Journal of Intensive Medicine 3 (2023) 73–78

Contents lists available at ScienceDirect

Journal of Intensive Medicine

journal homepage: www.elsevier.com/locate/jointm

Original Article

Relationship between PaO_2/FiO_2 and delirium in intensive care: A cross-sectional study

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ARTICLE INFO

Keywords:
Delirium
Intensive care unit
Partial pressure of oxygen (PaO_2)/Fraction of inspired oxygen (FiO_2)
Hypoxia
Risk factor
Non-linear relationship

ABSTRACT

Background: To investigate the relationship between partial pressure of oxygen (PaO_2)/fraction of inspired oxygen (FiO_2) and the probability of delirium in intensive care units (ICUs).

Methods: The investigation was a cross-sectional study that involved the collection of data from patients admitted to the Xiang Ya Hospital Cardiothoracic Surgical Care Unit and Comprehensive Intensive Care Unit from 01 September 2016 to 10 December 2016. Delirium was diagnosed using the simplified version of the Chinese Confusion Assessment Method (CAM) for the ICU. Demographic and medical data were obtained within 24 h of each patient admitted in the ICU. The PaO_2/FiO_2 of each patient was recorded 24 h after admission in the ICU. The patients were divided into three groups according to PaO_2/FiO_2 data : normal (PaO_2/FiO_2 ≥300 mmHg), slightly low (200 ≥PaO_2/FiO_2 <300 mmHg), and severely low (PaO_2/FiO_2 <200 mmHg). Baseline characteristics were compared in the three groups. Results of the unadjusted model, minimally adjusted model, and fully adjusted model are presented.

Results: A total of 403 participants were included in the study, of which 184 (45.7%) developed delirium. Age (P <0.001), Sequential Organ Failure Assessment (SOFA) score (P <0.001), Acute Physiology and Chronic Health Evaluation (APACHE) II score (P <0.001), mechanical ventilation time (P <0.001), history of hypertension (P=0.040), heart disease (P=0.040), sedation (P=0.001), and PaO_2/FiO_2 (P=0.006) were significantly associated with delirium in univariate analysis. Multivariate regression analysis models were used to further analyze the associations between PaO_2/FiO_2 and delirium. In the crude model, for 1 standard deviation (SD) increase in PaO_2/FiO_2, the odds ratio (OR) of delirium was 0.8 (95% confidence interval [CI]: 0.6–0.9), but there was no significant correlation in the fully adjusted model. There was a non-linear relationship between the PaO_2/FiO_2 and delirium in a generalized additive model. A two-piecewise linear regression model was used to calculate a PaO_2/FiO_2 threshold of 243 mmHg. On the left side of the threshold, the OR was 0.9 and the 95% CI was 0.9–1.0 (P=0.013) when PaO_2/FiO_2 increased by 1 SD.

Conclusions: PaO_2/FiO_2 was negatively associated with delirium when PaO_2/FiO_2 was below the identified threshold. As a readily available laboratory indicator, PaO_2/FiO_2 has potential value in the clinical evaluation of risk of delirium in ICU patients.

Introduction

Delirium is an acute occurrence of brain dysfunction that is characterized by acute onset of a fluctuating course of disorganized thinking, lack of attention, and an altered state of consciousness.[1] The prevalence of delirium is estimated to be 20–87%.[2,3] The differences in results between epidemiological studies may be related to differences in evaluation methods, types of sedation/analgesic drugs used, and the study populations. Delirium has been shown to prolong mechanical ventilation[4,5] and the length of hospitalization in intensive care units (ICUs),[4–6] and can also lead to long term cognitive dysfunction,[7,8] increased risk of mortality,[6,9] and increased ICU costs.[10]

The partial pressure of oxygen (PaO_2)/fraction of inspired oxygen (FiO_2) ratio was first proposed by Horovitz et al.[11] in 1974 to compare the oxygenation of patients with different inhaled oxygen concentrations. PaO_2/FiO_2 has since been demon-

