

Effects of Dexmedetomidine Administration on Outcomes in Critically Ill Patients with Acute Kidney Injury: A Propensity Score-Matching Analysis

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Research Article

Keywords: Acute kidney injury, Dexmedetomidine, Sedation, Critically ill, Mortality

Posted Date: June 18th, 2021

DOI: <https://doi.org/10.21203/rs.3.rs-609595/v1>

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Abstract

Background

Dexmedetomidine (DEX) had organ protection effects and could decrease mortality in animal models, but its association with mortality and length of stay (LOS) in ICU and hospital in critically ill patients was conflicting. Whether acute kidney injury (AKI) subgroup of critically ill patients could benefit from DEX was unknown. The present study aimed to evaluate the effects of DEX on clinical outcomes of critically ill patients with AKI.

Methods

Data were extracted from the Medical Information Mart for Intensive Care \times database (MIMIC \times). Propensity score matching (PSM) analysis (1:3), cox proportional hazards model, linear regression and logistic regression model were used to assess the effect of DEX on clinical outcomes.

Results

After PSM, 324 pairs of patients were matched between the patients with DEX administration and those without. DEX administration was associated with decreased in-hospital mortality [hazard ratio (HR) 0.287; 95% CI 0.151–0.542; $P < 0.001$] and 90-day mortality [HR 0.344; 95% CI 0.221–0.534; $P < 0.001$], and it was also associated with reduced length of stay (LOS) in ICU [4.54(3.13,7.72) versus 5.24(3.15,10.91), $P < 0.001$] and LOS in hospital [11.63(8.02,16.79) versus 12.09(7.83,20.44), $P = 0.002$]. Subgroup analysis showed the above associations existed only in mild and moderate AKI subgroups, but not in severe AKI subgroup. Nevertheless, DEX administration was not associated with the recovery of renal function [HR 1.199; 95% CI 0.851–1.688; $P = 0.300$].

Conclusions

DEX administration improved outcomes in critically ill patients with mild and moderate AKI and could be a good choice of sedation.

Background

Acute kidney injury (AKI) is characterized by abrupt decrease of kidney function, with increasing morbidity during the past decades. The morbidity and mortality of AKI in intensive care unit (ICU) patients are 50–59% and 14–51.7% respectively, of which 50% survivors suffered from irreversible declined renal function[1–3]. The etiologies of AKI in critically ill patients are diverse, including infection, ischemia, low cardiac output, toxins and so on[1]. Precise treatment is needed urgently, however few treatments have been proved to improve prognosis so far.

Dexmedetomidine (DEX) is a highly selective α_2 receptor agonist and a widely used sedative in ICU. DEX still has the effects of anti-inflammation, anti-oxidative stress, and reducing cell apoptosis. Previous studies confirmed that DEX could protect organs [4, 5] and decreased mortality [6] in sepsis or ischemia-reperfusion rat models, but its association with mortality and length of stay (LOS) in ICU and hospital in critically ill patients was conflicting [7–11]. Renal protection effect of DEX was observed both in animal models [5, 12] and critically ill patients [8, 10, 13].

However, whether the AKI subgroup of critically ill patients could benefit from DEX was unknown. The present study aimed to evaluate the effects of DEX on outcomes of critically ill patients with AKI, with outcomes defined as in-hospital and 90-day mortality, length of stay (LOS) in ICU and in hospital, and recovery of renal function.

Methods

Database introduction

The data of present study were extracted from a large critical care database— Medical Information Mart for Intensive Care III (MIMIC III) that was published by the Massachusetts Institute of Technology, with approval from the review boards of the Massachusetts Institute

of Technology and Beth Israel Deaconess Medical Center[14]. All patients in the database were de-identified for privacy protection, so the need for informed consent was waived. After successfully completing the National Institutes of Health (NIH) Web-based training course and the Protecting Human Research Participants examination (certification number 36211094), we were given the permission to extract data from MIMIC III.

Inclusion and exclusion criteria

We included adult patients receiving DEX for at least 6 hours during the first 48 hours after ICU admission. For patients who were admitted to ICU more than once, only the first ICU stay was considered. Patients who were younger than 18 years or those with known ESRD were excluded. In addition, patients who spent less than 48 hours in ICU were excluded.

AKI Definition

AKI was defined according to the Kidney Disease Improving Global Outcomes (KDIGO) criteria: an increase in serum creatinine (SCr) by ≥ 0.3 mg/dl (≥ 26.5 μ mol/l) within 48 h, or an increase in SCr to ≥ 1.5 times baseline within the prior 7 days, or urine volume < 0.5 ml/kg/h for 6 hours[15]. AKI stages were also defined according to KDIGO criteria[15]. The minimum SCr value within 7 days before admission was used as the baseline SCr[16]. When pre-admission SCr value was not available, the first SCr after admission was used as the baseline SCr[17]. In patients with deficient or insufficient urine output measurements, only the SCr criterion was applied.

Data extraction

Data extracted from MIMIC III using Structured Query Language (SQL) with Navicat Premium (version 12.0.28) included the demographic characteristics, comorbidities, simplified acute physiology score (SAPS), nonrenal sequential organ failure assessment score (SOFA), SCr value and urine output, use of dexmedetomidine, other sedatives, opioid agents, vasopressors and inotropes, nephrotoxic drugs and mechanical ventilation. Sepsis was defined as life-threatening organ dysfunction caused by a dysregulated host response to infection (sepsis 3.0)[18]. In the present study, patients with suspected or documented infection plus an acute increase of ≥ 2 SOFA points were recorded as sepsis. Use of vasopressor and inotropes was defined as the use of any of these agents, including vasopressin, norepinephrine, epinephrine, dobutamine, dopamine, and phenylephrine within 48 h after ICU admission. Use of nephrotoxic drugs was defined as the use of vancomycin, aminoglycoside and amphotericin. The estimated glomerular filtration rate (eGFR) was calculated using the Modification of Diet in Renal Disease study formula (MDRD) [19].

