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The impact of dexmedetomidine on mortality in critically ill patients with acute kidney injury: A retrospective propensity score matching analysis

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Author Contributions:

WW and JL designed the study. YJ and PZ conducted data collection. PG and HW conducted data analysis. WW wrote the manuscript. WW and JL analyzed and interpreted the result. All authors reviewed this manuscript.

Abstract:

Objectives This study sought to estimate the effect of dexmedetomidine (DEX) administration on acute kidney injury (AKI)-associated mortality in critically ill patients.

Design A retrospective cohort study.

Setting The study sourced its data from the Multiparameter Intelligent Monitoring in Intensive Care Database IV (MIMIC-IV), a comprehensive database of ICU patients.

Participants A total of 15754 critically ill patients with AKI were enrolled from the MIMIC-IV database.

Primary and secondary outcome In-hospital mortality and 180-day mortality.

Results 15754 critically ill AKI patients were included in our analysis. We found that DEX use decreased in-hospital mortality risk by 38% (HR: 0.62, 95% CI: 0.55-0.70). A significant decrease in in-hospital mortality was observed following treatment with DEX among critically ill patients with AKI stage 1 (15.6% vs. 10.7%, p< 0.001), stage 2 (18.5% vs. 14.7%, p = 0.017) but not stage 3 (27.6% vs. 26.6%, p = 0.848). Moreover, the 180-day mortality was reduced at AKI stage 1 (24.7% vs. 18.2%) and stage 2 (28.3% vs. 24.0%) but not stage 3 (39.1% vs. 38.3%).

Conclusions Our retrospective cohort study suggests that DEX significantly correlates with decreased risk-adjusted in-hospital and 180-day mortality in critically ill AKI patients. Nonetheless, future randomized controlled trials (RCTs) are warranted to validate our findings.

Keywords: Dexmedetomidine, AKI, Mortality, MIMIC-IV, Propensity score matching

Strengths and limitations of this study

- This study included 15754 patients, which is a very large sample size for a clinical study of critically ill patients with AKI.

- Additional confounding factors were adjusted and increased the reliability of our results and conducted a subgroup analysis of the association between DEX use and in-hospital mortality.
- This was a retrospective design and some data may be missing which slightly offsets the results, and we expect to further RCTs in the future.
- The conclusions are qualitative, not quantitative.

Introduction

Over the past few decades, the prevalence of acute kidney injury (AKI) has significantly increased and has gradually become a global health concern.[1] AKI is a common comorbidity among severely ill patients that require intensive care. Indeed, more than half of patients experience AKI during their stay in the intensive care unit (ICU).[2] AKI is related to adverse outcomes, increases CKD occurrence and kidney replacement therapy, and raises the risk of short- and long-term deaths,[3] causing huge social and economic burdens to patients and society. However, further research is warranted to optimize the management of AKI.[4]

In the context of critical care, effective sedation is of utmost importance for managing agitation and anxiety in patients.[5] The primary objective of sedation in the ICU is to achieve a state of calmness and cooperation in the patient, allowing for the easy awakening and clear communication of needs, particularly concerning pain management.[6] There is evidence to suggest that maintaining light sedation in patients in the ICU can lead to better outcomes. Current guidelines recommend dexmedetomidine (DEX) for sedation in an intensive care setting.[7] DEX is widely used in ICU as a highly selective alpha-2 agonist.[8] An increasing body of evidence suggests that DEX can inhibit the production of excess inflammation cytokine and protect renal function, which may positively impact the prognosis of AKI.[9-11] However, the renoprotective effects of DEX in critically ill patients have not been explore, the current literature consists mainly of basic-level studies or small sample population cohorts,

with a paucity of large-scale research. Hence, the present study aims to investigate DEX's effect on AKI-related mortality in critically ill patients.

Methods

Data sources

The study sourced its data from the Multiparameter Intelligent Monitoring in Intensive Care Database IV (MIMIC-IV), a comprehensive database of ICU patients.[12] We collected data on AKI patients from the MIMIC-IV database treated with or without DEX. This database contains a publicly available and real-world clinical database of patients at the Beth Israel Deaconess Medical Center from 2008 to 2019. Informed consent of patients was not required in this study since confidential patient information was already deleted. All reports followed the guidelines of Strengthening Epidemiological Observation and Research Report (STROBE).[13] A Collaborative Institutional Training Initiative (CITI) license (Certificate No. 11326088) was obtained by Wang W, who was entitled to extract data from the MIMIC-IV database in accordance with the relevant regulations.

Participants

This study included patients who were admitted to the ICU and diagnosed with acute kidney injury (AKI) according to the Kidney Disease Improving Global Outcomes (KDIGO) criteria.[14] The definition of baseline serum creatinine level (SCr) in this study was based on two criteria: 1) the minimum SCr level recorded within 7 days before ICU admission, or 2) if there was no SCr data available before admission, the first SCr level measured upon admission to the ICU was used as the baseline.[15] The study only considered data from the initial ICU admission for patients with multiple ICU stays. The MIMIC IV 2.0 database only contains data on adults older than 18. Patients who met any of the following criteria were excluded from the study: (1) death within 48 hours after admission to the ICU, (2) ICU stays less than 48 hours, and (3) missing more than 5% of potential risk variables that are associated with mortality.[16]

Covariates

The study included demographic characteristics and clinical characteristics with 24-hour average values. The Sequential Organ Failure Assessment (SOFA) score,[17] and

Simplified Acute Physiology Score (SAPS) II,[18] were calculated within the first 24 h after the ICU admission. During ICU admission, treatment measures (mechanical ventilation, continuous renal replacement therapy, vasopressors, sedative-analgesic medications, antibiotic and glucocorticoid use) were acquired (Table 1). These covariates, including clinical characteristics and basic demographic information, were based on other relevant studies.[19]

Table 1

Baseline characteristics for the two groups before and after matching.

Characteristic	Before PSM			After PSM		
	Non-DEX (n=12536)	DEX (n=3218)	SMD	Non- DEX (n=3196)	DEX (n=3196)	SMD
Age (y)	69.00 [58.00, 79.00]	63.00 [52.00, 73.00]	0.377	64.00 [53.00, 73.00]	63.00 [52.00, 73.00]	0.018
Gender			0.206			0.007
Male	6903 (55.1)	2095 (65.1)		2088 (65.3)	2077 (65.0)	
Female	5633 (44.9)	1123 (34.9)		1108 (34.7)	1119 (35.0)	
Laboratory measurements						
Hemoglobin (g/dL)	10.50 [8.90, 12.00]	10.40 [8.90, 12.20]	0.012	10.40 [8.80, 12.10]	10.40 [8.90, 12.20]	0.004
Platelet (10^9/L)	188.00 [137.00, 247.54]	174.00 [130.37, 229.46]	0.146	175.35 [127.48, 229.91]	173.90 [130.31, 229.50]	0.009
WBC ($\times 10^9$)	11.10 [8.30, 14.70]	11.86 [9.00, 15.50]	0.075	11.80 [8.70, 15.55]	11.86 [9.00, 15.48]	0.013
Creatinine (mg/dL)	1.10 [0.80, 1.60]	1.00 [0.80, 1.50]	0.108	1.00 [0.70, 1.50]	1.00 [0.80, 1.50]	0.001
BUN (mg/dL)	21.00 [15.00, 35.00]	19.00 [14.00, 28.06]	0.177	19.00 [13.00, 29.00]	19.00 [14.00, 28.06]	0.006

Lactate (mmol/L)	2.02 [1.41, 2.30]	1.83 [1.37, 2.43]	0.051	1.88 [1.38, 2.43]	1.83 [1.37, 2.43]	0.019
Vital signs						
Weight (kg)	80.80 [68.00, 96.00]	86.00 [71.60, 101.00]	0.095	85.00 [71.00, 100.00]	86.00 [71.60, 101.00]	0.041
Temperature (°C)	36.83 [36.57, 37.09]	36.91 [36.71, 37.30]	0.289	36.88 [36.66, 37.29]	36.91 [36.71, 37.29]	0.033
Respiratory rate (bpm)	18.83 [16.68, 21.64]	19.09 [16.96, 21.89]	0.069	18.97 [16.88, 21.72]	19.08 [16.95, 21.87]	0.031
Heart rate (bpm)	84.03 [74.35, 96.08]	84.47 [76.30, 96.94]	0.074	84.74 [75.56, 97.25]	84.41 [76.28, 96.85]	0.007
MAP (mmHg)	75.49 [69.80, 82.95]	75.66 [70.74, 81.85]	0.004	75.74 [70.47, 82.39]	75.64 [70.73, 81.84]	0.021
Spo2 (%)	97.25 [95.77, 98.59]	97.60 [96.20, 98.77]	0.131	97.72 [96.25, 98.93]	97.61 [96.20, 98.77]	0.031
Ethnicity			0.096			0.012
White	8516 (67.9)	2039 (63.4)		2048 (64.1)	2030 (63.5)	
other	4020 (32.1)	1179 (36.6)		1148 (35.9)	1166 (36.5)	
Admission type			0.223			0.018
Emergency	6720 (53.6)	1369 (42.5)		1393 (43.6)	1365 (42.7)	
other	5816 (46.4)	1849 (57.5)		1803 (56.4)	1831 (57.3)	
Need of support						
Vasopressors	1221 (9.7)	600 (18.6)	0.257	554 (17.3)	596 (18.6)	0.034
MV	2977 (23.7)	1069 (33.2)	0.211	1122 (35.1)	1068 (33.4)	0.036
CRRT	768 (6.1)	367 (11.4)	0.187	333 (10.4)	363 (11.4)	0.03
Comorbidities at ICU admission						
Congestive heart failure	4314 (34.4)	951 (29.6)	0.104	924 (28.9)	948 (29.7)	0.017
Cerebrovascular disease	2139 (17.1)	504 (15.7)	0.038	506 (15.8)	502 (15.7)	0.003

Chronic pulmonary	3331 (26.6)	914 (28.4)	0.041	901 (28.2)	907 (28.4)	0.004
Renal disease	3143 (25.1)	602 (18.7)	0.154	610 (19.1)	598 (18.7)	0.01
Liver disease	1701 (13.6)	488 (15.2)	0.046	504 (15.8)	487 (15.2)	0.015
Diabetes	4023 (32.1)	984 (30.6)	0.033	971 (30.4)	979 (30.6)	0.005
Severity of illness						
SOFA score	6.00 [3.00, 8.00]	8.00 [5.00, 11.00]	0.451	7.00 [5.00, 11.00]	8.00 [5.00, 11.00]	0.027
Respiration	0.00 [0.00, 2.00]	3.00 [0.00, 3.00]	0.596	2.00 [0.00, 3.00]	3.00 [0.00, 3.00]	0.028
Cardiovascular	1.00 [1.00, 3.00]	1.00 [1.00, 4.00]	0.29	1.00 [1.00, 4.00]	1.00 [1.00, 4.00]	0.015
Renal	1.00 [0.00, 2.00]	0.00 [0.00, 1.00]	0.11	0.00 [0.00, 1.00]	0.00 [0.00, 1.00]	0.016
Nervous	1.00 [0.00, 2.00]	2.00 [1.00, 3.00]	0.343	2.00 [1.00, 3.00]	2.00 [1.00, 3.00]	0.018
Liver	0.00 [0.00, 0.00]	0.00 [0.00, 0.00]	0.008	0.00 [0.00, 0.00]	0.00 [0.00, 0.00]	<0.001
Coagulation	0.00 [0.00, 1.00]	0.00 [0.00, 1.00]	0.156	0.00 [0.00, 1.00]	0.00 [0.00, 1.00]	0.001
SAPS II score	39.00 [31.00, 48.00]	40.00 [32.00, 50.00]	0.089	40.00 [31.00, 50.00]	40.00 [32.00, 50.00]	0.003
Sedative-analgesic medications						
Propofol	6289 (50.2)	2924 (90.9)	0.997	2902 (90.8)	2902 (90.8)	<0.001
Midazolam	3049 (24.3)	1262 (39.2)	0.324	1234 (38.6)	1246 (39.0)	0.008
Fentanyl	6018 (48.0)	2586 (80.4)	0.717	2601 (81.4)	2564 (80.2)	0.029
AKI stage			0.063			0.034
1	6722 (53.6)	1826 (56.7)		1812 (56.7)	1810 (56.6)	

2	4593 (36.6)	1102 (34.2)		1123 (35.1)	1096 (34.3)	
3	1221 (9.7)	290 (9.0)		261 (8.2)	290 (9.1)	
Sepsis	8011 (63.9)	2590 (80.5)	0.377	2550 (79.8)	2568 (80.4)	0.014
Antibiotic	9852 (78.6)	3016 (93.7)	0.449	2991 (93.6)	2994 (93.7)	0.004
Glucocorticoid	2186 (17.4)	544 (16.9)	0.014	530 (16.6)	543 (17.0)	0.011
Outcome						
In-hospital mortality	1930 (15.4)	432 (13.4)		563 (17.6)	431 (13.5)	
180-day mortality	3725 (29.7)	704 (21.9)		868 (27.2)	703 (22.0)	

Values are expressed as M±SD/median (IQR) or n (%).

PSM, Propensity Score Matching; DEX, Dexmedetomidine; SAPS, Simplified Acute Physiology Score; WBC, white blood cell; MAP, *Mean arterial pressure*; SOFA, The Sequential Organ Failure Assessment; MV, Mechanical ventilation; CRRT, continuous renal replacement therapy; AKI, Acute kidney disease.

Definitions and Outcomes

DEX use was defined as patients who received any dexmedetomidine treatment throughout hospitalization in the ICU, whatever the dosage. The primary outcome was in-hospital mortality and 180-day mortality of AKI patients in the ICU.

Statistical analysis

Our study presented continuous variables are described as mean ± standard deviaton for normally distributed or as the median and interquartile range (IQR) if not normally distributed, while the t-test or Mann-Whitney U test was utilized for comparison between groups, respectively. Categorical variables were presented using numbers and percentages (%), and the chi-square test or Fisher's exact test was adopted from group comparisons. We used propensity score matching (PSM) by 1:1 nearest neighbor matching to adjust the baseline difference between the groups. The caliper value was set to 0.2 between matching participants. The standardized mean difference (SMD) was calculated to determine the balance within the model (Table 1), and SMD greater than 0.1 was considered unbalanced.[20]

We used cox proportional hazards regression to assess the effect of DEX use on in-hospital mortality and 180-day mortality. Parameters with a p-value < 0.1 during univariate analysis and potential confounding factors were included in the multivariate

regression model. In the subgroup analysis, we classified patients based on age, gender, AKI stage, and sepsis incidence to assess the reliability of our findings. We conducted all statistical analyses using either R version 4.1.2, GraphPad Prism 6 software and MedCalc 20.1. The significance level was set at $P < 0.05$.

Results

Baseline population characteristics

15754 individuals diagnosed with AKI after ICU admission within 48h were selected for this analysis after excluding patients based on the exclusion criteria and classified in non-dexmedetomidine (non-DEX, n=12536) and dexmedetomidine (DEX, n=3218) groups (Fig.1). After PSM, the characteristics of 3196 patients in both groups were comparable (SMD< 0.1) (Table 1).

As presented in table 1, there were meaningful differences in age, gender, laboratory measurements, vital signs, admission type between the DEX group and the non-DEX group in the whole cohort. DEX treatment was more common in men and younger.

Primary Outcome

In-hospital mortality: We found that DEX use decreased in-hospital mortality risk by 38% among critically ill patients with AKI (HR: 0.62, 95% CI: 0.55-0.70) during PSM modeling and Cox proportional hazards regression (HR: 0.61, 95% CI: 0.55-0.68) (Fig.2, Supplementary table 1). A significant decrease in in-hospital mortality was observed among critically ill patients receiving DEX at AKI stage 1 (15.6% vs. 10.7%, p< 0.001), stage 2 (18.5% vs. 14.7%, p= 0.017) but not stage 3 (27.6% vs. 26.6%, p= 0.848) (Fig.3).

180-day mortality: DEX use also reduced 180-day mortality risk by 22% among critically ill patients with AKI (HR: 0.77, 95% CI: 0.69-0.85) during PSM modeling and Cox proportional hazards regression (HR: 0.68, 95% CI: 0.63-0.74) (Fig.2, Supplementary table 2). A significant decrease in 180-day mortality was observed among critically ill patients receiving DEX at AKI stage 1 (24.7% vs. 18.2%, p< 0.001), stage 2 (28.3% vs. 24.0%, p= 0.023) but not stage 3 (39.1% vs. 38.3%, p= 0.861) (Fig.3).

We also investigated the in-hospital and 180-day survival in critically patients

with AKI. The DEX group had significantly higher freedom from death at in-hospital (86.5 vs. 82.4%, $p < 0.001$) and 180-day (78.0 vs. 72.8%, $p < 0.001$) than the non-DEX group, respectively (Fig.4).

Overall, the use of DEX had a significant beneficial effect on the in-hospital mortality and 180-day mortality of AKI in critically ill patients.

Subgroup analysis

Subgroup analysis indicated that DEX use reduced in-hospital mortality of critically ill patients with AKI (Supplementary figure 1). There were no interactions between age, gender, sepsis, AKI stage, and DEX use, suggesting that these results were comparable for all populations.

Discussion

The present study showed that DEX use in severely ill AKI patients was linked with lower risk-adjusted in-hospital mortality and 180-day mortality. Consistent results were observed in different models. During subgroup analysis, after stratification according to age, gender, AKI stage, and sepsis, a strong correlation was still observed. Overall, we provide preliminary evidence that DEX has a beneficial effect on the prognosis of AKI in critically ill patients, providing the foothold to improve the outcomes of this patient population.