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https://doi.org/10.1016/j.jointm.2022.08.002
Received 18 January 2022; Received in revised form 24 July 2022; Accepted 10 August 2022. Managing Editor: Jingling Bao
Available online 1 October 2022

strated to be convenient and practical for assessing oxygenation and pulmonary shunting in clinical circumstances. It has commonly been used to diagnose adult respiratory distress syndrome (ARDS) via the evaluation of oxygenation criteria,[12–14] and it is the standard method for clinical experts to evaluate lung function. An acceptable threshold is 300 mmHg.[15] PaO_2/FiO_2 can reflect pathophysiological changes in hypoxia, and it can be used to assess disease progression and/or treatment outcomes.[16]

Previous studies have shown that sepsis, shock, sedation, age, and alcohol consumption are risk factors for delirium.[2,8,17] Additionally, hypoxemia is associated with cognitive impairment.[18–21] Few studies have investigated the associations between delirium and PaO_2/FiO_2. This study aimed to investigate the associations between PaO_2/FiO_2 and delirium.

Methods

Study population

This cross-sectional study involved data from patients admitted to the Cardiothoracic Surgical Care Unit (15 beds) and Comprehensive ICU (34 beds) at Xiangya Hospital from 01 September 2016 to 10 December 2016. For inclusion in the study, all patients were required to have stayed in the ICU for >24 h and to have been at least 18 years old during their stay in the ICU. Patients with a history of mental disorders were also included. Exclusion criteria were a lack of competency in Mandarin; a persistent disorder of consciousness before admission to the ICU (e.g., cerebrovascular accident, brain injury, brain death, intracranial infection, and coma caused by cardiac arrest); uncontrolled mental illness; intellectual disability; neuromuscular disorders; and lack of patient or family member consent to participate in the study.

Delirium and sedation assessments

Delirium diagnoses were conducted by two trained physicians in accordance with the simplified version of the Chinese Confusion Assessment Method for the ICU (CAM-ICU),[22] which was originally developed as a clinical assessment for the use of non-psychiatric doctors.[23] The CAM-ICU was then further improved by another group.[24] In this study, four key delirium features were assessed; (1) acute onset and fluctuating course, (2) inattention, (3) disorganized thinking, and (4) altered level of consciousness. Delirium was diagnosed if features (1) and (2) were present in addition to either feature (3) or (4). Two study assistants (ICU doctors) received training in the use of protocols for delirium detection, and they evaluated each patient for delirium at two fixed times every day (10:00–12:00 a.m. and 4:00–6:00 p.m.) until the patient was discharged. Level of consciousness was assessed using the Richmond Agitation-Sedation Scale (RASS),[25] which is based on a 10-point scale from −5 to +4. A RASS score of 0 indicates that the patient is awake and cooperative. A positive RASS score indicates agitation or aggression, ranging from +1 (mild agitation) to +4 (dangerous agitation). Negative RASS scores from −1 to −3 reflect responses to verbal commands, a score of −4 reflects responses to physical stimuli only, and a RASS score of −5 reflects no responses to either sound or physical stimuli. The CAM-ICU could not be administered when the RASS score was −4 or −5.

Compliance and reliability of assessors

Before the study was initiated, all assessors received CAM-ICU and RASS training. The study assistants diagnosed some patients to obtain prior experience and received interrater reliability evaluations from senior members of the group.

Data collection

Data were recorded for all patients who met the inclusion criteria. Demographic and medical data were obtained within 24 h of each patient admitted in the ICU, and included sex, age, medical history, Acute Physiology and Chronic Health Evaluation (APACHE) II scores, Sequential Organ Failure Assessment (SOFA) scores, and duration of mechanical ventilation. Arterial partial pressure of carbon dioxide ($PaCO_2$) and PaO_2 were measured using an arterial blood gas analyzer 24 h after admission to the ICU. FiO_2 was also recorded. Where multiple PaO_2/FiO_2 values were recorded, the lowest was used in analyses.

