Evaluation On The Safety of Anti-Platelet Agents In Patients With Acute Pancreatitis: A Retrospective Cohort Study

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Abstract

Background: Anti-platelet drug has not been paid much attention in guidelines for the treatment of acute pancreatitis, especially in patients with cardiovascular disease and receiving anti-platelet therapy, and its safety hasn't been evaluated by any guidelines or studies.

Methods: A total of 904 patients with acute pancreatitis were enrolled in this cohort study, they were divided into Anti-platelet therapy group (n=297) and non-Anti-platelet therapy group (n=607). The primary result was the mortality in the 14th-day, 28th-day, and 90th-day. Adverse events during treatment included septic shock, respiratory tract infection, urinary tract infection, abdominal infection, bleeding, kidney damage, respiratory distress, cardiac dysfunction, liver dysfunction, and renal dysfunction. Kaplan-meier, propensity score matching (PSM), subsequently, cox regression and subgroup analysis were performed.

Results: The mortality rates were 9.55% vs 4.71%, $P=0.012$, 13.34% vs 8.1%, $P=0.02$, 16.14% vs 13.13%, $P=0.235$, respectively, during the 14-day, 28-day, and 90-day follow-up periods. Risk ratio for death among anticoagulants versus non-anticoagulants after multivariate adjustment (HR=2.815, 2.819, 95%CI:1.021-4.667, 1.045-4.5

83, $p < 0.05$). According to the survival curves, there were significant differences in mortality after 14, 28, and 90 days between the anticoagulant and non-anticoagulant groups (log-rank $P < 0.05$). After PSM, 297 pairs were identified, and there was no significant difference in the risk of death between the anticoagulant and non-anticoagulant groups (all $P > 0.05$).

Conclusions: Anti-platelet therapy is not superior to non-prophylactic anti-platelet therapy in terms of reducing mortality and adverse events in acute pancreatitis, and there is no statistically significant difference in mortality and adverse events in the cohort of cardiovascular patients using anti-platelet drugs compared with those without using anti-platelet drugs.

1. Introduction

Acute pancreatitis is characterized by acute onset and rapid change of disease conditions. Patients with mild acute pancreatitis account for 80%, with the mortality rate of 1%-2%[1]. 20% of patients with mild acute pancreatitis can develop to those with acute severe pancreatitis, and 10%-20% of patients with acute severe pancreatitis died from septic shock caused by persistent organ failure and systemic inflammatory response [2, 3]. According to the Atlanta Conference in 2012, the high risk of death caused by acute severe pancreatitis consisted of two stages, in the first week and the first month, death results from systemic inflammatory response (SIRS) and persistent organ failure, respectively[4]. The incidence of portal vein and splenic vein thrombosis in patients with acute pancreatitis is about 13%, which can lead to liver failure, portal vein hypertension, spleen and intestinal necrosis in severe cases [5]. According to the guidelines, the use of thrombolytic drugs is not recommended because of the increased risk of bleeding after thrombolytic therapy. Anti-platelet drugs are the base of drugs for cardiovascular and cerebrovascular diseases, and the daily prophylactic use of anti-platelet drugs within the indication range in the cardiovascular and cerebrovascular disease population are recommended, however, the association between anti-platelet drug use and adverse events and outcomes in acute pancreatitis have been assessed by few studies or guideline. This study evaluated the difference of adverse events under the use of anti-platelet drugs and without the use of anti-platelet drugs in the course of the

prognosis of acute pancreatitis, and explores the security of patients with acute pancreatitis to use anti-platelet in cardiovascular disease.

