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Association between early vasopressor administration and in-hospital mortality in critically ill patients with acute pancreatitis: A cohort study from the MIMIC-IV database

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Abstract. – OBJECTIVE: This study aims to explore the association between early administration of vasopressors and in-hospital mortality in acute pancreatitis (AP) patients admitted to the ICU.

PATIENTS AND METHODS: The MIMIC-IV database was used to identify AP patients who had and had not received vasopressors. Univariate and multivariate logistic regression, propensity score matching (PSM), and inverse probability of treatment weighting (IPTW) were used for statistical analysis.

RESULTS: A total of 894 AP patients admitted to the ICU were included in the study. Among them, AP patients who received vasopressors were associated with an increased risk of in-hospital mortality in the unadjusted model (OR: 7.77, 95% CI 4.92-12.61, $p<0.001$), multivariable-adjusted model (OR: 2.51,95% CI 1.1-5.76, $p<0.05$), PSM model (OR: 2.58, 95% CI 1.03-6.85, $p<0.05$) and IPTW model (OR: 1.82, 95% CI 1.06-3.15, $p<0.05$) compared with patients who did not receive vasopressors. In the subgroup analysis, age (≥ 65 years old: OR: 2.5, 95% CI 0.82-7.91; <65 years old: OR: 4.63, 95% CI 0.84-26.41), male (OR: 1.19, 95% CI 0.35-4.03), ethnicity (white: OR: 2.49, 95% CI 0.81-7.62; non-white: OR: 4.28, 95% CI 0.85-23.7), usage of norepinephrine (OR: 2.29, 95% CI 0.91-5.78), and single-use of vasopressor (OR: 1.48, 95% CI 0.43-4.95) were not associated with in-hospital mortality in patients with AP, whereas vasopressin (OR: 4.27, 95% CI 1.24-15.13; $p<0.05$) and phenylephrine usage (OR: 4.75, 95% CI 1.66-13.95; $p<0.05$), combined vasopressor usage (OR: 4.41, 95% CI 1.55-12.96; $p<0.01$), and female usage (OR: 7.89, 95% CI 2.03-34.2; $p<0.01$) were associated with in-hospital mortality.

CONCLUSIONS: Early vasopressor use is significantly associated with increased in-hospital mortality among critically ill AP patients. This association might be greater in females, vasopressin, phenylephrine, and combined vasopressor users. Our results may benefit clinicians as they can guide the rational use of vasopressors in critically ill AP patients admitted to the ICU.

Key Words:
Vasopressors, Acute pancreatitis, Mortality, Increased, risk, ICU.

Introduction

Acute pancreatitis (AP) is a common gastroenterological disease that may cause organ dysfunction and is associated with high mortality. AP is defined as an acute abdominal disorder caused by activation of pancreatic enzymes by the pancreas itself and surrounding organs. It is characterized by the local inflammatory reaction of the pancreas and may lead to organ dysfunction[1]. Typical symptoms of AP include acute attacks of persistent severe upper abdominal pain, often radiating to the back, accompanied by abdominal distension, nausea, and vomiting, with the pain persisting even after vomiting. AP is one of the most common diseases in the emergency department with acute abdominal pain as the main complaint, and 0.3% of patients in the emergency department are initially diagnosed with AP[2]. Epidemiological investigation shows that the incidence rate of AP in the United States ranges from 13/100,000 to 45/100,000[3], and nearly 280,000 patients with AP are admitted annually. AP is the fifth major cause of hospital death, and the annual diagnosis and treatment cost exceeds 2.6 billion US dollars[4,5]. In 2007, a nationwide multicenter survey in China reported that the overall mortality rate of severe AP reached 11.8%, and 79% of

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the deaths occurred within two weeks after admission[6].

Vasopressors are a class of drugs with constricting effects on peripheral arterial and venous blood vessels. They can directly increase peripheral vascular resistance and raise the patient's blood pressure to ensure adequate blood oxygen supply to organs and tissues under constant cardiac output conditions. The commonly used vasopressors can be classified as catecholamines and vasoconstrictors. The former is most commonly used in emergencies, including dopamine, norepinephrine, epinephrine, m-diammonium, and norepinephrine (also known as phenylephrine). The latter mainly include vasopressin and its analogs. The biological half-life of catecholamines is very short (1-2 min), and the blood concentration in patients becomes stable 5-10 min after the start of infusion. In contrast, vasopressin takes a long time to reach a steady blood concentration. Generally, patients with low vascular resistance shock exhibit clear indications for using vasopressor drugs. Furthermore, vasopressors can even be used in extreme cases before volume replacement, to maintain the patient's minimum perfusion pressure. However, early use of vasopressor drugs may pose health risks[7]. Importantly, excessive volume supplementation may have adverse effects on patients. In contrast, a large number of clinical data suggest that patients with septic shock should be administered vasopressors at early stage[8]. In this regard, the safety of early use of vasopressors in patients with AP is not clear.

Therefore, this study aimed to explore the association between early administration of vasopressors and in-hospital mortality in patients with AP admitted to the ICU.

