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Effects of early hyperoxia in patients admitted to the general ward

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Article title

Effects of early hyperoxia in patients admitted to the general ward

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Authors' contributions

Jin Hee Jeong: Dr. Jeong conceptualized and designed the study, analyzed the data, drafted the initial manuscript, critically reviewed the manuscript, approved the final manuscript as submitted, and agreed to be accountable for all aspects of the work.

Dong Hoon Kim: Dr. Kim conceptualized and designed the study, coordinated and supervised data collection, critically reviewed the manuscript, approved the final manuscript as submitted, and agreed to be accountable for all aspects of the work.

Tae Yun Kim: Dr. Kim conceptualized and designed the study, interpreted data, critically reviewed the manuscript, approved the final manuscript as submitted, and agreed to be accountable for all aspects of the work.

Changwoo Kang: Dr. Kang interpreted data, critically reviewed the manuscript, approved the final manuscript as submitted, and agreed to be accountable for all aspects of the work.

Soo Hoon Lee: Dr. Lee interpreted data, critically reviewed the manuscript, approved the final manuscript as submitted, and agreed to be accountable for all aspects of the work.

Sang Bong Lee: Dr. Lee interpreted data, critically reviewed the manuscript, approved

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Effects of early hyperoxia in patients admitted to the general ward

Abstract

Introduction

We evaluated the association between hyperoxia induced by a noninvasive oxygen supply method for 3 days after emergency department (ED) arrival and the clinical outcomes after the fifth day of ED arrival.

Methods

In this retrospective observational cohort study, consecutive ED patients ≥ 16 years of age with available arterial blood gas analysis results who were admitted to our hospital with disease were enrolled from January 2010 to December 2016. The highest (PaO_{2MAX}), average (PaO_{2AVG}), and median (PaO_{2MED}) PaO_2 (arterial oxygen pressure) values within 72 h, and the area under the curve divided by the time elapsed between ED admittance and the last PaO_2 result (AUC_{72}), were used to assess hyperoxia. The primary outcome was the 90-day in-hospital mortality rate. The secondary outcomes were intensive care unit (ICU) transfer and respiratory failure after the fifth day of ED arrival, as well as new-onset cardiovascular, coagulation, hepatic, and renal dysfunction after the fifth day of ED arrival.

Results

Among the 10,141 patients, the mortality rate was 5.8%. The adjusted odds ratios (ORs) of in-hospital mortality for PaO_{2MAX}, PaO_{2AVG}, PaO_{2MED}, and AUC_{72} were 0.79 (95% CI, 0.61–1.02; P = 0.0715), 0.92 (95% CI, 0.69–1.24; P = 0.5863), 0.82 (95% CI, 0.61–1.11; P = 0.2005), and 1.53 (95% CI, 1.25–1.88; P <0.0001). All of the hyperoxia variables showed significant positive correlations with ICU transfer after the fifth day of ED arrival (P < 0.05). AUC_{72} was positively correlated with respiratory failure, as well as cardiovascular, hepatic, and renal dysfunction (P < 0.05). PaO_{2MAX} was positively correlated with cardiovascular dysfunction. PaO_{2MAX} and AUC_{72} were negatively correlated with coagulation dysfunction (P < 0.05).

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Conclusion

Hyperoxia during the first 3 days in patients outside the ICU is associated with in-hospital mortality and ICU transfer after the fifth day of ED arrival.

Keywords: Hyperoxia; Oxygen; Oxygen Inhalation Therapy

Strengths and limitation of this study

A retrospective observational cohort study of 10,141 patients visiting at the emergency department of a tertiary teaching hospital.

The relation between hyperoxia and clinical outcome was analyzed in the patients who were admitted to general ward.

The enrolled patients were limited to those who visited emergency department.

Because the NEWS was calculated using the initial values in the ED rather than ICU-based severity scores, the assessment of severity may have been inaccurate.