2. Materials And Methods

2.1 Data Sources

In this retrospective cohort study, the data of patients with acute pancreatitis were from Mimic-III, a large, single-center, public critical care database, which includes more than 40,000 ICU inpatients admitted to Beth Israel Deaconess Medical Center in Boston over a 14-year period from 2001 to 2012. To access this database, we passed relevant exams and were certified to access this database (number: 27714078). In this database, detailed information on ICU patient stays, including high-resolution monitoring data, therapeutic interventions including medications, discharge summaries, laboratory data, and radiology reports are contained. In terms of the International Classification of Diseases, the code of Acute Pancreatitis uses Version 9 (ICD-9) was 5770. We extracted clinical demographic characteristics, ICD-9 and other indicator codes, physiological indicators and laboratory tests, and the data was executed in mimic-III database through Structured Query Language (SQL). Supported by the Beth Israel Deaconess Medical Center (Boston, MA) and approved by the Institutional Review Board of MIT (Cambridge, MA), this study avoided informed consent and ethical requirements for patients because of the database and research design.

2.2 Criteria for the diagnosis

According to ICD-9 code 5770, 1216 patients with acute pancreatitis were retrieved. Only patients with first admission and first diagnosis of AP were included. Exclusion criteria : (1) Those who are less than 18 years old. (2) Those with chronic pancreatitis and pancreatic tumor. (3) Those with a history of severe immune system or coagulation disease. (4) Those whose return visit data i missed. (Figure 1)

2.3 Variables of the data

Variables included gender, height, weight, hypertension, diabetes, hyperlipidemia, chronic coronary atherosclerosis, coronary heart disease, hyperlipidemia, and whether invasive ventilation was performed. Laboratory materials included white blood cell count, platelet count, coagulation time, critical score (SAPS-II Score, Oasis Score, Sofa Score, GCS Score), complications include liver insufficiency, cardiac insufficiency, renal insufficiency, kidney injury, ARDS, abdominal infection, Respiratory infections, urinary tract infections, bleeding, septic shock, etc. Patients were treated with anti-platelet drugs (aspirin and clopidogrel). Variables of the result were the mortality after 14 days, mortality after 28 days, mortality after 90 days, and the incidence of adverse events.

2.5 Statistical Analysis

Statistical description and hypothesis testing: data were processed through the statistical software SPSS25.0 and R3.6.2 (SPSS, Chicago, Illinois, USA), which is internationally recognized. Descriptive statistics: Kolmogorov-Smirnov method was adopted to evaluate the characteristics of the distribution of the measurement data. Continuous data were presented as the median of the mean $\pm$ standard deviation or quartile range, and then it was compared using either the student T-test or the Mann-Whitney U test. The categorical variables were

expressed as numbers with percentages and compared using Pearson's χ^2 or Fisher's exact test. Kaplan-meier curve was adopted to show the cumulative incidence of events, and log-rank test was adopted for comparison. Moreover, cox proportional regression analysis was used to determine the relationship between anticoagulant use and mortality. Event risk in model 1 was adjusted for age and sex, BMI, and was further adjusted for multiple clinically relevant variables in Model 2, including age, sex, BMI, hypertension, diabetes and hyperlipidemia, liver insufficiency, cardiac insufficiency, renal insufficiency, kidney damage, ARDS, abdominal infection, respiratory infection, urinary tract infection, bleeding, septic shock, white blood cell count, platelet count, coagulation time, critical score (Saps- II Score, Oasis Score, Sofa Score, GCS Score). To minimize selection bias and control for the potential confounding effects of differences in baseline data, a propensity score matching (PSM) analysis between the anticoagulant and non-anticoagulant groups has been adopted, with its proportion of 1:1, subsequently, propensity score was calculated through the binary logistic regression model. It has been observed that the uneven distribution of risk at baseline was mainly due to differences in age, platelet count, and Sofa score, as well as chronic coronary syndrome and coronary heart disease. Therefore, these four factors were incorporated into the PSM model. Finally, 297 pairs were identified, and their characteristics and outcomes were compared again after PSM, in the bilateral analysis, when $P < 0.05$, it was considered statistically significant.

