Dexmedetomidine on the Prognosis of Patients With Sepsis-related Acute Kidney Injury

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Keywords. dexmedetomidine, sepsis, acute kidney injury, mortality, intensive care

Introduction. To investigate the effect of dexmedetomidine (DEX) on the prognosis and renal function recovery in patients with sepsis-associated AKI (SA-AKI).

Methods. A prospective observational study was conducted, enrolling patients with SA-AKI admitted to the ICU of Suzhou Municipal Hospital from July 2021 to June 2023. Patients were divided into a DEX group and a non-DEX group according to the sedation regimen.

Results. After matching, a total of 204 patients (102 in each group) were included, with balanced baseline (SMD < 10%). The primary endpoint: DEX significantly reduced the risk of 28-day mortality (adjusted HR = 0.556, 95% CI:0.317 to 0.975; *P* = .041), with a particularly significant benefit in patients with non-septic shock (HR = 0.372, *P* = .016) and AKI stage 1 (HR = 0.375, *P* = .035). Secondary endpoints: DEX significantly improved the rate of renal function recovery (adjusted OR = 2.841, 95% CI:1.427 to 5.656; *P* = .003), and the efficacy was modified by AKI stage (*P-interaction* = .005) and shock status (*P-interaction* = .006). The benefit was most prominent in patients with AKI stage 1 (*P* = .009) ; the benefit was clear in patients with non-septic shock (*P* = .011). There was a strong trend toward benefit in patients with septic shock (*P* = .054). There was no difference in ICU length of stay between the two groups (*P* > .05).

Conclusions. DEX significantly improves survival and promotes renal function recovery in patients with SA-AKI, particularly in patients with stage 1 AKI and non-septic shock. The potentially significant benefit observed in patients with septic shock warrants further validation in a larger sample.

RJCCN 2025; 1: 33-44
www.rjccn.org
DOI: 10.61882/rjccn.1.1.14

INTRODUCTION

Acute kidney injury (AKI) is a clinical syndrome characterized by an acute decline in renal function. Over the past few decades, the incidence of AKI has increased, reaching 20 to 35 % among hospitalized patients[1,2] and even higher in the intensive care unit (ICU), at approximately 40 to 60 %.[3,4] Sepsis is the cause of 40 to 70% of ICU AKI patients,[5,6] termed sepsis-associated acute kidney injury (SA-AKI). The mortality rate for these patients further increases to 30 to 60%, and hospital stays are also prolonged.[7,8]

Please cite this article as: Sixuan Z, Yanlin S, Yue Z, Biying Z, Aixiang Y. Dexmedetomidine on the Prognosis of Patients With Sepsis-related Acute Kidney Injury. RJCCN 2025; 1(1): 33-44

Dexmedetomidine (DEX) is a highly selective α2 receptor agonist and a widely used sedative and analgesic drug in the ICU. DEX also has anti-inflammatory, anti-oxidative stress, and apoptosis-reducing properties, and its renal protective effects have been confirmed in animal studies.[9-12] In recent years, clinical studies examining the protective effects of DEX on renal outcomes have begun, primarily in small cohort or retrospective studies.[13-14] However, high-quality prospective randomized controlled trials examining the effects of DEX on the prognosis of patients with SA-AKI are lacking. Therefore, this study aimed to investigate the effects of DEX on prognosis and renal function recovery in patients with SA-AKI through a prospective study.

MATERIALS AND METHODS

Prospective, observational study was used as the study design and ethics committee . This study was approved by the Ethics Committee of Suzhou Municipal Hospital (approval number: K-2021-GSKY20210201) and registered in the National Medical Research Registration and Filing Information System (registration number: MR-32-22-002262).

The research subjects included SA-AKI patients admitted to the ICUs of the three campuses of our hospital from July 2021 to June 2023 who agreed to participate in this study, and their families signed informed consent.

AKI diagnostic criteria: According to the 2012 KDIGO guidelines, AKI is diagnosed when one of the following three conditions is met: 1) Serum creatinine (SCr) increases by ≥ 0.3 mg/dL (≥ 26.5 μmol/L) within 48 hours; 2) SCr increases by ≥ 50% compared with the baseline value within 7 days; 3) Urine volume decreases [< 0.5 mL/(kg*h), lasting ≥ 6 hours].[2]

Diagnostic criteria for sepsis

Meet the following two conditions: 1) infection; 2) SOFA score ≥ 2 points.[15]

Diagnostic criteria for SA-AKI

Meeting both the diagnostic criteria for Sepsis and AKI.[6]

Inclusion Criteria

1) Age ≥ 18 years; 2) ICU hospitalization time ≥ 24 hours; 3) Meet the diagnostic criteria for SA-AKI; 4) Require sedation; 5) Have a physical examination or outpatient or inpatient renal function test report within 1 year before admission.

Exclusion Criteria

1) Chronic renal failure; 2) Bradycardia, II or III degree atrioventricular block; 3) Acute myocardial infarction, severe heart failure (NYHA grade 4); 4) Chronic liver failure (Child-Pugh B and C); 5) Drug addicts; alcohol addicts; 6) Mentally disabled patients; 7) Pregnant and lactating women.

Study Groups This study was divided into DEX group and non-DEX group; In the DEX group, a maintenance dose of 0.2 to 0.7 $\mu g \cdot kg^{-1} \cdot h^{-1}$ was used in addition to conventional treatment, while in the non-DEX group, midazolam or propofol was used as sedative in addition to conventional treatment.

