Original Article

Effect of sex on the association between arterial partial pressure of oxygen and in-hospital mortality in ICU patients with cardiogenic shock: a retrospective cohort study

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Background: Maintaining tissue perfusion and oxygen supply are essential for cardiogenic shock (CS) treatment. Sex has been reported to be associated with mortality and oxygen use in patients with CS. Males and females respond differently to hypoxia. We designed this cohort study to evaluate the effects of sex on the association between the arterial partial pressure of oxygen (PaO_2) and in-hospital mortality.

Methods: We used the Medical Information Mart for Intensive Care (MIMIC) IV database for this cohort study. The outcome was in-hospital mortality. The relationship between the PaO_2 and in-hospital mortality was compared with sex (via an interaction test) using multivariable Cox regression models. Presence of interaction between PaO_2 and sex was tested by using inter interaction terms.

Results: A total of 1,772 patients with CS were enrolled in this study. The association between PaO_2 and in-hospital mortality appeared to differ between males and females [hazard ratio (HR): 0.997, 95% confidence interval (CI): 0.995–0.999 *vs.* HR: 1.002, 95% CI: 0.999–1.003, P for interaction =0.002]. We repeated the analyses, based on different PaO_2 category (PaO_2 <60 mmHg; PaO_2 60–100 mmHg; PaO_2 >100 mmHg) and the results remained stable, P for interaction =0.008.

Conclusions: Sex affects the relationship between PaO_2 and in-hospital mortality in CS patients. Our findings may lead to the development of individualized therapies that focus on the use of different target oxygen partial pressures in different sexes to treat patients with CS.

Keywords: Sex; cardiogenic shock (CS); arterial partial pressure of oxygen; in-hospital mortality

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Introduction

Cardiogenic shock (CS) is a clinical syndrome of impaired tissue perfusion and oxygenation resulting from heart failure (1). In patients with CS caused by acute myocardial infarction, the mortality rate has reached 50% and has not decreased significantly over the last 2 decades (2).

Patients with CS require prompt and effective treatment (3). Clinicians use oxygen therapy, intra-aortic balloon pumps (4), and extracorporeal membrane oxygenation (5) to maintain tissue perfusion and oxygen supply (6). In previous studies, female patients with CS had a higher mortality rate than male through 2005–2014 (7) and through 2004–2018 (8) in American. In order to provide individualized treatment, it is important to determine the causes of the sex-dependent mortality differences in patients with CS.

Males and females respond differently to hypoxia (9,10). We hypothesized that sex-dependent mortality differences are due to the sex's response to partial pressure of oxygen (PaO_2). This cohort study was designed to determine whether sex and PaO_2 have an interactive effect on mortality. We present the following article in accordance with the STROBE reporting checklist (available at https://atm.amegroups.com/article/view/10.21037/atm-22-5141/rc) (11).

Methods

Data sources and setting

The Critical Care Databases in Medical Information Mart for Intensive Care IV (MIMIC-IV) were used for this population-based cohort study (https://physionet.org). The MIMIC-IV database has been updated from MIMIC-III (12). It includes data on 76,540 intensive care unit (ICU) stays between 2008 and 2019. The author ZN was granted approval to use this database (certification number 46644825). We also complied with all relevant ethical regulations regarding the use of the data in our study. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013).

Study population

The study population comprised adults with CS as defined by the International Classification of Diseases (ICD)-9 codes (code =785.51) or ICD-10 codes (code =R570) (13). The exclusion criteria included: (I) aged <18 years; (II) patients not admitted to ICU for the first time.

Exposure

PaO_2 value was obtained from the blood gas analysis results in Beth Israel Deaconess Medical Center. Due to the multiple measurements of PaO_2 in MIMIC-IV, the PaO_2 was taken as the median of those PaO_2 measurements at day 1. Additionally, we used the arithmetic mean of PaO_2 of day 1 for the sensitivity analysis. Sex data were extracted from the MIMIC-IV database directly.