Overwhelming literature substantiates that DEX can alleviate AKI caused by several factors. Wang et al. previously uncovered that DEX could ameliorate AKI in mice with sepsis by partially inhibiting oxidative stress and apoptosis by modulating the p75NTR/p38MAPK/JNK signaling pathways.[21] Zhao et al. further substantiated that DEX protected against lipopolysaccharide-induced AKI by promoting autophagy mediated by PI3K/AKI/mTOR pathway inhibition.[22] A meta-analysis by Loomba et al. demonstrated that DEX could confer postoperative renal protective effects with lower NGAL levels and increased creatine clearance in patients who received DEX. These effects correlated with reduced ICU length of stay and risk of AKI and mortality.[23] Shan et al. found that DEX could minimize AKI incidence in Stanford type B aortic dissection (TBAD) patients after endovascular aortic repair (EVAR).[24] A single-center RCT of 108 patients[25] showed that prior administration of DEX within 24 hours after

induction of anesthesia could reduce the incidence of AKI after aortic surgery under cardiopulmonary bypass. An RCT by Tang et al.[26] showed that DEX pretreatment attenuated AKI in patients. Animal studies further indicated that DEX could reduce cellular injury, improve renal function, and mitigate apoptosis in renal cells. Furthermore, Liu et al. revealed that DEX infusion in ICU patients with septic shock was linked to decreased AKI incidence and reduced ICU stay and CRRT performance. It is highly conceivable that the mechanism is related to anti-inflammatory effects and immunomodulation.[27]

Inflammation is key to AKI pathogenesis, progression, and prognosis. An increasing body of evidence suggests that DEX confers renoprotective effects and may be involved in the regulation of inflammation.[28-30] A meta-analysis by Ma et al.[31] that included 4842 patients showed that DEX decreased pro-inflammatory like cytokines interleukin-6, C-reactive, tumor necrosis factor-α, and increased anti-inflammatory cytokines like IL-10 in surgical patients. A sub-analysis of a multicenter RCT by Ohta et al.[32] suggested that sedation using DEX reduced inflammation in patients with sepsis requiring mechanical ventilation. Animal studies have shown that DEX may have a protective effect on cisplatin-induced AKI, and its potential mechanism may be related to the regulation of apoptosis and inflammatory response.[33] In addition, DEX can ameliorate microcirculation disorders by decreasing norepinephrine levels in the blood and increasing urine output and renal blood flow.[34] Since our study did not collect inflammatory indicators, the hypothesis that DEX may attenuate excessive inflammation could not be confirmed, emphasizing the need for future studies. Emerging evidence substantiates the benefits of DEX in AKI, but the prognosis and follow-up of AKI in critically ill patients have been largely understudied. In the present study, we consistently found that the in-hospital mortality of AKI patients in the DEX group was significantly lower than in the non-DEX group. At the same time, we found that the 180-day mortality of AKI patients was consistent with the in-hospital mortality, suggesting that DEX use is associated with survival benefits in this particular patient population. Our research provides a theoretical basis for clnicians to use DEX to manage critically ill patients with AKI.

Our subgroup analysis showed that DEX was effective in sepsis-associated-AKI (SA-AKI) patients, consistent with the literature.[35] Consistently, Hu et al. analyzed 2192 patients with SA-AKI and found that DEX use was related to decreased in-hospital mortality and improved renal function recovery of SA-AKI in critically ill patients. Unlike Hu's study is that our study included all types of AKI populations in the ICU. Our results showed that DEX use reduced in-hospital mortality of AKI in critically ill patients. Follow-up analysis showed that DEX use reduced the 180-day mortality of patients. Our findings suggest DEX is effective against sepsis-associated AKI and for AKI patients in general and improves the long-term prognosis. The role of DEX on more types of AKI subgroups warrants further exploration in severely ill subjects.

Our research has several limitations. First, data acquired from this database was adopted to maximize generalizability and power. Accordingly, there was no formal calculation of sample size in this study. Although the sample size of the subgroup was comparatively larger compared to previous studies, it may also increase the risk of false positive results during multiple subgroup analyses. In addition, our study's retrospective nature may have limited our findings' accuracy, and there could be other unknown potential confounding factors that we were unable to control for. However, we adjusted for many confounding factors, and PSM was conducted. Moreover, data analyzed in this study were acquired from a single-center observation database, emphasizing the need for a multicenter RCT to increase the robustness of our findings.

Conclusion

This retrospective cohort study showed that dexmedetomidine administration significantly reduces risk-adjusted in-hospital and 180-day mortality in critically ill patients with AKI. However, further RCTs are needed to develop the robustness of our findings.

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Figure Legends:

Fig.1. Flowchart of patients selection for the study. MIMIC-IV: Medical Information Mart for Intensive Care Database IV; ICU: intensive care unit.

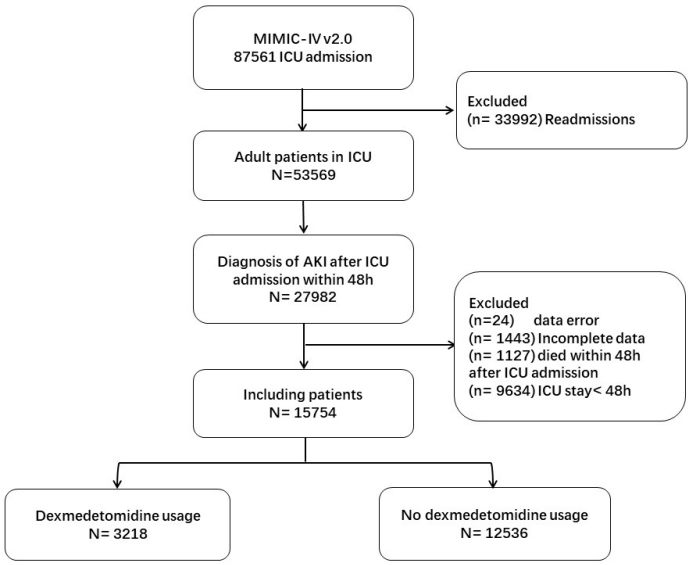
Fig.2. Association between in-hospital mortality, 180-day mortality and dexmedetomidine use of AKI patients evaluated by the Cox model. HR, hazard ratio; CI: confidence interval; Unadjusted: without adjustment; Multivarable adjusted: adjusted for all the baseline variables shown in Table 1.

PSM: propensity score matching.

Fig.3. In-hospital mortality and 180-day mortality of AKI in critically ill patients between the dexmedetomidine and non-dexmedetomidine group in different AKI stage.

Fig.4. Freedom from death at in-hospital and 180-day in critically ill patients with AKI between the two groups.

Supplementary figure 1. Subgroup analysis of the association between dexmedetomidine use and in-hospital mortality.



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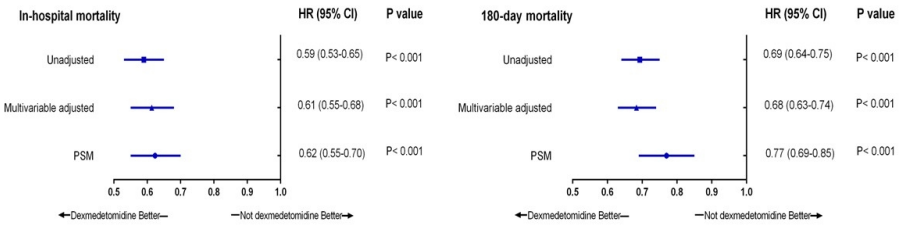
338x190mm (96 x 96 DPI)



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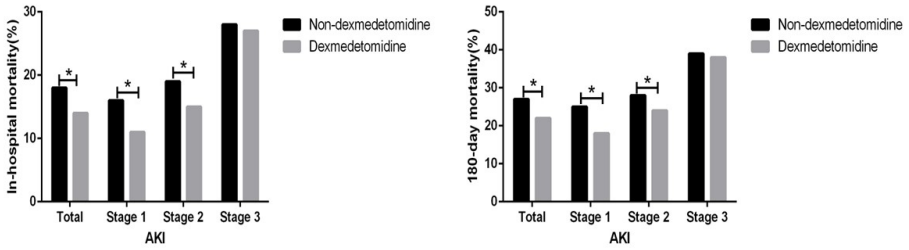

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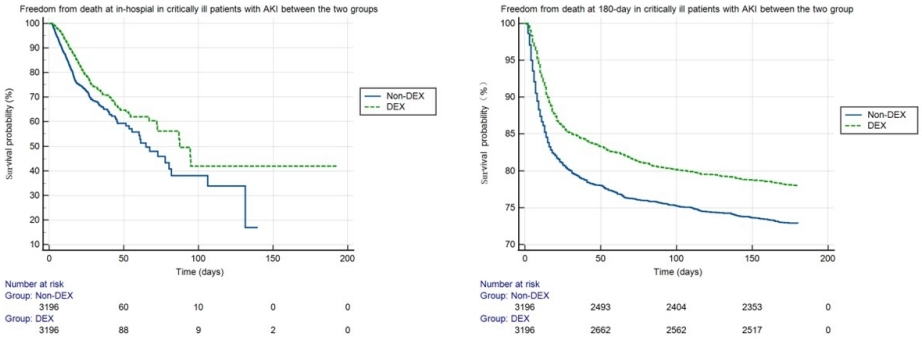


Fig.4. Freedom from death at in-hospital and 180-day in critically ill patients with AKI between the two groups.

338x190mm (96 x 96 DPI)

Supplementary table 1.

Cox logistic regression analysis of in-hospital mortality (before PSM)

	Univariable		Multivariable	
Variables	OR (95%CI)	*P* value	OR (95%CI)	*P* value
Need of support				
Vasopressors	2.636 (2.415, 2.877)	<0.001	1.394 (1.251, 1.553)	<0.001
MV	4.108 (3.782, 4.462)	<0.001	4.090 (3.710, 4.509)	<0.001
CRRT	1.863 (1.680, 2.065)	<0.001	0.845 (0.750, 0.952)	0.006
Comorbidities at ICU admission				
Congestive heart failure	1.151 (1.058, 1.251)	0.001	1.229 (1.125, 1.342)	<0.001
Cerebrovascular disease	1.437 (1.307, 1.581)	<0.001	1.547 [1.403, 1.705]	<0.001
Chronic pulmonary	1.056 (0.965, 1.155)	0.237		
Renal disease	1.101 (1.005, 1.206)	0.040	1.025 [0.928, 1.132]	0.629
Liver disease	1.651 (1.505, 1.812)	<0.001	1.120 (1.009, 1.244)	0.033
Diabetes	0.901 (0.825, 0.984)	<0.001	0.818 [0.746, 0.898]	<0.001
Severity of illness				
SOFA score	1.115 (1.105, 1.125)	<0.001	1.007 [0.993, 1.021]	0.350
SAPS II score	1.033 (1.031,	<0.001	1.018 (1.015, 1.021)	<0.001

	1.036)				
Sedative-analgesic medications					
Propofol	0.788	(0.725, 0857)	<0.001	0.465 (0.421, 0.513)	<0.001
Midazolam	1.680	(1.547, 1.823)	<0.001	0.838 (0.758, 0.928)	0.001
Fentanyl	1.724	(1.568, 1.895)	<0.001	1.309 (1.154, 1.486)	<0.001
AKI stage					
AKI stage 1	Ref			Ref	
AKI stage 2	1.142	(1.071, 1.217)	<0.001	1.044 (0.955, 1.142)	0.342
AKI stage 3	1.800	(1.646, 1.969)	<0.001	1.048 (0.928, 1.183)	0.453
Lactate (mmol/L)	1.314	(1.292, 1.337)	<0.001	1.224 (1.199, 1.250)	<0.001
Sepsis	1.871	(1.670, 2.096)	<0.001	1.574 (1.304, 1.901)	<0.001
Antibiotic	1.366	(1.191, 1.562)	<0.001	0.665 (0.533, 0.831)	<0.001
Glucocorticoid	0.719	(0.645, 0.801)	<0.001	0.709 (0.635, 0.791)	<0.001
DEX	0.585	(0.526, 0.650)	<0.001	0.610 (0.546, 0.680)	<0.001

PSM, Propensity Score Matching; DEX, Dexmedetomidine; SAPS, Simplified Acute Physiology Score; SOFA, The Sequential Organ Failure Assessment; MV, Mechanical ventilation; CRRT, continuous renal replacement therapy; AKI, Acute kidney disease.

Supplementary table 2.

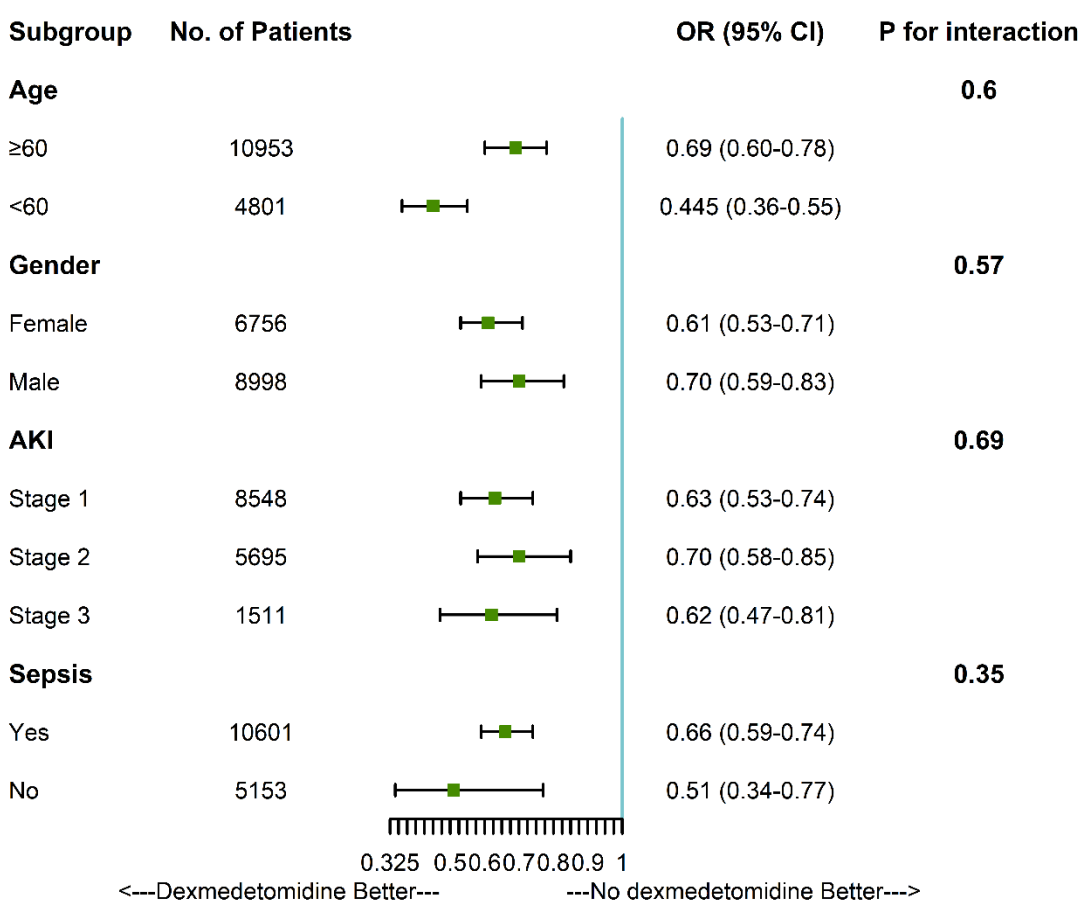
Cox logistic regression analysis of 180-day mortality (before PSM)

	Univariable		Multivariable	
Variables	OR (95%CI)	*P* value	OR (95%CI)	*P* value
Need of support				
Vasopressors	2.771 (2.579, 2.977)	<0.001	1.454 (1.331, 1.588)	<0.001
MV	2.626 (2.474, 2.788)	<0.001	2.565 (2.390, 2.752)	<0.001
CRRT	2.554 (2.345, 2.783)	<0.001	0.995 (0.899, 1.101)	0.920
Comorbidities at ICU admission				
Congestive heart failure	1.318 (1.240, 1.400)	<0.001	1.194 (1.120, 1.273)	<0.001
Cerebrovascular disease	1.423 (1.324, 1.530)	<0.001	1.581 (1.469, 1.701)	<0.001
Chronic pulmonary	1.129 (1.058, 1.204)	<0.001	1.104 (1.033, 1.180)	0.004
Renal disease	1.379 (1.293, 1.472)	<0.001	1.090 (1.017, 1.168)	0.015
Liver disease	1.881 (1.749, 2.022)	<0.001	1.249 (1.152, 1.355)	<0.001
Diabetes	0.982 (0.922, 1.046)	0.580		
Severity of illness				
SOFA score	1.129 (1.121, 1.136)	<0.001	1.013 (1.001, 1.024)	0.029
SAPS II score	1.039 (1.037,	<0.001	1.025 (1.023, 1.028)	<0.001

	1.041)				
Sedative-analgesic medications					
Propofol	0.715	(0.674, 0.758)	<0.001	0.448 (0.418, 0.482)	<0.001
Midazolam	1.809	(1.703, 1.923)	<0.001	0.910 (0.841, 0.986)	0.021
Fentanyl	1.492	(1.404, 1.586)	<0.001	1.242 (1.140, 1.352)	<0.001
AKI stage					
AKI stage 1	Ref			Ref	
AKI stage 2	1.142	(1.071, 1.217)	<0.001	1.076 (1.009, 1.148)	0.025
AKI stage 3	1.800	(1.646, 1.969)	<0.001	1.097 (0.999, 1.204)	0.051
Lactate (mmol/L)	1.250	(1.232, 1.268)	<0.001	1.155 (1.134, 1.176)	<0.001
Sepsis	2.060	(1.915, 2.215)	<0.001	1.664 (1.478, 1.874)	<0.001
Antibiotic	1.531	(1.404, 1.669)	<0.001	0.808 (0.703, 0.928)	0.003
Glucocorticoid	1.162	(1.079, 1.251)	<0.001	1.072 (0.994, 1.156)	0.071
DEX	0.693	(0.639, 0.751)	<0.001	0.683 (0.626,0.744)	<0.001

PSM, Propensity Score Matching; DEX, Dexmedetomidine; SAPS, Simplified Acute Physiology Score; SOFA, The Sequential Organ Failure Assessment; MV, Mechanical ventilation; CRRT, continuous renal replacement therapy; AKI, Acute kidney disease.

Supplementary figure 1



Supplementary figure 1. Subgroup analysis of the association between dexmedetomidine use and in-hospital mortality.

STROBE Statement—Checklist of items that should be included in reports of ***cohort studies***

	Item No	Recommendation	Page No
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	2
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	3
Objectives	3	State specific objectives, including any prespecified hypotheses	3
Methods			
Study design	4	Present key elements of study design early in the paper	4
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	4
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	4
		(*b*) For matched studies, give matching criteria and number of exposed and unexposed	5
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	4
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	5
Bias	9	Describe any efforts to address potential sources of bias	5
Study size	10	Explain how the study size was arrived at	5
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	5
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	4
		(*b*) Describe any methods used to examine subgroups and interactions	4
		(*c*) Explain how missing data were addressed	5
		(*d*) If applicable, explain how loss to follow-up was addressed	
		(*e*) Describe any sensitivity analyses	
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	6
		(b) Give reasons for non-participation at each stage	6
		(c) Consider use of a flow diagram	Yes
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	6
		(b) Indicate number of participants with missing data for each variable of interest	
		(c) Summarise follow-up time (eg, average and total amount)	
Outcome data	15*	Report numbers of outcome events or summary measures over time	6

Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included (*b*) Report category boundaries when continuous variables were categorized (*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	6 6
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	6
Discussion			
Key results	18	Summarise key results with reference to study objectives	7
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	9
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	9
Generalisability	21	Discuss the generalisability (external validity) of the study results	8.9
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	1

*Give information separately for exposed and unexposed groups.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at http://www.strobe-statement.org.