3. Results

3.1 Characteristics of the baseline

904 patients were enrolled in this cohort, of whom 297 received anti-platelet therapy and 607 did not receive it, as shown in Table 1. Before the PSM method, there were statistically significant differences in age, platelet count, Sofa score, cardiovascular disease, mortality after 14 days, and mortality after 28 days between the two groups. ($p < 0.05$). There was no significant difference in liver insufficiency, cardiac insufficiency, renal insufficiency, kidney injury, ARDS, abdominal cavity infection, respiratory system infection, urinary tract infection, bleeding and septic shock between 2 groups ($P > 0.05$). After PSM, 297 patients receiving anti-platelet therapy were matched with 297 patients not receiving anti-platelet drugs with a proportion of 1:1 (Figure 1).

3.2 Clinical Results

The mortality rates after 14 days, 28 days and 90 days were 9.55% vs 4.71%, $P = 0.012$, 13.34% VS 8.01%, $p = 0.02$, 16.14% VS 13.13%, $p = 0.235$ (table 1). Before PSM, it has also been shown in Kaplan-Meier curve (Figure 2) that there was a statistically significant difference in prognosis between two groups after 14 days and 28 days (log-rank $P = 0.012$ and 0.02 , respectively). There was no significant difference between the two groups after 90 days (Log-rank $P = 0.22$). After PSM, the demographic and confounding factors of 296 pairs became comparable (Table 1). After PSM, there was no significant difference in mortality and complication events between patients who took anti-platelet drugs and those who did not ($P > 0.05$) (Table 2). According to the Kaplan-meier curve (Figure 2), there was no significant difference in prognosis between these two groups on the 14 days, 28 days, and 90 days (log-rank $P = 0.082$, 0.066 , and 0.39 , respectively).

3.3 Relationship between anti-platelet therapy or non-anti-platelet therapy and efficacy

As is vividly shown in Cox regression analysis (Table 3), compared with anti-platelet drugs, patients in the unadjusted model at 14 days ($HR = 2.063$, 95%CI: 1.150-3.701, $P = 0.015$) and 28 days ($HR = 1.702$, 95%CI: 1.079-2.686, $P = 0.022$) presented an increased risk of death, even after multi-variable adjustment, and no anti-platelet

medication after 14 days (HR=2.185,95%CI: 1.021-4.667, P =0.044) or 28 days (HR=2.811,95%CI: 1.473-5.364, P =0.002) were not associated with increased risk of death. After PSM, there was no statistically significant increase in the risk of death after 14 days and 28 days compared with patients using anti-platelet drug in the unadjusted model and adjusted COX model. (P > 0.05).

3.4 Analysis of the subgroup

In the acute pancreatitis subgroup analysis, stratified by gender, age, BMI, hypertension, diabetes and hyperlipidemia, liver insufficiency, heart insufficiency, renal insufficiency, kidney injury, ARDS, and cardiovascular disease, among patients in the stratified group with cardiovascular disease, the risk of death of patients without receiving anti-platelet drugs was 2.460 times higher than those receiving anti-platelet drugs (P<0.05). There was no statistical significance in the other subgroups (P >0.05). In patients with cardiovascular disease after PSM, the risk of death was similar for both anti-platelet and non-anti-platelet users (P >0.05) (Table 4).

4. Discussion

In this study, no significant difference in mortality or complications were found in terms of acute pancreatitis between anti-platelet agents and those without anti-platelet agents, and these remained insignificant after PSM, multi-variable adjustment, and subgroup analysis, suggesting that anti-platelet use did not have a positive effect on the course of acute pancreatitis. Adverse events or mortality didn't increased after continuous use of anti-platelet agents in patients with acute pancreatitis in cardiovascular disease, and therefore should be continued according to guidelines for the course of the disease.

The treatment of acute pancreatitis, especially the treatment of SAP with multiple complications, is a complex process involving multiple disciplines such as surgery, gastroenterology, emergency department, intensive care medicine, infection department, interventional department, nutrition department and rehabilitation department, and the mode of multidisciplinary collaborative diagnosis and treatment should be adopted[7]. In the early treatment of acute pancreatitis, fluid therapy, analgesia and nutritional support, and treatment for etiology and early complications are included[8].