Covariates

Based on the published literature and clinical experience, we included the following variables in this study: demographic information (age, sex) (14), vital signs and laboratory tests (15) [heart rate, mean arterial pressure (MAP), respiratory rate, glucose, hemoglobin, platelet, white blood cell (WBC) count, bicarbonate, creatinine, sodium, potassium], the vasopressors used on the first day of ICU admission, disease comorbidities (16) (chronic pulmonary disease, hypertension, myocardial infarction, congestive heart failure, rheumatic disease, peptic ulcer disease, renal disease, and diabetes), and disease severity scores [the Oxford acute severity of illness score (OASIS)] (17), simplified acute physiology score (SOFA) (18), and simplified acute physiology score (SAPS) II (19). Illness severity (OASIS, SOFA and SAPS II scores) were calculated on the worst values in the first 24 hours in the ICU. The vasopressors included norepinephrine, epinephrine, phenylephrine, vasopressin, dopamine, dobutamine, and isoprenaline.

Highlight box

Key findings

- Sex affects the relationship between PaO_2 and in-hospital mortality in cardiogenic shock patients.

What is known and what is new?

- In previous studies, female patients with cardiogenic shock had a higher mortality rate than male. Males and females respond differently to hypoxia.
- Sex affects the relationship between PaO_2 and in-hospital mortality in cardiogenic shock patients.

What is the implication, and what should change now?

- This study may lead to the development of individualized therapies that focus on the use of different target oxygen partial pressures in males and females to treat patients with cardiogenic shock.

Outcome

The outcome of the study was in-hospital mortality during the study period.

Statistical analysis

A descriptive analysis was conducted for all the participants. The categorical variables are expressed as numbers and percentages. The continuous variables are expressed as means and standard deviations (SDs) if they had normal distributions or interquartile ranges if they had skewed distributions. We used the chi-square test and *t*-test, and Kruskal-Wallis test to compare categorical, normally distributed, and non-normally distributed continuous variables, respectively. We conducted Kaplan-Meier (K-M) and log-rank analyses to determine the survival curves for the different sexes.

Differences in the PaO_2 levels of the participants and survival (or non-survival) between the male and female patients were compared. Multiplicative interaction terms (sex × PaO_2) were incorporated into the models were used to test for interaction. The Wald test was used to test for statistical interaction. P for interaction <0.05 considered significant. Missing values are interpolated by median and mean. We also conducted 5 sets of multiple imputation data as a sensitivity analysis.

All the analyses were performed using the statistical software packages R 3.3.2 (http://www.R-project.org, The R Foundation) and Free Statistics software (version 1.7.1) (20). A 2-tailed test was performed, and a P value <0.05 was considered statistically significant.

Sensitivity analysis

The sensitivity analysis was performed using the arithmetic mean for the PaO_2 on day 1 after ICU admission. As sex-related hormones change with age, we excluded patients aged ≤50 years from the sensitivity analysis.

Results

Participants

Of the 53,150 adult patients with first hospital and ICU admissions in the MIMIC-IV database from 2008–2019. 2,027 patients with CS diagnosis met the inclusion exclusion criteria. 1,772 patients had at least one PaO_2 test within 24 hours (the flowchart was in Figure S1). Of these patients, 1,052 (59.4%) were male and 720 (40.6%) were female; 536 (30.2%) patients grouped in PaO_2 <60 mmHg, 539 (30.4%) patients grouped in PaO_2 60–100 mmHg, 697 (39.3%) patients grouped in PaO_2 >100 mmHg. As shown in *Table 1*, the comparison between males and females showed that there was no significant difference in heart rate, respiratory rate, glucose, WBC, bicarbonate, vasopressor use, ventilator use, peptic ulcer disease, DM, SAPS II score, and Charlson comorbidity index (all P>0.05). However, age, MAP, hemoglobin, platelets, Creatinine, Sodium, Potassium, Chronic pulmonary disease, hypertension, myocardial infarct, Congestive heart failure, Rheumatic disease, Renal disease, OASIS score, SOFA score, and in-hospital mobility were statistically significant differences between males and females (all P<0.05). The baseline factors including PaO_2 and other clinical covariates was presented in Table S1.