Data collected included gender, age, underlying diseases, type of ICU admission, primary infection site, APACHE II score, SOFA score, heart rate (HR), mean arterial pressure (MAP), white blood cell (WBC), high-sensitivity C-reactive protein (CRP), interleukin-6 (IL-6), procalcitonin (PCT), arterial lactate, albumin, alanine aminotransferase (ALT), blood urea nitrogen (BUN), creatinine (SCr), cystatin C, neutrophil gelatinase-associated lipocalin (NGAL), eGFR, mechanical ventilation (MV), continuous renal replacement therapy (CRRT), nephrotoxic drugs, vasoactive drugs, bacteremia, septic shock and AKI stage, 28-day survival, ICU stay time, and renal function recovery. Renal function recovery was defined as creatinine recovery to less than 1.5 times the baseline creatinine level or urine output > 0.5 mL/(kg*h).[13]

Statistical analysis was performed using STATA 18.0 software. Intergroup comparisons were performed using the chi-^{square} test or Fisher's exact test. Normally distributed quantitative data were expressed as mean ± standard deviation (x ± s), and t -tests or t' tests were performed depending on homogeneity of variance. Data with non-normal distribution, as confirmed by the Shapiro-Wilk test, were expressed as medians (interquartile ranges). Intergroup comparisons were performed using the Wilcoxon rank-sum test or the Kruskal-Wallis test. Propensity score matching (PSM) was

performed to minimize the influence of confounding factors. A 1:1 nearest neighbor matching algorithm with a caliper width of 0.01 was used without replacement. Variables with *a P* < .05 and factors strongly associated with disease severity and treatment decision-making were selected to generate propensity scores. Standardized mean differences (SMDs) were calculated to evaluate the efficacy of PSM in reducing intergroup differences. Cox regression, linear regression plus bootstrap, and logistic regression were used to analyze the effects of dexmedetomidine on 28-day mortality, ICU length of stay, and renal function recovery, respectively. All continuous variables were included in the models using their original units. Multivariate logistic regression with interaction terms (DEX × AKI stage, DEX × septic shock status) was used to assess heterogeneity in efficacy. Adjusted odds ratios (ORs) for stratified efficacy were calculated using linear combination analysis (LINCOM). *A P value* < .05 was considered statistically significant, and a *P-interaction* value < .05 was considered a significant stage effect.

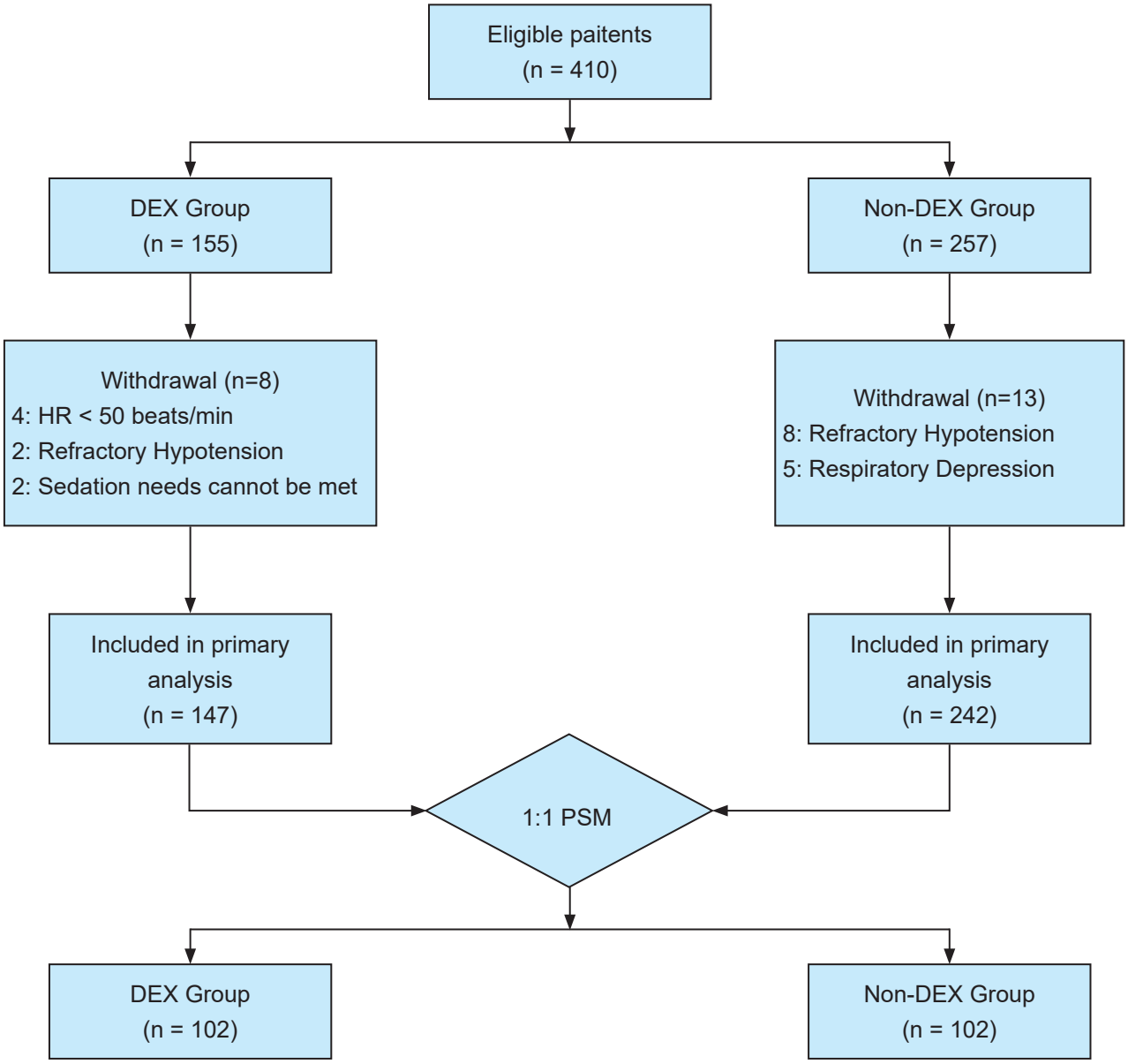

Figure 1. Flowchart of the SA-AKI Patient Study

RESULTS

General Information

A total of 389 patients with SA-AKI were included in the final analysis, with 147 in the DEX group and 242 in the non-DEX group (Figure 1). Of these, 276 were male and 113 were female, with an age range of 71.29 ± 15.81 years, a SOFA score of 6 (4, 8), and an APACHE II score of 21.20 ± 5.03. There were 188 patients with AKI stage 1, 124 with AKI stage 2, and 77 with AKI stage 3. Patient and demographic characteristics and baseline data for the two groups are shown in Table 1. Significant differences in WBC, CRP, PCT, albumin, cystatin C, and NGAL between the two groups were observed ($P < .05$); no other differences were observed between the two groups ($P > .05$) (Table 1).