Management of missing data

Variables with missing data are common in the MIMIC III database. The missing values were less than 10% for all variables in the present study (see additional file 1: Supplementary Table 1). Single imputation was used to impute the missing values including SCr, urine output and weight [20].

Outcomes

The primary endpoint was in-hospital mortality in the present study. The secondary endpoints included 90-day mortality, length of stay (LOS) in ICU, LOS in hospital and recovery of renal function. Recovery of renal function was defined as being discharged from ICU with serum creatinine below 1.5 times the baseline value and normal urine output (> 0.5 ml/kg/h).

Statistical analysis

Propensity score matching (PSM) analysis was used to minimize the effect of confounding factors. PSM was performed by a one-to-three greedy nearest neighbor matching algorithm using a caliper width of 0.01 without replacements. Variables including gender, age, ethnicity, admission type, chronic kidney disease (CKD), hypertension, diabetes mellitus (DM), chronic obstructive pulmonary disease (COPD), heart failure, liver disease, sepsis, SAPSII score, nonrenal SOFA score, SCr value and eGFR on admission, AKI stage, use of vasopressors and inotropes, vancomycin, aminoglycoside, amphotericin, opioid agents and other sedatives, and mechanical ventilation were selected to generate the propensity score. To evaluate the efficiency of PSM in reducing the differences between the two groups, standardized mean difference (SMD) was calculated. Finally, 324 matched pairs were generated and applied to the further analysis.

Continuous variables were expressed as median [interquartile range (IQR)]. Wilcoxon rank-sum test or Kruskal-Wallis test was used to identify the differences between groups. Categorical variables were expressed as the numbers and percentage and compared using the chi-square test or Fisher's exact test as appropriate.

Cox regression was used to evaluate the impact of DEX administration on mortality adjusting for confounding variables which were selected based on p value <0.05 in univariate analysis. Linear regression was used to evaluate the impact of DEX administration on LOS in ICU and in hospital, and the hazard ratios (HR) was calculated using the formula $HR = e^{bi}$. Logistic regression was used to evaluate the impact of DEX administration on recovery of renal function.

The statistical analysis was performed using Stata 16.0 (Stata Corp., College Station, TX, USA). A two-tailed test was performed, and p value <0.05 was considered statistically significant.

Results

Baseline characteristics

9784 patients were included according to the inclusion and exclusion criteria, of which 326 patients were exposed to DEX for at least 6 hours during the first 48 hours after ICU admission (Fig 1). After PSM, 324 patients who received DEX were matched with 972 patients who did not receive DEX.

The comparisons of the baseline characteristics between DEX group and non-DEX group were listed in Table 1. In unmatched cohort, there were significant differences in gender, age, admission types, hypertension, liver disease, sepsis, nonrenal SOFA score, SCr value and eGFR on admission, AKI stage, use of vasopressors and inotropes, vancomycin, opioid agents and other sedatives between DEX group and non-DEX group. After PSM, standardized differences for all variables were less than 10% and the propensity score distribution plot demonstrated successful propensity score matching between the two groups (Fig 2 and Fig 3). There was no significant difference between the two matched groups with regards to all covariates.

Relationship between DEX administration and outcomes

In unmatched cohort, DEX administration was associated with reduced in-hospital mortality (HR 0.264, 95% CI 0.145-0.479, $P < 0.001$) and 90-day mortality (HR 0.304, 95% CI 0.201–0.460, $P < 0.001$) after adjusting for confounding factors in Cox proportional hazards model. DEX administration was associated with reduced LOS in ICU (HR 0.156, 95% CI 0.073-0.329, $P < 0.001$) and LOS in hospital (HR 0.212, 95% CI 0.064-0.703, $P = 0.011$) in linear regression model. Nevertheless, we found that DEX administration was not associated with recovery of renal function in logistic regression model (HR 1.242, 95% CI 0.916–1.686, $P = 0.163$). (Table 2).

Similar to the results in unmatched cohort, DEX administration was associated with reduced in-hospital mortality (HR 0.287, 95% CI 0.151–0.542, $P < 0.001$) and 90-day mortality (HR 0.344, 95% CI 0.221–0.534, $P < 0.001$) (Table 2). Additionally, DEX administration was also associated with reduced LOS in ICU (HR 0.102, 95% CI 0.039–0.263, $P < 0.001$) and LOS in hospital (HR 0.141, 95% CI 0.040–0.500, $P = 0.002$), but it was not associated with the recovery of renal function (HR 1.199, 95% CI 0.851–1.688, $P = 0.300$) (Table 2).

Subgroup analysis

As shown in Fig 4, DEX administration was associated with decreased in-hospital mortality and 90-day mortality in AKI stage 1 to 2 subgroups, but it did not decrease the mortality in AKI stage 3 subgroup. In Fig 5, DEX administration was associated with reduced LOS in ICU in AKI stage 1 subgroup, but it was not associated with reduced LOS in ICU in AKI stage 2 to 3 subgroups. DEX administration was associated with reduced LOS in hospital in AKI stage 1 to 2 subgroups, but it was not associated with reduced LOS in hospital in AKI stage 3 subgroup. DEX administration was not associated with the recovery of renal function in AKI stage 1 subgroup (HR 1.010, 95% CI 0.632-1.612, $P = 0.968$), AKI stage 2 subgroup (HR 1.320, 95% CI 0.675-2.582, $P = 0.418$) and AKI stage 3 subgroup (HR 1.762, 95% CI 0.553-5.620, $P = 0.338$).