Primary outcome

The patients had an overall in-hospital mortality rate of 40.9% (724/1,772). The mortality rates of males and females were 38.5% (405/1,052) and 44.3% (319/720), respectively. The mortality rates of patients in the PaO_2 <60 mmHg group, 60–100 mmHg group and the PaO_2 >100 mmHg group were 43.1% (231/536), 43.4% (234/539) and 37.2% (259/697), respectively.

The surviving males had a significantly higher PaO_2 than non-surviving males (90.5 *vs.* 81.0 mmHg, P=0.007, *Figure 1*), while the PaO_2 did not differ among the survival and non-survival in females (88.0 *vs.* 83.5 mmHg, P=0.692, *Figure 1*). In the K-M analysis, PaO_2 >100 mmHg was associated with lower in-hospital mortality in male patients compared with other groups (Log rank test P=0.00037, *Figure 2*). However, the mortality rates were similar among the three groups of female patients (Log rank test P=0.92, *Figure 2*).

In multivariate Cox regression analyses, after adjusted all confounders in *Table 1*, we found sex modified the effect of association between PaO_2 and in-hospital mortality no matter in continuous Variable or categorical variables (*Table 2*). The hazard ratio (HR) between PaO_2 and in-hospital mortality in males and females were HR: 0.997, 95% confidence interval (CI): 0.995–0.999 and HR: 1.002, 95% CI: 0.999–1.003, respectively, P for interaction =0.002. We repeated the analyses, based on different PaO_2 category (PaO_2 <60 mmHg; PaO_2 60–100 mmHg; PaO_2 >100 mmHg) and the results remained stable, P for interaction =0.008. We also found an interaction between sex, PaO_2 and in-hospital mortality using a restricted cubic spline (*Figure 3*).

Table 1 Baseline characteristics of the participants

Variables	Total (n=1,772)	Males (n=1,052)	Females (n=720)	P value
Age (years)	70.6±14.6	68.9±14.8	73.1±13.9	<0.001
Heart rate (bpm)	89.4±18.2	88.9±18.3	90.0±18.2	0.23
MAP (mmHg)	60.5±36.2	62.1±37.2	58.1±34.4	0.02
Respiratory rate (bpm)	21.0±4.2	21.2±4.2	20.8±4.1	0.06
Glucose (mmol/L)	152.8 (124.1, 202.7)	152.8 (125.6, 203.2)	152.7 (122.3, 202.4)	0.38
Hemoglobin (g/L)	10.1±2.4	10.4±2.5	9.6±2.1	<0.001
Platelets ($\times10^{12}$)	166.0 (115.0, 227.0)	161.0 (112.0, 221.0)	170.5 (120.2, 235.0)	0.02
WBC ($\times10^{9}$)	15.1 (11.0, 20.2)	15.2 (11.0, 20.5)	15.0 (10.9, 20.0)	0.54
Bicarbonate (mmol/L)	18.5±5.5	18.7±5.3	18.3±5.7	0.21
Creatinine (mg/dL)	1.8 (1.2, 2.8)	2.0 (1.3, 3.0)	1.6 (1.1, 2.3)	<0.001
Sodium (mmol/L)	135.3±5.7	135.0±5.7	135.9±5.5	<0.001
Potassium (mmol/L)	5.0±1.0	5.1±1.0	4.9±1.0	<0.001
Vasopressor use, n (%)	1,382 (78.0)	833 (79.2)	549 (76.2)	0.16
Ventilator use, n (%)	1,017 (57.4)	607 (57.7)	410 (56.9)	0.752
Chronic pulmonary disease, n (%)	539 (30.4)	290 (27.6)	249 (34.6)	<0.001
Hypertension, n (%)	478 (27.0)	257 (24.4)	221 (30.7)	0.004
Myocardial infarct, n (%)	881 (49.7)	550 (52.3)	331 (46.0)	0.009
Congestive heart failure, n (%)	1,358 (76.6)	843 (80.1)	515 (71.5)	<0.001
Rheumatic disease, n (%)	71 (4.0)	22 (2.1)	49 (6.8)	<0.001
Peptic ulcer disease, n (%)	40 (2.3)	28 (2.7)	12 (1.7)	0.22
Renal disease, n (%)	693 (39.1)	441 (41.9)	252 (35.0)	<0.001
DM, n (%)	698 (39.4)	413 (39.3)	285 (39.6)	0.93
OASIS score	38.9±9.9	38.4±10.2	39.6±9.5	0.01
SOFA score	9.0 (6.0, 12.0)	9.0 (6.0, 13.0)	9.0 (6.0, 12.0)	<0.001
SAPS II score	48.6±15.8	48.1±16.0	49.2±15.4	0.18
Charlson comorbidity index	7.0 (5.0, 9.0)	7.0 (5.0, 9.0)	7.0 (5.0, 9.0)	0.89
In-hospital mortality	724 (40.9)	405 (38.5)	319 (44.3)	0.02