Patients and Methods

Data Sources

The data used for analysis was obtained from a large US-based critical care database named Medical Information Mart for Intensive Care IV (MIMIC-IV, version 2.0), which contains integrated comprehensive, de-identified clinical data of ICU patients admitted to the ICU in the Beth Israel Deaconess Medical Center (Boston, MA, USA) between 2012 and 2019. To gain access to the database, we had to complete the National Institutes of Health's web-based course and pass the examinations (certificate record id: 39508701). Informed consent and ethics approval was not applicable as all patients' data were publicly available and anonymous. All reports were compliant with the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines.

Study Population

All patients diagnosed with AP in the MIMIC database who were admitted to the ICU and older than 18 years were included in the study. The first admission was considered if a patient was enrolled in the ICU more than once. Patients who were discharged or died within 24 h after ICU admission or had missing outcome data (in-hospital mortality) were excluded.

Extraction of Variables

Collected clinical variables included (1) demographic characteristics including gender, age, and ethnicity; (2) vital parameters, including heart rate, systolic blood pressure (SBP), diastolic blood pressure (DBP), and mean arterial pressure (MAP); (3) scoring system including Sequential Organ Failure Assessment (SOFA) score, Simplified Acute Physiology Score II (SAPS II), and Systemic inflammatory response syndrome (SIRS) score; (4) comorbidities including congestive heart failure, myocardial infarct, cerebrovascular disease, peripheral vascular disease, chronic pulmonary disease, dementia, rheumatic disease, peptic ulcer disease, liver disease, renal disease, paraplegia, diabetes, metastatic solid tumor, malignant cancer, acquired immune deficiency syndrome (AIDS), hypertension, acute kidney injury (AKI), and obesity; (5) ICU fluid input on the first day of admission and treatment measure including mechanical ventilation and renal replacement therapy (RRT). Based on the ethnicity variable, patients were divided as white and non-white. SOFA score associated with the greatest severity of illness was calculated within the first 24 h after ICU admission. The Kidney Disease: Improving Global Outcomes (KDIGO) criteria were used to define AKI. Vital parameter values were the mean of repeated measurements within 24 h of ICU admission. Treatment measures were collected from ICU admission to discharge or death. There were less than 2% missing values for all screening variables, including heart rate, SBP, DBP, MBP, and the first-day ICU input (**Supplementary Figure 1**). Using the 'mice' R package (The R Foundation for Statistical Computing, Vienna, Austria)[9], a single imputation method was performed to impute the missing values.

The main exposure was the early administration of vasopressors [24 h before ICU admission (-24 h to 0)]. In-hospital mortality was the endpoint of this study.

Statistical Analysis

Continuous variables are expressed as the median and interquartile range (IQR), whereas categorical variables are expressed as the number and percentage (%). Wilcoxon test or Chi-squared tests were used as appropriate for two-group comparisons.

Unadjusted and adjusted odds ratios (ORs) and corresponding 95% confidence intervals (95% CIs) were evaluated by univariate and multivariate regression analysis. The confounding variables for mortality outcomes, shown in Table I, were selected based on the literature and clinical knowledge.

Propensity score matching (PSM) was performed to identify similar patients using a nearest neighbor-matching algorithm with a maximum caliper of 0.05 of the propensity score. AP patients with vasopressor administration at an early stage were matched with a similar cohort of AP patients without vasopressor administration in a 1:2 ratio for confounders shown in Table I. To evaluate the efficacy of an unadjusted cohort and PSM, standardized mean differences (SMDs) were computed and are presented in **Supplementary Figure 2**. The matched cohort was analyzed based on logistic regression to compare in-hospi-