It has been suggested in previous studies that platelets play an important role in maintaining the integrity of blood vessel walls and in hemostasis, thrombosis and wound healing, furthermore, it is of vital importance in the process of blood coagulation by regulating hemostasis and coagulation generation. However, in addition, it has been proved in more and more studies that platelets are related to inflammatory response and can even participate in systemic inflammatory response syndrome [10-15]. Platelets and their products are directly or indirectly involved in the occurrence and development of inflammatory reactions, which may results from the fact that platelets can recognize pathogenic microorganisms related to inflammation and various signals generated during inflammation. Activated platelets can produce a large number of cytokines and chemokines, thus producing a variety of immune effects and regulatory functions [16]. There is no or low expression of CD40L on the surface of resting platelets. When invaded by pathogens, platelets are activated and can induce the expression of CD40L, which can subsequently act on endothelial cells and lymphocytes, triggering a variety of inflammatory reactions. Namely, the combination of CD40 and CD40L activate various inflammatory cells to produce various pro-inflammatory factors such interleukin-1 and interleukin-2, and simultaneously leads to the release of local adhesion molecules, including intercellular adhesion molecule-1, vascular cell adhesion

molecule-1 and P-selectin, and regulates the chemoattraction and exudation of leukocytes to inflammatory sites, which is also a further participation in the inflammatory process [17,18]. After being stimulated by inflammation, platelets are activated and can produce and release a variety of chemical agonists that regulate inflammation, such as PF4, β -TG, MIP-1 α , etc. Platelets directly or indirectly play an important role in the process of inflammation with the assistance of these cytokines/chemokines [19].

Until today, few studies have demonstrated the role of anti-platelet agents in acute pancreatitis. According to Akyazi et al, long-term pre-processing of aspirin preconditioning can prevent or improve certain hematologic, serological, and histological changes associated with AP. Guotao Lu et al. It is reported that the protection of acinar cells from necrosis in the early stage of AP plays a critical role in the pathologic process of AP. Aspirin reduces the level of COX in pancreatic tissue and protects pancreatic acinar cells from necrosis and reduces the severity of SAP. Clinically, aspirin may be a potential therapeutic intervention in the treatment of SAP [20]. According to a study in Taiwan, the risk for 5000 patients enrolled in a cohort study using aspirin developing acute pancreatitis was 8 times higher than those not taking aspirin [22]. Therefore, the use of anti-platelet drugs is controversial in clinic.

According to guidelines, patients with a history of atherosclerotic cardiovascular disease should receive aspirin for secondary prevention. For patients with atherosclerotic cardiovascular disease, clopidogrel (75 mg/ day) is recommended if they are confirmed allergic to aspirin. A combination of anti-platelet agents (low-dose aspirin combined with a P2Y₁₂ inhibitor) can be adopted for up to one year after the appearance of acute coronary syndrome, and there may be greater benefits if prolonging the time of using it. For diabetes patients with increased cardiovascular risk, aspirin (75-162 mg/ day) can be used for primary prevention after fully communicating with them on the benefits and potential risk of aspirin. Aspirin can reduce the risk of cardiovascular disease and death in patients with a history of myocardial infarction or stroke [23]. Due to systemic inflammatory reaction in patients with acute pancreatitis, their whole body is under the condition of hypercoagulability. Anti-platelet drugs can help prevent the expansion of formed thrombosis and prevent the formation of new thrombosis or embolism. In addition, they are mainly used for the prevention and treatment of thrombotic diseases. Guidelines for the use of anticoagulants and anti-platelet agents in acute pancreas have always been conservative, as drug use increases the risk of bleeding and mortality. In this cohort research, a subset of patients with cardiovascular disease, including those with chronic coronary syndrome and coronary heart disease, were eligible for anti-platelet therapy based on European and Chinese guidelines, and patient mortality or the incidence of adverse events can't be increased because of the use of anti-platelet therapy. Therefore, patients with cardiovascular diseases can take prophylactic anti-platelet drugs according to the guidelines on the basis of bleeding and platelet evaluation during the whole treatment process. When it comes to the deficiency of this paper, there is only a small amount of data in this study, therefore, multi-centered data is required to support the conclusion.