Data are means ± SD, n (%), and median (IQR). MAP, mean artery pressure; WBC, white blood cell; DM, diabetes mellitus; OASIS, Oxford Acute Severity of Illness Score; SOFA, Sequential Organ Failure Assessment; SAPS, simplified acute physiology score; SD, standard deviation; IQR, interquartile range.

Sensitivity analysis

We found similar results based on the arithmetic means of PaO_2 on day 1 (Table S2). After excluding 162 patients aged ≤50 years, the results remained stable (Table S3). In multiple imputation, the results remain similar (Table S4).

Discussion

In this cohort study, our findings confirmed that among male participants with CS in the MIMIC-IV database, the survival rate of the PaO_2 >100 mmHg group was significantly higher than that of the PaO_2 60–100 mmHg

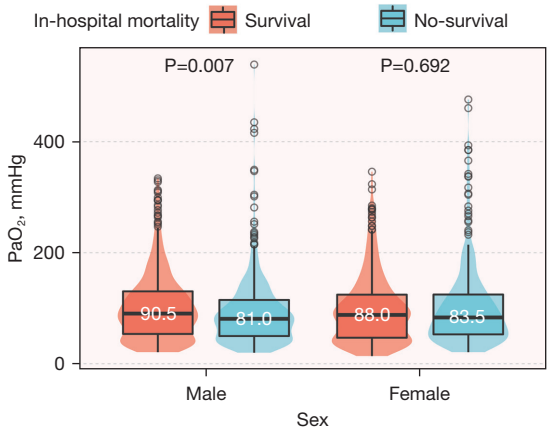

Figure 1 Distribution of the PaO_2 in terms of survival and death by sex.

group and the PaO_2 <60 mmHg group. However, this effect was not observed in the female participants. After adjusting for potential confounders, the PaO_2 was found to be inversely associated with in-hospital mortality in male CS patients, but not in female CS patients. In a further analysis, hyperoxemia was found to be associated with lower in-hospital mortality in males. We also found an interactive effect between sex and the PaO_2 on in-hospital mortality, which suggests that there is an important difference in the responses of males and females to hyperoxemia. Our study confirmed previous findings on gender differences in CS, which reported that in patients with CS, females were older than males, which have a higher severity of illness and a higher in-hospital mortality rates than males (7,8).