Discussion

DEX inhibits the release of norepinephrine from the locus coeruleus and competitively binds to α_2 receptors, which can relieve sympathetic excitement storms and anxiety, and has a mild analgesic and sedative effect. Since it does not act on the midbrain reticular ascending system and GABA receptors, patients sedated with DEX are more likely to wake up and respiratory inhibition is less common. Besides sedative effect, DEX has the effects of anti-inflammation, anti-oxidative stress, and reducing cell apoptosis[21].

In sepsis or ischemia-reperfusion rat models, DEX had protective effects on heart[22], lung[4], liver[23], kidney[5] and intestine[24] by inhibiting the inflammatory responses and hence reduced the mortality of model rats[6]. However, its association with mortality and LOS in ICU and in hospital in critically ill patients was conflicting[7–11]. Some studies indicated that DEX administration could decrease the mortality of patients[7, 8] and reduce the LOS in ICU[9, 10] and in hospital[11]. However, other studies showed that DEX had nothing to do with mortality [25–27] and LOS in hospital[11, 25, 26]. The effect of DEX might be related to age. One study showed that early application of DEX failed to decrease the 90-day mortality in mechanically ventilated patients [28], and then stratified analysis showed that DEX decreased the 90-day mortality in elderly patients, but increased the 90-day mortality rate in young patients[29]. In this retrospective cohort study of critically ill patients with AKI, we selected two matched groups receiving and not receiving DEX for at least 6 hours in the first 48 hours after ICU admission. Our results demonstrated DEX administration was associated significantly with decreased in-hospital and 90-day mortality and reduced LOS in ICU and in hospital in critically ill patients with AKI. The results were robust after adjusting for confounding variables.

Subgroup analysis showed DEX administration was associated with decreased in-hospital and 90-day mortality, reduced LOS in hospital in patients with AKI stage 1 to 2, but the above associations did not exist in patients with AKI stage 3. DEX administration was associated with reduced LOS in ICU in patients with AKI stage 1, but the above association did not exist in patients with AKI stage 2 to 3. The results seemed to indicate that patients with severe renal impairment could not benefit from DEX. The underlying reason was unknown. DEX is mainly metabolized by the liver and excreted by the kidney. Patients with severely impaired renal function cannot effectively and timely eliminate the metabolites of DEX. One previous study showed that the effective sedation time of DEX in patients with severe impaired renal function (Ccr < 30ml/min) was longer than that in the control group[21]. Therefore, the excretion disorder of DEX in patients with AKI stage 3 might offset its benefit.

Renal protection effect of DEX was confirmed in animal models[12, 30]. In patients after heart and lung surgeries[7, 13] and in patients with severe sepsis[10], the renal protective effect of DEX was also observed. However, DEX administration was not associated with the recovery of renal function in critically ill patients with AKI in this study. Recovery of renal function was defined as being discharged from ICU with serum creatinine below 1.5 times the baseline value and normal urine output (> 0.5 ml/kg/h), which was a short-term renal outcome indicator. We did not observe the long-term effect of DEX administration on kidney in critically ill patients with AKI. Moreover, the dose of DEX was not considered, which might impact the effect.

This study was the first to evaluate the effect of DEX administration on clinical outcomes in critically ill patients with AKI. But there are still a few limitations in this study. First, although we have incorporated many confounding factors and made a PSM to reduce bias, there were still some possible confounding factors not incorporated because of the missing data such as body mass index (BMI). Second, heterogeneity of treatment strategies might affect the outcomes of patients. Finally, this study was a single-centered retrospective study, and multicenter randomized controlled trials were needed to confirm the conclusions.

Conclusions

DEX administration decreased mortality and reduced the length of ICU stay and hospital stay in critically ill patients with mild and moderate AKI, but the beneficial effect did not exist in critically ill patients with severe AKI. DEX administration could not improve short-term renal outcome, while its effect on long-term renal outcome needs further investigation. In summary, DEX administration could improve clinical outcomes in critically ill patients with AKI, and it could be a good choice of sedation.

Abbreviations

DEX: Dexmedetomidine, AKI: Acute kidney injury, MIMIC δ : Medical Information Mart for Intensive Care δ database, PSM: Propensity score matching, LOS: Length of stay, ICU: Intensive care unit, NIH: National Institutes of Health, ESRD: End stage renal disease, KDIGO: Kidney Disease Improving Global Outcomes, Scr: Serum creatinine, SQL: Structured Query Language, SAPS δ : Simplified acute physiology score δ , SOFA: Sequential organ failure assessment score, eGFR: Estimated glomerular filtration rate, CKD: chronic kidney disease, hypertension, DM: Diabetes mellitus, COPD: Chronic obstructive pulmonary disease, SMD: Standardized mean difference, GABA: γ -aminobutyric acid.

Declarations

Ethics approval and consent to participate

The establishment of this database was approved by the Massachusetts Institute of Technology (Cambridge, MA) and Beth Israel Deaconess Medical Center (Boston, MA). Consent was obtained for data extraction. Therefore, ethics approval and informed consent were both waived for this study.

Consent for publication

Not applicable.

Availability of data and materials

The datasets presented in this study are available in the MIMIC δ database (<https://physionet.org/content/mimiciii/1.4/>).