A total of 389 patients with SA-AKI were included in the final study analysis, including 147 patients in the DEX group and 242 patients in the Non-DEX group. After propensity score matching (1:1 nearest neighbor matching, caliper value = 0.01), 102 pairs of patients were successfully matched (204 cases).

After propensity score matching (1:1 nearest neighbor matching, caliper value = 0.01), 102 pairs of patients were successfully matched (204 patients). Forty-five patients in the DEX group were excluded due to a lack of sufficiently similar controls. After matching, the SMDs for all covariates were < 10% (Figure 2). The Rubin's B value decreased from 98.2% before matching to 27.5%, and the R value improved from 0.81 to 0.89, indicating that matching effectively eliminated baseline confounding. No statistically significant differences were found between the groups (all $P > .05$) (Table 1).

Comparison of Main Observation Indicators of Clinical Data Between the Two Groups

Univariate COX regression analysis compared the 28-day mortality rate between the DEX group and the non-DEX group. The results showed that the 28-day mortality risk in the DEX group was 0.528 times that of the non-DEX group, which means the risk was reduced by 47.2%, and this association was statistically significant ($P = .022$). After adjusting for age, APACHE II score, SOFA score, arterial lactate, MV, and CRRT, multivariate COX regression analysis showed that the 28-day mortality risk in the DEX group was still reduced

Table 1. Baseline Characteristics of Patients with SA-AKI in the Two Groups

Observation indicators	Before PSM			After PSM		
	DEX Group n = 147	Non-DEX group n = 242	*P*	DEX Group n = 102	Non-DEX group n = 102	*P*
Age, y	71.50 ± 17.01	71.15 ± 15.08	.397	71.69 ± 16.75	70.59 ± 14.95	.622
Gender (male), n (%)	99 (67.35)	177 (73.14)	.222	67 (65.69)	72 (70.59)	.452
Underlying diseases, n (%)						
Hypertension	81 (57.45)	137 (56.61)	.874	57 (55.88)	53 (51.96)	.574
Diabetes	57 (40.43)	94 (38.84)	.760	40 (39.22)	37 (36.27)	.665
chronic obstructive pulmonary disease	17 (12.06)	27 (11.16)	.790	12 (11.76)	9 (8.82)	.489
Heart failure	28 (19.86)	46 (19.01)	.688	20 (19.61)	17 (18.14)	.586
Cerebrovascular disease	25 (17.73)	46 (19.01)	.756	17 (16.67)	19 (18.63)	.713
Tumor	8 (5.67)	17 (6.53)	.606	6 (5.88)	7 (6.86)	.774
Type of ICU admission, n (%)			.704			.326
Emergency non-surgical admission	58 (39.46)	98 (40.50)		40 (39.22)	38 (37.25)	
Inpatient non-surgical transfer	51 (34.69)	84 (34.71)		34 (33.33)	37 (36.27)	
Emergency surgery admission	17 (11.56)	34 (14.05)		20 (19.61)	11 (10.78)	
Elective surgery transfer	21 (14.29)	26 (10.74)		14 (13.73)	10 (9.80)	

Table 1. Continued

Observation indicators	Before PSM			After PSM		
	DEX Group n = 147	Non-DEX group n = 242	*P*	DEX Group n = 102	Non-DEX group n = 102	*P*
Primary infection site, n (%)			.351			.100
Lungs	72 (48.98)	112 (46.28)		54 (52.94)	43 (42.16)	
Digestive system	32 (21.77)	42 (17.36)		24 (23.53)	19 (18.63)	
urinary system	19 (12.93)	32 (13.22)		9 (8.82)	14 (13.73)	
Skin and soft tissue	5 (3.40)	14 (5.79)		3 (2.94)	6 (5.88)	
central nervous system	1 (0.68)	9 (3.72)		0 (0.00)	5 (4.90)	
Other	18 (12.24)	33 (13.64)		12 (11.76)	15 (14.71)	
Bacteremia, n (%)	21 (14.29)	40 (16.53	.555	15 (14.71)	15 (14.71)	.555
Septic shock, n (%)	49 (33.33)	89 (36.78)	.491	38 (37.25)	37 (36.27)	.885
SOFA	6 (4,8)	6 (4,8)	.056	6 (4,8)	6 (4,9)	.708
APACHE II	20.89 ± 4.97	21.38 ± 5.07	.347	21.32 ± 5.09	21.44 ± 5.28	.872
Heart rate, beats / min	101 (88,114)	99.5 (83,109)	.105	99.5 (86,112)	103 (88,112)	.607
Mean arterial pressure, mmHg	70 (59,77)	68 (58,77)	.261	70 (58,79)	70 (60,78)	.709
Mechanical ventilation, n (%)	91 (61.90)	157 (64.88)	.554	67 (65.69)	67 (65.69)	.554
CRRT, n (%)	40 (27.21)	67 (27.92)	.880	29 (28.43)	30 (29.41)	.877
Nephrotoxic drug use, n (%)			.983			.893
Vancomycin	15 (10.20)	23 (9.50)		9 (8.82)	10 (9.80)	
Polymyxins	6 (4.08)	11 (4.55)		4 (3.92)	4 (3.92)	
contrast agents	5 (3.40)	11 (4.55)		4 (3.92)	6 (5.88)	
Other	5 (3.40)	8 (3.31)		3 (2.94)	5 (4.90)	
Vasoactive drugs, n (%)	49 (33.33)	89 (36.78)	.491	38 (37.25)	37 (36.27)	.885
WBC, × 10^9/L	13.04 ± 4.72	14.10 ± 5.16)	.040	13.52 ± 4.76	13.80 ± 4.92	.696
CRP, mg/L	42.54 ± 6.42	40.42 ± 6.55	.002	41.82 ± 6.02	41.93 ± 6.08	.890
IL-6, pg/mL	99.91 (84.63,110.88)	99.06 (85.69,109.85)	.700	100.56 (87.77,109.98)	97.99 (84.32,110.39)	.446
PCT, ng/mL	5.31 (4.67,6.16)	5.02 (4.31,5.82)	.011	5.20 (4.61,6.01)	5.10 (4.58,5.76)	.426
Lactic acid, mmol/L	4.80 (3.43,6.60)	4.89 (3.41,8.40)	.246	4.89 (3.62,7.10)	4.08 (3.35,7.20)	.327
Albumin, g/L	30.49 (28.50,34.39)	31.67 (29.13,34.98)	.030	30.73 (28.63,34.73)	31.10 (28.25,34.07)	.837
ALT, U/L	56.16 (51.07,61.12)	56.08 (51.28,60.57)	.844	57.019 (52.26,60.76)	56.43 (50.96,60.36)	.424
BUN, mmol/L	9.42 (8.23,11.46)	9.51 (8.20,11.38)	.605	9.22 (8.26, 11.18)	9.18 (7.95,11.20)	.563
Creatinine, μmol/L	149.76 (125.26,203.33)	161.83 (131.63,208.42)	.168	153.46 (130.41,203.56)	160.52 (129.42,208.42)	.858
Cystatin C, mg/L	2.14 (1.68,2.59)	2.30 (1.86,3.47)	.003	2.21 (1.73,2.66)	2.06 (1.68,2.50)	.276
NGAL, ng/mL	206.78 (198.05,215.72)	202.98 (193.47,211.24)	.006	205.38 (196.53,212.61)	203.63 (194.88,212.63)	.673
eGFR, mL/min/ 1.73m^2	38.19 (27.44,47.34)	36.67 (27.43,45.01)	.334	37.00 (26.25,44.41)	37.73 (26.58,46.73)	.955
AKI stage, n (%)			.567			.672
AKI stage 1	76 (51.70)	112 (46.28)		49 (48.04)	50 (49.02)	
AKI stage 2	43 (29.25)	81 (33.47)		35 (34.31)	30 (29.41)	
AKI stage 3	28 (19.05)	49 (20.25)		18 (17.65)	22 (21.57)	