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The impact of dexmedetomidine on mortality in critically ill patients with acute kidney injury: A retrospective propensity score matching analysis

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The impact of dexmedetomidine on mortality in critically ill patients with acute kidney injury: A retrospective propensity score matching analysis

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Abstract:

Objectives This study sought to estimate the effect of dexmedetomidine (DEX) administration on mortality in critically ill patients with acute kidney injury (AKI).

Design A retrospective cohort study.

Setting The study sourced its data from the Multiparameter Intelligent Monitoring in Intensive Care Database IV (MIMIC-IV), a comprehensive database of ICU patients.

Participants A total of 15754 critically ill patients with AKI were enrolled from the MIMIC-IV database.

Primary and secondary outcome Primary outcome was in-hospital mortality and secondary outcome was 180-day mortality.

Results 15754 critically ill AKI patients were included in our analysis. We found that DEX use decreased in-hospital mortality risk by 38% (HR: 0.62, 95% CI: 0.55-0.70). A significant decrease in in-hospital mortality was observed following treatment with DEX among critically ill patients with AKI stage 1 (15.6% vs. 10.7%, p< 0.001), stage

2 (18.5% vs. 14.7%, p = 0.017) but not stage 3 (27.6% vs. 26.6%, p = 0.848). Moreover, the 180-day mortality was reduced at AKI stage 1 (24.7% vs. 18.2%) and stage 2 (28.3% vs. 24.0%) but not stage 3 (39.1% vs. 38.3%).

Conclusions Our retrospective cohort study suggests that DEX significantly correlates with decreased risk-adjusted in-hospital and 180-day mortality in critically ill AKI patients. Nonetheless, future randomized controlled trials (RCTs) are warranted to validate our findings.

Keywords: Dexmedetomidine, AKI, Mortality, MIMIC-IV, Propensity score matching

Strengths and limitations of this study

- This study included 15754 patients, which is a very large sample size for a clinical study of critically ill patients with AKI.
- Additional confounding factors were adjusted and increased the reliability of our results and conducted a subgroup analysis of the association between DEX use and in-hospital mortality.
- This was a retrospective design without long-term follow-up, so the results may be biased.
- The data of this study was from a MIMIC-IV database, and some data may be missing which slightly offsets the results.

Introduction

Over the past few decades, the prevalence of acute kidney injury (AKI) has significantly increased and has gradually become a global health concern.[1] AKI is a common comorbidity among severely ill patients that require intensive care. Indeed, more than half of patients experience AKI during their stay in the intensive care unit

(ICU).[2] AKI is related to adverse outcomes, increases CKD occurrence and kidney replacement therapy, and raises the risk of short- and long-term deaths,[3] causing huge social and economic burdens to patients and society. However, further research is warranted to optimize the management of AKI.[4]

In the context of critical care, effective sedation is of utmost importance for managing agitation and anxiety in patients.[5] The primary objective of sedation in the ICU is to achieve a state of calmness and cooperation in the patient, allowing for the easy awakening and clear communication of needs, particularly concerning pain management.[6] There is evidence to suggest that maintaining light sedation in patients in the ICU can lead to better outcomes. Current guidelines recommend dexmedetomidine (DEX) for sedation in an intensive care setting.[7] DEX is widely used in ICU as a highly selective alpha-2 agonist.[8] An increasing body of evidence suggests that DEX can inhibit the production of excess inflammation cytokine and protect renal function, which may positively impact the prognosis of AKI.[9-11] However, the renoprotective effects of DEX in critically ill patients have not been explored, based on the above characteristics of DEX, we assume that the use of DEX can reduce the mortality rate of AKI patients. The current literature consists mainly of basic-level studies or small samples of other population cohorts, with a paucity of large-scale research[12-13]. Hence, the present study aims to investigate DEX's effect on AKI-related mortality in critically ill patients based on a large sample of critical care public databases.

Methods

Data sources

The study sourced its data from the Multiparameter Intelligent Monitoring in Intensive Care Database IV (MIMIC-IV), a comprehensive database of ICU patients.[14] We collected data on AKI patients from the MIMIC-IV database treated with or without DEX. This database contains a publicly available and real-world clinical database of patients at the Beth Israel Deaconess Medical Center from 2008 to 2019. Informed consent of patients was not required in this study since confidential patient information was already deleted. All reports followed the guidelines of Strengthening

Epidemiological Observation and Research Report (STROBE).[15] A Collaborative Institutional Training Initiative (CITI) license (Certificate No. 11326088) was obtained by Wang W, who was entitled to extract data from the MIMIC-IV database in accordance with the relevant regulations.

Participants

This study included patients who were admitted to the ICU and diagnosed with acute kidney injury (AKI) according to the Kidney Disease Improving Global Outcomes (KDIGO) criteria.[16] The definition of baseline serum creatinine level (SCr) in this study was based on two criteria: 1) the minimum SCr level recorded within 7 days before ICU admission, or 2) if there was no SCr data available before admission, the first SCr level measured upon admission to the ICU was used as the baseline.[17] The MIMIC IV 2.0 database only contains data on adults older than 18. Patients who met any of the following criteria were excluded from the study: (1) death within 48 hours after admission to the ICU, (2) ICU stays less than 48 hours.

Covariates

The study included demographic characteristics and clinical characteristics with 24-hour average values. The Sequential Organ Failure Assessment (SOFA) score,[18] and Simplified Acute Physiology Score (SAPS) II,[19] were calculated within the first 24 h after the ICU admission. We collected the following clinical information of each patient: demographics, laboratory measurements, vital signs, ethnicity, admission type, need of support, comorbidities at ICU admission, severity of illness, sedative-analgesic medications use, AKI stage, sepsis, antibiotic use, glucocorticoid use(Table 1). These covariates, including clinical characteristics and basic demographic information, were based on other relevant studies and clinical practice.[20-21]

Data definitions

Extracted data from MIMIC-IV on the first day of ICU admission, including age, gender, laboratory measurements, vital signs, ethnicity, admission type, vasopressors, mechanical ventilation (MV), continuous renal replacement therapy (CRRT), comorbidities, SOFA score, SAPS II score. We also collected information on whether DEX, propofol, midazolam, fentanyl, antibiotics, and glucocorticoids were used during

ICU hospitalization. Sepsis was defined as a life-threatening organ dysfunction caused by a dysregulation of host response to infection (Sepsis 3.0)[22], which refers to patients with documented or suspected infections and acute changes in the SOFA score ≥ 2 points.

DEX use was defined as patients who received any dexmedetomidine treatment throughout hospitalization in the ICU.

Outcomes

In-hospital mortality refers to the death of patients during this hospitalization, which was recorded by the hospital[23]. In the MIMIC-IV database, this type of patients will be marked with a 'hospital expire flag' to indicate the hospital death during this hospitalization. If a patient has been hospitalized multiple times, we only select the first check-in record. The primary outcome was in-hospital mortality and the second outcome was 180-day mortality of AKI patients in the ICU.

Statistical analysis

Our study presented continuous variables described as mean±standard deviaton for normally distributed or as the median and interquartile range (IQR) if not normally distributed, while the t-test or Mann-Whitney U test was utilized for comparison between groups, respectively. Categorical variables were presented using numbers and percentages (%), and the chi-square test or Fisher's exact test was adopted from group comparisons. We used propensity score matching (PSM) by 1:1 nearest neighbor matching to adjust the baseline difference between the groups. The caliper value was set to 0.2 between matching participants. The standardized mean difference (SMD) was calculated to determine the balance within the model (Table 1), and SMD greater than 0.1 was considered unbalanced.[24]

We used Cox proportional hazards regression and binary logistic regression to assess the effect of DEX use on in-hospital mortality and 180-day mortality. In the subgroup analysis, we used binary logistic regression analysis of in-hospital mortality to assess the effect of DEX use on in-hospital mortality in subgroup populations. Parameters with a p-value< 0.1 during univariate analysis and potential confounding

factors were included in the multivariate regression model. In the subgroup analysis, we classified patients based on age, gender, AKI stage, and sepsis incidence to assess the reliability of our findings. We conducted all statistical analyses using either R version 4.1.2, GraphPad Prism 6 software, or MedCalc 20.1. The significance level was set at $p< 0.05$.

Patient and public involvement

None.

Results

Baseline population characteristics

15754 individuals diagnosed with AKI after ICU admission within 48h were selected for this analysis after excluding patients based on the exclusion criteria (Figure 1). In the whole cohort, the median age of patients was 68 (57 ± 78) years old, with 8998 (57.1%) males and 6756 (42.9%) females. 8548 (54.3%) patients were diagnosed with AKI stage 1, 5695 (36.1%) with AKI stage 2, and 1511 (9.6%) with AKI stage 3.

In this study, patients were classified into non-dexmedetomidine (non-DEX, n=12536) and dexmedetomidine (DEX, n=3218) groups. Compared with the non-DEX group, the DEX group was younger (63 vs 69 y, $p< 0.001$), heavier weight (86.0 vs 80.8 kg, $p< 0.001$), higher wbc (11.9 vs 11.1 $\times 10^9$, $p< 0.001$), temperature (36.9 vs 36.8 ℃, $p< 0.001$), Spo2 (97.6 vs 97.3 %, $p< 0.001$), sofa score (8.0 vs 6.0, $p< 0.001$) and SAPS II score (40.0 vs 39.0, $p< 0.001$), faster respiratory rate (19.1 vs 18.8 bpm, $p< 0.001$) and heart rate (84.5 vs 84.0 bpm, $p= 0.001$), lower platelet (174.0 vs 188.0 10^9/L, $p< 0.001$), creatinine (1.0 vs 1.1 mg/dL, $p< 0.001$), bun (19.0 vs 21.0 mg/dL, $p< 0.001$), lactate (1.83 vs 2.02 mmol/L, $p= 0.001$), congestive heart failure (29.6% vs 34.4%, $p< 0.001$) and renal disease (18.7% vs 25.1%, $p< 0.001$), more female (65.1% vs 55.1%, $p< 0.001$), white ethnicity (63.4% vs 67.9%, $p< 0.001$), emergency admission (42.5% vs 53.6, $p< 0.001$), vasopressin use (18.6 vs 9.7 %, $p< 0.001$), MV (33.2% vs 23.7%, $p< 0.001$), CRRT (11.4% vs 6.1%, $p< 0.001$), chronic pulmonary (28.4% vs 26.6%, $p= 0.039$), liver disease (15.2% vs 13.6%, $p= 0.021$), propofol use (90.0% vs 50.2%, $p< 0.001$), midazolam use (39.2% vs 24.3%, $p< 0.001$) fentanyl use (80.4% vs 48.0, $p<$

0.001) AKI stage 1 (56.7% vs 53.6%, p= 0.006), sepsis (80.5% vs 63.9%, p< 0.001) and antibiotics use (93.7% vs 78.6%, p< 0.001). After PSM, the characteristics of 3196 patients in both groups were comparable (SMD< 0.1) (Table 1).

Table 1. Baseline characteristics for the two groups before and after matching.

Characteristic	Before PSM			After PSM		
	Non-DEX (n=12536)	DEX (n=3218)	SMD	Non- DEX (n=3196)	DEX (n=3196)	SMD
Age (y)	69.00 [58.00, 79.00]	63.00 [52.00, 73.00]	0.377	64.00 [53.00, 73.00]	63.00 [52.00, 73.00]	0.018
Gender, male, n (%)	6903 (55.1)	2095 (65.1)	0.206	2088 (65.3)	2077 (65.0)	0.007
Laboratory measurements						
Hemoglobin (g/dL)	10.50 [8.90, 12.00]	10.40 [8.90, 12.20]	0.012	10.40 [8.80, 12.10]	10.40 [8.90, 12.20]	0.004
Platelet ($\times 10^9$/L)	188.00 [137.00, 247.54]	174.00 [130.37, 229.46]	0.146	175.35 [127.48, 229.91]	173.90 [130.31, 229.50]	0.009
WBC ($\times 10^9$)	11.10 [8.30, 14.70]	11.86 [9.00, 15.50]	0.075	11.80 [8.70, 15.55]	11.86 [9.00, 15.48]	0.013
Creatinine (mg/dL)	1.10 [0.80, 1.60]	1.00 [0.80, 1.50]	0.108	1.00 [0.70, 1.50]	1.00 [0.80, 1.50]	0.001
BUN (mg/dL)	21.00 [15.00, 35.00]	19.00 [14.00, 28.06]	0.177	19.00 [13.00, 29.00]	19.00 [14.00, 28.06]	0.006
Lactate (mmol/L)	2.02 [1.41, 2.30]	1.83 [1.37, 2.43]	0.051	1.88 [1.38, 2.43]	1.83 [1.37, 2.43]	0.019
Vital signs						
Weight (kg)	80.80 [68.00, 96.00]	86.00 [71.60, 101.00]	0.095	85.00 [71.00, 100.00]	86.00 [71.60, 101.00]	0.041
Temperature (°C)	36.83 [36.57, 37.09]	36.91 [36.71, 37.30]	0.289	36.88 [36.66, 37.29]	36.91 [36.71, 37.29]	0.033
Respiratory rate (bpm)	18.83 [16.68, 21.64]	19.09 [16.96, 21.89]	0.069	18.97 [16.88, 21.72]	19.08 [16.95, 21.87]	0.031
Heart rate (bpm)	84.03 [74.35, 96.08]	84.47 [76.30, 96.94]	0.074	84.74 [75.56, 97.25]	84.41 [76.28, 96.85]	0.007
MAP (mmHg)	75.49 [69.80, 82.95]	75.66 [70.74, 81.85]	0.004	75.74 [70.47, 82.39]	75.64 [70.73, 81.84]	0.021
Spo2 (%)	97.25 [95.77, 98.59]	97.60 [96.20, 98.77]	0.131	97.72 [96.25, 98.93]	97.61 [96.20, 98.77]	0.031
Ethnicity, white, n (%)	8516 (67.9)	2039 (63.4)	0.096	2048 (64.1)	2030 (63.5)	0.012
Admission type, emergency, n (%)	6720 (53.6)	1369 (42.5)	0.223	1393 (43.6)	1365 (42.7)	0.018
Need of support, n (%)						
Vasopressors	1221 (9.7)	600 (18.6)	0.257	554 (17.3)	596 (18.6)	0.034
MV	2977 (23.7)	1069 (33.2)	0.211	1122 (35.1)	1068 (33.4)	0.036

CRRT	768 (6.1)	367 (11.4)	0.187	333 (10.4)	363 (11.4)	0.030
Comorbidities at ICU admission, n (%)						
Congestive heart failure	4314 (34.4)	951 (29.6)	0.104	924 (28.9)	948 (29.7)	0.017
Cerebrovascular disease	2139 (17.1)	504 (15.7)	0.038	506 (15.8)	502 (15.7)	0.003
Chronic pulmonary	3331 (26.6)	914 (28.4)	0.041	901 (28.2)	907 (28.4)	0.004
Renal disease	3143 (25.1)	602 (18.7)	0.154	610 (19.1)	598 (18.7)	0.010
Liver disease	1701 (13.6)	488 (15.2)	0.046	504 (15.8)	487 (15.2)	0.015
Diabetes	4023 (32.1)	984 (30.6)	0.033	971 (30.4)	979 (30.6)	0.005
Severity of illness						
SOFA score	6.00 [3.00, 8.00]	8.00 [5.00, 11.00]	0.451	7.00 [5.00, 11.00]	8.00 [5.00, 11.00]	0.027
SAPS II score	39.00 [31.00, 48.00]	40.00 [32.00, 50.00]	0.089	40.00 [31.00, 50.00]	40.00 [32.00, 50.00]	0.003
Sedative-analgesic medications, n (%)						
Propofol	6289 (50.2)	2924 (90.9)	0.997	2902 (90.8)	2902 (90.8)	<0.001
Midazolam	3049 (24.3)	1262 (39.2)	0.324	1234 (38.6)	1246 (39.0)	0.008
Fentanyl	6018 (48.0)	2586 (80.4)	0.717	2601 (81.4)	2564 (80.2)	0.029
AKI stage, n (%)			0.063			0.034
1	6722 (53.6)	1826 (56.7)		1812 (56.7)	1810 (56.6)	
2	4593 (36.6)	1102 (34.2)		1123 (35.1)	1096 (34.3)	
3	1221 (9.7)	290 (9.0)		261 (8.2)	290 (9.1)	
Sepsis, n (%)	8011 (63.9)	2590 (80.5)	0.377	2550 (79.8)	2568 (80.4)	0.014
Antibiotic, n (%)	9852 (78.6)	3016 (93.7)	0.449	2991 (93.6)	2994 (93.7)	0.004
Glucocorticoid, n (%)	2186 (17.4)	544 (16.9)	0.014	530 (16.6)	543 (17.0)	0.011
Outcome, n (%)						
In-hospital mortality	1930 (15.4)	432 (13.4)		563 (17.6)	431 (13.5)	
180-day mortality	3725 (29.7)	704 (21.9)		868 (27.2)	703 (22.0)	

Values are expressed as M±SD/median (IQR) or n (%).

PSM, Propensity Score Matching; DEX, Dexmedetomidine; SAPS, Simplified Acute Physiology Score; WBC, white blood cell; MAP, *Mean arterial pressure*; SOFA, The Sequential Organ Failure Assessment; MV, Mechanical ventilation; CRRT, continuous renal replacement therapy; AKI, Acute kidney disease.

Primary Outcome

In-hospital mortality: We found that DEX use decreased in-hospital mortality risk by 38% among critically ill patients with AKI (HR: 0.62, 95% CI: 0.55-0.70) during PSM modeling. Moreover, Cox proportional hazards regression (HR: 0.61, 95% CI: 0.55-0.68) (Fig.2, Supplementary table 1) and binary logistic regression (OR: 0.64, 95% CI: 0.56-0.73) (Supplementary table 2) were consistent with the trend of PSM modeling. A significant decrease in in-hospital mortality was observed among critically ill patients receiving DEX at AKI stage 1 (15.6% vs. 10.7%, p< 0.001), stage 2 (18.5% vs. 14.7%, p= 0.017) but not stage 3 (27.6% vs. 26.6%, p= 0.848) (Fig.3).

Second Outcome

180-day mortality: DEX use also reduced 180-day mortality risk by 22% among critically ill patients with AKI (HR: 0.77, 95% CI: 0.69-0.85) during PSM modeling. Moreover, Cox proportional hazards regression (HR: 0.68, 95% CI: 0.63-0.74) (Fig.2, Supplementary table 3) and binary logistic regression (OR: 0.64, 95% CI: 0.57-0.71) (Supplementary table 4) were consistent with the trend of PSM modeling. A significant decrease in 180-day mortality was observed among critically ill patients receiving DEX at AKI stage 1 (24.7% vs. 18.2%, p< 0.001), stage 2 (28.3% vs. 24.0%, p= 0.023) but not stage 3 (39.1% vs. 38.3%, p= 0.861) (Fig.3).