Competing interests

All the authors declare that they have no competing interests.

Funding

This study was supported by the Project of Gusu School, Nanjing Medical University [grant number: GSKY20210201] and Project Suzhou Science and Technology Development Plan [grant number: SYSD2018149]. None of these funding agencies have contributed to the study design, collection, management, analysis and interpretation of the data, or in the preparation, review or approval of the manuscript.

Authors' contributions

AY: Conceptualization, Methodology, Writing-Original draft, Funding acquisition. JY: Supervision, Formal analysis. BZ: Writing-Original draft preparation. JQ and LJ: Data curation, Software. ZJ: Software. GL: Supervision, Writing- Reviewing and Editing. All the authors have read and approved the final manuscript.

Acknowledgements

Not applicable.

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Tables

Table 1 Unmatched and matched covariates: Non-DEX versus DEX

Variables	Unmatched Cohort			Matched Cohort		
	Non-DEX group	DEX group	P value	Non-DEX group	DEX group	P value
	(n=9458)	(n=326)		(n=972)	(n=324)	
Age	68.72(56.39,77.27)	65.04(55.04,75.04)	0.006	65.32(54.39,75.13)	65.16(54.97,75.06)	0.912
Gender, male, n (%)	5270(55.72)	223(68.40)	<0.001	620(63.79)	221(68.21)	0.149
Ethnicity, n (%)			0.218			0.691
white	6705(70.89)	244(74.85)		703(72.33)	242(74.69)	
black	686(7.25)	17(5.21)		59(6.07)	17(5.25)	
others	2067(21.85)	65(19.94)		210(21.60)	65(20.06)	
Admission type, n (%)			<0.001			0.223
Elective	1373(14.52)	116(35.58)		306(31.48)	114(35.19)	
Emergency	7700(81.41)	205(62.88)		658(67.70)	205(63.27)	
Urgent	385(4.07)	5(1.53)		8(0.82)	5(1.54)	
Co-morbidities, n (%)						
CKD	1385(14.64)	49(15.03)	0.846	141(14.51)	48(14.81)	0.892
Hypertension	4609(48.73)	194(59.51)	<0.001	561(57.72)	193(59.57)	0.558
Diabetes mellitus	3077(32.53)	110(33.74)	0.647	331(34.05)	110(33.95)	0.973
COPD	414(4.38)	17(5.21)	0.469	54(5.56)	16(4.94)	0.670
Heart failure	3913(41.37)	121(37.12)	0.125	385(39.61)	121(37.35)	0.470
Liver disease	1083(11.45)	23(7.06)	0.014	74(7.61)	23(7.10)	0.761
Sepsis, n (%)	1432(15.14)	15(4.60)	<0.001	40(4.12)	15(4.63)	0.691
SAPS 2 on ICU admission	40(31,50)	37.5(31,48)	0.053	38(30,48)	37.5(31,48)	0.884
Nonrenal SOFA on ICU admission	4(2,6)	5(4,7)	<0.001	5(3,7)	5(4,7)	0.560
Vasopressor, n (%)	4958(52.42)	252(77.30)	<0.001	741(76.23)	250(77.16)	0.734
Inotropes, n (%)	908(9.60)	60(18.40)	<0.001	186(19.14)	59(18.21)	0.712
Use of nephrotoxic drugs, n (%)						
Vancomycin	5655(59.79)	252(77.30)	<0.001	769(79.12)	250(77.16)	0.457
Aminoglycoside	508(5.37)	18(5.52)	0.906	60(6.17)	17(5.25)	0.541
Amphotericin	36(0.38)	1(0.31)	1.000	1(0.10)	1(0.31)	0.438
Use of opioid agent, n (%)	1415(14.96)	89(27.30)	<0.001	279(28.70)	88(27.16)	0.593
Use of other sedatives, n (%)	5072(53.63)	310(95.09)	<0.001	930(95.68)	308(95.06)	0.642
Mechanical ventilation, n (%)	6434(68.03)	315(96.63)	<0.001	938(96.50)	313(96.60)	0.930
Serum creatinine on ICU admission, (mg/dl)	1.2(0.9,1.8)	1.0(0.8,1.3)	<0.001	1.1(0.8,1.4)	1.0(0.8,1.3)	0.345
eGFR on ICU	55.28(34.31,81.14)	69.13(50.04,84.17)	<0.001	63.80(47.29,85.49)	69.23(49.72,84.70)	0.416

admission, (ml/min/1.73m ²) ^a				
AKI stage, n (%)			<0.001	0.109
stage 1	4610(48.74)	206(63.19)	590(60.70)	204(62.96)
stage 2	2989(31.60)	80(24.54)	290(29.84)	80(24.69)
stage 3	1859(19.66)	40(12.27)	92(9.47)	40(12.35)

Data are presented as n (%), or median (interquartile range). DEX, dexmedetomidine; CKD, chronic kidney diseases; COPD, chronic obstructive pulmonary disease; ICU, intensive care unit; SAPS II, simplified acute physiology score II; SOFA, sequential organ failure assessment; eGFR, estimated glomerular filtration rate

^aeGFR was calculated using MDRD formula

Table 2 Association between DEX administration and outcomes in critically ill patients with AKI