Abbreviations: APACHE II, acute physiology and chronic health evaluation score or acute physiology and chronic health evaluation II score; SOFA, sequential organ failure assessment; CRRT, continuous renal replacement therapy; NGAL, neutrophil gelatinase-associated lipocalin; AKI, acute kidney injury.

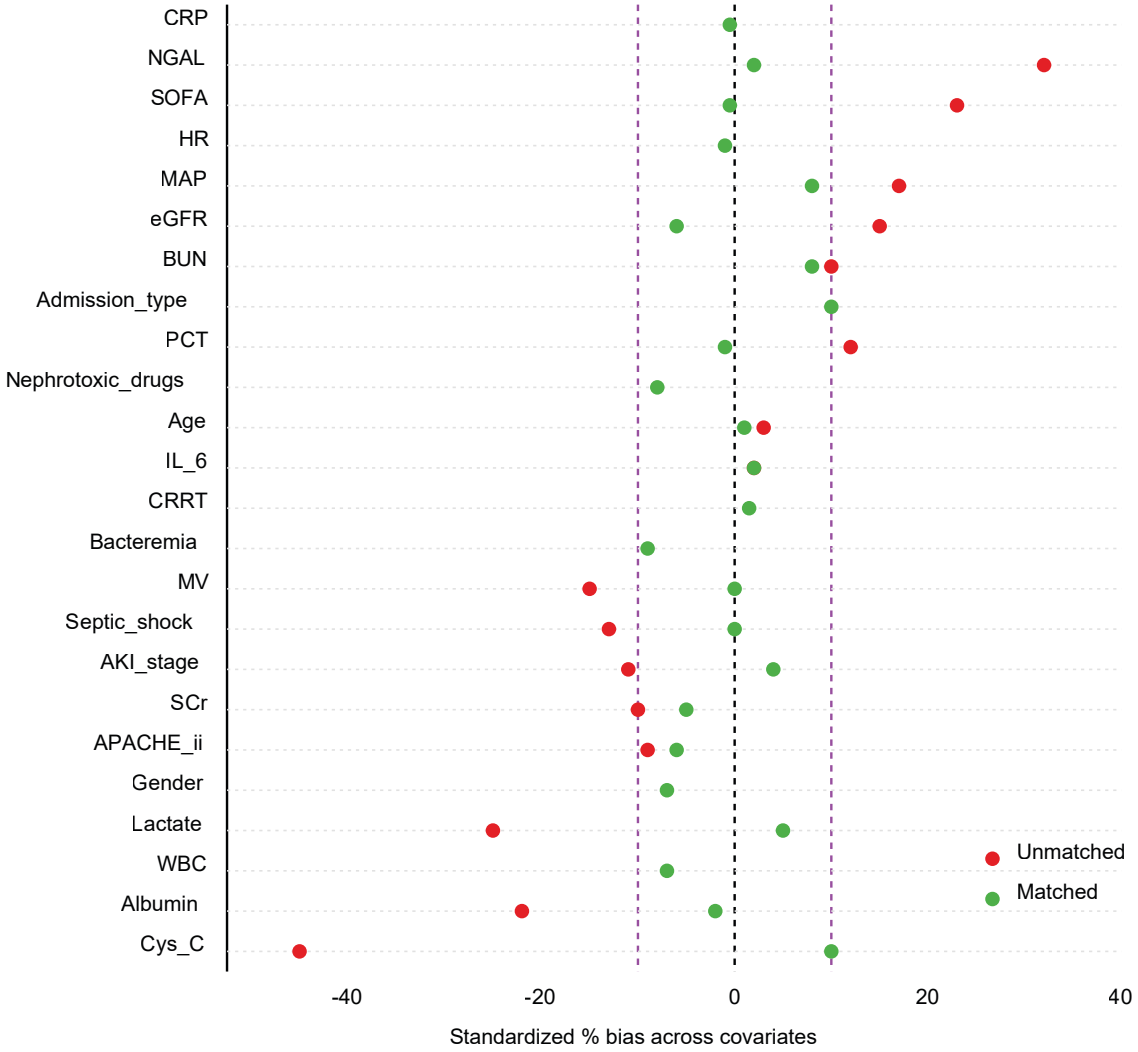

Figure 2. The standardized mean difference between the two groups before and after PSM. After propensity score matching (1:1 nearest neighbor matching, caliper value = 0.01), SMD of all covariates were less than 10%.