We conducted a check on the goodness of fit of the model and found that p< 0.05, indicates a good fit of the model. We also investigated the in-hospital and 180-day survival in critical patients with AKI. The DEX group had significantly higher freedom from death at in-hospital (86.5 vs. 82.4%, p < 0.001) and 180-day (78.0 vs. 72.8%, p < 0.001) than the non-DEX group, respectively (Fig.4).

Overall, the use of DEX had a significant beneficial effect on the in-hospital mortality and 180-day mortality of AKI in critically ill patients.

Subgroup analysis

Subgroup analysis indicated that DEX use reduced in-hospital mortality of critically ill patients with AKI (Supplementary Figure 1). There were no interactions between age, gender, sepsis, AKI stage, and DEX use, suggesting that these results were

comparable for all populations.

Discussion

The present study showed that DEX use in severely ill AKI patients was linked with lower risk-adjusted in-hospital mortality and 180-day mortality. Consistent results were observed in different models. During subgroup analysis, after stratification according to age, gender, AKI stage, and sepsis, a strong correlation was still observed. Overall, we provide preliminary evidence that DEX has a beneficial effect on the prognosis of AKI in critically ill patients, providing the foothold to improve the outcomes of this patient population.

Overwhelming literature substantiates that DEX can alleviate AKI caused by several factors. Wang et al. previously uncovered that DEX could ameliorate AKI in mice with sepsis by partially inhibiting oxidative stress and apoptosis by modulating the p75NTR/p38MAPK/JNK signaling pathways.[25] Zhao et al. further substantiated that DEX protected against lipopolysaccharide-induced AKI by promoting autophagy mediated by PI3K/AKI/mTOR pathway inhibition.[26] A meta-analysis by Loomba et al. demonstrated that DEX could confer postoperative renal protective effects with lower NGAL levels and increased creatine clearance in patients who received DEX. These effects correlated with reduced ICU length of stay and risk of AKI and mortality.[27] Shan et al. found that DEX could minimize AKI incidence in Stanford type B aortic dissection (TBAD) patients after endovascular aortic repair (EVAR).[28] A single-center RCT of 108 patients[29] showed that prior administration of DEX within 24 hours after induction of anesthesia could reduce the incidence of AKI after aortic surgery under cardiopulmonary bypass. An RCT by Tang et al.[30] showed that DEX pretreatment attenuated AKI in patients. Animal studies further indicated that DEX could reduce cellular injury, improve renal function, and mitigate apoptosis in renal cells. Furthermore, Liu et al. revealed that DEX infusion in ICU patients with septic shock was linked to decreased AKI incidence and reduced ICU stay and CRRT performance. It is highly conceivable that the mechanism is related to anti-inflammatory effects and immunomodulation.[31]

Inflammation is key to AKI pathogenesis, progression, and prognosis. An

increasing body of evidence suggests that DEX confers renoprotective effects and may be involved in the regulation of inflammation.[32-34] A meta-analysis by Ma et al.[35] that included 4842 patients showed that DEX decreased pro-inflammatory like cytokines interleukin-6, C-reactive, tumor necrosis factor-α, and increased anti-inflammatory cytokines like IL-10 in surgical patients. A sub-analysis of a multicenter RCT by Ohta et al.[36] suggested that sedation using DEX reduced inflammation in patients with sepsis requiring mechanical ventilation. Animal studies have shown that DEX may have a protective effect on cisplatin-induced AKI, and its potential mechanism may be related to the regulation of apoptosis and inflammatory response.[37] In addition, DEX can ameliorate microcirculation disorders by decreasing norepinephrine levels in the blood and increasing urine output and renal blood flow.[38] Since our study did not collect inflammatory indicators, the hypothesis that DEX may attenuate excessive inflammation could not be confirmed, emphasizing the need for future studies. Emerging evidence substantiates the benefits of DEX in AKI, but the prognosis and follow-up of AKI in critically ill patients have been largely understudied. In the present study, we consistently found that the in-hospital mortality of AKI patients in the DEX group was significantly lower than in the non-DEX group. At the same time, we found that the 180-day mortality of AKI patients was consistent with the in-hospital mortality, suggesting that DEX use is associated with survival benefits in this particular patient population. Our research provides a theoretical basis for clinicians to use DEX to manage critically ill patients with AKI. In our research results, we also found that propofol reduced the risk of in-hospital mortality and 180-day mortality, and we speculate that this may be due to the renal protective effect of propofol[39-40].

Our subgroup analysis showed that DEX was effective in sepsis-associated-AKI (SA-AKI) patients, consistent with the literature.[21] Consistently, Hu et al. analyzed 2192 patients with SA-AKI and found that DEX use was related to decreased in-hospital mortality and improved renal function recovery of SA-AKI in critically ill patients. Unlike Hu's study is that our study included all types of AKI populations in the ICU. Our results showed that DEX use reduced in-hospital mortality of AKI in critically ill patients. Follow-up analysis showed that DEX use reduced the 180-day

mortality of patients. Our findings suggest DEX is effective against sepsis-associated AKI and for AKI patients in general and improves the long-term prognosis. The role of DEX on more types of AKI subgroups warrants further exploration in severely ill subjects. Our study found that using DEX in critically ill patients with AKI can reduce in-hospital mortality and 180-day mortality. Shehabi et al.[41] found that early use of DEX sedation can reduce the 90-day mortality in elderly patients with critically ill mechanical ventilation in the SPICE III trial, whether the patient has surgery or not. On the contrary, a higher likelihood of an increase in 90-day mortality was observed in younger patients of non-surgical status. However, it has not been thoroughly researched for the use of DEX sedation in critically ill patients with AKI, and this study can serve as a supplement to such patients in the SPICE III trial.

Our research has several limitations. First, data acquired from this database was adopted to maximize generalizability and power. Accordingly, there was no formal calculation of sample size in this study. Although the sample size of the subgroup was comparatively larger compared to previous studies, it may also increase the risk of false positive results during multiple subgroup analyses. Second, our study's retrospective nature may have limited our findings' accuracy, and there could be other unknown potentially confounding factors that we were unable to control for. Third, we adjusted for many confounding factors, and PSM was conducted. Moreover, data analyzed in this study were acquired from a single-center observation database, emphasizing the need for a multicenter RCT to increase the robustness of our findings. Forth, due to the lack of admission diagnosis recorded in the MIMIC database, it is difficult for us to accurately identify the etiology of AKI in each patient. Therefore, the AKI patients defined in this study are actually unselected AKI. Although it is difficult to determine the exact cause of AKI and the reason why patients are admitted to the ICU, we have made necessary adjustments for other confounding factors that affect patient mortality. Our conclusion is stable and reliable, and may only apply to unselected AKI in critically ill patients. Fifth, This study did not consider the dosage and duration of DEX use, and further attention is needed in future studies.

Conclusion

This retrospective cohort study showed that dexmedetomidine administration significantly reduces risk-adjusted in-hospital and 180-day mortality in critically ill patients with AKI. However, further RCTs are needed to develop the robustness of our findings.

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Competing interests None declared.

Patient and public involvement Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

Data availability statement Data are available upon reasonable request.

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Figure Legends:

Fig.1. Flowchart of patients selection for the study. MIMIC-IV: Medical Information Mart for Intensive Care Database IV; ICU: intensive care unit.

Fig.2. Association between in-hospital mortality, 180-day mortality and dexmedetomidine use of AKI patients evaluated by the Cox model. HR, hazard ratio; CI: confidence interval; Unadjusted: without adjustment; Multivarable adjusted: adjusted for all the baseline variables shown in Table 1. PSM: propensity score matching.

Fig.3. In-hospital mortality and 180-day mortality of AKI in critically ill patients between the dexmedetomidine and non-dexmedetomidine group in different AKI stage.

Fig.4. Freedom from death at in-hospital and 180-day in critically ill patients with AKI between the two groups.

Supplementary figure 1. Subgroup analysis of the association between dexmedetomidine use and in-hospital mortality.

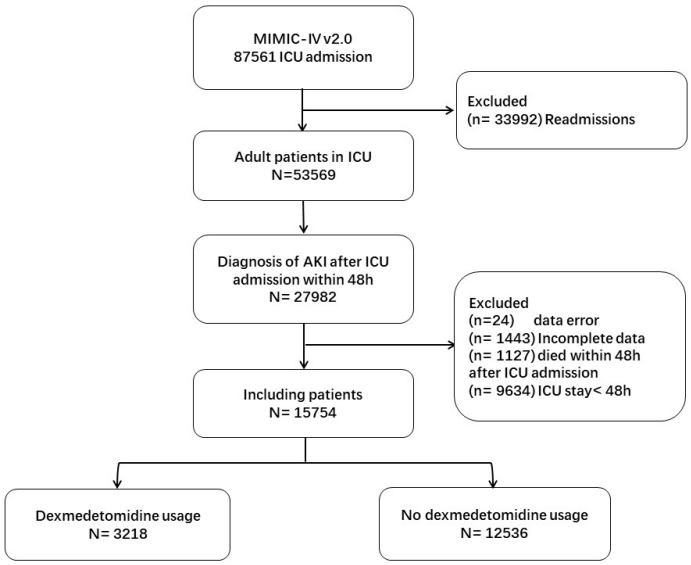

Fig.1. Flowchart of patients selection for the study. MIMIC-IV: Medical Information Mart for Intensive Care Database IV; ICU: intensive care unit.

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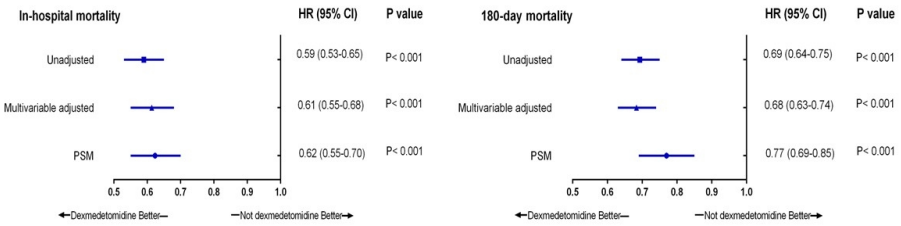

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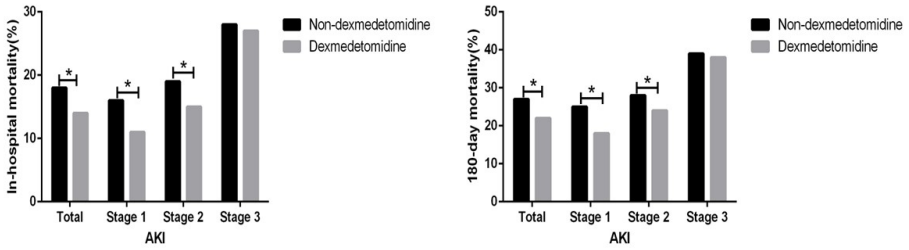

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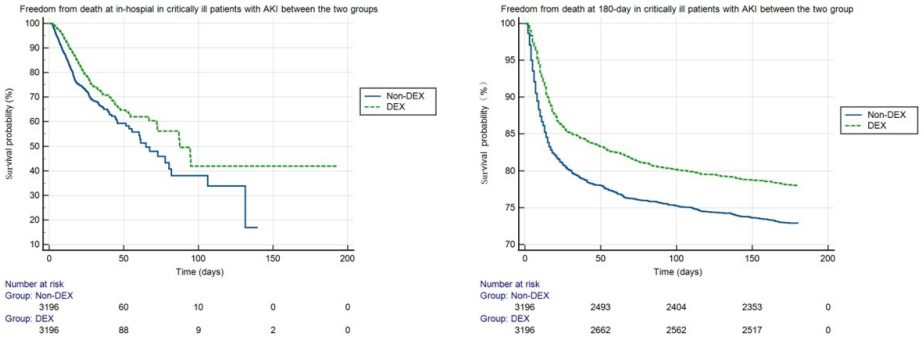


Fig.4. Freedom from death at in-hospital and 180-day in critically ill patients with AKI between the two groups.

338x190mm (96 x 96 DPI)

Supplementary table 1.

Cox logistic regression analysis of in-hospital mortality (before PSM)

	Univariable		Multivariable	
Variables	HR (95%CI)	*P* value	HR (95%CI)	*P* value
Need of support				
Vasopressors	2.636 (2.415, 2.877)	<0.001	1.394 (1.251, 1.553)	<0.001
MV	4.108 (3.782, 4.462)	<0.001	4.090 (3.710, 4.509)	<0.001
CRRT	1.863 (1.680, 2.065)	<0.001	0.845 (0.750, 0.952)	0.006
Comorbidities at ICU admission				
Congestive heart failure	1.151 (1.058, 1.251)	0.001	1.229 (1.125, 1.342)	<0.001
Cerebrovascular disease	1.437 (1.307, 1.581)	<0.001	1.547 [1.403, 1.705]	<0.001
Chronic pulmonary	1.056 (0.965, 1.155)	0.237		
Renal disease	1.101 (1.005, 1.206)	0.040	1.025 [0.928, 1.132]	0.629
Liver disease	1.651 (1.505, 1.812)	<0.001	1.120 (1.009, 1.244)	0.033
Diabetes	0.901 (0.825, 0.984)	<0.001	0.818 [0.746, 0.898]	<0.001
Severity of illness				
SOFA score	1.115 (1.105, 1.125)	<0.001	1.007 [0.993, 1.021]	0.350
SAPS II score	1.033 (1.031, 1.036)	<0.001	1.018 (1.015, 1.021)	<0.001
Sedative-analgesic medications				
Propofol	0.788 (0.725, 0857)	<0.001	0.465 (0.421, 0.513)	<0.001
Midazolam	1.680 (1.547, 1.823)	<0.001	0.838 (0.758, 0.928)	0.001
Fentanyl	1.724 (1.568, 1.895)	<0.001	1.309 (1.154, 1.486)	<0.001
AKI stage				
AKI stage 1	Ref		Ref	
AKI stage 2	1.142 (1.071, 1.217)	<0.001	1.044 (0.955, 1.142)	0.342
AKI stage 3	1.800 (1.646, 1.969)	<0.001	1.048 (0.928, 1.183)	0.453
Lactate (mmol/L)	1.314 (1.292, 1.337)	<0.001	1.224 (1.199, 1.250)	<0.001
Sepsis	1.871 (1.670, 2.096)	<0.001	1.574 (1.304, 1.901)	<0.001
Antibiotic	1.366 (1.191, 1.562)	<0.001	0.665 (0.533, 0.831)	<0.001

Glucocorticoid	0.719 (0.645, 0.801)	<0.001	0.709 (0.635, 0.791)	<0.001
DEX	0.585 (0.526, 0.650)	<0.001	0.610 (0.546, 0.680)	<0.001

PSM, Propensity Score Matching; DEX, Dexmedetomidine; SAPS, Simplified Acute Physiology Score; SOFA, The Sequential Organ Failure Assessment; MV, Mechanical ventilation; CRRT, continuous renal replacement therapy; AKI, Acute kidney disease.

Supplementary table 2.

Binary logistic regression analysis of in-hospital mortality (before PSM)

	Univariable		Multivariable	
Variables	OR (95%CI)	*P* value	OR (95%CI)	*P* value
Need of support				
Vasopressors	5.730 (5.151, 6.375)	<0.001	2.040 (1.766, 2.357)	<0.001
MV	6.194 (5.645, 6.796)	<0.001	5.022 (4.468, 5.644)	<0.001
CRRT	4.960 (4.367, 5.633)	<0.001	1.320 (1.106, 1.575)	0.002
Comorbidities at ICU admission				
Congestive heart failure	1.186 (1.083, 1.299)	<0.001	1.294 (1.156, 1.448)	<0.001
Cerebrovascular disease	1.668 (1.500, 1.854)	<0.001	2.302 (2.029, 2.612)	<0.001
Chronic pulmonary	1.069 (0.969, 1.178)	0.182		
Renal disease	1.206 (1.092, 1.333)	<0.001	1.010 (0.890, 1.146)	0.881
Liver disease	2.612 (2.350, 2.905)	<0.001	1.442 (1.253, 1.659)	<0.001
Diabetes	0.886 (0.806, 0.975)	0.013	0.776 (0.691, 0.871)	<0.001
Severity of illness				
SOFA score	1.222 (1.209, 1.236)	<0.001	1.041 (1.021, 1.060)	<0.001
SAPS II score	1.054 (1.051, 1.057)	<0.001	1.029 (1.024, 1.033)	<0.001
Sedative-analgesic medications				
Propofol	1.129 (1.032, 1.235)	0.008	0.462 (0.406, 0.526)	<0.001
Midazolam	2.938 (2.685, 3.215)	<0.001	1.062 (0.935, 1.206)	0.353
Fentanyl	2.914 (2.638, 3.218)	<0.001	1.499 (1.296, 1.734)	<0.001
AKI stage				
AKI stage 1	Ref		Ref	
AKI stage 2	1.149 (1.044, 1.265)	0.004	1.080 (0.967, 1.207)	0.174

AKI stage 3	2.139 (1.873, 2.442)	<0.001	1.105 (0.937, 1.305)	0.236
Lactate (mmol/L)	1.496 (1.449, 1.545)	<0.001	1.258 (1.212, 1.305)	<0.001
Sepsis	3.145 (2.794, 3.539)	<0.001	1.878 (1.527, 2.310)	<0.001
Antibiotic	2.246 (1.949, 2.587)	<0.001	0.723 (0.566, 0.923)	0.009
Glucocorticoid	0.961 (0.855, 1.080)	0.505		
DEX	0.852 (0.762, 0.953)	0.005	0.639 (0.556,0.734)	<0.001

PSM, Propensity Score Matching; DEX, Dexmedetomidine; SAPS, Simplified Acute Physiology Score; SOFA, The Sequential Organ Failure Assessment; MV, Mechanical ventilation; CRRT, continuous renal replacement therapy; AKI, Acute kidney disease.

Supplementary table ~~32~~3.