	Non-DEX group	DEX group	P value	HR	Lower 95%CI	Upper 95%CI
Pre-matched cohort	n=9458	n=326				
Primary outcome						
In-hospital mortality, n (%)	1771(18.72)	11(3.37)	<0.001	0.264	0.145	0.479
Secondary outcomes						
90-day mortality, n (%)	2676(28.29)	23(7.06)	<0.001	0.304	0.201	0.460
LOS in ICU stay, [median (IQR)]	4.44(2.94,8.36)	4.54(3.13,7.86)	<0.001	0.156	0.073	0.329
LOS in hospital, [median (IQR)]	10.84(6.94,18.06)	11.63(8.06,16.76)	0.011	0.212	0.064	0.703
Recovery of renal function, n (%)	7098(75.05)	271(83.13)	0.163	1.242	0.916	1.686
Post-matched cohort	n=972	n=324				
Primary outcome						
In-hospital mortality, n (%)	122(12.55)	11(3.40)	<0.001	0.287	0.151	0.542
Secondary outcomes						
90-day mortality, n (%)	174(17.90)	23(7.10)	<0.001	0.344	0.221	0.534
LOS in ICU, [median (IQR)]	5.24(3.15,10.91)	4.54(3.13,7.72)	<0.001	0.102	0.039	0.263
LOS in hospital, [median (IQR)]	12.09(7.83,20.44)	11.63(8.02,16.79)	0.002	0.141	0.040	0.500
Recovery of renal function, n (%)	785(80.76)	269(83.02)	0.300	1.199	0.851	1.688

DEX, dexmedetomidine; AKI, acute kidney injury; ICU, intensive care unit; LOS, length of stay; IQR interquartile; HR, hazard ratio; 95% CI, 95% confidence interval

^aCox regression was used to evaluate the impact of DEX administration on mortality outcomes adjusting for confounding variables selected based on P value <0.05 in univariate analysis.

^bLinear regression was used to evaluate the impact of DEX administration on length of stay. HR was calculated using the formula $HR = e^{\beta_i}$

°Recovery of renal function was defined as being discharged from ICU with serum creatinine below 1.5 times the baseline value and normal urine output (> 0.5 ml/kg/h). Impact of DEX administration on the recovery of renal function was evaluated using logistic regression model.

Figures

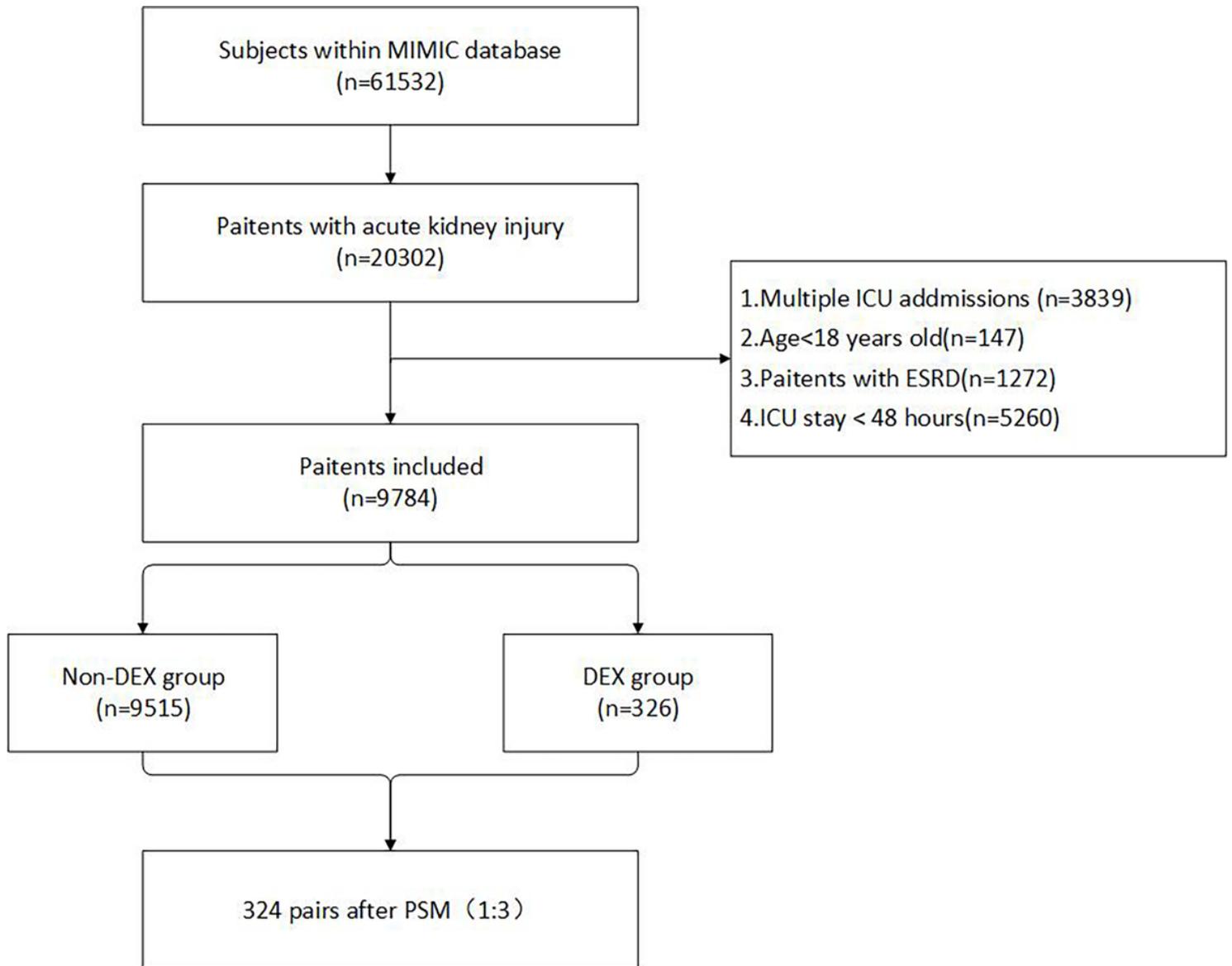


Figure 1

Patient distribution in the MIMIC database and exclusion criteria. MIMIC: Medical Information Mart for Intensive Care, ICU: intensive care unit, ESRD: end stage renal disease, PSM: propensity-score matching