4. Conclusion

In the observational analysis in patients with acute pancreatitis, preventive anti-platelet therapy is not better than the preventive anti-platelet therapy in terms of reduced mortality, and simultaneously, it did not lead to reduced adverse events, in patients with cardiovascular under the acute pancreatitis and receiving anti-platelet agents, preventive anti-platelet therapy can also be used as a secondary drug for prevention.

Declarations

Ethical Approval

This study was conducted in accordance with the declaration of Helsinki. All patients or family members involved in the study had signed informed consent. The study was approved by the Human Research Ethics Committees of The Affiliated Changzhou No.2 People's Hospital of Nanjing Medical University.

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Competing interests

There is no conflict of interest in this paper.

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Tables

Table1: Baseline characteristics and clinical outcomes in pancreatitis patients treated with anti-platelet drug

variable	No use drugs(n=607)	use drugs(n=297)	p-value
Gender n(%)			0.249
male	331(54.53%)	174(58.58%)	
female	276(45.47%)	123(41.42%)	
Age,(years)	62.26±45.67	72.58±44.93	0.04
BMI,(kg/m ²)	28.59±8.44	28.55±8.59	0.957
Hypertension, n(%)	248(40.85%)	129(43.43%)	0.46
Diabetes, n (%)	165(27.18%)	83(27.94%)	0.809
Dyslipidemia, n (%)	54(8.89%)	33(11.11%)	0.298
Cardiovascular disease(CHD,CCS),n(%)	194(31.96%)	116(39.06%)	0.035
Invasive ventilation,n(%)	152(25.04%)	77(12.69%)	0.774
PLT,($\times 10^9$)	296.82±150.90	319.01±158.54	0.041
WBC,($\times 10^9$)	12.15±5.96	12.16±5.60	0.967
PT,($\times 10^9$)	15.49±6.12	15.41±5.10	0.855
Sapsii score	37.02±15.80	35.2±14.9	0.97
Oasis score	32.66±9.38	32.25±9.48	0.539
Sofa score	5.4±3.71	4.69±3.50	0.04
Gcs score	13.83±2.45	13.96±2.15	0.444
14-day mortality,n(%)	58(9.55%)	14(4.71%)	0.012
28-day mortality,n(%)	81(13.34%)	24(8.08%)	0.02
90-day mortality,n(%)	98(16.14%)	39(13.13%)	0.235
AKI,n(%)	230(37.89%)	145(48.82%)	0.02
ARDS,n(%)	57(9.39%)	26(8.75%)	0.756
Live-dysfunction,n(%)	76(12.52%)	30(10.10%)	0.288
Kidney-dysfunction,n(%)	243(40.03%)	127(42.76%)	0.433
Heart-dysfunction,n(%)	140(23.06%)	68(28.90%)	0.955
Septic shock,n(%)	69(11.37%)	34(11.45%)	0.971
Urinary-tract-infection,n(%)	82(13.51%)	52(17.51%)	0.112
Intra-abdominal infectonal,n(%)	167(27.51%)	100(33.67%)	0.057
Respiratory infection,n(%)	64(10.54%)	22(7.41%)	0.131
Bleeding,n(%)	6(0.98%)	3(0.101%)	0.987

BMI:body mass index;CHD:coronary heart disease;CCS:Chronic Coronary Syndrome ;PLT

⌘Platelet ;WBC:White Blood Cell ;PT:Prothrombin time ;Saps-ii score=simplified Acute physiology score II ;Sofa score=Sequential Organ Failure Assessment;GAS=Glasgow Coma scale ;Oasis score=Oxford Acute severity of illness score;AKI=Acute Renal Injury;ARDS=Acute Respiratory Distress Syndrome