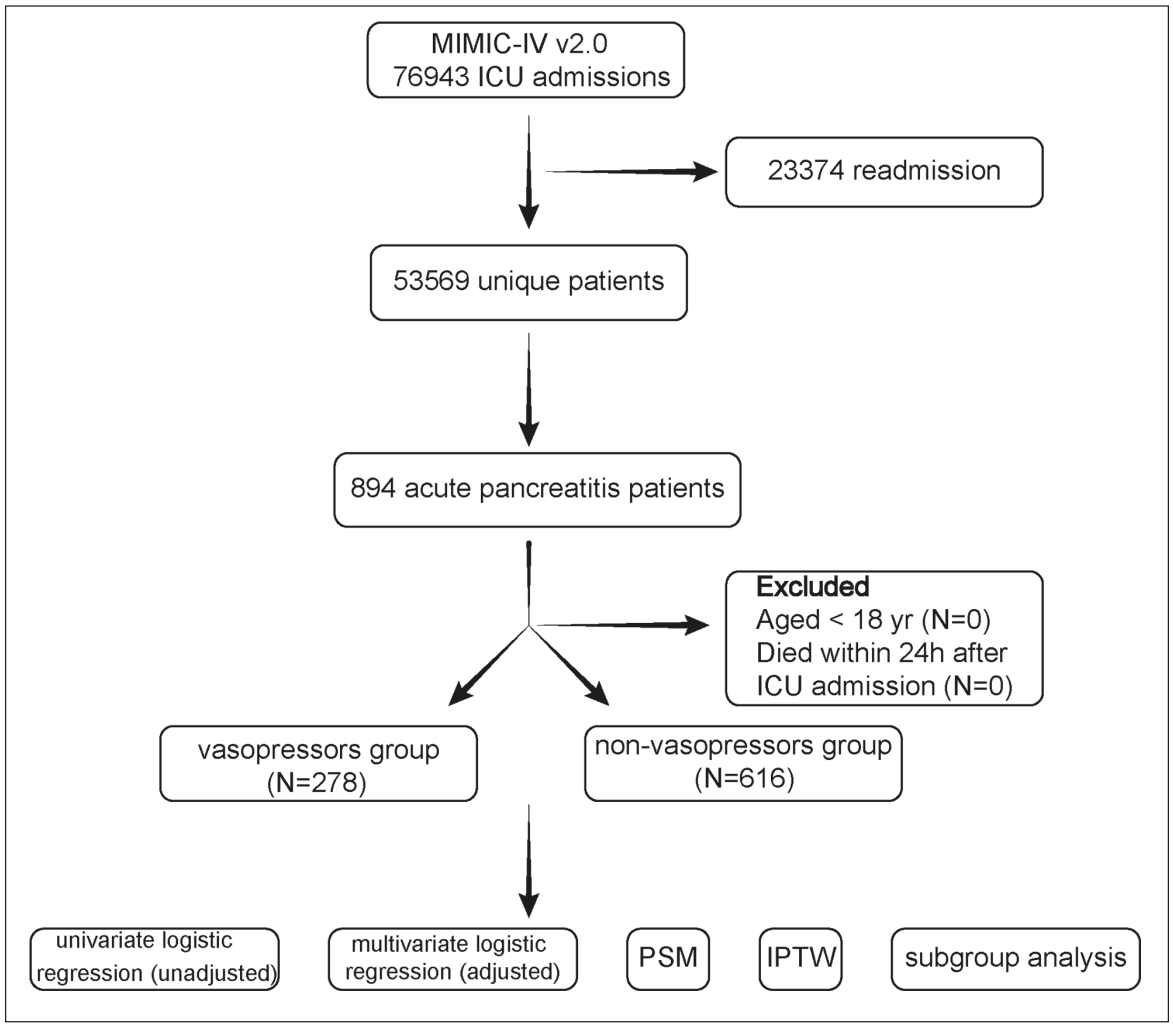

Figure 1. Flowchart of this study. MIMIC-IV: Medical Information Mart for Intensive Care Database IV; PSM: propensity score matching; IPTW: inverse probability of treatment weighting.

Table I. Baseline characteristics between groups before and after PSM and IPTW.

Variables	Entire cohort		p	After PSM		p	After IPTW		p
	Non-vasopressors	Vasopressors		Non-vasopressors	Vasopressors		Non-vasopressors	Vasopressors	
Gender (%)			0.18			0.858			0.565
Female	246 (39.9)	125 (45.0)		38 (50.0)	33 (47.1)		411.6 (47.7)	321.3 (53.1)	
Male	370 (60.1)	153 (55.0)		38 (50.0)	37 (52.9)		451.2 (52.3)	283.9 (46.9)	
Age [median (IQR)]	57.84 (45.78, 71.74)	62.84 (50.39, 75.72)	0.002	66.69 (46.35, 78.25)	66.78 (51.78, 76.70)	0.969	63.37 (47.26, 80.68)	60.37 (48.09, 73.01)	0.485
Ethnicity (%)			0.001			0.593			
Non-white	205 (33.3)	126 (45.3)		27 (35.5)	21 (30.0)		245.2 (28.4)	230.2 (38.0)	0.163
White	411 (66.7)	152 (54.7)		49 (64.5)	49 (70.0)		617.5 (71.6)	375.0 (62.0)	
Heart rate [median (IQR)]	92.98 (79.95, 107.44)	96.12 (81.10, 108.56)	0.118	94.28 (79.85, 107.39)	95.62 (81.97, 106.17)	0.736	97.19 (82.62, 106.27)	96.79 (81.74, 111.60)	0.462
SBP [median (IQR)]	128.08 (115.40, 141.30)	108.67 (102.28, 116.94)	<0.001	117.54 (106.26, 128.13)	114.00 (104.78, 124.05)	0.291	122.58 (107.21, 137.04)	116.50 (107.03, 128.97)	0.172
DBP [median (IQR)]	71.40 (63.08, 81.78)	60.43 (54.81, 66.55)	<0.001	64.00 (55.10, 70.31)	63.47 (57.35, 68.87)	0.959	67.99 (55.27, 77.92)	66.03 (58.39, 72.50)	0.502
MAP [median (IQR)]	85.08 (76.74, 94.42)	74.17 (69.90, 80.92)	<0.001	78.10 (71.44, 84.71)	75.32 (70.68, 84.89)	0.575	81.28 (70.99, 91.86)	79.41 (71.91, 86.97)	0.556
SOFA [median (IQR)]	4.00 (2.00, 6.00)	11.00 (8.00, 15.00)	<0.001	7.00 (6.00, 10.00)	7.00 (6.00, 9.75)	0.674	5.00 (3.00, 9.00)	7.00 (5.00, 11.00)	0.002
SAPS II [median (IQR)]	28.00 (20.00, 37.00)	47.00 (36.00, 58.75)	<0.001	42.00 (33.00, 48.00)	40.00 (32.00, 51.00)	0.922	33.00 (23.00, 47.00)	40.00 (30.00, 54.00)	0.202
SIRS [median (IQR)]	3.00 (2.00, 3.00)	3.00 (3.00, 4.00)	<0.001	3.00 (2.00, 4.00)	3.00 (3.00, 4.00)	0.862	3.00 (2.00, 4.00)	3.00 (3.00, 4.00)	0.787
MV (%)			<0.001			0.461			0.006
No	514 (83.4)	69 (24.8)		27 (35.5)	30 (42.9)		558.8 (64.8)	207.6 (34.3)	
Yes	102 (16.6)	209 (75.2)		49 (64.5)	40 (57.1)		304.0 (35.2)	397.6 (65.7)	
Myocardial infarct (%)			0.118			0.66			0.273
No	561 (91.1)	243 (87.4)		69 (90.8)	61 (87.1)		675.2 (78.3)	536.0 (88.6)	
Yes	55 (8.9)	35 (12.6)		7 (9.2)	9 (12.9)		187.6 (21.7)	69.2 (11.4)	
Congestive heart failure (%)			<0.001			0.78			0.225
No	530 (86.0)	211 (75.9)		59 (77.6)	52 (74.3)		752.3 (87.2)	499.0 (82.4)	
Yes	86 (14.0)	67 (24.1)		17 (22.4)	18 (25.7)		110.5 (12.8)	106.2 (17.6)	
Peripheral vascular disease (%)			0.1			0.847			0.261
No	586 (95.1)	256 (92.1)		70 (92.1)	66 (94.3)		827.1 (95.9)	561.2 (92.7)	
Yes	30 (4.9)	22 (7.9)		6 (7.9)	4 (5.7)		35.6 (4.1)	44.0 (7.3)	