Statistical analysis

Continuous variables were analyzed using descriptive statistics (mean ±standard deviation [SD] or median and minimum–maximum). Categorical data were analyzed as frequencies and percentages via chi-squared tests. PaO_2/FiO_2 data were divided into three groups: normal (PaO_2/FiO_2 ≥300 mmHg), slightly low (200≥ PaO_2/FiO_2 <300 mmHg), and severely low (PaO_2/FiO_2 <200 mmHg). Baseline characteristics were compared in the three groups. Results of the unadjusted model, minimally adjusted model, and fully adjusted model are presented, in accordance with the recommendations of the Strengthening the Reporting of Observational Studies in Epidemiology statement.[26] Adjusted variables were selected based on clinical judgment and published studies. If the influence of a confounder changed by >10%, it was incorporated into the adjusted model.[27] Generalized additive models were then used to investigate non-linear relationships between PaO_2/FiO_2 and delirium after adjustment for potential confounders. A two-piecewise linear regression model was used to calculate the threshold effect of PaO_2/FiO_2 on delirium based on a smoothing plot. A recursive method was used to automatically calculate the inflection point if the ratio between PaO_2/FiO_2 and delirium was notable in the smoothed curve and gave the maximum model likelihood. All data were analyzed using R software (http://www.R-project.org) and EmpowerStats software (www.empowerstats.com, X&Y Solutions, Inc., Boston, MA, USA). P <0.05 was considered statistically significant.

Results

Participants

A total of 813 patients were admitted to the two ICUs during the enrollment period. After excluding patients who did not meet the relevant criteria, a total of 403 patients were included in the study (Figure 1). The average age of the participants was

Table 1
Baseline characteristics of the study participants according to PaO_2/FiO_2 cohort.

Variables	PaO_2/FiO_2 (mmHg)			*P*-value
	<200 (*n*=72)	200–300 (*n*=128)	≥300 (*n*=203)	
Age (years)	57.5 ± 13.9	56.3 ± 15.2	52.4 ± 17.1	0.037
Sex				0.231
Female	48 (66.7)	73 (57.1)	112 (55.2)	
Male	24 (33.3)	55 (43.0)	91 (44.8)	
Smoking habits	20 (27.8)	44 (34.4)	54 (26.6)	0.303
Drinking habits	6 (8.3)	20 (15.6)	24 (11.8)	0.304
Delirium	47 (65.3)	55 (43.0)	82 (40.4)	0.001
Comorbidities				
Hypertension	35 (48.6)	42 (32.8)	52 (25.6)	0.002
Heart disease	22 (30.6)	35 (27.3)	46 (22.7)	0.358
History of CVA	1 (1.4)	6 (4.7)	5 (2.5)	0.348
Diabetes	5 (6.9)	17 (13.3)	17 (8.4)	0.233
COPD	10 (13.9)	12 (9.4)	9 (4.4)	0.024
Treatment measures				
Postoperative surgery	47 (65.3)	92 (71.9)	177 (87.2)	<0.001
Sedation	56 (77.8)	89 (69.5)	146 (71.9)	0.454
Mechanical ventilation	62 (86.1)	98 (76.6)	167 (82.3)	0.214
Mechanical ventilation time (h)	11.8 (0.0–234.0)	1 5.5 (0.0–274.0)	5.5 (0.0–98.0)	<0.001
Biochemical indicators				
PaO_2 (mmHg)	66.9 ± 12.7	98.8 ± 27.3	160.2 ± 44.2	<0.001
$PaCO_2$ (mmHg)	39.8 ± 7.6	38.8 ± 9.7	37.9 ± 7.1	0.202
Lac (mmol/L)	1.6 (0.4–15.0)	1.2 (0.3–15.0)	1.4 (0.3–15.0)	0.830
HCO_3^- (mmol/L)	25.2 ± 4.6	26.5 ± 16.5	24.1 ± 5.6	0.119
BUN (mmol/L)	9.0 (1.8–29.6)	8.11 (1.4–64.0)	6.00 (1.3–45.0)	0.004
Creatinine (mmol/L)	112.5 (46.7–723.0)	101.0 (43.5–626.0)	90.7 (28.0–178.0)	0.115
Criticality assessment				
SOFA score	8.0 (0.0–21.0)	5.0 (0.0–25.0)	4.0 (0.0–18.0)	<0.001
APACHE II score	12.5 (3.0–29.0)	11.00 (0.0–32.0)	9.0 (0.0–28.0)	<0.001

