acute kidney injury: a systemic review and meta-analysis. Sci Rep. 2022;12(1):20365.
29. Mo M, Pan L, Huang Z, Liang Y, Liao Y, Xia N. Development and validation of a prediction model for survival in diabetic patients with acute kidney injury. Front Endocrinol (Lausanne). 2021;12:737996.
30. Gonçalves JG, de Bragança AC, Canale D, Shimizu MH, Sanches TR, Moysés RM, Andrade L, Seguro AC, Volpini RA. Vitamin D deficiency aggravates chronic kidney disease progression after ischemic acute kidney injury. PLoS ONE. 2014;9(9):e107228.
31. Zapatero A, Dot I, Diaz Y, Gracia MP, Pérez-Terán P, Climent C, Masclans JR, Nolla J. Severe vitamin D deficiency upon admission in critically ill patients is related to acute kidney injury and a poor prognosis. Med Intensiva (Engl Ed). 2018;42(4):216–24.
32. Wang Y, Yang S, Zhou Q, Zhang H, Yi B. Effects of vitamin D supplementation on renal function, inflammation and glycemic control in patients with diabetic nephropathy: a systematic review and meta-analysis. Kidney Blood Press Res. 2019;44(1):72–87.
33. Xu S, Chen YH, Tan ZX, Xie DD, Zhang C, Xia MZ, Wang H, Zhao H, Xu DX, Yu DX. Vitamin D3 pretreatment alleviates renal oxidative stress in lipopolysaccharide-induced acute kidney injury. J Steroid Biochem Mol Biol. 2015;152:133–41.

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