(HR = 0.556, 95% CI: 0.317 to 0.975 ; *P* = .041)**.** Linear regression plus bootstrap analysis compared the ICU length of stay between the two groups. No statistically significant difference was found in ICU length of stay between the two groups in either univariate analysis or multivariate analysis with the inclusion of covariates (both *P* > .05). Univariate logistic regression analysis showed that the rate of renal function recovery was significantly higher in patients receiving DEX than in those not receiving it (OR = 2.117, 95% CI: 1.1193 to 3.757; *P* = .001). After adjusting for the above key covariates, multivariate analysis still showed that the favorable association of renal function recovery was further strengthened in the DEX group (OR = 2.841, 95% CI: 1.427 to 5.656; *P* = .003) (Table 2).

Multivariate adjustment analysis revealed differences in 28-day mortality, ICU length of stay, and renal function recovery among subgroups according to AKI clinical stage and the presence or absence of septic shock. Among patients with AKI stage 1, the DEX group had a 62.5 % lower 28-day mortality compared with the non- DEX group (HR = 0.375, 95% CI: 0.151 to 0.931; *P* = .035). There was no statistically significant difference between the two groups in AKI stage 2 and stage 3 (*P* = .461). While DEX did not reduce 28-day mortality in patients with septic shock, the risk of 28 -day mortality in the DEX group was significantly higher at 62.8% in the non-septic

Table 2. Relationship Between Dexmedetomidine and Prognosis of Patients with SA-AKI

Prognostic indicators	Dexmedetomidine group	Non-dexmedetomidine group	Univariate analysis		Multivariate adjustment analysis*	
			Effect size (95% CI)	*P*	Effect size (95% CI)	*P*
Before PSM	n = 147	n = 242				
28-day mortality rate, n (%)	29 (19.73)	77 (31.82)	HR = 0.639 (0.417 to 0.980)	.040	HR = 0.629 (0.386 to 0.1.026)	.063
ICU stay,† d	9.0 (4.00 to 15.00)	9.0 (5.0 to 18.00)	GMR = 0.971 (0.809 to 1.135)	.738	GMR = 0.976 (0.795 to 1.156)	.797
Renal function recovery rate, n (%)	98 (66.67)	138 (57.02)	OR = 1.507 (0.983 to 2.310)	.060	OR = 1.841 (1.035 to 3.275)	.038
After PSM	n = 102	n = 102				
28-day mortality rate, n (%)	19 (18.63)	40 (39.22)	HR = 0.528 (0.306 to 0.913)	.022	HR = 0.556 (0.317 to 0.975)	.041
ICU stay,† d	8.0 (4.00 to 15.00)	8.0 (5.0 to 19.00)	GMR = 0.893 (0.672 to 1.115)	.374	GMR = 0.903 (0.702 to 1.113)	.403
Renal function recovery rate, n (%)	72 (70.59)	53 (51.96)	OR = 2.117 (1.193 to 3.757)	.001	OR = 2.841 (1.427 to 5.656)	.003

Note: Cox regression was used to analyze 28-day mortality; linear regression + Bootstrap was used to analyze ICU stay; and logistic regression was used to analyze renal function recovery rate.
*Adjustment factors: Before PSM, age, sex, SOFA score, APACHE II score, HR, MAP, MV, CRRT, WBC, CRP, PCT, arterial lactate, albumin, BUN, SCr, cystatin C, NGAL, eGFR, and bacteremia, septic shock, and AKI stage were adjusted; after PSM, age, SOFA score, APACHE II score, arterial lactate, MV, and CRRT were adjusted;
†ICU length of stay was skewed and analyzed after natural logarithm transformation. The effect value was the geometric mean ratio (GMR); the 95% CI was calculated using the bootstrap percentile method (1000 replicates).

shock group (HR = 0.372, 95% CI: 0.166 to 0.833; *P* = .016) (Figure 3). There was no statistically significant difference in the ICU length of stay between the two groups at different AKI stages or with or without septic shock (all *P* > .05).

Multivariate COX regression was adjusted to analyze the difference in 28-day mortality between subgroups. The 28-day mortality of AKI stage 1 patients in the DEX group was 62.5% lower than that in the non-DEX group (HR = 0.375, 95% CI: 0.151 to 0.931; *P* = .035). There was no significant difference in AKI stage 2 and AKI stage 3 between the two groups (*P* = .461). For patients with septic shock, DEX did not reduce 28-day mortality, but in the non-septic shock group, the risk of 28-day mortality in the DEX group was 62.8%, and the difference was statistically significant (HR = 0.372, 95% CI: 0.166 to 0.833; *P* = .016) (Figure 4).

Multivariate logistic regression showed that AKI stage significantly modified the effect of DEX on renal function recovery (*P-interaction* = .005). Stratified analysis showed that in patients with AKI stage 1, DEX was independently associated with a significant increase in the rate of renal function recovery (adjusted OR = 4.814, 95% CI: 1.473 to 15.735; *P* = .009); no significant independent effect of DEX was observed in patients with AKI stage 2 (adjusted OR = 1.628, 95% CI: 0.517 to 5.126; *P* = .405); In patients with stage 3 AKI, the point estimate for DEX suggested a potential benefit (adjusted OR = 3.038), but the confidence interval (95% CI: 0.422 to 21.871) was wide and included 1, so the result did not reach statistical significance (*P* = .270). Septic shock status was also a significant modifier of the DEX effect (*P-interaction* = .006). In patients without septic shock, DEX was independently associated with a significantly increased rate of renal function recovery (adjusted OR = 3.048, 95% CI: 1.291 to 7.198; *P* = .011). In patients with septic shock, DEX showed a strong trend toward benefit (adjusted OR = 3.966), but the result was marginally statistically significant (95% CI: 0.978 to 16.079; *P* = .054) (Table 3 and Figure 5).