Evidence of an association between the PaO_2 and mortality in patients with CS is still limited. However, several studies have examined this association in critical care patients. For example, the SRLF Trial Group found that the severity of hypoxemia was an independent risk factor for mortality among ICU patients (percentage of male patients: 68%) (21). Zhang *et al.* found that lower PaO_2 levels were associated with a high mortality risk in sepsis patients (percentage of male patients: 55%) (22). Martín-Fernández *et al.* reported that oxygenation with a PaO_2 >100 mmHg was independently associated with a lower 90-day mortality rate, and a shorter ICU stay and intubation time in critically ill postsurgical sepsis/septic shock patients (percentage of male patients: 60%) (23). In Baekgaard 's study, early hyperoxemia in trauma patients was found to be associated with reduced adjusted in-hospital mortality (percentage of male patients: 78%) (24). These results are only partially consistent with our findings. The possible effects of sex on hypoxia and mortality have been overlooked. In these studies, males represented the majority of patients (55–78%) (20-23). There were no sexes stratification in these studies, and males account for the majority of the study population (20-23). As a result, it was likely that the total effect of PaO_2 on mortality was only depended on the effect of male population.

Several studies have reported there may be some differences in responses to changes in the PaO_2 between the sexes. Camacho-Cardenosa's found that the ventilatory response to hypoxia was more pronounced in males than females (9). This may be because males have relatively higher sympathetic responses to hypoxia exposure than females (10). Another study found that, at rest, morbidly obese males have poorer pulmonary gas exchange and pulmonary diffusion than morbidly obese females (25). In type B acute aortic dissection, being male was found to be independently associated with a minimum PaO_2/FiO_2 (26).

Unlike female patients, in our cohort, the male patients with hyperoxemia had reduced in-hospital mortality rates. There are significant differences between sexes, which can affect the relationship between PaO_2 and mortality. However, the differences between sex-related hormones may be an important part on the relationship between hyperoxia and mortality. For example, the sex hormone androgen, which controls mitochondrial function, is higher in males than in females (27). Several studies suggest that androgen activity is important for the maintenance of normal mitochondrial architecture in both males and females (28-30). Sex difference in androgen levels may lead to males making better use of oxygen than females. In addition, high level of the testosterone, another sex hormone that is elevated in males, have been shown to be associated with better outcomes in coronavirus 2019 patients (31). Moreover, sex-related hormones change with age. Age may be a significant confounding factor in our study. However, the association between hyperoxia and mortality in males and females was still different in the older patients (i.e., those aged >50 years).

Our study provides valuable clinical evidence that sex affects the relationship between hyperoxia and mortality. As a result of our findings, we may be able to develop individualized therapies for treating patients with CS that utilize different target oxygen partial pressures based on their sexes.