Data were expressed as mean ± SD, *n* (%), and median (minimum–maximum).
APACHE: Acute Physiology and Chronic Health Evaluation; BUN: Blood urea nitrogen; COPD: Chronic obstructive pulmonary disease; CVA: Cerebral vascular accident; Lac: Arterial blood lactic acid; FiO_2: Fraction of inspired oxygen; $PaCO_2$: Arterial partial pressure of carbon dioxide; PaO_2: Partial pressure of oxygen; SD: Standard deviation; SOFA: Sequential Organ Failure Assessment.

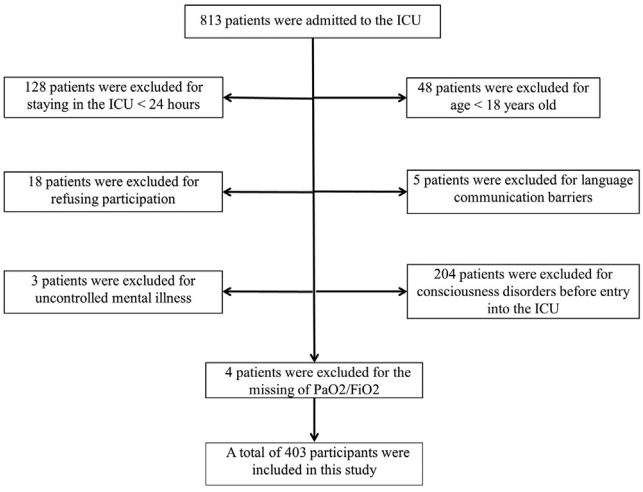

Figure 1. Flowchart of study participants.
FiO_2: Fraction of inspired oxygen; ICU: Intensive care unit; PaO_2: Partial pressure of oxygen.

54.5±16.0 years, and 57.8% (233/403) patients were female. Of the 403 patients, 184 (45.7%) developed delirium.

Characteristics of the study participants by PaO_2/FiO_2

Characteristics of the patients in the different PaO_2/FiO_2 subgroups are shown in Table 1. There were no significant differences in sex, heart disease, history of cerebral vascular accident (CVA), diabetes, smoking habits, drinking habits, sedation, or mechanical ventilation between the different PaO_2/FiO_2 groups. With respect to laboratory indicators, there were also no significant differences in arterial blood pH, arterial blood lactic acid (Lac), or $PaCO_2$ 24 h after admission, or bicarbonate and creatinine. The mean age in the severe PaO_2/FiO_2 decrease group was significantly greater than that in the other groups (*P*=0.037). In the severe decrease of PaO_2/FiO_2 group, the patients were older and they exhibited higher frequencies of hypertension, chronic obstructive pulmonary disease (COPD), postoperative surgery, and delirium, and higher mechanical ventilation times, SOFA scores, APACHE II scores, PaO_2, and blood urea nitrogen (BUN). Patients with lower PaO_2/FiO_2 tended to be older and have higher SOFA and APACHE II scores.

Factors associated with delirium in univariate analysis

Variables associated with delirium in univariate analysis are shown in Table 2. PaO_2/FiO_2 value was significantly associated with delirium (odds ratio [OR]=0.8, 95% confidence interval [CI] =: 0.6–0.9, *P*=0.006). Age (OR=1.1, 95% CI:1.0–1.1, *P* <0.001), SOFA score (OR=1.1, 95% CI: 1.1–1.2, *P* <0.001), APACHE II score (OR=1.2, 95% CI: 1.1–1.2, *P* <0.001), and mechanical ventilation time (OR=1.1, 95% CI: 1.0–1.1, *P* <0.001) were positively associated with delirium, as were hypertension, heart disease, history of CVA, postoperative surgery, and seda-

Table 2
Factors correlated to delirium by univariate analysis.