Cox logistic regression analysis of 180-day mortality (before PSM)

	Univariable		Multivariable	
Variables	HR (95%CI)	*P* value	HR (95%CI)	*P* value
Need of support				
Vasopressors	2.771 (2.579, 2.977)	<0.001	1.454 (1.331, 1.588)	<0.001
MV	2.626 (2.474, 2.788)	<0.001	2.565 (2.390, 2.752)	<0.001
CRRT	2.554 (2.345, 2.783)	<0.001	0.995 (0.899, 1.101)	0.920
Comorbidities at ICU admission				
Congestive heart failure	1.318 (1.240, 1.400)	<0.001	1.194 (1.120, 1.273)	<0.001
Cerebrovascular disease	1.423 (1.324, 1.530)	<0.001	1.581 (1.469, 1.701)	<0.001
Chronic pulmonary	1.129 (1.058, 1.204)	<0.001	1.104 (1.033, 1.180)	0.004
Renal disease	1.379 (1.293, 1.472)	<0.001	1.090 (1.017, 1.168)	0.015
Liver disease	1.881 (1.749, 2.022)	<0.001	1.249 (1.152, 1.355)	<0.001
Diabetes	0.982 (0.922, 1.046)	0.580		
Severity of illness				
SOFA score	1.129 (1.121, 1.136)	<0.001	1.013 (1.001, 1.024)	0.029
SAPS II score	1.039 (1.037, 1.041)	<0.001	1.025 (1.023, 1.028)	<0.001

Sedative-analgesic medications				
Propofol	0.715 (0.674, 0.758)	<0.001	0.448 (0.418, 0.482)	<0.001
Midazolam	1.809 (1.703, 1.923)	<0.001	0.910 (0.841, 0.986)	0.021
Fentanyl	1.492 (1.404, 1.586)	<0.001	1.242 (1.140, 1.352)	<0.001
AKI stage				
AKI stage 1	Ref		Ref	
AKI stage 2	1.142 (1.071, 1.217)	<0.001	1.076 (1.009, 1.148)	0.025
AKI stage 3	1.800 (1.646, 1.969)	<0.001	1.097 (0.999, 1.204)	0.051
Lactate (mmol/L)	1.250 (1.232, 1.268)	<0.001	1.155 (1.134, 1.176)	<0.001
Sepsis	2.060 (1.915, 2.215)	<0.001	1.664 (1.478, 1.874)	<0.001
Antibiotic	1.531 (1.404, 1.669)	<0.001	0.808 (0.703, 0.928)	0.003
Glucocorticoid	1.162 (1.079, 1.251)	<0.001	1.072 (0.994, 1.156)	0.071
DEX	0.693 (0.639, 0.751)	<0.001	0.683 (0.626,0.744)	<0.001

PSM, Propensity Score Matching; DEX, Dexmedetomidine; SAPS, Simplified Acute Physiology Score; SOFA, The Sequential Organ Failure Assessment; MV, Mechanical ventilation; CRRT, continuous renal replacement therapy; AKI, Acute kidney disease.

Supplementary table 4.

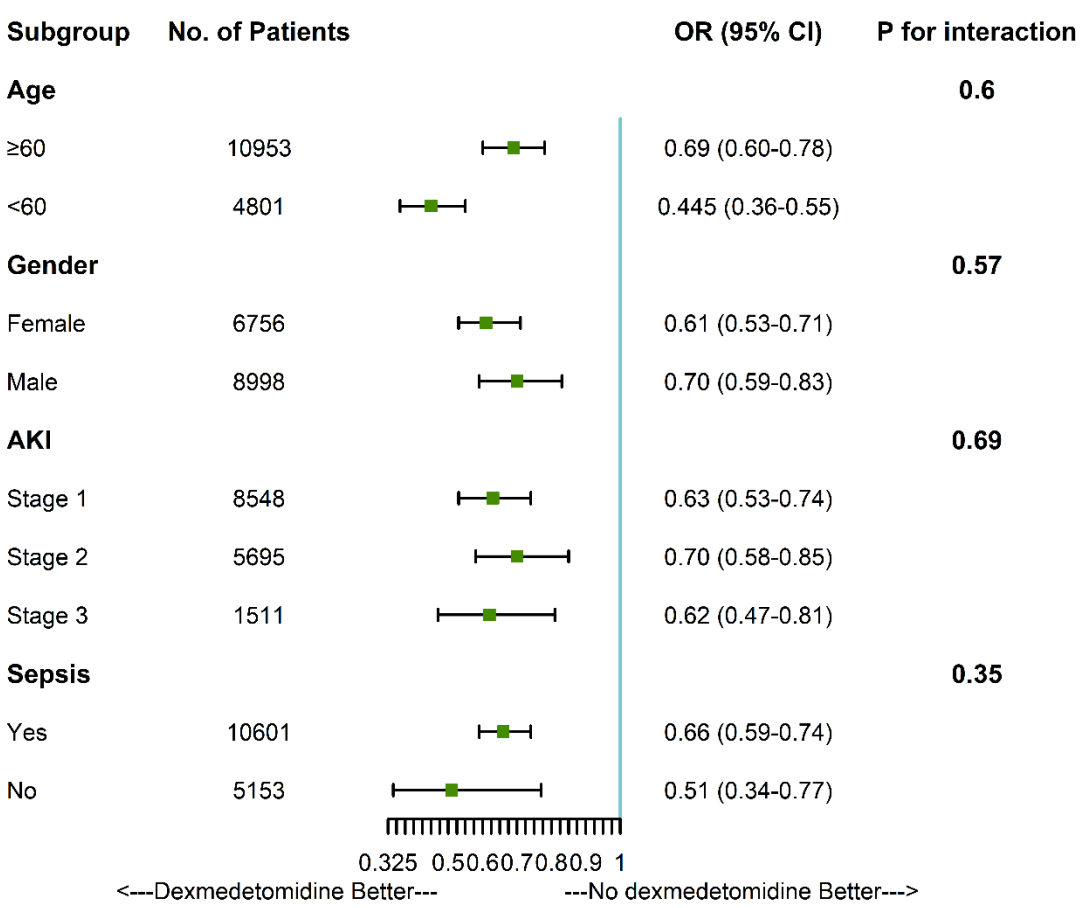
Binary logistic regression analysis of 180-day mortality (before PSM)

	Univariable		Multivariable	
Variables	OR (95%CI)	*P* value	OR (95%CI)	*P* value
Need of support				
Vasopressors	3.346 (3,028, 3.697)	<0.001	1.604 (1.407, 1.828)	<0.001
MV	2.960 (2.744, 3.193)	<0.001	3.059 (2.777, 3.371)	<0.001
CRRT	3.273 (2.896, 3.699)	<0.001	1.117 (0.954, 1.309)	0.170
Comorbidities at ICU admission				
Congestive heart failure	1.416 (1.318, 1.523)	<0.001	1.284 (1.178, 1.401)	<0.001
Cerebrovascular disease	1.504 (1.376, 1.643)	<0.001	1.926 (1.740, 2.131)	<0.001

Chronic pulmonary	1.171 (1.084, 1.265)	<0.001	1.156 (1.057, 1.264)	0.002
Renal disease	1.511 (1.397, 1.635)	<0.001	1.114 (1.014, 1.225)	0.025
Liver disease	2.125 (1.936, 2.332)	<0.001	1.458 (1.298, 1.638)	<0.001
Diabetes	0.993 (0.922, 1.070)	0.860		
Severity of illness				
SOFA score	1.156 (1.145, 1.166)	<0.001	1.012 (0.997, 1.028)	<0.001
SAPS II score	1.052 (1.049, 1.054)	<0.001	1.039 (1.035, 1.043)	<0.001
Sedative-analgesic medications				
Propofol	0.663 (0.618, 0.711)	<0.001	0.335 (0.302, 0.371)	<0.001
Midazolam	2.017 (1.871, 2.173)	<0.001	1.020 (0.918, 1.133)	0.709
Fentanyl	1.563 (1.456, 1.678)	<0.001	1.346 (1.206, 1.501)	<0.001
AKI stage				
AKI stage 1	Ref		Ref	
AKI stage 2	1.170 (1.085, 1.261)	<0.001	1.116 (1.026, 1.215)	0.011
AKI stage 3	2.014 (1.797, 2.256)	<0.001	1.151 (1.007, 1.314)	0.039
Lactate (mmol/L)	1.349 (1.310, 1.389)	<0.001	1.173 (1.135, 1.213)	<0.001
Sepsis	2.293 (2.112, 2.489)	<0.001	1.790 (1.560, 2.053)	<0.001
Antibiotic	1.630 (1.478, 1.797)	<0.001	0.827 (0.704, 0.971)	0.021
Glucocorticoid	1.236 (1.131, 1.352)	<0.001	1.244 (1.124, 1.376)	<0.001
DEX	0.662 (0.604, 0.726)	<0.001	0.636 (0.569,0.711)	<0.001

PSM, Propensity Score Matching; DEX, Dexmedetomidine; SAPS, Simplified Acute Physiology Score; SOFA, The Sequential Organ Failure Assessment; MV, Mechanical ventilation; CRRT, continuous renal replacement therapy; AKI, Acute kidney disease.

Supplementary figure 1



Supplementary figure 1. Subgroup analysis of the association between dexmedetomidine use and in-hospital mortality.

STROBE Statement—Checklist of items that should be included in reports of ***cohort studies***

	Item No	Recommendation	Page No
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	2
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	3
Objectives	3	State specific objectives, including any prespecified hypotheses	3
Methods			
Study design	4	Present key elements of study design early in the paper	4
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	4
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	4
		(*b*) For matched studies, give matching criteria and number of exposed and unexposed	5
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	4
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	5
Bias	9	Describe any efforts to address potential sources of bias	5
Study size	10	Explain how the study size was arrived at	5
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	5
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	4
		(*b*) Describe any methods used to examine subgroups and interactions	4
		(*c*) Explain how missing data were addressed	5
		(*d*) If applicable, explain how loss to follow-up was addressed	
		(*e*) Describe any sensitivity analyses	
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	6
		(b) Give reasons for non-participation at each stage	6
		(c) Consider use of a flow diagram	Yes
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	6
		(b) Indicate number of participants with missing data for each variable of interest	
		(c) Summarise follow-up time (eg, average and total amount)	
Outcome data	15*	Report numbers of outcome events or summary measures over time	6

Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included (*b*) Report category boundaries when continuous variables were categorized (*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	6 6
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	6
Discussion			
Key results	18	Summarise key results with reference to study objectives	7
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	9
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	9
Generalisability	21	Discuss the generalisability (external validity) of the study results	8.9
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	1

*Give information separately for exposed and unexposed groups.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at http://www.strobe-statement.org.

Dear Prof. Shivali Fulchand:

Thank you very much for providing us with the opportunity to revise our manuscript. The red part that has been revised according to your comments.

We are grateful to the editor and reviewers for their constructive comments and helpful suggestions. Responding to the critics, we have conducted additional analyses as requested. We also gave more detail about the methodology. We believe that our manuscript has been substantially improved and hope it is now acceptable for the BMJ Open.

I assure you that all authors have read and approved the submission of the revised manuscript. Also, this work containing the original research has not been published previously nor is under consideration for publication elsewhere.

Please let me know if you might have any further questions.

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Editor

Editor point 1: Please revise the 'Strengths and limitations of this study' section of your manuscript (after the abstract). This section should contain up to five short bullet points, no longer than one sentence each, that relate specifically to the methods. The novelty, aims, results or expected impact of the study should not be summarised here.

Author response 1: Thank you for your comments. We have made necessary modifications to 'Strengths and limitations of this study' section according to your suggestion (**Lines 41-52**).

Editor point 2: We have noticed that Tables embedded in the main document have more than 2 pages. Please be informed that we allow a maximum 2 pages for tables embedded in the main document therefore please can you amend your table in order to fit in the Journal's structured format for tables.

Author response 2: Thank you for your comments. We have made necessary changes to the table style according to your suggestion to ensure that readers can obtain the best viewing experience (**Lines 207-211**). Thank you again.

Reviewer

Reviewer: 1

Point 1: Abstract:

Define in-hospital mortality with a time-frame (e.g. 30 days?) or definition (any time within the same hospital stay as the original ICU admission?)

Author response 1: Thank you for your reminder this issue. In this study, two types of outcome events were defined, namely in-hospital mortality and 180-day mortality. In-hospital mortality refers to the death of a patient during this hospitalization, which was recorded by the hospital. In the MIMIC-IV database, this type of patients was marked with a "hospital expire flag" to indicate the hospital death during this hospitalization. If a patient has been hospitalized multiple times, we only select the patient's first check-in record. We have provided a more detailed explanation of the

outcome events, especially the in-hospital mortality in the resubmit manuscript (**Lines 139-145**). Thank you again.

Point 2: Strengths and limitations:

'The conclusions are qualitative, not quantitative'. May need some expanding- it is not immediately clear what is meant by this, especially as quantitative results are provided.

Author response 2: Thank you for pointing out this issue. We agree with this suggestion and we have made modifications to the 'strengths and limitations' in the resubmit manuscript to appear more rigorous (**Lines 41-52**). Thank you again.

Point 3: Introduction

Please provide references to the previously-conducted research, which you mention towards the end of the final paragraph. I think you should be upfront about causal effect estimation, since that is what you are trying to achieve here via covariate adjustment.

Author response 3: Thank you for your reminder. We have attached the relevant references to the previous literature mentioned in the introduction section. At the same time, we have supplemented our research hypotheses and intentions based on your suggestions (**Lines 74-80**). Thank you very much for your careful guidance.

Point 4: Methods

Source of acute kidney injury/reason for admission to ICU is not reported, which could be significant (E.g. after surgery or sepsis).

Patients who were missing more than 5% of potential risk variables that are associated with mortality were excluded; what were these variables? I note you reference Zhao et al. (2020), who define a similar population, but it is not clear exactly which variables were used to identify this- was it only for missing covariates?

Table 1 should be in the results section.

Author response 4: Thank you for your reminder. This is indeed an issue that cannot be ignored. The etiology of AKI and the reason why patients are admitted to the ICU are important confounding factors. However, due to the lack of admission diagnosis

recorded in the MIMIC database, it is difficult for us to accurately identify the cause of AKI in each patient. Therefore, the AKI patients we defined in this study are actually 'unselected AKI'. Although it is difficult to determine the exact cause of AKI and the reason why patients are admitted to the ICU, we have made necessary adjustments for other confounding factors that affect patient mortality. Our conclusion is stable and reliable, but as you mentioned, our conclusion may only apply to 'unselected AKI'. We have provided additional clarification on this issue in the limitations section (**Lines 323-329**).

Patients who missed more than 5% of potential risk variables related to mortality were excluded from the study, which referred to the description of a similar population defined by Zhao et al. (2020), but was not specifically described in the references. Therefore, this sentence was deleted from our resubmitted manuscript (**Lines 104-105**).

At the same time, we reset Table 1 in the results section and made necessary formatting adjustments to the table (**Lines 207-211**). Thank you very much for your careful guidance.

Point 5: Covariates-defined based on reference 19 (Early administration of glucocorticoid for thyroid storm: analysis of a national administrative database; Senda et al., 2020)- it is not clear why you believe similar adjustment sets would apply here. Common causes of the exposure (DEX use) and outcome (mortality) should be adjusted for here, ideally informed via drawing out the hypothesised causal relationships using a directed acyclic graph.

Author response 5: Thank you for your reminder. When selecting covariates, we prioritize variables that are accurately related to outcome events. The determination of these variables is mainly based on clinical practice and previous literature. We realized that selecting this literature was not appropriate, so we replaced it with other literature that could better explain the selection of covariates (reference 20-21). At the same time, we also carefully considered the included covariates based on the actual situation of the MIMIC database (in fact, there are some important variables that we

cannot obtain from the database, including the etiology of AKI and the reason for admission to the ICU you mentioned earlier) and the variables presented in this study were ultimately determined. We have revised our references to make readers aware of our covariate selection principles (**Lines 116-118**). Thank you again.

Point 6: Exposure: DEX use was defined as patients who received any dexmedetomidine treatment throughout hospitalization in the ICU, whatever the dosage. I'm not sure how much variability could be in the use of DEX. The target trial framework would have helped with defining the exposure. Would you expect to see differential effects between those with 1-2 exposures compared with extended periods of sedation- and what might be the variables that need to be adjusted for in this scenario (i.e. greater exposure to sedatives may be more unwell)?

Author response 6: Thank you for your reminder. Due to the complexity of dealing with the database dose (e.g: differences in DEX usage days and hard to homogenize), we finally consider whether to use DEX for patients as a categorical variable to explore its impact on the outcome. At the same time, we referred to the definition in reference [20] Tao (2021) et al. 'Effects of ondansetron use on outputs of acute kidney injury in critically ill patients: An analysis based on the MIMIC-IV database' for description. The dosage and duration of DEX use may indeed be potential factors affecting outcomes, and we supplemented this issue in the limitations section (**Lines 329-330**). Thank you very much for pointing out this issue.

Point 7: Outcome: in-hospital mortality and 180-day mortality of AKI patients in the ICU. Is there any distinction between AKI mortality and all-cause mortality? I note in the objectives in the abstract, you refer to kidney-related mortality, but it is not clear whether that is the outcome ultimately used.

Author response 7: Thank you for your reminder. In fact, we can only trace the all-cause death of the patient from the MIMIC database, and we cannot identify the kidney-related mortality. We have modified the corresponding expression in the objectives in the abstract. Thank you again (**Lines 17-19**).

Point 8: Statistical analysis: there is an error in the reference #20 (year published is

2010, not 2015). Please specify which covariates were included in the propensity score model. The propensity score approach itself seems reasonable, but I am concerned the model could be misspecified due to potential errors in defining the exposure, and no justification for confounder selection.

Author response 8: Thank you for your careful reminder. We are very sorry for our incorrect reference cite and we have corrected the incorrect reference. We indicate these variables in the covariates section of the revised manuscript. These variables are baseline characteristics of patients and are closely related to outcome events (specifically referring to the research of Tao et al in reference 20-21 and clinical practice). After balancing these variables, we believe that our outcomes will be more reliable and stable (**Lines 421-426**). We have also corrected our definition of exposure in the objectives section (**Lines 17-19**). Thank you very much for your careful guidance.

Point 9: Consider use of an alternate outcome model. Although Cox proportional hazards models are commonly used because covariate adjustment is relatively straightforward, they cannot give causal estimates (see https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3653612/). Also, if you are using all-cause mortality, you do not need to account for competing risks, but if you do conduct an analysis using kidney-related mortality only, you will need to consider the competing risk of all-cause mortality.

Author response 9: Thank you for your suggestion. We have carefully read the literature you recommended. Indeed, there are certain drawbacks to using Cox regression models for causal reasoning. The PSM analysis in this study is actually a method of adjusting observational data, which can reduce the impact of potential confounding variables between intervention factors and outcomes. According to your suggestion, we additionally performed binary logistic regression to better causal inference. Finally, we found that the use of DEX is still an independent risk factor for reducing mortality. We have supplemented the above results in the resubmit manuscript (**Supplementary table 2 and 4**). Thank you again.

Point 10: Results:

Since you mention that DEX is guideline recommended, it is interesting that the treatment group- especially since it is comprised of any exposure to DEX over the period of interest Refer to statistically significant results as such (not just significant). Ensure results are summarised appropriately-for example include error bars on Figure 3.

Author response 10: The question you raised is very interesting, but in fact, the guide we mentioned was released in 2013, so we have updated the guide reference [7] (2022) (**Lines 367-369**). In order to minimize bias as much as possible, we also used statistical methods such as PSM and regression analysis to correct for possible confounding factors, which made the conclusions of this study (based on real-world data) more credible. Our Figure 3 references the drawing method of Tao et al. in reference [20]. Thank you for your thoughtful suggestions (**Lines 421-423**).