DISCUSSION

Sepsis-associated acute kidney injury (SA-AKI) is an important driver of high mortality in ICU patients, and its treatment strategy optimization urgently needs breakthroughs. This study systematically

evaluated the effect of dexmedetomidine on the prognosis of SA-AKI patients through a prospective observational design. After PSM correction for confounding, we found that : DEX significantly

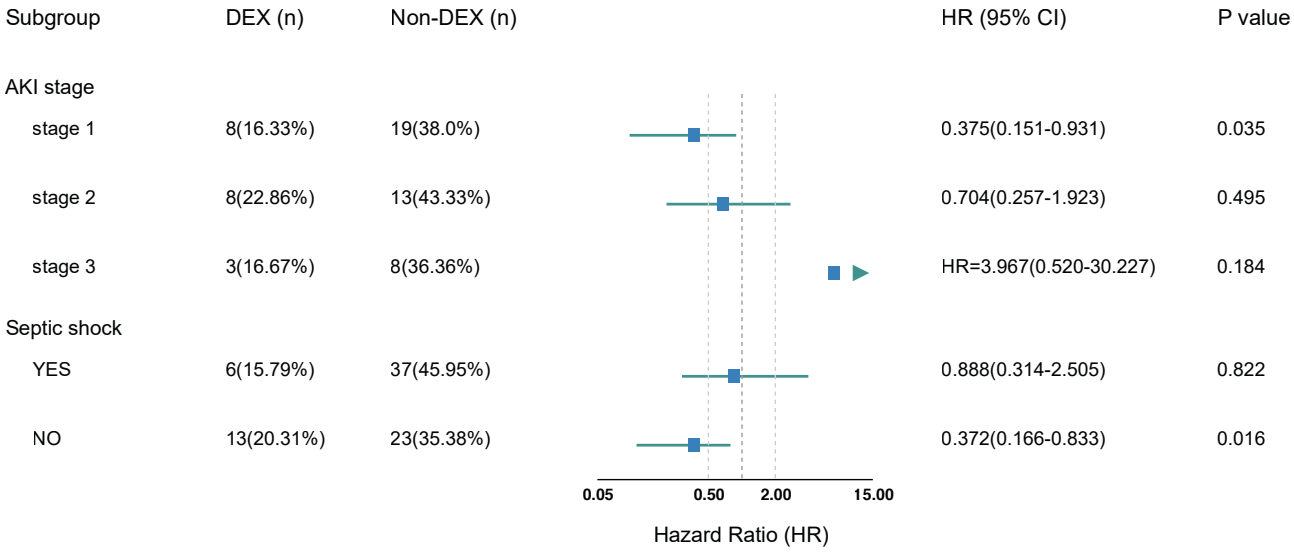

Figure 3. Risk of 28-day mortality risk in two groups of SA-AKI patients according to AKI stage and whether they had septic shock.

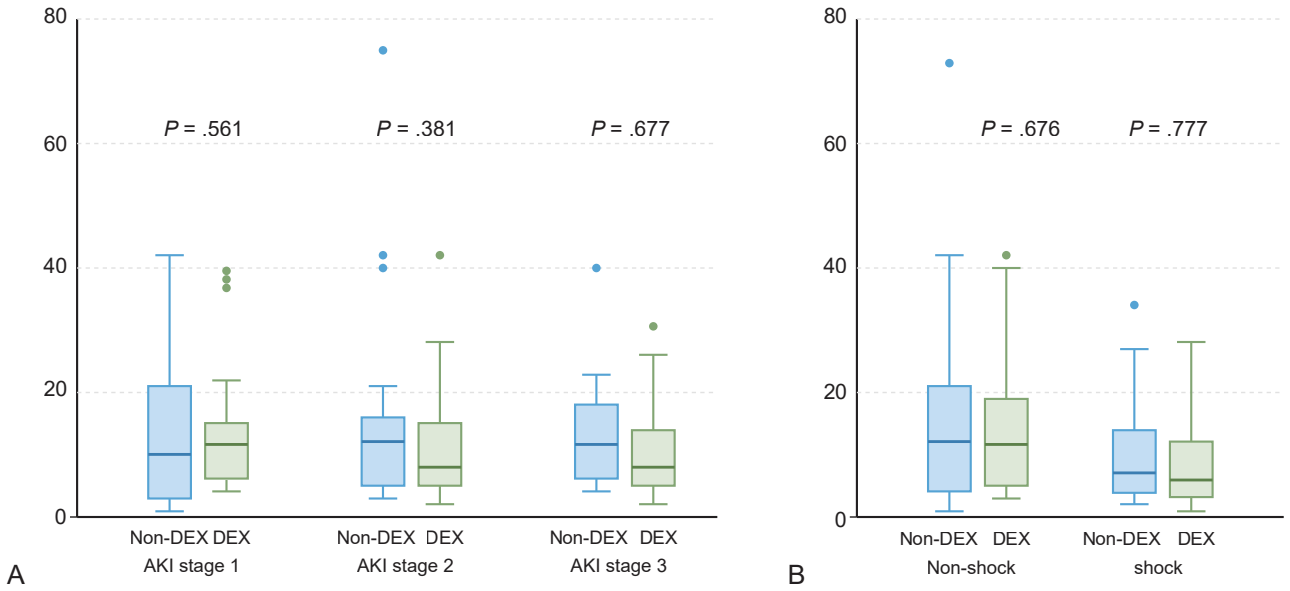

Figure 4. Comparison of ICU stay time between the two groups of SA-AKI patients with different AKI stages and whether they had septic shock: A) There was no significant difference in the length of ICU stay between the two groups of SA-AKI patients at different AKI stages ($P > .05$).