Table continued

Table I. ***(Contined).*** Baseline characteristics between groups before and after PSM and IPTW.

Variables	Entire cohort		*p*	After PSM		*p*	After IPTW		*p*
	Non-vasopressors	Vasopressors		Non-vasopressors	Vasopressors		Non-vasopressors	Vasopressors	
Cerebrovascular disease (%)			0.001			1			0.288
No	590 (95.8)	250 (89.9)		71 (93.4)	65 (92.9)		824.5 (95.6)	562.8 (93.0)	
Yes	26 (4.2)	28 (10.1)		5 (6.6)	5 (7.1)		38.2 (4.4)	42.4 (7.0)	
Dementia (%)			0.705			0.943			0.002
No	596 (96.8)	271 (97.5)		75 (98.7)	68 (97.1)		725.9 (84.1)	595.2 (98.4)	
Yes	20 (3.2)	7 (2.5)		1 (1.3)	2 (2.9)		136.8 (15.9)	10.0 (1.6)	
Chronic pulmonary disease (%)			0.602			0.95			0.948
No	494 (80.2)	218 (78.4)		60 (78.9)	54 (77.1)		703.8 (81.6)	491.6 (81.2)	
Yes	122 (19.8)	60 (21.6)		16 (21.1)	16 (22.9)		159.0 (18.4)	113.6 (18.8)	
Rheumatic disease (%)			0.321			1			0.864
No	597 (96.9)	265 (95.3)		74 (97.4)	69 (98.6)		842.0 (97.6)	589.6 (97.4)	
Yes	19 (3.1)	13 (4.7)		2 (2.6)	1 (1.4)		20.8 (2.4)	15.6 (2.6)	
Peptic ulcer disease (%)			0.101			0.495			0.224
No	593 (96.3)	260 (93.5)		67 (88.2)	65 (92.9)		829.7 (96.2)	567.2 (93.7)	
Yes	23 (3.7)	18 (6.5)		9 (11.8)	5 (7.1)		33.1 (3.8)	38.0 (6.3)	
Paraplegia (%)			0.352			1			0.689
No	605 (98.2)	276 (99.3)		74 (97.4)	68 (97.1)		850.0 (98.5)	592.3 (97.9)	
Yes	11 (1.8)	2 (0.7)		2 (2.6)	2 (2.9)		12.7 (1.5)	12.9 (2.1)	
Renal disease (%)			0.007			1			0.198
No	535 (86.9)	221 (79.5)		61 (80.3)	57 (81.4)		759.1 (88.0)	499.9 (82.6)	
Yes	81 (13.1)	57 (20.5)		15 (19.7)	13 (18.6)		103.7 (12.0)	105.3 (17.4)	
Malignant cancer (%)			0.197			1			0.65
No	577 (93.7)	253 (91.0)		69 (90.8)	63 (90.0)		808.1 (93.7)	559.0 (92.4)	
Yes	39 (6.3)	25 (9.0)		7 (9.2)	7 (10.0)		54.6 (6.3)	46.2 (7.6)	
Metastatic solid tumor (%)			0.304			1			0.938
No	593 (96.3)	272 (97.8)		73 (96.1)	67 (95.7)		837.2 (97.0)	588.2 (97.2)	
Yes	23 (3.7)	6 (2.2)		3 (3.9)	3 (4.3)		25.5 (3.0)	17.0 (2.8)	
AIDS (%)			0.789			0.967			0.97
No	610 (99.0)	274 (98.6)		76 (100.0)	69 (98.6)		856.3 (99.3)	600.8 (99.3)	
Yes	6 (1.0)	4 (1.4)		0 (0.0)	1 (1.4)		6.4 (0.7)	4.4 (0.7)	
Charlson comorbidity index [median (IQR)]	4.00 (2.00, 6.00)	5.00 (3.00, 7.00)	<0.001	5.00 (3.00, 7.00)	5.00 (4.00, 7.00)	0.565	5.00 (2.42, 7.00)	5.00 (3.00, 6.00)	0.786

Table continued

Table I. ***(Contined)*****.** Baseline characteristics between groups before and after PSM and IPTW.