Point 11: Discussion

Seems reasonable based on results. Good discussion of previous findings. Ensure absolute risk discussed as well as relative risk.

Author response 11: Thank you for your affirmation and suggestion. We have made necessary modifications to this study based on your suggestions to ensure that the risks reported are true and reasonable. We once again express our gratitude to you. Your carefully suggestions and guidance have made the conclusions we have drawn more reliable and stable. Thank you very much.

Reviewer: 2

Point 1: Abstract:

“acute kidney injury (AKI)-associated mortality”: This would be almost impossible to define from such database. It would assume the study analysed “all-cause mortality in patients with AKI at ICU admission”.

Author response 1: Thank you for your reminder. We are very sorry for our incorrect writing. In fact, we can only trace the all-cause mortality of patients from the MIMIC

database and cannot identify kidney-related mortality. We have modified the corresponding wording in the objectives (**Lines 17-19**) and emphasized the limitations in the section (**Lines 323-329**). Thank you for your careful guidance.

Point 2: Introduction:

"Current guidelines recommend dexmedetomidine (DEX) for sedation in an intensive care setting." The cited reference is outdated, there are more recent guidelines for ICU sedation.

Author response 2: Thank you very much for your suggestion. We have carefully read the latest guide and referenced it [7] in the appropriate location (**Lines 367-369**).Thank you again.

Point 3: Methods:

«The primary outcome was in-hospital mortality and 180-day mortality of AKI patients in the ICU»: Were these co-primary outcomes? If not, one should be declared the primary outcome and the other one is a secondary outcome. Of note, in the abstract, in-hospital mortality is declared to be the primary and 180-day mortality a secondary outcome. This should be clarified.

Author response 3: Thank you for your suggestion. Indeed, there can usually only be one primary outcome. We have followed your suggestion to clearly define primary outcome as in-hospital mortality and secondary outcome as 180-day mortality (**Lines 25-26**) (**Lines 144-145**). Thank you for pointing out this issue.

Point 4: PSM analysis was performed, but most results presented for whole cohort. The authors should clearly indicate which results are from the PSM cohort and which are from the whole cohort. They should also justify their decision to report results for the whole cohort, especially if there are substantial differences between the whole cohort and the PSM cohort.

Author response 4: Thank you for your reminder. We have re described the results section according to your suggestion and provided a detailed explanation of the results before and after PSM. In fact, the variables we selected for inclusion in PSM are all baseline characteristics of patients and are closely related to outcome events. After

careful baseline balancing, the two groups of patients achieved 'post-hoc randomization', which simulated prospective RCT and made the results more reliable (**Lines 173-197**). Thank you very much.

Point 5: For PSM, "The choice of covariate was based on other relevant studies": The study cited is a retrospective cohort study of 811 patients on the effect of glucocorticoids on the survival of patients with thyroid storm that used a different statistical approach except for PSM. I respectfully disagree that this is the best approach to select the covariates.

Author response 5: Thank you for your reminder. The variables we selected were baseline characteristics of patients and were closely related to outcome events. When selecting covariates, the determination of these variables was mainly based on clinical practice and previous literature. We re-emphasized the basis for selecting covariates in the methodology section. Based on your suggestion, we realized that choosing this literature was not appropriate, so we have replaced it with other literature that can better explain covariate selection and we will no longer cite this literature in the resubmit manuscript (**Lines 112-118**). We are very sorry for our incorrect reference cite and thank you for your careful guidance.

Point 6: Results:

Even the unadjusted HR for death was highly significant in favor of DEX. This is very surprising, as no adjustment was made for time, dose and duration of DEX. This might point to selection bias of giving DEX to patients who are more stable and more likely to survive. This should be explained and addressed in the discussion.

Author response 6: Thank you for your reminder. Due to the complexity of dealing with the database dose (e.g: differences in DEX usage days and hard to homogenize), we finally consider whether to use DEX for patients as a categorical variable to explore its impact on the outcome. At the same time, we referred to the definition in reference [20] Tao (2021) et al. 'Effects of ondansetron use on outputs of acute kidney injury in critically ill patients: An analysis based on the MIMIC-IV database' for description (**Lines 421-423**). The dosage and duration of DEX use may indeed be

potential factors affecting outcomes, and we supplemented this issue in the limitations section (**Lines 329-330**). Thank you again.

Point 7: It looks like, in the Cox logistic regression analysis, propofol reduces the OR of death compared to no propofol–this is a very unexpected finding and hard to believe, and should be explained. The proportional hazards assumption should be checked and the authors should assess the risk of overfitting the model, e.g. include the number of events per variable. Finally, the authors could have reported the model's goodness of fit to facilitate the interpretation of the results.

Author response 7:

Thank you for your suggestion. We found in the literature that propofol has a renal protective effect. Therefore, we suspect that reducing the risk of in-hospital mortality and 180-day mortality may be through renal protection. We also added a discussion on the results of propofol in the discussion section of the resubmit manuscript (**Lines 292-294**).

As for the model's goodness of fit, we have fitted the Cox models of in-hospital mortality and 180-day mortality and found that both models were $P<0.05$, indicating good fit. We have also added the results to the resubmit manuscript. (**Lines 231-232**). Thank you for your careful guidance.

Point 8: The authors selected the potential risk variables that are associated with mortality from a study furosemide, not necessarily including AKI patients. The actual variables included in the model and the rationale to select them should be reported.

Author response 8: Thank you for your reminder. When selecting covariates, we prioritize variables that are accurately related to the outcome event. The determination of these variables is mainly based on clinical practice and previous literature. We have referred to other literature that can better explain the selection of covariates in our resubmitted manuscript (references 20-21) (**Lines 421-426**). We matched the baseline characteristics of patients and factors that can affect AKI, and AKI can increase patient mortality. Therefore, we also matched at the baseline. Thank you for pointing out this issue.

Point 9: The authors did not report any adjustments for multiple subgroup analyses, which increases the risk of a type-I error.

Author response 9: Thank you for your reminder. We have adjusted the variables for subgroup analysis, but missed the explanation in the manuscript. Therefore, we have provided additional explanations in the statistical analysis section of the resubmit manuscript (**Lines 157-169**). Thank you for your careful guidance.

Point 10: Table 1:

At baseline, propofol was given to 50% and 90% of patients in the non-Dex and DEX group. However only 23% and 33% of these patients received mechanical ventilation. This is very unusual if not implausible, as propofol is usually given to sedate ventilated patients. How exactly were the baseline variables defined? At ICU admission or within the first 24 hours? Differences in the exact definition of these variables are important and might influence the validity and interpretation of the statistical model.

Author response 10: Thank you for your reminder. Mechanical ventilation we included was based on the first day of ICU admission. Our baseline is also based on data from the first day of ICU admission, and whether to use propofol or other medications for treatment is record during the period of ICU admission, so these seemingly unreasonable results may appear. Therefore, we provide a detailed definition of the sources of these variables in the data definition section (**Lines 127-136**). Thank you for pointing out this issue.

Point 11: Figure 4

There must be an error with the numbers in the graph on the left in Fig 4: It looks like the majority of patients have died. Were the patients discharged alive counted as events rather than censored?

Author response 11: Thank you for your suggestion. We carefully examined our original data and we define the follow-up time for in-hospital mortality using the length of hospital stay, which is different from the 180-day mortality follow-up time. Therefore, there is a difference in the shape of the graphs produced by the two.

This is due to the specificity of the follow-up time for in-hospital mortality, but the trend of the results is consistent. There is a literature [23] that introduces the variable of in-hospital mortality (Hospital mortality was considered as a time-to-event variable. The event was death during hospitalization. A patient was censored when he or she was discharged alive. Patients were followed during their hospital stay.), so we cited it in the article. Thank you again for your reminder (**Lines 140-141**).

Point 12: Discussion:

Timing and dose of the intervention, type and duration of surgery, unmeasured patient characteristics, and perioperative therapeutic strategies are important confounders in this study, and this should be mentioned in the discussion. Moreover, the results should be put into perspective of the SPICE III trial and it's relevant post-hoc analyses.

Author response 12: Thank you for your reminder. Due to the complexity of dealing with the database dose (e.g: differences in DEX usage days and hard to homogenize), we finally consider whether to use DEX for patients as a categorical variable to explore its impact on the outcome. At the same time, we referred to the definition in reference [20] Tao (2021) et al. 'Effects of ondansetron use on outputs of acute kidney injury in critically ill patients: An analysis based on the MIMIC-IV database' for description (**Lines 421-423**). The dosage and duration of DEX use may indeed be potential factors affecting outcomes, and we supplemented this issue in the limitations section and we will continue to focus on this issue in our future research (**Lines 329-330**).

Our study found that using DEX in critically ill patients with AKI can reduce in-hospital mortality and 180-day mortality. Shehabi et al [41] in a SPICE III trial found that early use of DEX sedation can reduce the 90-day mortality in elderly patients with critically ill mechanical ventilation, whatever the patient has surgery or not. On the contrary, a higher likelihood of an increase in 90-day mortality was observed in younger patients of non-surgical status. However, it has not been thoroughly research

for the use of DEX sedation in critically ill patients with AKI, and this study can serve as a supplement to such patients in the SPICE III trial. We also added a discussion in the resubmit manuscript (**Lines 305-312**). Thank you again for your careful guidance.

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The impact of dexmedetomidine on mortality in critically ill patients with acute kidney injury: A retrospective propensity score matching analysis

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The impact of dexmedetomidine on mortality in critically ill patients with acute kidney injury: A retrospective propensity score matching analysis

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Abstract:

Objectives This study sought to estimate the effect of dexmedetomidine (DEX) administration on mortality in critically ill patients with acute kidney injury (AKI).

Design A retrospective cohort study.

Setting The study sourced its data from the Multiparameter Intelligent Monitoring in Intensive Care Database IV (MIMIC-IV), a comprehensive database of ICU patients.

Participants A total of 15754 critically ill patients with AKI were enrolled from the MIMIC-IV database.

Primary and secondary outcome Primary outcome was in-hospital mortality and secondary outcome was 180-day mortality.

Results 15754 critically ill AKI patients were included in our analysis. We found that DEX use decreased in-hospital mortality risk by 38% (HR: 0.62, 95% CI: 0.55-0.70) and 180-day mortality risk by 23% (HR: 0.77, 95% CI: 0.69-0.85). After adjusting for confounding factors, DEX can reduce all three stages of AKI in in-hospital mortality.

Conclusions Our retrospective cohort study suggests that DEX significantly correlates with decreased risk-adjusted in-hospital and 180-day mortality in critically ill AKI patients. Nonetheless, future randomized controlled trials (RCTs) are warranted to validate our findings.

Keywords: Dexmedetomidine, AKI, Mortality, MIMIC-IV, Propensity score matching

Strengths and limitations of this study

- This study included 15754 patients, which is a very large sample size for a clinical study of critically ill patients with AKI.
- Additional confounding factors were adjusted and increased the reliability of our results and conducted a subgroup analysis of the association between DEX use and in-hospital mortality.
- This retrospective study was unable to conduct long-term follow-up, so we look forward to future multicenter clinical studies to make up for this deficiency and further verify the stability of the results in this study.
- The data of this study was from a MIMIC-IV database, and some data may be missing which slightly offsets the results.

Introduction

Over the past few decades, the prevalence of acute kidney injury (AKI) has significantly increased and has gradually become a global health concern.[1] AKI is a common comorbidity among severely ill patients that require intensive care. Indeed, more than half of patients experience AKI during their stay in the intensive care unit (ICU).[2] AKI is related to adverse outcomes, increases CKD occurrence and kidney replacement therapy, and raises the risk of short- and long-term deaths,[3] causing huge

social and economic burdens to patients and society. However, further research is warranted to optimize the management of AKI.[4]

In the context of critical care, effective sedation is of utmost importance for managing agitation and anxiety in patients.[5] The primary objective of sedation in the ICU is to achieve a state of calmness and cooperation in the patient, allowing for the easy awakening and clear communication of needs, particularly concerning pain management.[6] There is evidence to suggest that maintaining light sedation in patients in the ICU can lead to better outcomes. Current guidelines recommend dexmedetomidine (DEX) for sedation in an intensive care setting.[7] DEX is widely used in ICU as a highly selective alpha-2 agonist.[8] An increasing body of evidence suggests that DEX can inhibit the production of excess inflammation cytokine and protect renal function, which may positively impact the prognosis of AKI.[9-11]However, the renoprotective effects of DEX in critically ill patients have not been explored, based on the above characteristics of DEX, we assume that the use of DEX can reduce the mortality rate of AKI patients. The current literature consists mainly of basic-level studies or small samples of other population cohorts, with a paucity of large-scale research.[12-13] Hence, the present study aims to investigate DEX's effect on AKI-related mortality in critically ill patients based on a large sample of critical care public databases.

Methods

Data sources

The study sourced its data from the Multiparameter Intelligent Monitoring in Intensive Care Database IV (MIMIC-IV), a comprehensive database of ICU patients.[14] We collected data on AKI patients from the MIMIC-IV database treated with or without DEX. This database contains a publicly available and real-world clinical database of patients at the Beth Israel Deaconess Medical Center from 2008 to 2019. Informed consent of patients was not required in this study since confidential patient information was already deleted. All reports followed the guidelines of Strengthening Epidemiological Observation and Research Report (STROBE).[15] A Collaborative Institutional Training Initiative (CITI) license (Certificate No. 11326088)

was obtained by Wang W, who was entitled to extract data from the MIMIC-IV database in accordance with the relevant regulations.

Participants

This study included patients who were admitted to the ICU and diagnosed with acute kidney injury (AKI) according to the Kidney Disease Improving Global Outcomes (KDIGO) criteria.[16] The definition of baseline serum creatinine level (SCr) in this study was based on two criteria: 1) the minimum SCr level recorded within 7 days before ICU admission, or 2) if there was no SCr data available before admission, the first SCr level measured upon admission to the ICU was used as the baseline.[17] The MIMIC IV 2.0 database only contains data on adults older than 18. Patients who met any of the following criteria were excluded from the study: (1) death within 48 hours after admission to the ICU, (2) ICU stays less than 48 hours.

Covariates

The study included demographic characteristics and clinical characteristics with 24-hour average values. The Sequential Organ Failure Assessment (SOFA) score,[18] and Simplified Acute Physiology Score (SAPS) II,[19] were calculated within the first 24 h after the ICU admission. We collected the following clinical information of each patient: demographics, laboratory measurements, vital signs, ethnicity, admission type, need of support, comorbidities at ICU admission, severity of illness, sedative-analgesic medications use, AKI stage, sepsis, antibiotic use, glucocorticoid use(Table 1). These covariates, including clinical characteristics and basic demographic information, were based on other relevant studies and clinical practice.[20-22]

Data definitions

Extracted data from MIMIC-IV on the first day of ICU admission, including age, gender, laboratory measurements, vital signs, ethnicity, admission type, vasopressors, mechanical ventilation (MV), continuous renal replacement therapy (CRRT), comorbidities, SOFA score, SAPS II score. We also collected information on whether DEX, propofol, midazolam, fentanyl, antibiotics, and glucocorticoids were used during ICU hospitalization. Sepsis was defined as a life-threatening organ dysfunction caused by a dysregulation of host response to infection (Sepsis 3.0),[23] which refers to

patients with documented or suspected infections and acute changes in the SOFA score ≥ 2 points.

DEX use was defined as patients who received any dexmedetomidine treatment throughout hospitalization in the ICU.

Outcomes

In-hospital mortality refers to the death of patients during this hospitalization, which was recorded by the hospital.[24] In the MIMIC-IV database, this type of patients will be marked with a 'hospital expire flag' to indicate the hospital death during this hospitalization. If a patient has been hospitalized multiple times, we only select the first check-in record. The primary outcome was in-hospital mortality and the second outcome was 180-day mortality of AKI patients in the ICU.

Statistical analysis

Our study presented continuous variables described as mean±standard deviaton for normally distributed or as the median and interquartile range (IQR) if not normally distributed, while the t-test or Mann-Whitney U test was utilized for comparison between groups, respectively. Categorical variables were presented using numbers and percentages (%), and the chi-square test or Fisher's exact test was adopted from group comparisons. We used propensity score matching (PSM) by 1:1 nearest neighbor matching to adjust the baseline difference between the groups. The caliper value was set to 0.2 between matching participants. The standardized mean difference (SMD) was calculated to determine the balance within the model (Table 1), and SMD greater than 0.1 was considered unbalanced.[25]

We used Cox proportional hazards regression and binary logistic regression to assess the effect of DEX use on in-hospital mortality and 180-day mortality. In the subgroup analysis, we used binary logistic regression analysis of in-hospital mortality to assess the effect of DEX use on in-hospital mortality in subgroup populations. Parameters with a p-value< 0.1 during univariate analysis and potential confounding factors were included in the multivariate regression model. In the subgroup analysis, we classified patients based on age, gender, AKI stage, and sepsis incidence to assess

the reliability of our findings. We conducted all statistical analyses using either R version 4.1.2, GraphPad Prism 6 software, or MedCalc 20.1. The significance level was set at $p< 0.05$.

Patient and public involvement

None.

Results

Baseline population characteristics

15754 individuals diagnosed with AKI after ICU admission within 48h were selected for this analysis after excluding patients based on the exclusion criteria (Figure 1). In the whole cohort, the median age of patients was 68 years old, with 8998 (57.1%) males and 6756 (42.9%) females. 8548 (54.3%) patients were diagnosed with AKI stage 1, 5695 (36.1%) with AKI stage 2, and 1511 (9.6%) with AKI stage 3.

In this study, patients were classified into non-dexmedetomidine (non-DEX, n=12536) and dexmedetomidine (DEX, n=3218) groups. Compared with the non-DEX group, the DEX group was younger, heavier weight, higher wbc, temperature, Spo2, sofa score and SAPS II score, faster respiratory rate and heart rate, lower platelet, creatinine, bun, lactate, congestive heart failure and renal disease, more female, white ethnicity, emergency admission, vasopressin use, MV, CRRT, chronic pulmonary, liver disease, propofol use, midazolam use fentanyl use AKI stage 1, sepsis and antibiotics use. After PSM, the characteristics of 3196 patients in both groups were comparable (SMD< 0.1) (Table 1).

Table 1. Baseline characteristics for the two groups before and after matching.