Introduction

Supplemental oxygen is a fundamental therapy for hypoxic patients, and is frequently ordered in various clinical settings. Physicians tend to believe that oxygen is a safe and beneficial treatment option in non-hypoxic patients, and even in patients with hyperoxia.[1] However, hyperoxia is positively correlated with poor outcomes. Patients in the intensive care unit (ICU) with high arterial oxygen pressure (PaO_2) and a high fraction of inspired oxygen (FiO_2) have a higher mortality rate than normoxic patients.[2] Hyperoxia is associated with the in-hospital mortality rate of patients resuscitated from cardiac arrest.[3-5] In addition, hyperoxia is associated with poor outcomes in patients with stroke, spontaneous SAH, and traumatic brain injury. [6-8] A recent randomized clinical study reported better outcomes in normoxic compared to hyperoxic ICU patients.[9]

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Despite the evidence that hyperoxia is harmful in critical clinical settings, therapeutic strategies that prevent hyperoxia cannot be translated to non-ICU settings because related studies involved only ICU patients.[2,6,9] Many patients in the emergency department (ED) require supplemental oxygen, and some need mechanical ventilation and so are admitted to the ICU. However, in most ED patients, oxygen therapy is administered using a noninvasive method such as a facial mask or nasal prong; such patients are then admitted to the general ward. The only study of the association between hyperoxia and clinical outcomes in the ED reported that hyperoxia was harmful in patients diagnosed with sepsis.[10] However, that study involved a small number of patients, a limited disease spectrum, and a single arterial blood gas analysis (ABGA) result. No studies have evaluated the associations between hyperoxia and mortality in patients admitted to the general ward. We hypothesized that hyperoxia induced by a noninvasive oxygen supply method during the early treatment period would have adverse effects somewhat later in patients admitted to the general ward.

We evaluated the association between hyperoxia during the first 3 days after ED arrival and clinical outcomes after the fifth day of ED arrival.

Method

Study design and setting

We conducted a single-center retrospective observational cohort study at Gyeongsang National University Hospital, a tertiary teaching hospital located in the south-central region of the Republic of Korea, from January 2010 to December 2016. This study was approved by our Institutional Review Board. All patients admitted to the ED are enrolled in the National Emergency Department Information System (NEDIS). The NEDIS was developed in 2003 to establish a national database of ED patients.[11,12] The quality of the data are examined annually by the National

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Emergency Medical Center, a government-funded, national ED control agency. In our ED, triage nurses and attending physicians enter into the NEDIS the patients' data, including basic demographic and temporal parameters, physiologic parameters at ED arrival, symptoms, diagnosis, treatment details (including drugs and procedures), outcomes, and other information. The data are organized using the standard NEDIS registry format in the hospital electronic medical records (EMRs). The validity of all data are checked by function modules within the system before the data are saved.

Participants

All consecutive patients ≥ 16 years of age with available ABGA results in the ED who were admitted to the hospital with disease (not injury) during the study period were enrolled. We excluded patients with fewer than two partial pressure of oxygen (PaO_2) results within 72 h of ED arrival. We also excluded patients with a maximum value of PaO_2 within 72 h (PaO_{2MAX}) of < 60 mmHg because we wished to compare hyperoxic and normoxic patients. Because we intended to assess delayed effects of hyperoxia, we also excluded patients who died prior to day 5 after ED arrival and who showed complications in the first 5 days (ICU transfer and respiratory failure, as well as new-onset cardiovascular, hepatic, renal, and coagulation dysfunction).

The other exclusion criteria were transfer to other facilities after admission, discharge with no hope of recovery, left the hospital against medical advice, and a hospital stay duration > 90 days. Patients diagnosed with acute myocardial infarction were also excluded because supplemental oxygen is no longer recommended as a routine therapy in normoxic patients with acute myocardial infarction.[13]

Data collection

The data were extracted from the hospital EMR system. The demographic parameters recorded were age and sex. The physiological parameters were systolic blood