Variables	Entire cohort		*p*	After PSM		*p*	After IPTW		*p*
	Non-vasopressors	Vasopressors		Non-vasopressors	Vasopressors		Non-vasopressors	Vasopressors	
Diabetes (%)			0.969			0.503			0.2
No	443 (71.9)	201 (72.3)		59 (77.6)	50 (71.4)		534.4 (61.9)	448.7 (74.1)	
Yes	173 (28.1)	77 (27.7)		17 (22.4)	20 (28.6)		328.3 (38.1)	156.5 (25.9)	
Liver disease (%)			0.871			0.654			0.629
No	492 (79.9)	220 (79.1)		64 (84.2)	56 (80.0)		702.8 (81.5)	475.7 (78.6)	
Yes	124 (20.1)	58 (20.9)		12 (15.8)	14 (20.0)		159.9 (18.5)	129.5 (21.4)	
Obesity (%)			0.469			0.848			0.968
No	544 (88.3)	240 (86.3)		67 (88.2)	60 (85.7)		774.0 (89.7)	542.2 (89.6)	
Yes	72 (11.7)	38 (13.7)		9 (11.8)	10 (14.3)		88.7 (10.3)	63.0 (10.4)	
Hypertension (%)			0.472			1			0.209
No	317 (51.5)	151 (54.3)		41 (53.9)	37 (52.9)		375.6 (43.5)	328.5 (54.3)	
Yes	299 (48.5)	127 (45.7)		35 (46.1)	33 (47.1)		487.1 (56.5)	276.7 (45.7)	
AKI (%)			<0.001			0.907			0.014
None	319 (51.8)	28 (10.1)		12 (15.8)	12 (17.1)		342.8 (39.7)	94.2 (15.6)	
Stage 1	86 (14.0)	23 (8.3)		7 (9.2)	7 (10.0)		96.8 (11.2)	89.7 (14.8)	
Stage 2	142 (23.1)	86 (30.9)		35 (46.1)	28 (40.0)		177.4 (20.6)	256.3 (42.3)	
Stage 3	69 (11.2)	141 (50.7)		22 (28.9)	23 (32.9)		245.8 (28.5)	165.0 (27.3)	
RRT (%)			<0.001			1			0.003
No	601 (97.6)	242 (87.1)		73 (96.1)	67 (95.7)		842.8 (97.7)	564.1 (93.2)	
Yes	15 (2.4)	36 (12.9)		3 (3.9)	3 (4.3)		19.9 (2.3)	41.1 (6.8)	
First-day input [median (IQR)]	7,600.00 (4,707.50, 11,500.00)	17,405.50 (12,070.00, 26,962.50)	<0.001	11,185.00 (6,580.00, 16,172.50)	12,180.00 (8,428.00, 16,490.00)	0.199	9,338.17 (5,400.00, 16,492.16)	12,837.64 (9,078.59, 18,077.87)	0.108

PSM: propensity score matching; IPTW: inverse probability treatment weighted; SOFA: sequential organ failure assessment; SAPS II: simplified acute physiology score II; SIRS: systemic inflammatory response syndrome; SBP: systolic blood pressure; DBP: diastolic blood pressure; MAP: mean arterial pressure; MV: mechanical ventilation; AIDS: acquired immunodeficiency syndrome; AKI: acute kidney injury; RRT: renal replacement treatment; IQR: interquartile range; *p* by Chi-squared test [N (%)] or Wilcoxon test [median (IQR)].