Characteristic	Before PSM			After PSM		
	Non-DEX (n=12536)	DEX (n=3218)	SMD	Non- DEX (n=3196)	DEX (n=3196)	SMD
Age (y)	69.00 [58.00, 79.00]	63.00 [52.00, 73.00]	0.377	64.00 [53.00, 73.00]	63.00 [52.00, 73.00]	0.018
Gender, male, n (%)	6903 (55.1)	2095 (65.1)	0.206	2088 (65.3)	2077 (65.0)	0.007
Laboratory measurements						
Hemoglobin (g/dL)	10.50 [8.90, 12.00]	10.40 [8.90, 12.20]	0.012	10.40 [8.80, 12.10]	10.40 [8.90, 12.20]	0.004
Platelet ($\times 10^9$/L)	188.00 [137.00, 247.54]	174.00 [130.37, 229.46]	0.146	175.35 [127.48, 229.91]	173.90 [130.31, 229.50]	0.009

WBC ($\times 10^9$)	11.10 [8.30, 14.70]	11.86 [9.00, 15.50]	0.075	11.80 [8.70, 15.55]	11.86 [9.00, 15.48]	0.013
Creatinine (mg/dL)	1.10 [0.80, 1.60]	1.00 [0.80, 1.50]	0.108	1.00 [0.70, 1.50]	1.00 [0.80, 1.50]	0.001
BUN (mg/dL)	21.00 [15.00, 35.00]	19.00 [14.00, 28.06]	0.177	19.00 [13.00, 29.00]	19.00 [14.00, 28.06]	0.006
Lactate (mmol/L)	2.02 [1.41, 2.30]	1.83 [1.37, 2.43]	0.051	1.88 [1.38, 2.43]	1.83 [1.37, 2.43]	0.019
Vital signs						
Weight (kg)	80.80 [68.00, 96.00]	86.00 [71.60, 101.00]	0.095	85.00 [71.00, 100.00]	86.00 [71.60, 101.00]	0.041
Temperature (°C)	36.83 [36.57, 37.09]	36.91 [36.71, 37.30]	0.289	36.88 [36.66, 37.29]	36.91 [36.71, 37.29]	0.033
Respiratory rate (bpm)	18.83 [16.68, 21.64]	19.09 [16.96, 21.89]	0.069	18.97 [16.88, 21.72]	19.08 [16.95, 21.87]	0.031
Heart rate (bpm)	84.03 [74.35, 96.08]	84.47 [76.30, 96.94]	0.074	84.74 [75.56, 97.25]	84.41 [76.28, 96.85]	0.007
MAP (mmHg)	75.49 [69.80, 82.95]	75.66 [70.74, 81.85]	0.004	75.74 [70.47, 82.39]	75.64 [70.73, 81.84]	0.021
Spo2 (%)	97.25 [95.77, 98.59]	97.60 [96.20, 98.77]	0.131	97.72 [96.25, 98.93]	97.61 [96.20, 98.77]	0.031
Ethnicity, white, n (%)	8516 (67.9)	2039 (63.4)	0.096	2048 (64.1)	2030 (63.5)	0.012
Admission type, emergency, n (%)	6720 (53.6)	1369 (42.5)	0.223	1393 (43.6)	1365 (42.7)	0.018
Need of support, n (%)						
Vasopressors	1221 (9.7)	600 (18.6)	0.257	554 (17.3)	596 (18.6)	0.034
MV	2977 (23.7)	1069 (33.2)	0.211	1122 (35.1)	1068 (33.4)	0.036
CRRT	768 (6.1)	367 (11.4)	0.187	333 (10.4)	363 (11.4)	0.030
Comorbidities at ICU admission, n (%)						
Congestive heart failure	4314 (34.4)	951 (29.6)	0.104	924 (28.9)	948 (29.7)	0.017
Cerebrovascular disease	2139 (17.1)	504 (15.7)	0.038	506 (15.8)	502 (15.7)	0.003
Chronic pulmonary	3331 (26.6)	914 (28.4)	0.041	901 (28.2)	907 (28.4)	0.004
Renal disease	3143 (25.1)	602 (18.7)	0.154	610 (19.1)	598 (18.7)	0.010
Liver disease	1701 (13.6)	488 (15.2)	0.046	504 (15.8)	487 (15.2)	0.015
Diabetes	4023 (32.1)	984 (30.6)	0.033	971 (30.4)	979 (30.6)	0.005
Severity of illness						
SOFA score	6.00 [3.00, 8.00]	8.00 [5.00, 11.00]	0.451	7.00 [5.00, 11.00]	8.00 [5.00, 11.00]	0.027
SAPS II score	39.00 [31.00, 48.00]	40.00 [32.00, 50.00]	0.089	40.00 [31.00, 50.00]	40.00 [32.00, 50.00]	0.003

Sedative-analgesic medications, n (%)						
Propofol	6289 (50.2)	2924 (90.9)	0.997	2902 (90.8)	2902 (90.8)	<0.001
Midazolam	3049 (24.3)	1262 (39.2)	0.324	1234 (38.6)	1246 (39.0)	0.008
Fentanyl	6018 (48.0)	2586 (80.4)	0.717	2601 (81.4)	2564 (80.2)	0.029
AKI stage, n (%)			0.063			0.034
1	6722 (53.6)	1826 (56.7)		1812 (56.7)	1810 (56.6)	
2	4593 (36.6)	1102 (34.2)		1123 (35.1)	1096 (34.3)	
3	1221 (9.7)	290 (9.0)		261 (8.2)	290 (9.1)	
Sepsis, n (%)	8011 (63.9)	2590 (80.5)	0.377	2550 (79.8)	2568 (80.4)	0.014
Antibiotic, n (%)	9852 (78.6)	3016 (93.7)	0.449	2991 (93.6)	2994 (93.7)	0.004
Glucocorticoid, n (%)	2186 (17.4)	544 (16.9)	0.014	530 (16.6)	543 (17.0)	0.011
Outcome, n (%)						
In-hospital mortality	1930 (15.4)	432 (13.4)		563 (17.6)	431 (13.5)	
180-day mortality	3725 (29.7)	704 (21.9)		868 (27.2)	703 (22.0)	

Values are expressed as M±SD/median (IQR) or n (%).

PSM, Propensity Score Matching; DEX, Dexmedetomidine; SAPS, Simplified Acute Physiology Score; WBC, white blood cell; MAP, *Mean arterial pressure*; SOFA, The Sequential Organ Failure Assessment; MV, Mechanical ventilation; CRRT, continuous renal replacement therapy; AKI, Acute kidney disease.

Primary Outcome

In-hospital mortality: We found that DEX use decreased in-hospital mortality risk by 38% among critically ill patients with AKI (HR: 0.62, 95% CI: 0.55-0.70) during PSM modeling. Moreover, Cox proportional hazards regression (HR: 0.61, 95% CI: 0.55-0.68) (Fig.2, Supplementary table 1) and binary logistic regression (OR: 0.64, 95% CI: 0.56-0.73) (Supplementary table 2) were consistent with the trend of PSM modeling. A significant decrease in in-hospital mortality was observed among critically ill patients receiving DEX at AKI stage 1 (15.6% vs. 10.7%, p< 0.001), stage 2 (18.5% vs. 14.7%, p= 0.017) but not stage 3 (27.6% vs. 26.6%, p= 0.848) (Fig.3).

Second Outcome

180-day mortality: DEX use also reduced 180-day mortality risk by 23% among

critically ill patients with AKI (HR: 0.77, 95% CI: 0.69-0.85) during PSM modeling. Moreover, Cox proportional hazards regression (HR: 0.68, 95% CI: 0.63-0.74) (Fig.2, Supplementary table 3) and binary logistic regression (OR: 0.64, 95% CI: 0.57-0.71) (Supplementary table 4) were consistent with the trend of PSM modeling. A significant decrease in 180-day mortality was observed among critically ill patients receiving DEX at AKI stage 1 (24.7% vs. 18.2%, p< 0.001), stage 2 (28.3% vs. 24.0%, p= 0.023) but not stage 3 (39.1% vs. 38.3%, p= 0.861) (Fig.3).

We conducted a check on the goodness of fit of the model and found that p< 0.05, indicates a good fit of the model. We also investigated the in-hospital and 180-day survival in critical patients with AKI. The DEX group had significantly higher freedom from death at in-hospital (86.5 vs. 82.4%, p < 0.001) and 180-day (78.0 vs. 72.8%, p < 0.001) than the non-DEX group, respectively (Fig.4).

Overall, the use of DEX had a significant beneficial effect on the in-hospital mortality and 180-day mortality of AKI in critically ill patients.

Subgroup analysis

Subgroup analysis indicated that DEX use reduced in-hospital mortality of critically ill patients with AKI (Supplementary Figure 1). There were no interactions between age, gender, sepsis, AKI stage, and DEX use, suggesting that these results were comparable for all populations.

Discussion

The present study showed that DEX use in severely ill AKI patients was linked with lower risk-adjusted in-hospital mortality and 180-day mortality. Consistent results were observed in different models. During subgroup analysis, after stratification according to age, gender, AKI stage, and sepsis, a strong correlation was still observed. Overall, we provide preliminary evidence that DEX has a beneficial effect on the prognosis of AKI in critically ill patients, providing the foothold to improve the outcomes of this patient population.

Overwhelming literature substantiates that DEX can alleviate AKI caused by several factors. Ruegg et al. in a review summarized the role of dexmedetomidine in preventing acute kidney injury in intensive care.[26] Wang et al. previously uncovered

that DEX could ameliorate AKI in mice with sepsis by partially inhibiting oxidative stress and apoptosis by modulating the p75NTR/p38MAPK/JNK signaling pathways.[27] Zhao et al. further substantiated that DEX protected against lipopolysaccharide-induced AKI by promoting autophagy mediated by PI3K/AKI/mTOR pathway inhibition.[28] A meta-analysis by Loomba et al. demonstrated that DEX could confer postoperative renal protective effects with lower NGAL levels and increased creatine clearance in patients who received DEX. These effects correlated with reduced ICU length of stay and risk of AKI and mortality.[29] Shan et al. found that DEX could minimize AKI incidence in Stanford type B aortic dissection (TBAD) patients after endovascular aortic repair (EVAR).[30] A single-center RCT of 108 patients[31] showed that prior administration of DEX within 24 hours after induction of anesthesia could reduce the incidence of AKI after aortic surgery under cardiopulmonary bypass. An RCT by Tang et al.[32] showed that DEX pretreatment attenuated AKI in patients. Animal studies further indicated that DEX could reduce cellular injury, improve renal function, and mitigate apoptosis in renal cells. Furthermore, Liu et al. revealed that DEX infusion in ICU patients with septic shock was linked to decreased AKI incidence and reduced ICU stay and CRRT performance. It is highly conceivable that the mechanism is related to anti-inflammatory effects and immunomodulation.[33]

Inflammation is key to AKI pathogenesis, progression, and prognosis. An increasing body of evidence suggests that DEX confers renoprotective effects and may be involved in the regulation of inflammation.[34-36] A meta-analysis by Ma et al.[37] that included 4842 patients showed that DEX decreased pro-inflammatory like cytokines interleukin-6, C-reactive, tumor necrosis factor-α, and increased anti-inflammatory cytokines like IL-10 in surgical patients. A sub-analysis of a multicenter RCT by Ohta et al.[38] suggested that sedation using DEX reduced inflammation in patients with sepsis requiring mechanical ventilation. Animal studies have shown that DEX may have a protective effect on cisplatin-induced AKI, and its potential mechanism may be related to the regulation of apoptosis and inflammatory response.[39] In addition, DEX can ameliorate microcirculation disorders by

decreasing norepinephrine levels in the blood and increasing urine output and renal blood flow.[40] Since our study did not collect inflammatory indicators, the hypothesis that DEX may attenuate excessive inflammation could not be confirmed, emphasizing the need for future studies. Emerging evidence substantiates the benefits of DEX in AKI, but the prognosis and follow-up of AKI in critically ill patients have been largely understudied. In the present study, we consistently found that the in-hospital mortality of AKI patients in the DEX group was significantly lower than in the non-DEX group. At the same time, we found that the 180-day mortality of AKI patients was consistent with the in-hospital mortality, suggesting that DEX use is associated with survival benefits in this particular patient population. Our research provides a theoretical basis for clinicians to use DEX to manage critically ill patients with AKI. In our research results, we also found that propofol reduced the risk of in-hospital mortality and 180-day mortality, and we speculate that this may be due to the renal protective effect of propofol,[41-42] this finding may also be due to the fact that propofol may be give more often to patients who are hemodynamically more stable and therefore more like to survive. The commonly used sedative drugs in ICU are propofol, dexmedetomidine, and midazolam, which can be used alone or in combination. There was no statistically significant difference in the use of propofol between the two groups after PSM, and we also adjusted for propofol as a confounding factor in the logistic regression analysis, and the interference of propofol on death outcomes was excluded.

Our subgroup analysis showed that DEX was effective in sepsis-associated-AKI (SA-AKI) patients, consistent with the literature.[21] Consistently, Hu et al. analyzed 2192 patients with SA-AKI and found that DEX use was related to decreased in-hospital mortality and improved renal function recovery of SA-AKI in critically ill patients. Unlike Hu's study is that our study included all types of AKI populations in the ICU. Our results showed that DEX use reduced in-hospital mortality of AKI in critically ill patients. Follow-up analysis showed that DEX use reduced the 180-day mortality of patients. Our findings suggest DEX is effective against sepsis-associated AKI and for AKI patients in general and improves the long-term prognosis. The role of DEX on more types of AKI subgroups warrants further exploration in severely ill

subjects. Our study found that using DEX in critically ill patients with AKI can reduce in-hospital mortality and 180-day mortality. In the figure 3 we conducted a chi-square test from group comparisons and the impact of confounding factors was not included. In the subgroup analysis in the supplementary figures we used binary logistic regression analysis and include the influence of confounding factors. After adjusting for confounding factors, DEX can reduce all three stages of AKI in in-hospital mortality. Shehabi et al.[43] found that early use of DEX sedation can reduce the 90-day mortality in elderly patients with critically ill mechanical ventilation in the SPICE III trial, whether the patient has surgery or not. On the contrary, a higher likelihood of an increase in 90-day mortality was observed in younger patients of non-surgical status. However, it has not been thoroughly researched for the use of DEX sedation in critically ill patients with AKI, and this study can serve as a supplement to such patients in the SPICE III trial.

Our research has several limitations. First, data acquired from this database was adopted to maximize generalizability and power. Accordingly, there was no formal calculation of sample size in this study. Although the sample size of the subgroup was comparatively larger compared to previous studies, it may also increase the risk of false positive results during multiple subgroup analyses. Second, our study's retrospective nature may have limited our findings' accuracy, and there could be other unknown potentially confounding factors that we were unable to control for. Third, we adjusted for many confounding factors, and PSM was conducted. Moreover, data analyzed in this study were acquired from a single-center observation database, emphasizing the need for a multicenter RCT to increase the robustness of our findings. Forth, due to the lack of admission diagnosis recorded in the MIMIC database, it is difficult for us to accurately identify the etiology of AKI in each patient. Therefore, the AKI patients defined in this study are actually unselected AKI. Although it is difficult to determine the exact cause of AKI and the reason why patients are admitted to the ICU, we have made necessary adjustments for other confounding factors that affect patient mortality. Our conclusion is stable and reliable, and may only apply to unselected AKI in critically ill patients. Fifth, this study did not consider the dosage and duration of DEX use, and

further attention is needed in future studies. Sixth, in this study we did not consider changes in exposure or covariates over time. Due to the large number and heterogeneity of patients, it is difficult to quantify or qualitatively measure the changes in exposure or covariates of all patients over time. We focus on the measurement indicators of patients at admission, and only by analyzing this time point can we have significant value in promoting and applying our conclusions in clinical practice.

Conclusion

This retrospective cohort study showed that dexmedetomidine administration is associated with reduced risk-adjusted in-hospital and 180-day mortality in critically ill patients with AKI. However, further RCTs are needed to develop the robustness of our findings.

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Contributors WW and JL designed the study. YJ and PZ conducted data collection. PG and HW conducted data analysis. WW wrote the manuscript. WW and JL analyzed and interpreted the result. All authors reviewed this manuscript.

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Competing interests None declared.

Patient and public involvement Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

Data availability statement Data are available upon reasonable request.

Patient consent for publication Not required.

Ethics approval Considering that this study was based on the analysis of an anonymous third-party public database with prior approval from the Institutional Review Board, no ethical review was required.

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Figure Legends:

Fig.1. Flowchart of patients selection for the study. MIMIC-IV: Medical Information Mart for Intensive Care Database IV; ICU: intensive care unit.

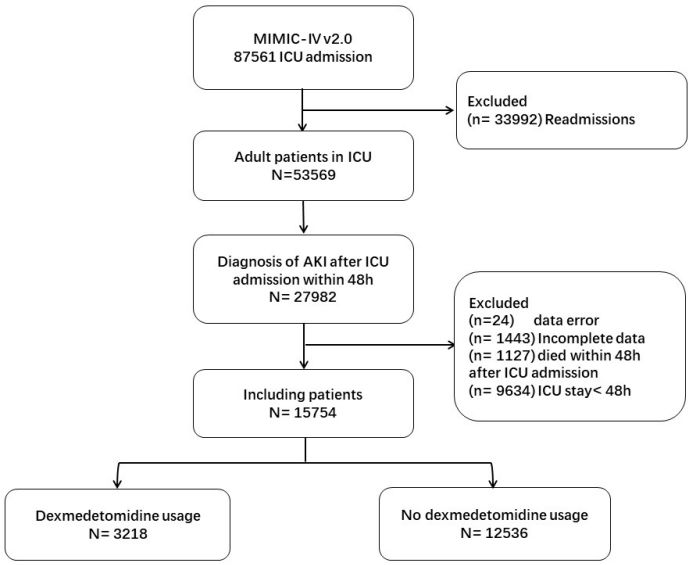
Fig.2. Association between in-hospital mortality, 180-day mortality and dexmedetomidine use of AKI patients evaluated by the Cox model. HR, hazard ratio; CI: confidence interval; Unadjusted: without adjustment; Multivarable adjusted: adjusted for all the baseline variables shown in Table 1. PSM: propensity score matching.

Fig.3. In-hospital mortality and 180-day mortality of AKI in critically ill patients between the

dexmedetomidine and non-dexmedetomidine group in different AKI stage.

Fig.4. Freedom from death at in-hospital and 180-day in critically ill patients with AKI between the two groups.

Supplementary figure 1. Subgroup analysis of the association between dexmedetomidine use and in-hospital mortality.