Table 3. Multivariate Logistic Regression Analysis of the Effect of DEX on Renal Function Recovery Rate in Patients with SA-AKI: Interaction Between AKI Stage and Septic Shock

Variable	OR (95% CI)	*P*
Dexmedetomidine × AKI stage interaction	4.384 (1.551 to 12.394)	.005
AKI stage 1	4.814 (1.473 to 15.735)	.009
AKI stage 2	1.628 (0.517 to 5.126)	.405
AKI stage 3	3.038 (0.422 to 21.871)	.270
Dexmedetomidine × septic shock interaction	3.461 (1.429 to 8.383)	.006
Septic shock	3.966 (0.978 t 16.079)	.054
Non-septic shock	3.048 (1.291 to 7.198)	.011

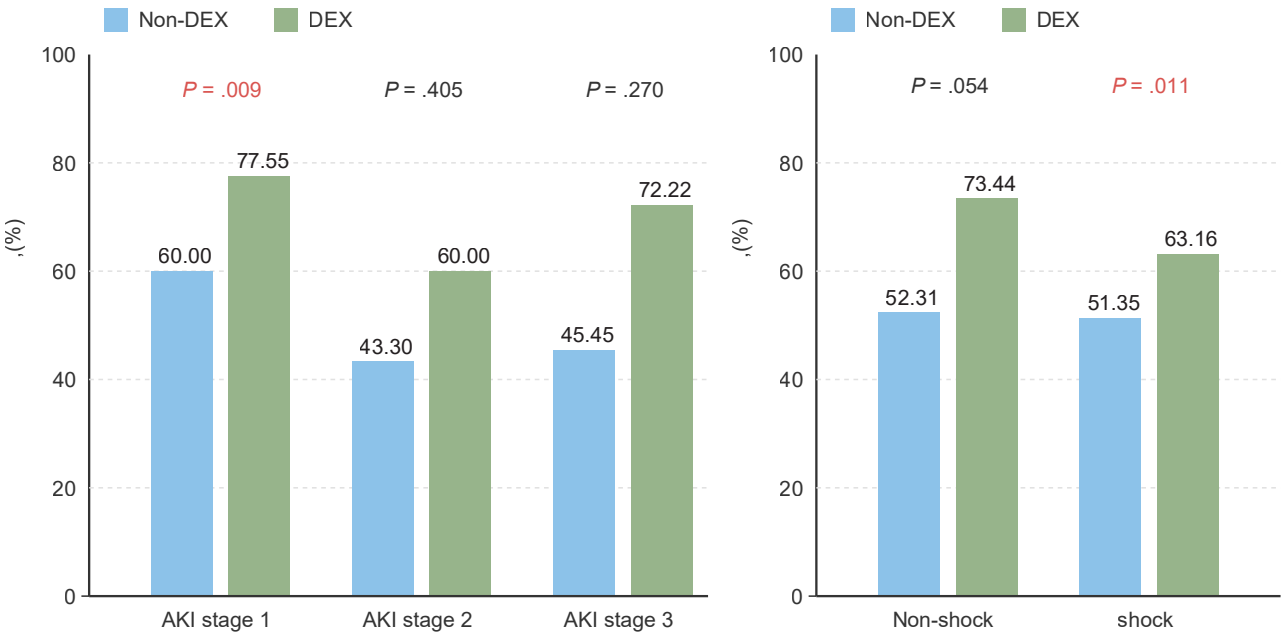

Figure 5. Comparison of renal function recovery rates in the two groups of SA-AKI patients with different AKI stages and whether they had septic shock. In AKI stage 1 patients, DEX was independently associated with a significantly increased rate of renal function recovery (adjusted OR = 4.814, 95% CI: 1.473 to 15.735; *P* = .009) (95% CI: 1.291 to 7.198; *P* = .011).

reduced the 28-day all-cause mortality of SA-AKI patients (adjusted HR = 0.556), and this survival benefit was particularly significant in patients with non-septic shock (HR = 0.372) and AKI stage 1 patients (HR = 0.375); DEX significantly improved the renal function recovery rate (adjusted OR = 2.841), and the efficacy was significantly modified by AKI stage and shock status . AKI stage 1 patients benefited the most (OR = 4.814), non-septic shock patients showed a clear benefit (OR = 3.048), and a strong benefit trend was also observed in septic shock patients (OR = 3.966, *P* = .054); DEX did not significantly shorten ICU length of stay. These results provide high-quality evidence for the use of DEX in personalized sedation therapy for SA-AKI.

The survival benefit of DEX in patients with SA-AKI may be due to its multiple protective mechanisms. The pathophysiological mechanism of sepsis-induced AKI has been preliminarily explored. Multiple mechanisms may lead to the occurrence of SA-AKI, including systemic and renal inflammation in sepsis, renal hypoperfusion and microcirculatory dysfunction, complement activation, RAAS dysregulation, mitochondrial dysfunction, etc.,[6] among which renal inflammatory response and microcirculatory dysfunction are crucial.[16] Animal studies have shown that DEX prevents SA-AKI by inhibiting the expression of sepsis-induced inflammatory factors.[10,17] The study by Yu-Chang *et al.* confirmed that DEX has the effect of improving the renal microcirculation of septic rats.[18] Yuan Zhao *et al.* reported that DEX can protect LPS-induced acute kidney injury by affecting autophagy, apoptosis or ferroptosis.[9,10,19,20] In recent years, clinical studies have also shown the renal protective effect of DEX. DEX can improve the prognosis of SA-AKI by reducing the level of norepinephrine in the blood, improving microcirculatory disorders, and weakening sympathetic nerve tension.[14]

Several studies have shown that SA-AKI is associated with a higher mortality rate,[6,21,22] but the effect of DEX on the prognosis of patients with sepsis is still uncertain. A large retrospective cohort study[23] showed that DEX could reduce the 28-day mortality rate in mechanically ventilated patients with sepsis, but in another retrospective study of 331 patients with sepsis, DEX had no statistically significant effect on the 30-day mortality rate in patients with sepsis.[24] In another multicenter randomized controlled trial (DESIRE) of septic patients receiving mechanical ventilation, DEX had no statistically significant effect on the 28-day

mortality of patients (23 vs. 31%; HR = 0.69, 95% CI: 0.38 to 1.22, P = .20).[25] However, in a subgroup analysis of critically ill patients with APACHE II scores ≥ 23, DEX could reduce the 28-day mortality and hospital mortality of patients with sepsis (22 vs. 42%, P = .03; 28% and 52%, P = .01).[7] Consistent with our study, Hu's retrospective study also found that DEX can reduce the in-hospital mortality of SA-AKI patients (28.3 vs. 41.3%, HR = 0.56; P < .001), and is beneficial to shorten the ICU stay and hospital stay of SA-AKI patients (*both* P < .001). In addition, the renal function recovery rate in the DEX group was also higher (61.8 vs. 55.8%, HR = 1.35, P = .01).[14] The failure to shorten the ICU stay in our study may be due to the fact that the average age of the patients included in this study was higher (71.29 years old) and the high proportion of stage 1 in the AKI stage (48.33 %), which may weaken the improvement effect of DEX on hospital stay. In addition, our study found that DEX had a significant effect on SA-AKI. The 62.5% reduction in mortality in stage 1 patients confirms the importance of early intervention: at this stage, renal injury is primarily functional, and DEX may inhibit AKI progression by improving renal perfusion and alleviating subclinical damage. The survival benefit was even more significant in patients with non-septic shock (adjusted HR = 0.372), suggesting that DEX may exert a stronger protective effect in SA-AKI in the setting of non- septic shock by stabilizing hemodynamics and alleviating non-infectious inflammatory responses.