Our study also had some limitations. First, as with

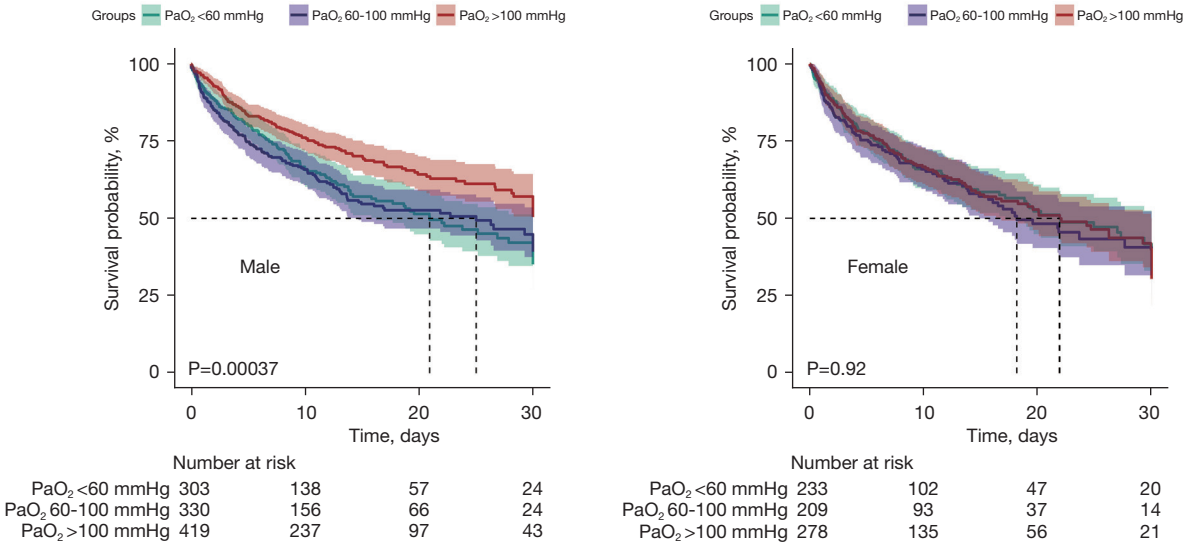

Figure 2 K-M analysis of different oxygen partial pressure category in males and females. K-M, Kaplan-Meier.

Table 2 Sex modified the effect of the association between the PaO_2 and in-hospital mortality

Variable	Crude model, HR (95% CI)	P value	Adjusted model, HR (95% CI)	P value	P for interaction
Continuous variable					
PaO_2 (mmHg)					
Male	0.998 (0.996–0.999)	0.039	0.997 (0.995–0.999)	0.007	0.002
Female	1.001 (0.999–1.003)	0.307	1.002 (0.999–1.003)	0.102	
Categorical variables					
Male					
PaO_2 <60 mmHg	Ref.		Ref.		0.008
PaO_2 60–100 mmHg	1.030 (0.811–1.307)	0.810	0.806 (0.625–1.039)	0.095	
PaO_2 >100 mmHg	0.664 (0.521–0.846)	0.001	0.557 (0.427–0.727)	<0.001	
Female					
PaO_2 <60 mmHg	Ref.		Ref.		
PaO_2 60–100 mmHg	1.046 (0.789–1.387)	0.753	1.134 (0.838–1.534)	0.415	
PaO_2 >100 mmHg	1.005 (0.773–1.305)	0.972	1.069 (0.800–1.429)	0.652	

In adjusted model, we adjusted for all the confounders in *Table 1*.

all retrospective analyses, some unadjusted confounding variables may have affected results. However, we did adjust for possible confounders. Second, as the study population only comprised patients with CS, it may not be generalizable to patients without CS. Third, in terms of sexes, there are significant differences. Further studies are necessary to confirm whether any of these factors may affect the relationship between PaO_2 and mortality.

Conclusions

Sex affects the relationship between the PaO_2 and in-

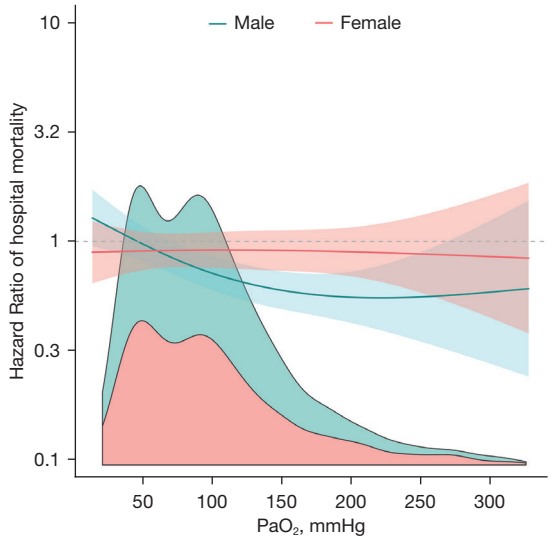

Figure 3 Interactive effect of sex and the PaO_2 on in-hospital mortality. The blue line and red line represent the estimated values of males and females, respectively. The light color represents the corresponding 95% CI. The blue and red peaks represent the distributions for males and females, respectively.

hospital mortality in CS. Our findings may lead to the development of individualized therapies that focus on the use of different target oxygen partial pressures in different sexes to treat patients with CS.

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Footnote

Reporting Checklist: The authors have completed the STROBE reporting checklist. Available at https://atm.amegroups.com/article/view/10.21037/atm-22-5141/rc

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://atm.amegroups.com/article/view/10.21037/atm-22-5141/coif). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013).

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