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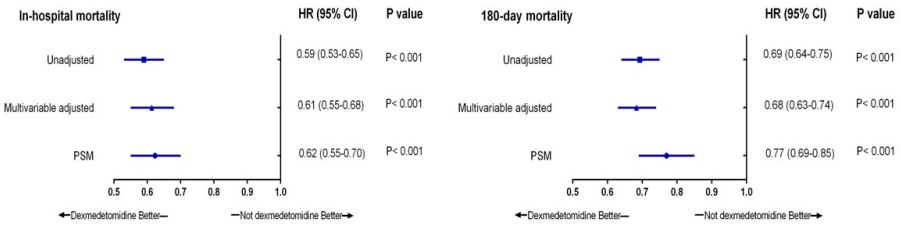

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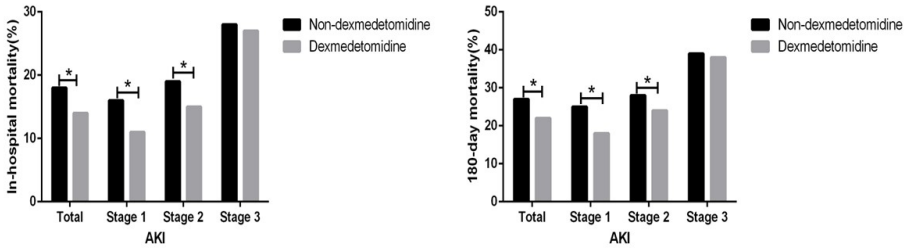


Fig.3. In-hospital mortality and 180-day mortality of AKI in critically ill patients between the dexmedetomidine and non-dexmedetomidine group in different AKI stage.

338x190mm (96 x 96 DPI)

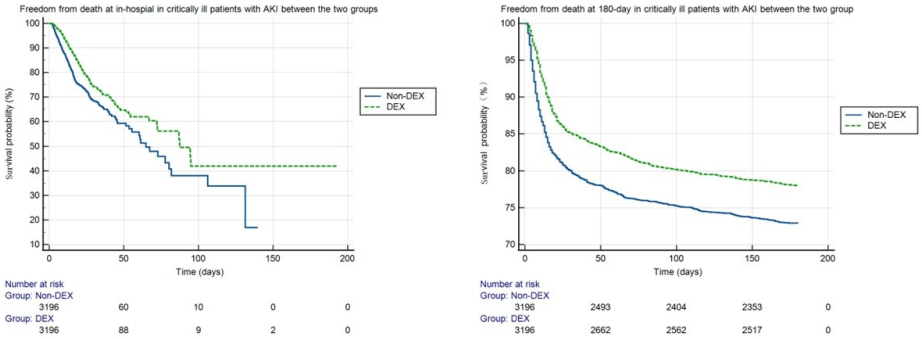


Fig.4. Freedom from death at in-hospital and 180-day in critically ill patients with AKI between the two groups.

338x190mm (96 x 96 DPI)

Supplementary table 1.

Cox logistic regression analysis of in-hospital mortality (before PSM)

	Univariable		Multivariable	
Variables	HR (95%CI)	*P* value	HR (95%CI)	*P* value
Need of support				
Vasopressors	2.636 (2.415, 2.877)	<0.001	1.394 (1.251, 1.553)	<0.001
MV	4.108 (3.782, 4.462)	<0.001	4.090 (3.710, 4.509)	<0.001
CRRT	1.863 (1.680, 2.065)	<0.001	0.845 (0.750, 0.952)	0.006
Comorbidities at ICU admission				
Congestive heart failure	1.151 (1.058, 1.251)	0.001	1.229 (1.125, 1.342)	<0.001
Cerebrovascular disease	1.437 (1.307, 1.581)	<0.001	1.547 [1.403, 1.705]	<0.001
Chronic pulmonary	1.056 (0.965, 1.155)	0.237		
Renal disease	1.101 (1.005, 1.206)	0.040	1.025 [0.928, 1.132]	0.629
Liver disease	1.651 (1.505, 1.812)	<0.001	1.120 (1.009, 1.244)	0.033
Diabetes	0.901 (0.825, 0.984)	<0.001	0.818 [0.746, 0.898]	<0.001
Severity of illness				
SOFA score	1.115 (1.105, 1.125)	<0.001	1.007 [0.993, 1.021]	0.350
SAPS II score	1.033 (1.031, 1.036)	<0.001	1.018 (1.015, 1.021)	<0.001
Sedative-analgesic medications				
Propofol	0.788 (0.725, 0857)	<0.001	0.465 (0.421, 0.513)	<0.001
Midazolam	1.680 (1.547, 1.823)	<0.001	0.838 (0.758, 0.928)	0.001
Fentanyl	1.724 (1.568, 1.895)	<0.001	1.309 (1.154, 1.486)	<0.001
AKI stage				
AKI stage 1	Ref		Ref	
AKI stage 2	1.142 (1.071, 1.217)	<0.001	1.044 (0.955, 1.142)	0.342
AKI stage 3	1.800 (1.646, 1.969)	<0.001	1.048 (0.928, 1.183)	0.453
Lactate (mmol/L)	1.314 (1.292, 1.337)	<0.001	1.224 (1.199, 1.250)	<0.001
Sepsis	1.871 (1.670, 2.096)	<0.001	1.574 (1.304, 1.901)	<0.001
Antibiotic	1.366 (1.191, 1.562)	<0.001	0.665 (0.533, 0.831)	<0.001

Glucocorticoid	0.719 (0.645, 0.801)	<0.001	0.709 (0.635, 0.791)	<0.001
DEX	0.585 (0.526, 0.650)	<0.001	0.610 (0.546, 0.680)	<0.001

PSM, Propensity Score Matching; DEX, Dexmedetomidine; SAPS, Simplified Acute Physiology Score; SOFA, The Sequential Organ Failure Assessment; MV, Mechanical ventilation; CRRT, continuous renal replacement therapy; AKI, Acute kidney disease.

Supplementary table 2.

Binary logistic regression analysis of in-hospital mortality (before PSM)

	Univariable		Multivariable	
Variables	OR (95%CI)	*P* value	OR (95%CI)	*P* value
Need of support				
Vasopressors	5.730 (5.151, 6.375)	<0.001	2.040 (1.766, 2.357)	<0.001
MV	6.194 (5.645, 6.796)	<0.001	5.022 (4.468, 5.644)	<0.001
CRRT	4.960 (4.367, 5.633)	<0.001	1.320 (1.106, 1.575)	0.002
Comorbidities at ICU admission				
Congestive heart failure	1.186 (1.083, 1.299)	<0.001	1.294 (1.156, 1.448)	<0.001
Cerebrovascular disease	1.668 (1.500, 1.854)	<0.001	2.302 (2.029, 2.612)	<0.001
Chronic pulmonary	1.069 (0.969, 1.178)	0.182		
Renal disease	1.206 (1.092, 1.333)	<0.001	1.010 (0.890, 1.146)	0.881
Liver disease	2.612 (2.350, 2.905)	<0.001	1.442 (1.253, 1.659)	<0.001
Diabetes	0.886 (0.806, 0.975)	0.013	0.776 (0.691, 0.871)	<0.001
Severity of illness				
SOFA score	1.222 (1.209, 1.236)	<0.001	1.041 (1.021, 1.060)	<0.001
SAPS II score	1.054 (1.051, 1.057)	<0.001	1.029 (1.024, 1.033)	<0.001
Sedative-analgesic medications				
Propofol	1.129 (1.032, 1.235)	0.008	0.462 (0.406, 0.526)	<0.001
Midazolam	2.938 (2.685, 3.215)	<0.001	1.062 (0.935, 1.206)	0.353
Fentanyl	2.914 (2.638, 3.218)	<0.001	1.499 (1.296, 1.734)	<0.001
AKI stage				
AKI stage 1	Ref		Ref	
AKI stage 2	1.149 (1.044, 1.265)	0.004	1.080 (0.967, 1.207)	0.174

AKI stage 3	2.139 (1.873, 2.442)	<0.001	1.105 (0.937, 1.305)	0.236
Lactate (mmol/L)	1.496 (1.449, 1.545)	<0.001	1.258 (1.212, 1.305)	<0.001
Sepsis	3.145 (2.794, 3.539)	<0.001	1.878 (1.527, 2.310)	<0.001
Antibiotic	2.246 (1.949, 2.587)	<0.001	0.723 (0.566, 0.923)	0.009
Glucocorticoid	0.961 (0.855, 1.080)	0.505		
DEX	0.852 (0.762, 0.953)	0.005	0.639 (0.556,0.734)	<0.001

PSM, Propensity Score Matching; DEX, Dexmedetomidine; SAPS, Simplified Acute Physiology Score; SOFA, The Sequential Organ Failure Assessment; MV, Mechanical ventilation; CRRT, continuous renal replacement therapy; AKI, Acute kidney disease.

Supplementary table 3.

Cox logistic regression analysis of 180-day mortality (before PSM)

	Univariable		Multivariable	
Variables	HR (95%CI)	*P* value	HR (95%CI)	*P* value
Need of support				
Vasopressors	2.771 (2.579, 2.977)	<0.001	1.454 (1.331, 1.588)	<0.001
MV	2.626 (2.474, 2.788)	<0.001	2.565 (2.390, 2.752)	<0.001
CRRT	2.554 (2.345, 2.783)	<0.001	0.995 (0.899, 1.101)	0.920
Comorbidities at ICU admission				
Congestive heart failure	1.318 (1.240, 1.400)	<0.001	1.194 (1.120, 1.273)	<0.001
Cerebrovascular disease	1.423 (1.324, 1.530)	<0.001	1.581 (1.469, 1.701)	<0.001
Chronic pulmonary	1.129 (1.058, 1.204)	<0.001	1.104 (1.033, 1.180)	0.004
Renal disease	1.379 (1.293, 1.472)	<0.001	1.090 (1.017, 1.168)	0.015
Liver disease	1.881 (1.749, 2.022)	<0.001	1.249 (1.152, 1.355)	<0.001
Diabetes	0.982 (0.922, 1.046)	0.580		
Severity of illness				
SOFA score	1.129 (1.121, 1.136)	<0.001	1.013 (1.001, 1.024)	0.029
SAPS II score	1.039 (1.037, 1.041)	<0.001	1.025 (1.023, 1.028)	<0.001

Sedative-analgesic medications				
Propofol	0.715 (0.674, 0.758)	<0.001	0.448 (0.418, 0.482)	<0.001
Midazolam	1.809 (1.703, 1.923)	<0.001	0.910 (0.841, 0.986)	0.021
Fentanyl	1.492 (1.404, 1.586)	<0.001	1.242 (1.140, 1.352)	<0.001
AKI stage				
AKI stage 1	Ref		Ref	
AKI stage 2	1.142 (1.071, 1.217)	<0.001	1.076 (1.009, 1.148)	0.025
AKI stage 3	1.800 (1.646, 1.969)	<0.001	1.097 (0.999, 1.204)	0.051
Lactate (mmol/L)	1.250 (1.232, 1.268)	<0.001	1.155 (1.134, 1.176)	<0.001
Sepsis	2.060 (1.915, 2.215)	<0.001	1.664 (1.478, 1.874)	<0.001
Antibiotic	1.531 (1.404, 1.669)	<0.001	0.808 (0.703, 0.928)	0.003
Glucocorticoid	1.162 (1.079, 1.251)	<0.001	1.072 (0.994, 1.156)	0.071
DEX	0.693 (0.639, 0.751)	<0.001	0.683 (0.626,0.744)	<0.001

PSM, Propensity Score Matching; DEX, Dexmedetomidine; SAPS, Simplified Acute Physiology Score; SOFA, The Sequential Organ Failure Assessment; MV, Mechanical ventilation; CRRT, continuous renal replacement therapy; AKI, Acute kidney disease.

Supplementary table 4.

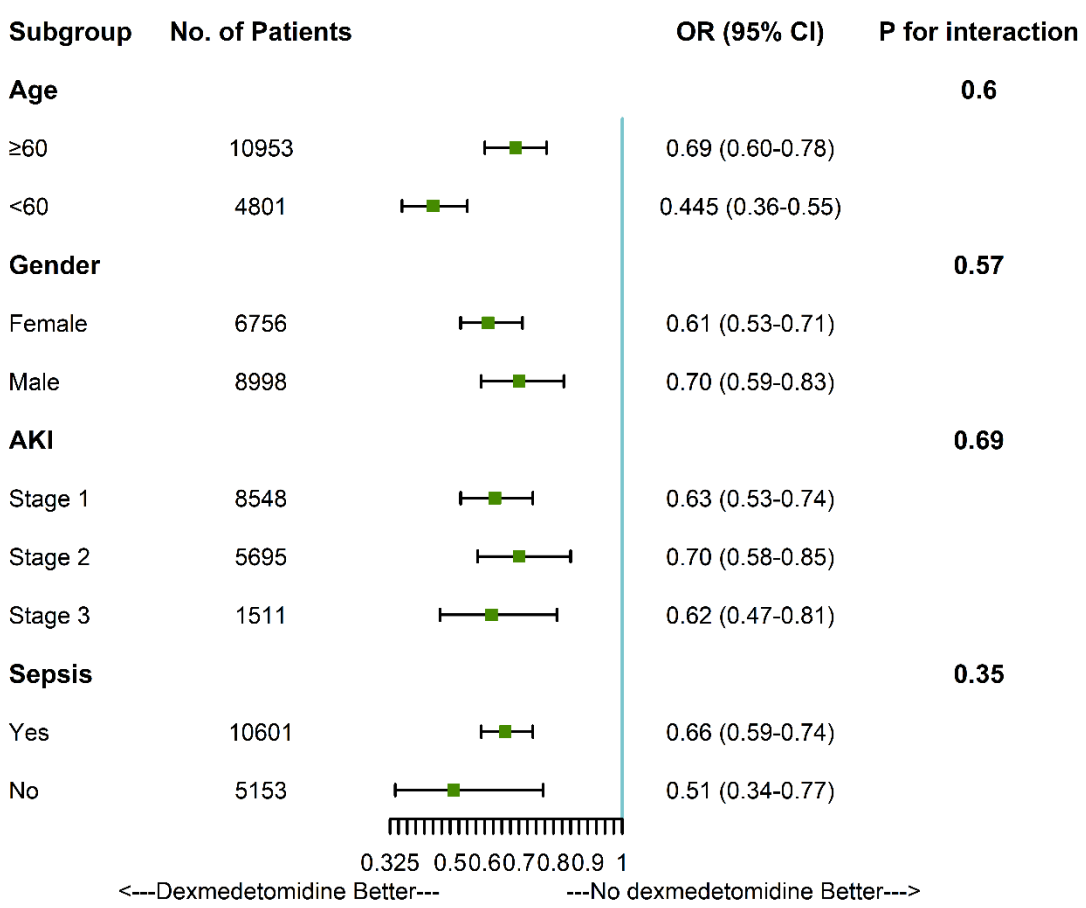
Binary logistic regression analysis of 180-day mortality (before PSM)

	Univariable		Multivariable	
Variables	OR (95%CI)	*P* value	OR (95%CI)	*P* value
Need of support				
Vasopressors	3.346 (3,028, 3.697)	<0.001	1.604 (1.407, 1.828)	<0.001
MV	2.960 (2.744, 3.193)	<0.001	3.059 (2.777, 3.371)	<0.001
CRRT	3.273 (2.896, 3.699)	<0.001	1.117 (0.954, 1.309)	0.170
Comorbidities at ICU admission				
Congestive heart failure	1.416 (1.318, 1.523)	<0.001	1.284 (1.178, 1.401)	<0.001
Cerebrovascular disease	1.504 (1.376, 1.643)	<0.001	1.926 (1.740, 2.131)	<0.001

Chronic pulmonary	1.171 (1.084, 1.265)	<0.001	1.156 (1.057, 1.264)	0.002
Renal disease	1.511 (1.397, 1.635)	<0.001	1.114 (1.014, 1.225)	0.025
Liver disease	2.125 (1.936, 2.332)	<0.001	1.458 (1.298, 1.638)	<0.001
Diabetes	0.993 (0.922, 1.070)	0.860		
Severity of illness				
SOFA score	1.156 (1.145, 1.166)	<0.001	1.012 (0.997, 1.028)	<0.001
SAPS II score	1.052 (1.049, 1.054)	<0.001	1.039 (1.035, 1.043)	<0.001
Sedative-analgesic medications				
Propofol	0.663 (0.618, 0.711)	<0.001	0.335 (0.302, 0.371)	<0.001
Midazolam	2.017 (1.871, 2.173)	<0.001	1.020 (0.918, 1.133)	0.709
Fentanyl	1.563 (1.456, 1.678)	<0.001	1.346 (1.206, 1.501)	<0.001
AKI stage				
AKI stage 1	Ref		Ref	
AKI stage 2	1.170 (1.085, 1.261)	<0.001	1.116 (1.026, 1.215)	0.011
AKI stage 3	2.014 (1.797, 2.256)	<0.001	1.151 (1.007, 1.314)	0.039
Lactate (mmol/L)	1.349 (1.310, 1.389)	<0.001	1.173 (1.135, 1.213)	<0.001
Sepsis	2.293 (2.112, 2.489)	<0.001	1.790 (1.560, 2.053)	<0.001
Antibiotic	1.630 (1.478, 1.797)	<0.001	0.827 (0.704, 0.971)	0.021
Glucocorticoid	1.236 (1.131, 1.352)	<0.001	1.244 (1.124, 1.376)	<0.001
DEX	0.662 (0.604, 0.726)	<0.001	0.636 (0.569,0.711)	<0.001

PSM, Propensity Score Matching; DEX, Dexmedetomidine; SAPS, Simplified Acute Physiology Score; SOFA, The Sequential Organ Failure Assessment; MV, Mechanical ventilation; CRRT, continuous renal replacement therapy; AKI, Acute kidney disease.

Supplementary figure 1



Supplementary figure 1. Subgroup analysis of the association between dexmedetomidine use and in-hospital mortality.

STROBE Statement—Checklist of items that should be included in reports of ***cohort studies***

	Item No	Recommendation	Page No
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	2
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	3
Objectives	3	State specific objectives, including any prespecified hypotheses	3
Methods			
Study design	4	Present key elements of study design early in the paper	4
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	4
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	4
		(*b*) For matched studies, give matching criteria and number of exposed and unexposed	5
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	4
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	5
Bias	9	Describe any efforts to address potential sources of bias	5
Study size	10	Explain how the study size was arrived at	5
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	5
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	4
		(*b*) Describe any methods used to examine subgroups and interactions	4
		(*c*) Explain how missing data were addressed	5
		(*d*) If applicable, explain how loss to follow-up was addressed	
		(*e*) Describe any sensitivity analyses	
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	6
		(b) Give reasons for non-participation at each stage	6
		(c) Consider use of a flow diagram	Yes
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	6
		(b) Indicate number of participants with missing data for each variable of interest	
		(c) Summarise follow-up time (eg, average and total amount)	
Outcome data	15*	Report numbers of outcome events or summary measures over time	6

Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included (*b*) Report category boundaries when continuous variables were categorized (*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	6 6
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	6
Discussion			
Key results	18	Summarise key results with reference to study objectives	7
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	9
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	9
Generalisability	21	Discuss the generalisability (external validity) of the study results	8.9
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	1

*Give information separately for exposed and unexposed groups.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at http://www.strobe-statement.org.