Variables	Statistics	OR (95% CI)	*P*-value
Age (years)	54.5 ± 16.0	1.1 (1.0–1.1)	<0.001
Sex			
Female	233(57.8)	1.0	
Male	170 (42.2)	1.4 (0.9–2.0)	0.135
Smoking habits	118 (29.3)	0.7 (0.4–1.1)	0.084
Drinking habits	50 (12.4)	0.9 (0.5–1.7)	0.802
Comorbidities			
Hypertension	129 (32.0)	1.9 (1.3–2.9)	0.041
Heart disease	103 (25.6)	1.6 (1.0–2.5)	0.041
History of CVA	12 (3.0)	6.2 (1.4–28.8)	0.019
Diabetes	31 (7.7)	2.0 (0.9–4.2)	0.073
COPD	31 (7.7)	2.0 (0.9–4.2)	0.073
Treatment measures			
Postoperative surgery	316 (78.4)	0.5 (0.3–0.8)	0.003
Sedation	291 (72.2)	2.5 (1.5–3.9)	0.001
Mechanical ventilation	327 (81.1)	1.6 (0.9–2.6)	0.088
Mechanical ventilation time (h)	7 (0–274)	1.1 (1.0–1.1)	<0.001
Biochemical indicators			
PaO_2 (mmol/L)	124.0 ± 51.9	1.0 (1.1–1.0)	0.127
$PaCO_2$ (mmol/L)	38.5 ± 8.1	1.0 (0.9–1.0)	0.131
Lac (mmol/L)	2.3 ± 2.5	1.2 (1.1–1.3)	0.001
HCO_3^- (mmol/L)	25.1 ± 10.3	1.0 (0.9–1.0)	0.864
PaO_2/FiO_2 (per SD mmHg)	0.0 ± 1.0	0.8 (0.6–0.9)	0.006
BUN (mmol/L)	8.8 ± 6.6	1.1 (1.0–1.1)	0.001
Creatinine (mmol/L)	126.7 ± 104.5	1.0 (1.0–1.0)	0.050
Criticality score			
SOFA score	4.0 (0.0–25.0)	1.1 (1.1–1.2)	<0.001
APACHE II score	11(0.0–32.0)	1.2 (1.1–1.2)	<0.001
Prognosis			
Time of hospital stay (days)	19.9 ± 15.0	1.0 (0.9–1.0)	0.466
ICU time	4.0 ± 4.2	1.2 (1.1–1.3)	<0.001
Outcome			
Death	32 (7.9)	1.0	
Survival	371 (92.1)	0.30 (0.1–0.7)	0.003

Statistic data were expressed as mean ± SD, *n* (%), and median (minimum–maximum).
APACHE: Acute Physiology and Chronic Health Evaluation; BUN: Blood urea nitrogen; CI: Confidence interval; COPD: Chronic obstructive pulmonary disease; CVA: Cerebral vascular accident; Lac: Arterial blood lactic acid; FiO_2: Fraction of inspired oxygen; ICU: Intensive care unit; OR: Odds ratio; $PaCO_2$: Arterial partial pressure of carbon dioxide; PaO_2: Partial pressure of oxygen; SD: Standard deviation; SOFA: Sequential Organ Failure Assessment.

tion. Sex, diabetes, history of COPD, smoking habits, drinking habits, mechanical ventilation, and $PaCO_2$ were not associated with delirium.

Relationships between PaO_2/FiO_2 and delirium

Multivariate regression analysis models were used to analyze the associations between PaO_2/FiO_2 and delirium. Results derived from the crude model, adjusted model I, and fully adjusted model II are shown in Table 3. In the crude model, for 1 SD increase in PaO_2/FiO_2, the OR of delirium was 0.8 (95% CI: 0.6–0.9). There was no obvious change in effect size in model I, which was adjusted for age and sex (OR=0.8, 95% CI: 0.6–1.0, *P*=0.038). There was no significant association between PaO_2/FiO_2 and delirium in model II, which was adjusted for sex, age, hypertension, heart disease, history of CVA, diabetes, smoking habits, drinking habits, chronic pulmonary dysfunction, infection, blood pressure at admission, postoperative surgery, mechanical ventilation, mechanical ventilation time, $PaCO_2$, sedation, APACHE II score, and SOFA score (OR=1.00, 95% CI: 0.8–1.4, *P*=0.855).