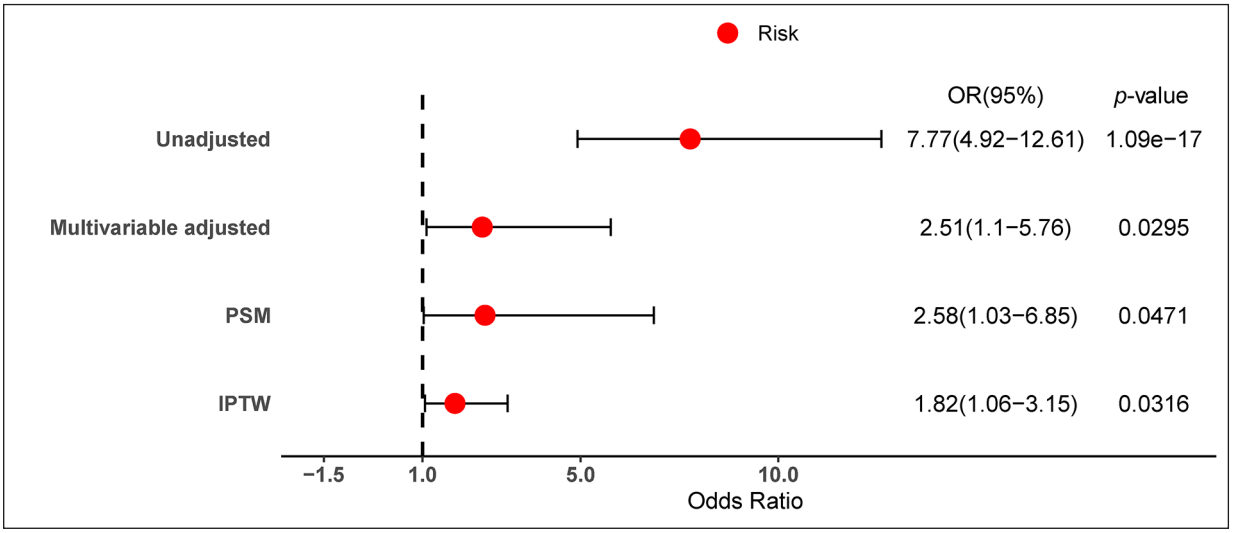

Figure 2. Forrest plot of the association between vasopressor use and in-hospital morality. OR: odds ratio; CI: confidence interval; ICU: intensive care unit; Unadjusted: univariate logistic regression without adjustment; Multivariable adjusted: multivariate logistic regression after adjusting for all the variables in Table I; PSM: propensity score matching; IPTW: inverse probability of treatment weighting.

tal mortality between early vasopressor users and vasopressor non-users.

As study groups were derived in a nonrandomized manner, inverse probability treatment weighted (IPTW) was used for sensitivity analysis to ensure the validity of our conclusions. A pseudo-population was created using IPTW, in which covariates were independent of treatment, to balance early vasopressor users and vasopressor non-users. The probability of assigning patients to either of the two groups was determined based on a logistic regression model containing the confounder variables shown in Table I. Subsequently, the weight for each patient was calculated based on the inverse of the probability of group assignment. SMDs were calculated to examine covariate balance before and after IPTW (**Supplementary Figure 3**). A weighted multivariate logistic regression model was generated to compare in-hospital mortality between early vasopressor users and vasopressor non-users.

As for subgroup analysis, multivariate logistic regression was performed among age, gender, single or combined use of vasopressor, categories of vasopressor and in-hospital mortality modified by confounder variables shown in Table I in the entire population. The results of univariate and multivariate logistic regression were described as ORs with 95% CIs. The data were obtained using Structured Query Language (SQL) with pgAdmin (version 4). Statistical analysis was performed using R 4.2.1 software (The R Foundation for Statistical Computing, Vienna, Austria) and SPSS v. 23.0 (IBM Corp., Armonk, NY, USA). A p-value < 0.05 was considered statistically significant.

Results

Population and Baseline Characteristics

The flowchart is shown in Figure 1. A total of 894 eligible patients with AP admitted to the ICU, and corresponding clinical variables and outcomes were screened according to the exclusion and inclusion criteria (Table I). The missing data in the clinical variables are shown in **Supplementary Figure 1**. Of these, 278 AP patients received vasopressors at an early stage (31.1%) during their time in the ICU, and 616 acute pancreatitis patients did not (68.9%).

Table I shows the baseline characteristics for the vasopressor user and vasopressors non-user groups. In general, the vasopressor user group had higher SOFA score [11 (IQR 8-15) *vs.* 4 (IQR 2-6); $p<0.001$], SAPS II score [47 (IQR 36-58.75) *vs.* 28 (IQR 20-37); $p<0.001$], SIRS score [3 (IQR 3-4) *vs.* 3 (IQR 2-3); $p<0.001$], charlson comorbidity index [5 (IQR 3-7) *vs.* 4 (IQR 2-6); $p<0.001$], and first-day input [17,405.50 (IQR 12,070-26,962.5) ml *vs.* 7,600 (IQR 4,707.5-11,500) ml; $p<0.001$],

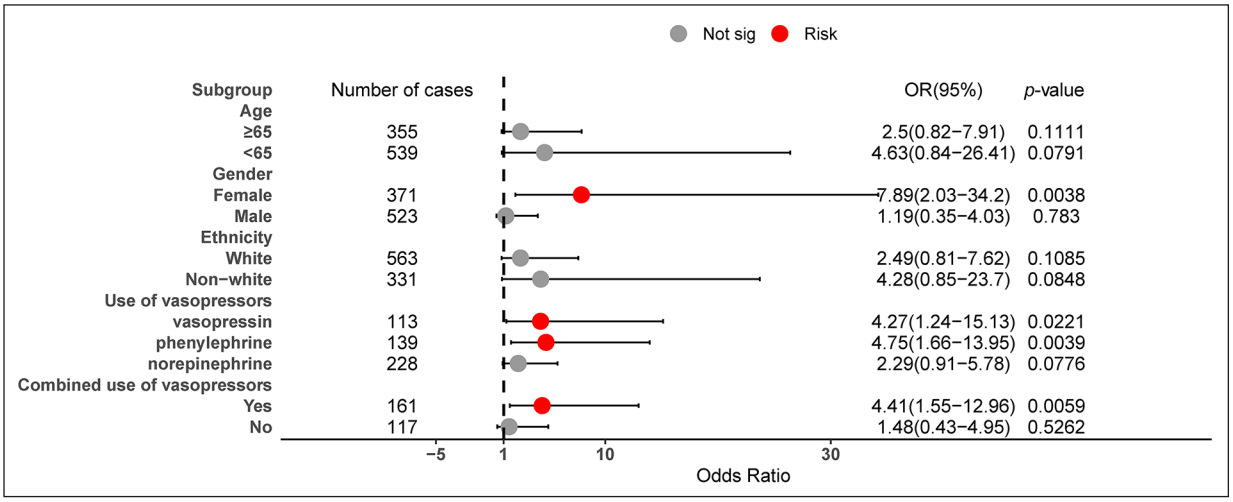

Figure 3. Subgroup analysis of association between vasopressors use and in-hospital mortality of patients with acute pancreatitis admitted to the ICU. OR: odds ratio, CI: confidence interval.