Table2 Distribution of clinically relevant variables and adverse events before and after propensity score matching in patients treated with anti-platelet drug

variable	Pre-PSM			Post-PSM		
Baseline data	No drugs(n=607)	Use drugs(n=297)	p-value	No Use drugs(n=297)	Use drugs(n=297)	p-value
Gender n(%)			0.249		72.58±44.93	0.99
male	331(54.53%)	174(58.58%)		154(51.85%)	174(58.59%)	
female	276(45.47%)	123(41.42%)		143(48.15%)	123(41.41%)	
Age,years	62.26±45.67	72.58±44.93	0.04	68.50±57.68	72.58±44.93	0.337
Hypertension, n(%)	28.59±8.44	28.55±8.59	0.957	126(42.42%)	129(43.43%)	0.804
Diabetes, n (%)	165(27.18%)	83(27.94%)	0.809	80(26.93%)	83(27.95%)	0.991
Dyslipidemia, n (%)	54(8.89%)	33(11.11%)	0.298	24(7.07%)	33(11.11%)	0.21
Coronary,n(%)	194(31.96%)	116(39.06%)	0.035	119(40.06%)	116(39.06%)	0.801
Invasive ventilation,n(%)	152(25.04%)	77(12.69%)	0.774	73(24.58%)	77(25.93%)	0.706
PLT,($\times 10^9$)	296.82±150.90	319.01±158.54	0.041	299.32±152.47	319.01±158.54	0.124
WBC,($\times 10^9$)	12.15±5.96	12.16±5.60	0.967	12.06±6.05	12.17±5.61	0.356
PT,($\times 10^9$)	15.49±6.12	15.41±5.10	0.855	14.90±3.62	15.41±5.10	0.356
Saps-ii score	37.02±15.80	35.2±14.9	0.97	38.17±15.24	35.20±14.90	0.016
Oasis score	32.66±9.38	32.25±9.48	0.539	33.16±8.95	32.25±9.48	0.225
Sofa score	5.4±3.71	4.69±3.50	0.04	5.59±3.78	4.69±3.50	0.03
Gcs score	13.83±2.45	13.96±2.15	0.444	13.6±2.79	13.96±2.15	0.079
14-day mortality,n(%)	58(9.55%)	14(4.71%)	0.012	26(8.75%)	14(4.71%)	0.049
28-day mortality,n(%)	81(13.34%)	24(8.08%)	0.02	39(13.13%)	24(8.08%)	0.046
90-day mortality,n(%)	98(16.14%)	39(13.13%)	0.235	47(15.82%)	39(13.13%)	0.351
AKI,n(%)	230(37.89%)	145(48.82%)	0.02	114(38.38%)	145(48.82%)	0.01
ARDS,n(%)	57(9.39%)	26(8.75%)	0.756	23(7.74%)	26(8.75%)	0.665
Live-dysfunction,n(%)	76(12.52%)	30(10.10%)	0.288	35(11.78%)	30(10.10%)	0.511
Kidney-dysfunction,n(%)	243(40.03%)	127(42.76%)	0.433	125(42.08%)	127(42.76%)	0.868
Heart-dysfunction,n(%)	140(23.06%)	68(28.90%)	0.955	69(23.23%)	68(22.89%)	0.922

Septic shock,n(%)	69(11.37%)	34(11.45%)	0.971	32(10.77%)	34(11.45%)	0.794
Urinary-tract-infection,n(%)	82(13.51%)	52(17.51%)	0.112	37(12.45%)	52(17.51%)	0.085
Intra-abdominal infection,n(%)	167(27.51%)	100(33.67%)	0.057	82(27.60%)	100(33.67%)	0.109
Respiratory infection,n(%)	64(10.54%)	22(7.41%)	0.131	32(10.77%)	22(7.41%)	0.119
Bleeding,n(%)	6(0.98%)	3(0.101%)	0.987	4(1.34%)	3(1.01%)	0.942