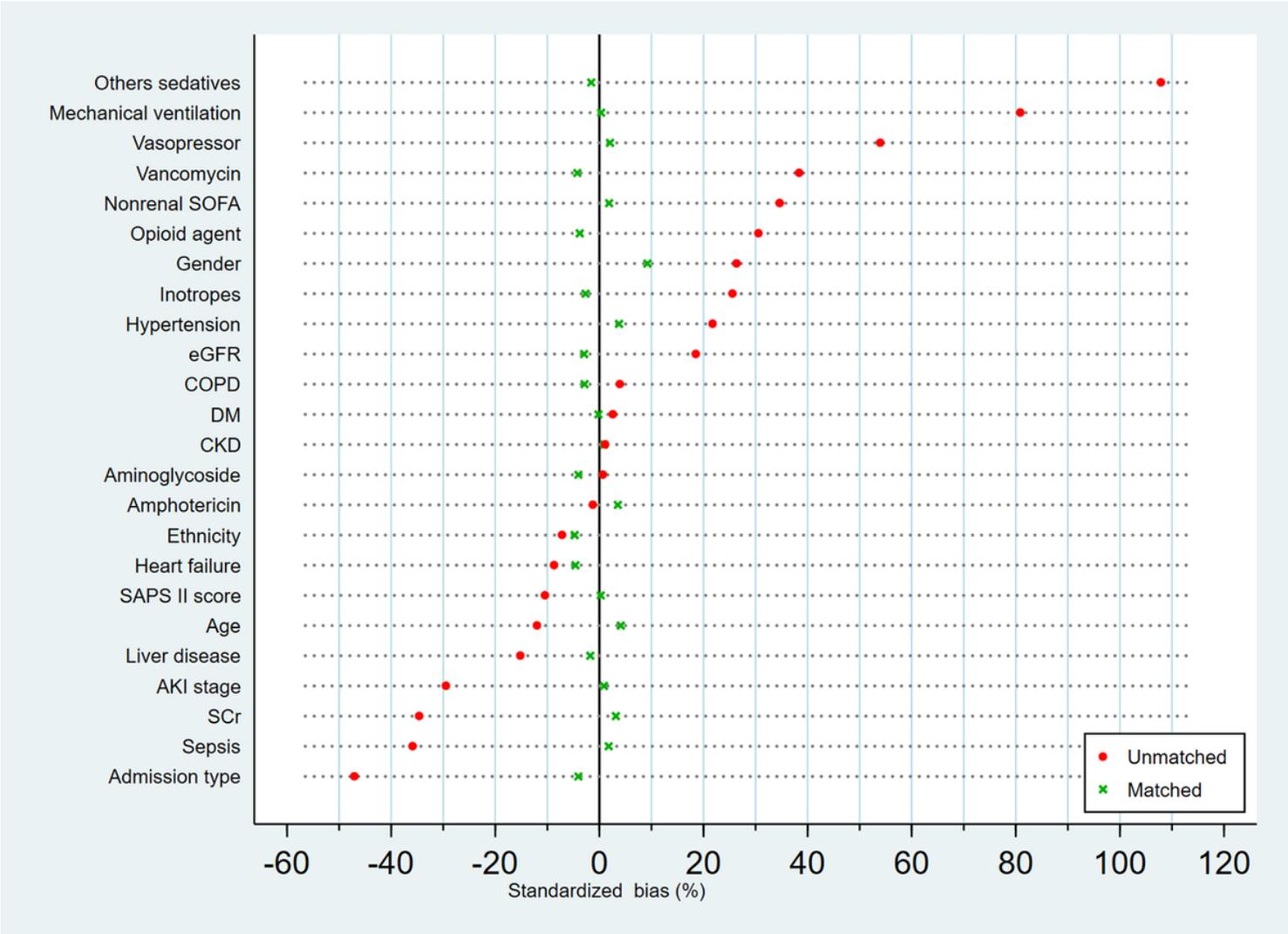


Figure 2

Standardized bias before and after PSM. PSM: propensity-score matching

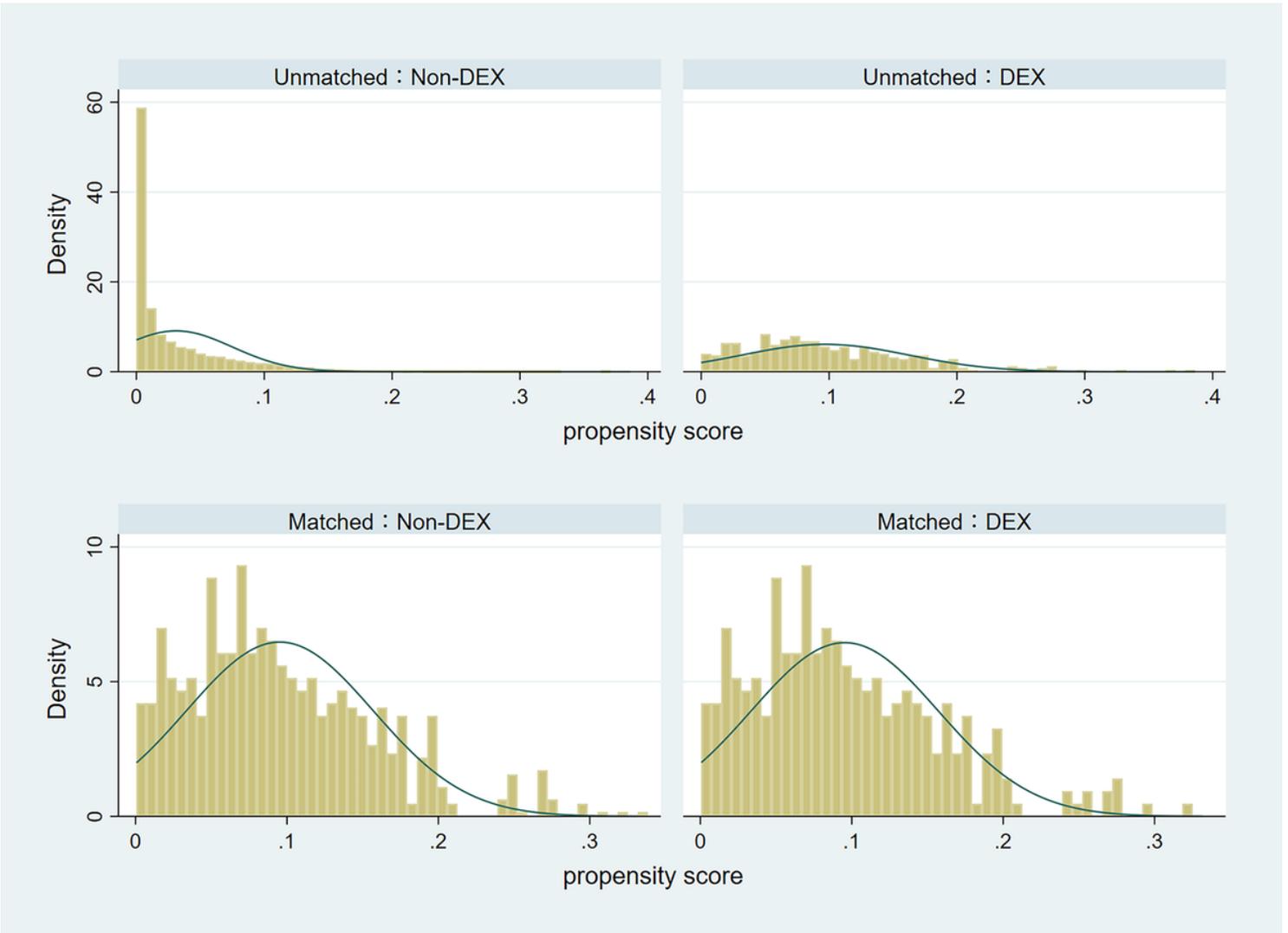


Figure 3

Propensity score distribution plot before and after PSM. PSM: propensity-score matching