and severe vital signs [SBP: 108.67 (IQR 102.28-116.94) mmHg *vs.* 128.08 (IQR 115.4-141.3) mmHg, $p<0.001$; DBP: 60.43 (IQR 54.81-66.55) mmHg *vs.* 71.4 (IQR 63.08-81.78) mmHg, $p<0.001$; MAP: 74.17 (IQR 69.90-80.92) mmHg *vs.* 85.08 (IQR 76.74-94.42) mmHg, $p<0.001$] than the vasopressor non-user group, indicating that the patients in the vasopressor group were more critically ill than the vasopressor non-user group. Besides, there was a significant difference in age, ethnicity, congestive heart failure, cerebrovascular disease, renal disease, AKI, mechanical ventilation, and RRT between the vasopressor user and the vasopressor non-user group. After PSM and IPTW, differences in almost all the confounding variables were insignificant between the two groups (Table I). The SMDs before and after PSM and IPTW are shown in **Supplementary Figures 2** and **3**.

Relationship Between Early Vasopressors Use and in-Hospital Mortality

AP patients who received vasopressors at early stage were associated with an increased risk of in-hospital mortality in the unadjusted model (OR: 7.77, 95% CI 4.92-12.61, $p<0.001$) compared with patients who did not receive vasopressors. Taking confounding factors into account, the OR for early vasopressor administration was 2.51 (95% CI 1.1-5.76, $p<0.05$) in the multivariate logistic regression. PSM (OR: 2.58, 95% CI 1.03-6.85, $p<0.05$) and IPTW (OR: 1.82, 95% CI 1.06-3.15, $p<0.05$) models also demonstrated that early vasopressors use would increase in-hospital mortality (Figure 2).

Subgroup Analysis

The details of vasopressor categories and mortalities were shown in Table II. After adjusting for confounding factors based on multivariate logistic regression, the variables of age (≥ 65 years old: OR: 2.5, 95% CI 0.82-7.91; <65 years old: OR: 4.63, 95% CI 0.84-26.41), male (OR: 1.19, 95% CI 0.35-4.03), ethnicity (white: OR: 2.49, 95% CI 0.81-7.62; non-white: OR: 4.28, 95% CI 0.85-23.7), norepinephrine usage (OR: 2.29, 95% CI 0.91-5.78), and single-use of vasopressors (OR: 1.48, 95% CI 0.43-4.95) were not associated with in-hospital mortality in patients with AP. In contrast, use of vasopressin (OR: 4.27, 95% CI 1.24-15.13; $p<0.05$) or phenylephrine (OR: 4.75, 95% CI 1.66-13.95; $p<0.05$), combined use of vasopressors (OR: 4.41, 95% CI 1.55-12.96; $p<0.01$), females (OR: 7.89, 95% CI 2.03-34.2; $p<0.01$) in the vasopressor group were associated with an increased risk of in-hospital mortality compared with that in the vasopressor nonuser group (Figure 3). Owing to a limited number of milrinone, dobutamine, epinephrine, and dopamine users, they were not included in the subgroup analysis.

Discussion

AP is characterized by a high mortality rate in intensive care unit. Early administration of vaso-

pressors has been associated with reduced mortality risk in patients with shock[10]. However, the relationship between the early use of vasopressors and mortality in patients with AP remains unclear. In an attempt to clarify this relationship, this study included 894 AP patients from the MIMIC database; of these, 278 AP patients received vasopressors in the early stage during their ICU stay, whereas 616 AP patients did not. Results showed that early use of vasopressors was associated with increased mortality risk in patients with AP, particularly female user, vasopressin users or phenylephrine users, and combined vasopressor users were prone to death.

The early use mentioned in the study refers to vasopressor usage in the pre-shock stage in patients with AP, as we found that almost all patients in the vasopressor group admitted to the ICU who were administered vasopressors during this time/stage did not develop shock. Therefore, the administration start time of vasopressors is very important. A retrospective cohort[11] including 539 patients requiring vasopressors within 72 h of admission suggested that vasopressors were associated with increased mortality in patients and that vasopressors may play a causal role in adverse outcomes. In addition, Mecek et al[12,13] reported that the additional use of vasopressors played a vital role in predicting death. Our results reported similar findings although the population previously studied was that of patients with septic shock. However, norepinephrine administration was significantly delayed in those who died. It continued to be independently associated with 28-day mortality [OR 1.39 (1.14-1.71) for every hour delay] when adjusted for treatment, and illness severity characteristics[14]. Besides, the delayed administration of vasopressors may result in excessive intravenous fluid therapy, which may be harmful and even increase the hospital death rate[15,16]. The rats in a shock model could also benefit from the early use of vasopressors[17]. The reason that these conclusions differ from our results is that the included patients or animal models are in late stage of shock. So far, there was no clear mechanism explaining this observation and our results. Some evidence suggested that the powerful vasoconstricting properties of vasopressors could contribute to poor liver, heart, extremities, and digits perfusion, potentially impacting patient outcomes[18-20]. Moreover, high doses of vasopressor drugs may be associated with a higher risk of complications, including myocardial ischemia, decreased cardiac function, arrhythmias, increased tissue oxygen consumption, and pulmonary hypertension[21].