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pressure, heart rate, breathing rate, body temperature, arterial oxyhemoglobin saturation, and mental status (assessed as alert, verbal, pain, and unresponsive [AVPU]). We also extracted data from the Prehospital Record and List of Therapeutic Management sections of the EMR to determine whether a given patient had received supplemental oxygen therapy. The National Early Warning Score (NEWS) was calculated in each patient to access the severity of illness.[14] The PaO_2 results determined by arterial blood gas analysis within 72 h of ED arrival were collected. Temporal parameters between ED arrival and hospital discharge (dates of ED arrival, admission, ICU transfer, beginning of ventilator care, death, and discharge) and final outcome (discharge, transfer, death, or other) were also collected. Because we assessed complications of hyperoxia using the Sequential Organ Failure Assessment (SOFA) score components (cardiovascular, hepatic, renal, and coagulation dysfunction), we evaluated the platelet count, and serum creatinine and bilirubin levels, at ED arrival and after the fifth day of ED arrival, and determined whether a given patient received vasopressors. We also evaluated use of mechanical ventilation therapy after the fifth day of ED arrival to assess respiratory failure. Because the PaO_2/FIO_2 ratio could not be accurately calculated in the ED and general ward, respiratory failure was defined as the need for endotracheal intubation.

Hyperoxia variables

Among the hyperoxia metrics described by Helmerhorst *et al*. [15], the highest (PaO_{2MAX}), average (PaO_{2AVG}), and median (PaO_{2MED}) PaO_2 values within 72 h, and the area under the curve divided by the time elapsed between ED arrival and the last PaO_2 result (AUC_{72}) were used in this study. Using the PaO_{2MED} as the starting value (t = 0; ED arrival time) and the value at 72 h (t = 72), the AUC_{72} was calculated using the trapezoid rule. Because no definition of hyperoxia has been established, we used the following upper quintile values: 137 mmHg for PaO_{2MAX}, 105 mmHg for PaO_{2AVG},

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103 mmHg for PaO_{2MED}, and 174 mmHg for AUC_{72}.

Study outcome

The primary outcome was the 90-day in-hospital mortality rate. The secondary outcomes were ICU transfer and respiratory failure after the fifth day of ED arrival, and new-onset cardiovascular, coagulation, hepatic, and renal dysfunction (SOFA sub-score ≥ 2) after the fifth day of ED arrival.

Data analysis

Age was categorized into 16–39, 40–79, and ≥80 years. All continuous variables showed a skewed distribution, and are presented as medians with interquartile ranges (IQRs). The Mann-Whitney U-test was used to compare continuous variables, and Pearson's χ^2 test for categorical variables.

Univariate logistic regression was performed using demographic and physiological data and the NEWS, laboratory parameter values (platelet, creatinine, and bilirubin levels, and initial PaO_2), and hyperoxia variable values. Adjusted odds ratios (ORs) were calculated for each hyperoxia variable that had a $P < 0.01$ in univariate logistic regression to assess their association with in-hospital mortality.

The secondary outcomes (ICU transfer, respiratory failure and new-onset cardiovascular, hepatic, renal, and coagulation dysfunction after the fifth day) were subjected to the same analyses as the primary outcome. The PaO_{2MAX}, PaO_{2AVG}, PaO_{2MED}, and AUC_{72} values were subjected to multivariate analyses.

All P-values were two-sided, and a P-value of < 0.05 was considered indicative of statistical significance. Analyses were performed using MedCalc version 17 (MedCalc Software BVBA, Ostend, Belgium) and Stata version 13 (StataCorp, LP, College Station, TX).

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Results

Baseline

Of the 228,326 patients who arrived at the ED during the study period, 32,821 met the inclusion criteria. After applying the exclusion criteria, 10,141 patients were eligible for analysis (Figure 1). Males accounted for 59.6% (6,040) of patients, and the median age of the study population was 69 (IQR 57–78) years old. The baseline characteristics of the patients are shown in Table 1.