Non-linear relationships between PaO_2/FiO_2 and the risk of delirium were investigated using a generalized additive model (Figure 2). The relationship between PaO_2/FiO_2 and the probability of delirium was non-linear after adjustment for sex, age, ICU time, outcome, history of CVA, hypertension, smoking habits, postoperative surgery, SOFA score, APACHE II score, mechanical ventilation duration, sedation, $PaCO_2$, lactic acid, and BUN. A two-piecewise linear regression model was used to calculate a PaO_2/FiO_2 threshold of 243 mmHg. On the left of the threshold inflection point, there was a negative relationship between PaO_2/FiO_2 and delirium (OR=0.9, 95% CI: 0.9–1.0, *P*=0.013). On the right of the threshold inflection point, there was no significant relationship (OR=1.3, 95% CI: 0.9–1.9, *P*=0.091).

Discussion

The pathophysiology of delirium in critically ill patients remains unclear. To our knowledge, delirium is related to both the disease itself and interaction between treatments and the ICU environment. Previous studies indicate that hypoxia is an independent risk factor for acute brain injury and may induce long-term cognitive impairment.[19,28,29] McMorris et al.[21] reported that low PaO_2 (35–60 mmHg) was an important predictor of cognitive impairment, and other studies suggest that cognitive impairments due to hypoxia are associated with hip-

Table 3
Relationship between PaO_2/FiO_2 and delirium in different models.

Variables	Crude model*		Adjust I model†		Adjust II model‡	
	OR (95% CI)	*P*-value	OR (95% CI)	*P*-value	OR (95% CI)	*P*-value
PaO_2/FiO_2 (per SD)	0.8 (0.6–0.9)	0.006	0.8(0.6–1.0)	0.038	1.0 (0.8–1.4)	0.855
Fitted groups						
<200	Ref		Ref		Ref	
200–300	0.4 (0.2–0.7)	0.003	0.4 (0.2–0.7)	0.001	0.5 (0.2–1.1)	0.079
≥300	0.4 (0.2–0.6)	0.001	0.4 (0.2–0.7)	0.001	0.9 (0.7–1.4)	0.434
P for trend		0.001		0.007		0.783

*Crude model: We did not adjust other covariates.
†Adjusted I model: We adjusted for sex and age.
‡Adjusted II model: We adjusted for sex, age, ICU time, outcome, hypertension, history of CVA, heart disease, smoking habits, postoperative surgery, SOFA score, APACHE II score, mechanical ventilation time, sedation, $PaCO_2$, Lac, BUN.
APACHE: Acute Physiology and Chronic Health Evaluation; BUN: Blood urea nitrogen; CI: Confidence interval; CVA: Cerebral vascular accident; FiO_2: Fraction of inspired oxygen; ICU: Intensive care unit; Lac: Arterial blood lactic acid; OR: Odds ratio; $PaCO_2$: Arterial partial pressure of carbon dioxide; PaO_2: Partial pressure of oxygen; Ref: Reference; SD: Standard deviation; SOFA: Sequential Organ Failure Assessment.