Table II. Use and non-use of vasopressors and outcomes in patients with acute pancreatitis.

Variables	Number of cases
Use of vasopressors	278
Single use	117
Combined use	161
Death	73
Alive	205
Non-use of vasopressors	616
Death	27
Alive	589
Categories	
Milrinone	12
Dobutamine	14
Vasopressin	113
Phenylephrine	139
Norepinephrine	228
Epinephrine	30
Dopamine	21

Notably, the results of our subgroup analysis showed that compared with vasopressor non-users, combined vasopressor usage and vasopressin or phenylephrine usage were associated with increased mortality risk in patients with AP, while norepinephrine usage and single use of vasopressors were not. The explanation of our results may be related to the pathogenesis of AP. Hypovolemia in AP is caused by a specific inflammatory response, unlike hypovolemia caused by trauma or bleeding. Different causes stimulate acinar cells to secrete IL-1β. In addition, inflammatory factors such as IL-6 induce CD4+ T cells to invade and differentiate into the pancreatic parenchyma, thereby secreting IL-17, inducing neutrophils and macrophages to gather in the inflammatory zone, causing damage to the acinar and surrounding cells[22]. Moreover, inflammatory factors induce the seep out of electrolytes and small molecule proteins in the lumen out into the tissue gap, resulting in insufficient volume in the vascular lumen, blood concentration, and elastase hydrolysis of elastin in the vascular wall, causing microcirculation embolism, leading to insufficient perfusion of pancreas, end organs, and even multiple organ dysfunction in severe cases[23]. Therefore, proper fluid resuscitation can correct fluid loss, maintain sufficient intravascular volume, and improve microcirculation perfusion and tissue oxygenation. According to guidelines for the diagnosis and treatment of AP in China, aggressive fluid resuscitation is the first-line treatment for AP, only if

the patient with persistent hypotension can be administered norepinephrine during or after fluid resuscitation to raise blood pressure[24]. Different types of vasopressors have different targets and indications. Norepinephrine is a strong α-receptor agonist, with a weak effect on β1 receptors and little effect on β2 receptors. Importantly, norepinephrine, widely recognized as the first-line treatment for shock, can significantly increase systemic vascular resistance and mean arterial pressure in septic shock patients, with low alteration of the heart rate[25]. Phenylephrine is a synthetic adrenergic drug that mainly excites α-receptor, and its pressor effect is weaker and more durable than norepinephrine. Routine use of phenylephrine in shock patients is not recommended, because it may cause reflex bradycardia and tissue ischemia of internal organs and decrease cardiac output[26]. Dopamine should be used with caution in patients with shock because it may increase the risk of tachyarrhythmia[27], including atrial fibrillation, ventricular tachycardia, and even ventricular fibrillation[21]. In addition, a study[28] showed no significant difference in mortality between patients who started to use vasopressin at the same time as low-dose noradrenaline and those who used noradrenaline alone. These results are in line with our findings.

Limitations

Nevertheless, our studies had several limitations. First, given its retrospective observational design, the patient's exposure history and laboratory tests were incomplete, resulting in some missing values in the study. Besides, all patients recruited were admitted to the same unit, and the results may be affected by the unique practice of the unit. Therefore, multicenter trials are needed to validate the results. Second, PSM analysis lost many observations and lead to data loss, resulting in the non-representativeness of the remaining samples and selective bias. Moreover, the baseline scores of the two groups were not completely balanced through IPTW analysis, and there were still some differences in variables. Third, there may have been some unmeasured confounders that might have affected the severity of the disease and affected vasopressor use in this study. Finally, the early and late administered vasopressors in patients with AP are not compared due to the limited data source.

Conclusions

Early vasopressor use is significantly associated with increased in-hospital mortality among critically ill AP patients. This association might be greater in females, vasopressin and phenylephrine users, and combined vasopressor users. Our results may help clinicians rationally guide the use of vasopressors in critically ill AP patients.

Conflict of Interest

The Authors declare that they have no conflict of interests.

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Authors' Contributions

Q. Peng: conceptualization, methodology, software; H. Shi: data curation, writing-original draft preparation; Y. S. He and S. Y. Sun: software, validation; all authors: reviewing.

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Informed Consent

Not applicable.

Availability of Data and Materials

The data set analyzed to generate the findings for this study are available from the corresponding author upon reasonable request.

Ethics Approval

MIMIC-IV database used in our study was approved by the Institutional Review Boards (IRB) of the Massachusetts Institute of Technology and does not contain protected health information.

Informed Consent

Informed consent was not applicable as all patients' data were publicly available and anonymous.

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