Table 1. Baseline characteristics of patients

Characteristics	Total	Missing data, n (%)
Number of patients	10,141	
Age	69.0 (57.0 – 78.0)	0 (0)
Age category, n (%)		
16-39	786 (7.8)	0 (0)
40-79	7,434 (73.3)	0 (0)
≥80	1,921 (18.9)	0 (0)
Male, n (%)	6040 (59.6)	0 (0)
Physiologic variables		
Systolic blood pressure, mmHg	130 (110-150)	0 (0)
Heart rate, per minute	90 (78 - 108)	0 (0)
Breath rate, per minute	20 (20-22)	4 (0.0)
Body temperature, °C	36.7 (36.4 - 37.2)	10 (0.1)
SaO_2, %	96 (93 - 98)	230 (2.3)
Consciousness (alert), n (%)	9,076 (89.5)	0 (0)

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Supplemental oxygen, n (%)	4,012 (39.6)	0 (0)
NEWS	4 (1-7)	236 (2.3)
Initial laboratory results		
Platelet, $x10^3/mm^3$	220 (162-287)	56 (0.6)
Creatinine, mg/dl	0.87 (0.66-1.31)	61 (0.6)
Bilirubin, mg/dl	0.68 (0.43-1.10)	80 (0.8)
PO_2, mmHg	76 (59-96)	371 (3.7)
Hyperoxia variables results		
PaO_{2MAX}	99.0 (83.0 – 126.0)	0 (0)
PaO_{2AVG}	81.0 (68.9 – 99.0)	0 (0)
PaO_{2MED}	80.0 (67.5 – 97.5)	0 (0)
AUC_{72}	63.8 (23.2 – 153.2)	0 (0)
Mortality, n (%)	584 (5.8)	0 (0)

SaO_2, Oxyhemoglobin saturation; NEWS, National Early Warning Score; PO_2, Partial pressure of Oxygen; PaO_{2Max}, highest value of PO_2 within 72 hours ; PaO_{2AVG}, average value of PO_2 within 72 hours; PaO_{2MED} , median value of PO_2 within 72 hours; AUC_{72}, area under the curve divided by elapsed time between ED arrival and the last result of PO_2 within 72 hours

Data are medians (interquartile range) unless stated otherwise.

Primary outcome

The results of univariate regression analyses are shown in Table 2. Patient age, sex, and all physiologic variables were significant. Regarding the initial values of the laboratory parameters, bilirubin and PaO_2 were significant. The unadjusted ORs of PaO_{2MAX}, PaO_{2AVG}, PaO_{2MED}, and AUC_{72} were 0.64 (95% CI, 0.51–0.82; P = 0.0003), 0.57 (95% CI, 0.45–0.74; P < 0.0001), 0.54 (95% CI, 0.42–0.69; P < 0.0001), and 1.59

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(95% CI, 1.32–1.92); P < 0.0001), respectively.

Because the values of the NEWS components (systolic blood pressure, heart rate, breath rate, body temperature, SaO2, supplemental oxygen, and consciousness) had P-values of < 0.01 in univariate analyses, we subjected NEWS to multivariate regression analyses. The adjusted ORs of PaO_{2MAX}, PaO_{2AVG}, PaO_{2MED}, and AUC_{72} were 0.79 (95% CI, 0.61–1.02; P = 0.0715), 0.92 (95% CI, 0.69–1.24; P = 0.5863), 0.82 (95% CI, 0.61–1.11; P = 0.2005) and 1.53 (95% CI, 1.25–1.88; P < 0.0001), respectively (Table 3).

Table 2. Univariate analysis of independent variables for 90 day in-hospital mortality

Variable	Odds ratio	P
Age 40 - 79	2.63 (1.63 - 4.24)	0.0001
Age ≥ 80	3.20 (1.94 - 5.27)	<0.0001
Female	0.54 (0.45 - 0.65)	<0.0001
Systolic blood pressure	0.99 (0.99 - 0.99)	<0.0001
Heart rate	1.01 (1.01 - 1.02)	<0.0001
breathing rate	1.07 (1.05 - 1.09)	<0.0001
Body temperature	0.90 (0.83 - 0.98)	0.0143
SaO_2	0.96 (0.96 - 0.97)	<0.0001
Consciousness (non-alert)	1.96 (1.57 - 2.45)	<0.0001
Supplemental oxygen	1.97 (1.66 - 2.33)	<0.0001
NEWS	1.14 (1.11 - 1.16)	<0.0001
Platelet	1.00 (1.00 - 1.00)	0.0659
Creatinine	0.97 (0.93 - 1.01)	0.1875
Bilirubin	1.15 (1.12 - 1.17)	<0.0001
Initial PO_2	0.99 (0.99 - 1.00)	0.0005