Table3 Impact of use drug vs. No use drug on the event risk at Cox analysis

Event risk	Pre-PSM		Post-PSM	
	HR (95% CI)	P-Value	HR (95% CI)	p-value
14-day mortality Unadjusted	2.063[1.150-3.701]	0.015	1.854[0.964-3.567]	0.064
Adjusted model 1	2.189[1.045-4.583]	0.038	1.418[0.593-3.395]	0.433
Adjusted model 2	2.185[1.021-4.667]	0.044	1.213[0.483-3.049]	0.681
28-day mortality Unadjusted	1.702[1.079-2.686]	0.22	1.654[0.992-2.756]	0.054
Adjusted model 1	2.397[1.269-4.525]	0.007	1.821[0.884-3.751]	0.104
Adjusted model 2	2.811[1.473-5.364]	0.002	1.735[0.815-3.693]	0.153

HR=Hazard Ratio ;CI: confidence interval PSM:Propensity matching analysis

Table 4 .Association between treatment with use drug vs. No use drug and mortality in subgroups.

Subgroups	Pre-PSM			post-PSM	
		HR(95%CI)	P-Value	HR(95%CI)	P-Value
Sex	male	3.391(1.318-8.720)	0.011	2.541(0.883-7.351)	0.84
	female	0.471(0.619-2.821)	0.471	1.409(0.610-3.256)	0.422
Age,yrs	≥60	1.928(1.015-3.662)	0.045	1.761(0.838-3.701)	0.135
	<60	7.650(1.035-56.551)	0.46	6.618(0.847-51.686)	0.072
BMI,kg/m2	BMI≥25	2.178(0.890-5.328)	0.088	1.312(0.441-3.905)	0.625
	BMI<25	1.644(0.459-5.894)	0.445	1.467(0.351-6.138)	0.6
Hypertension	Yes	2.085(0.980-4.789)	0.083	1.827(0.719-4.460)	0.205
	No	2.072(0.910-4.717)	0.81	1.892(0.755-4.742)	0.174
Diabetes	Yes	1.765(0.904-3.446)	0.096	2.106(0.527-8.420)	0.292
	No	3.173(0.925-10.772)	0.64	1.783(0.848-3.746)	0.127
AKI	Yes	1.436(0.473-4.364)	0.523	2.589(0.988-5.567)	0.356
	No	2.915(1.465-5.801)	0.002	1.275(0.360-4.519)	0.706
ARDS	Yes	1.376(0.278-6.817)	0.696	1.134(0.160-8.055)	0.900
	No	2.174(1.159-4.078)	0.015	1.975(0.982-3.965)	0.56
Hyperlipemia	Yes	1.225(0.111-13.510)	0.868	1.405(0.088-22.459)	0.81
	No	2.907(1.146-3.839)	0.16	1.855(0.945-3.644)	0.73
Cardiovascular disease(CHD,CCS),n(%)	Yes	2.460(1.157-5.233)	0.019	2.106(1.013-4.920)	0.830
	No	1.418(0.545-3.690)	0.474	1.323(0.459-3.812)	0.605
Invasive ventilation	Yes	2.386(0.807-7.050)	0.116	1.923(0.563-6.570)	0.297
	No	1.944(0.970-	0.641	1.833(0.846-	0.124

		3.894		3.972)	
Liver-dysfunction	Yes	1.434(0.298-6.903)	0.653	1.313(0.219-7.856)	0.766
	No	2.169(1.155-4.073)	0.016	1.943(0.962-3.926)	0.064
kidney_dysfunction	Yes	1.335(0.518-3.440)	0.015	1.210(0.407-3.60)	0.730
	No	2.560(1.202-5.453)	0.55	2.332(0.998-5.362)	0.051
heart-dysfunction	Yes	1.060(0.403-2.788)	0.07	0.826(0.252-2.707)	0.753
	No	2.807(1.322-5.962)	0.906	2.623(0.687-5.956)	0.132

Figures

Figure 1

Study flowchart.

(a)

(b)

(c)

(d)

(e)

(f)

Figure 2

survival curve in the two groups before and after PSM. Before PSM(a-c). **a** the 14-day mortality(use drug group vs. No use drug group). **b** the 28-days mortality **c** the 90-days mortality.after PSM(d-f).**d** the 14-day mortality(use drug group vs. No use drug group). **e**.the 28-days mortality. **f**. the 90-days mortality.

Supplementary Files

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