This study reported that DEX significantly improved the renal function recovery rate in SA-AKI patients (adjusted OR = 2.841), and found key effect modifiers: the modifying effect of AKI stage (*P-interaction* = .005) and the modifying effect of shock state (*P-interaction* = .006). Among them, patients with AKI stage 1 benefited the most (adjusted OR = 4.814), which may be due to the fact that AKI stage 1 is mainly characterized by functional damage (insufficient renal perfusion, microcirculatory disorders), and DEX can reduce or even reverse early damage through α_2 receptor-mediated vascular regulation and anti-inflammatory effects ; DEX can inhibit TLR4/ NOX4/ NF-κB pathway, activate Keap1-Nrf2 pathway, enhance AMPK/mTOR pathway, and other anti-oxidative stress, improve renal cortical perfusion, reduce renal damage, and promote its recovery.[9] These mechanisms may play a key role in the reversible injury stage (AKI stage 1). The beneficial effect of DEX on the recovery of renal function in SA-AKI patients was weakened in AKI stages 2 and 3, and there was no statistical difference. This may be related to the irreversible increase in renal structural damage (such as tubular necrosis and interstitial fibrosis) in AKI stages 2 and 3, which makes recovery more difficult,[26-28] suggesting that DEX still needs to be combined with renal repair strategies (such as stem cell therapy) in the sedation treatment of severe SA- AKI.[29] In addition, the study showed that DEX has a clear benefit in non-septic shock SA-AKI (OR = 3.048), while the benefit in septic shock SA-AKI is not significant, which may be related to the vascular regulation and anti-inflammatory effects of DEX . However, patients with septic shock have more severe inflammation and poor vasodilation ability, and DEX is difficult to correct such severe pathophysiological changes. However, there is still great potential for patients with septic shock SA-AKI (OR = 3.966, P = .054). Although it did not reach statistical significance, the effect size suggests its clinical importance. This is different from the report by Lulan Li[30] that DEX reduced the 90-day mortality rate in patients with septic shock (OR = 0.60, 95% CI: 0.37 to 0.94; P = *.030).* The complexity of the immune disorder in sepsis and the potential residual confounding in this study (such as pathogen virulence and antibiotic response) may have weakened the statistical power of our study.

In the study, DEX did not shorten the ICU stay of SA-AKI patients. It is possible that although DEX accelerates the recovery of renal function in SA-AKI patients, the overall recovery of critically ill patients is affected by the function of multiple organs, which is consistent with the findings of Hu *et al.*[14] However, the mortality rate in the septic shock group was not significantly reduced. Severe sepsis is often complicated by immune paralysis and secondary infection. The immunomodulatory effect of DEX may have a "biphasic effect," and caution is warranted regarding the risk of DEX-induced

bradycardia or hypotension, which could offset its benefits in hemodynamically unstable patients.

This study avoided recall bias associated with retrospective studies through a prospective design. Strict PSM matching (SMD < 10%, Rubin's B < 30%) minimized confounding. Interaction analyses revealed a modifier effect of AKI stage and the presence of septic shock on the efficacy of DEX, promoting more precise treatment strategies for SA-AKI. However, this study was conducted in ICUs across three campuses of our hospital, not a truly multicenter study. Furthermore, the dose and duration of DEX were not analyzed, potentially leading to unmeasured confounding bias. Limited sample size in the subgroups of the study resulted in wide confidence intervals, requiring further validation in prospective, multicenter, and larger studies. Sedation in the non-DEX group was not performed using a single sedative agent, midazolam or propofol, potentially influencing the results. Furthermore, the study did not investigate long-term patient outcomes. Future studies may consider exploring the ultra-early application of DEX within 6 hours after the diagnosis of SA-AKI, which can be combined with new biomarkers (such as urinary NGAL and [IGFBP7·TIMP-2]) to dynamically evaluate the efficacy.[31] More attention should be paid to the dosage and duration of DEX application in SA-AKI patients.

CONCLUSIONS

In summary, DEX significantly improves survival and renal function recovery in patients with SA-AKI, particularly those with stage 1 AKI and non-septic shock. The potentially significant benefit observed in patients with septic shock warrants further validation with a larger sample size. It is suggested that for hemodynamically stable patients with SA-AKI (especially those with KDIGO stage 1) requiring sedation, early use of dexmedetomidine may exert renal protection through multiple mechanisms, potentially becoming a key adjunctive strategy to improve prognosis.

ACKNOWLEDGEMENTS

Conflict of Interest

All authors declare no conflicts of interest.

Author Contribution Statement

Zhou Sixuan, Sun Yanlin, and Zhuang Yue were responsible for patient recruitment, data collection, and paper writing. Zhou Biying was responsible for data analysis. Yang Aixiang was responsible for experimental design, paper guidance, and paper review.

Authors' Contributions

ZHOU Sixuan, SUN Yanlin, and ZHUANG Yue were responsible for patient recruitment, data collection, and academic paper writing. ZHOU Biying performed data analysis. YANG Aixiang provided experimental design, paper guidance, and manuscript review.

Funding

This research was supported by the following grants: Nanjing Medical University Gusu College Research Project (GSKY20210201); the Collaborative Chronic Disease Management Research Project of Traditional Chinese and Western Medicine (CXZH2024152).

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Received July 2025
Revised August 2025
Accepted September 2025