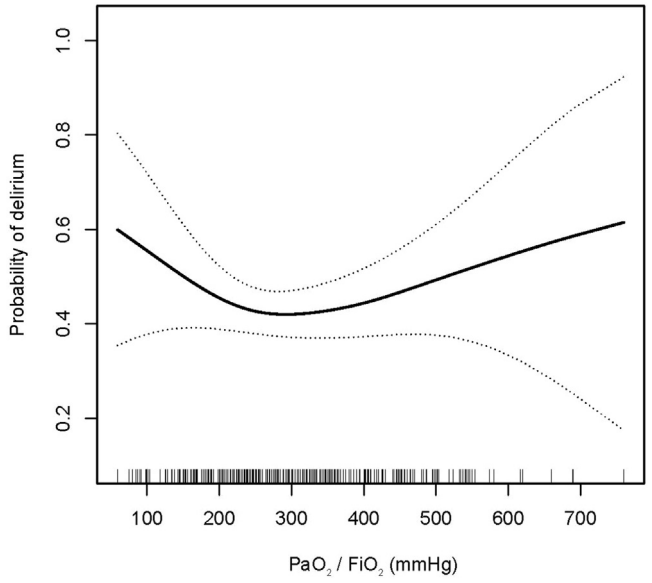

Figure 2. Relationship between PaO_2/FiO_2 and the probability of delirium. There was a non-linear relationship between PaO_2/FiO_2 and the probability of delirium after adjusting for the followings: sex, age, ICU time, outcome, hypertension, history of CVA, heart disease, smoking habits, postoperative surgery, SOFA score, APACHE II score, mechanical ventilation time, sedation, $PaCO_2$, lactic acid, and BUN. Solid line indicates the cubic spline functions between variables. Imaginary lines represent the 95% CI from the fit.
APACHE: Acute Physiology and Chronic Health Evaluation; BUN: Blood urea nitrogen; CI: Confidence interval; CVA: Cerebral vascular accident; FiO_2: Fraction of inspired oxygen; ICU: Intensive care unit; $PaCO_2$: Arterial partial pressure of carbon dioxide; PaO_2: Partial pressure of oxygen; SOFA: Sequential Organ Failure Assessment.

pocampal atrophy or other neuropathological changes.[30,31] Central nervous system impairments are well documented in disorders characterized by acute hypoxic insults, acute ARDS,[19] COPD,[32] and obstructive sleep apnea syndrome.[33] Of the 184 patients with delirium in this study, only 23 were not mechanically ventilated. Mechanical ventilation is a risk factor for delirium, which may be related to sedation and hypoxia. Therefore, we adjusted for mechanical ventilation, duration of mechanical ventilation, and sedation as potential confounders. No previous study has investigated the relationship between PaO_2/FiO_2 and delirium. PaO_2/FiO_2 can reflect pathophysiological changes in hypoxia, and it can be used to assess disease progression and/or treatment outcomes. The reason why PaO_2/FiO_2 >243 mmHg had no relationship with delirium may be related to the small sample size.

The current study had several limitations. First, not all participants underwent mechanical ventilation, which may have led to limitations in the PaO_2/FiO_2 evaluations. Second, delirium was only evaluated twice a day. Such discontinuous monitoring and evaluation may have resulted in a lower recorded incidence of delirium than the actual incidence. Third, the use of sedatives and analgesics in patients with ARDS or hypoxia can reduce oxygen consumption. However, previous studies indicate that delirium is associated with the prolonged use of sedatives and analgesics. This was not confirmed in this study. To ensure the credibility of our results, sedation and other covariates were adjusted for in multivariate regression analysis models and the analysis of a threshold effect.

Conclusions

There is a non-linear relationship between PaO_2/FiO_2 and the risk of delirium. PaO_2/FiO_2 is negatively correlated with risk of delirium when it is <243 mmHg. As a readily available laboratory indicator, PaO_2/FiO_2 has potential value in the clinical evaluation of ICU patients with delirium. The results of this study require confirmation with other studies, particularly large prospective studies.

Ethical Statement

Each patient who participated in the survey provided a signed informed consent form, or had a family member sign an informed consent form. The study was approved by the Ethics Committee of Xiang Ya Hospital of Central South University (Approval Number: AF/SC-07/02.0).

Data Availability Statement

Readers can access the data supporting the conclusions of the study from the Mendeley Data. Ai, Yuhang (2020), "Risk factors for ICU delirium," Mendeley Data, http://dx.doi.org/10.17632/5gx8j6wgs5.1.

Funding

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Conflicts of Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper. All the authors of the manuscript have agreed to publish.

Acknowledgments

We thank LetPub (www.letpub.com) for its linguistic assistance during the preparation of this manuscript.

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