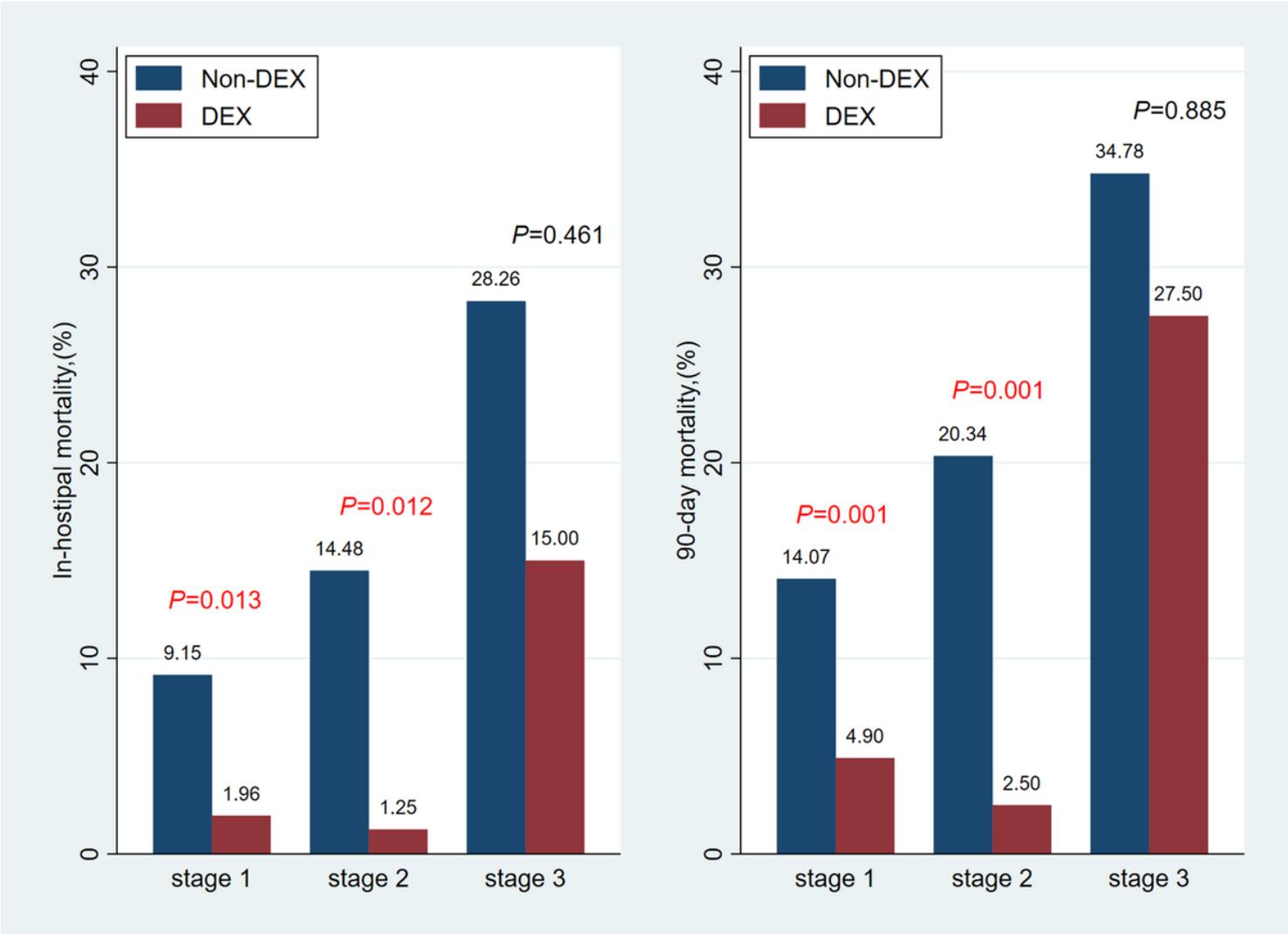


Figure 4

Mortality by stage of AKI between Non-DEX group and DEX group after PSM. DEX: dexmedetomidine PSM: propensity-score matching

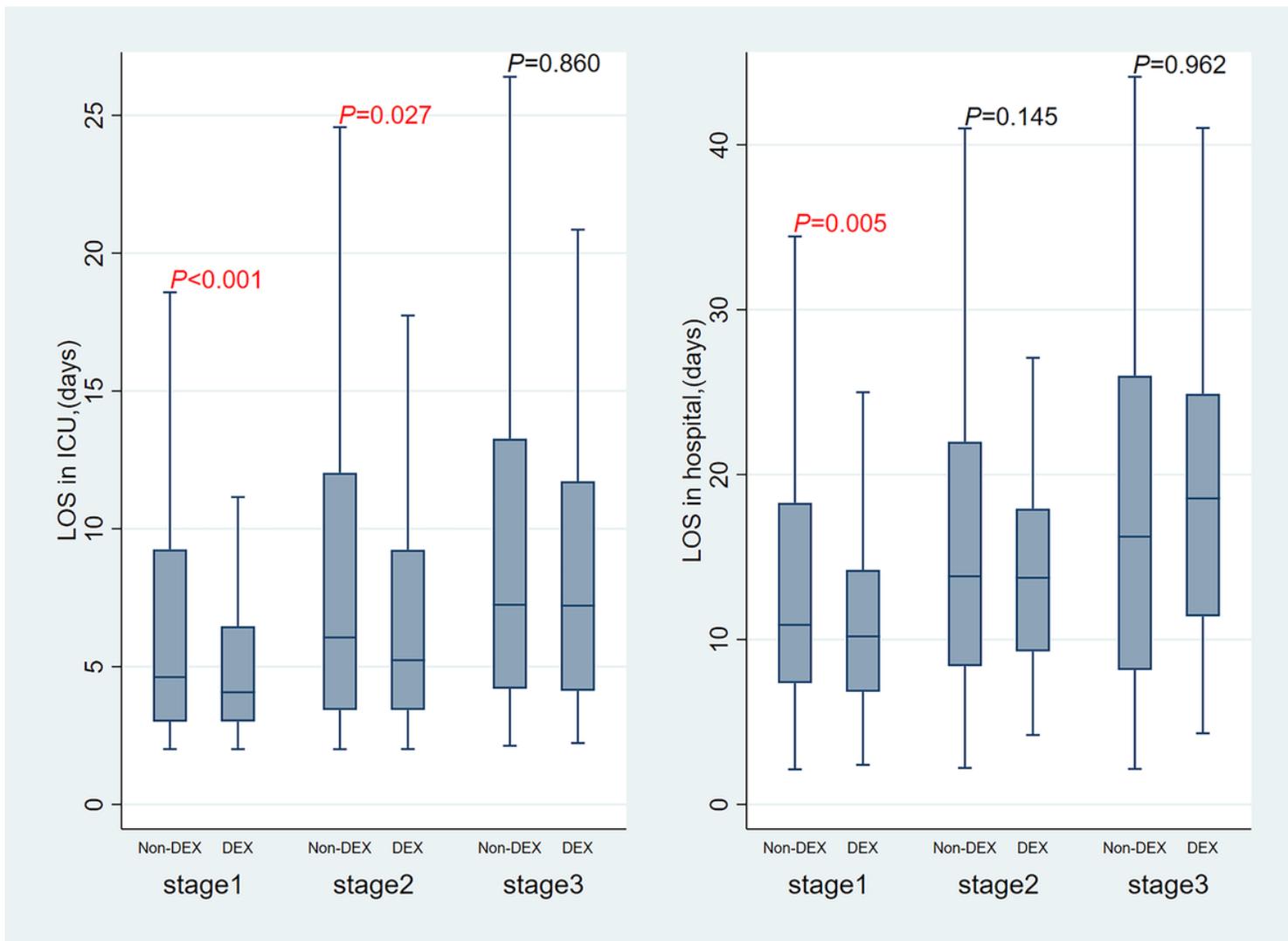


Figure 5

LOS by stage of AKI between Non-DEX group and DEX group after PSM. LOS: length of stay, DEX: dexmedetomidine PSM: propensity-score matching

Supplementary Files

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- [Additionalfile1.docx](#)