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PaO_{2MAX}	0.64 (0.51 - 0.82)	0.0003
PaO_{2AVG}	0.57 (0.45 - 0.74)	<0.0001
PaO_{2MED}	0.54 (0.42 - 0.69)	<0.0001
AUC_{72}	1.59 (1.32 – 1.92)	<0.0001

SaO_2, Oxyhemoglobin saturation; NEWS, National Early Warning Score; PO_2, Partial pressure of Oxygen; PaO_{2Max}, highest value of PO_2 within 72 hours ; PaO_{2AVG}, average value of PO_2 within 72 hours; PaO_{2MED} , median value of PO_2 within 72 hours; AUC_{72}, area under the curve divided by elapsed time between ED arrival and the last result of PO_2 within 72 hours

Table 3. Adjusted odds ratio of hyperoxia variables for 90 day in-hospital mortality

Variable	Odds ratio [a]	P
PaO_{2MAX}	0.79 (0.61 – 1.02)	0.0715
PaO_{2AVG}	0.92 (0.69 - 1.24)	0.5863
PaO_{2MED}	0.82 (0.61 - 1.11)	0.2005
AUC_{72}	1.53 (1.25 - 1.88)	<0.0001

[a] Adjusted by age, sex, NEWS, initial bilirubin and initial

PO_2, Partial pressure of Oxygen; PaO_{2Max}, highest value of PO_2 within 72 hours ; PaO_{2AVG}, average value of PO_2 within 72 hours; PaO_{2MED} , median value of PO_2 within 72 hours; AUC_{72}, area under the curve divided by elapsed time between ED arrival and the last result of PO_2 within 72 hours

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Secondary outcomes

All of the hyperoxia variables were significantly positively correlated with ICU transfer after the fifth day of ED arrival (Table 4). Among the hyperoxia variables, AUC_{72} had the highest OR for ICU transfer (4.03; 95% CI, 3.25–5.01; P < 0.0001). AUC_{72} was positively correlated with respiratory failure as well as cardiovascular, hepatic, and renal dysfunction. PaO_{2MAX} was positively correlated with cardiovascular dysfunction. PaO_{2MAX} and AUC_{72} were negatively correlated with coagulation dysfunction (0.64; 95% CI, 0.43–0.94; P = 0.022 and 0.67; 95% CI, 0.48–0.92; P = 0.015).

Table 4. Hyperoxia variables and adjusted odds ratio (95% CI) for secondary outcomes

Variable	ICU transfer [a]	Respiratory failure [b]	Cardiovascular dysfunction [c]	Hepatic dysfunction [d]	Renal dysfunction [e]	Coagulation dysfunction [f]
	358 (3.5)	68 (0.7)	386 (3.8)	678 (8.7)	983 (12.6)	408 (5.0)
PaO_{2MAX}	2.81 [g] (2.26 - 3.50)	1.45 (0.85 - 2.47)	1.39 [i] (1.09 - 1.78)	0.99 (0.74 - 1.33)	0.95 (0.72 - 1.26)	0.64 [i] (0.43 – 0.94)
PaO_{2AVG}	2.04 [g] (1.61 - 2.57)	1.13 (0.63 - 2.01)	1.13 (0.87 - 1.47)	0.96 (0.70 - 1.34)	1.13 (0.84 - 1.53)	1.08 (0.74 - 1.59
PaO_{2MED}	1.51 [h] (1.18 – 1.94)	0.66 (0.34 - 1.30)	1.02 (0.78 - 1.33)	1.02 (0.74 - 1.40)	0.97 (0.72 - 1.31)	1.17 (0.81 – 1.69)
AUC_{72}	4.03 [g] (3.25 –	2.40 [h] (1.46 – 3.95)	1.63 [h] (1.29 – 2.07)	1.53 [i] (1.18 - 1.97)	1.33 [i] (1.05 - 1.68)	0.67 [i] (0.48 –

5.01) 0.92)

[a] Adjusted by systolic blood pressure, heart rate, body temperature, consciousness and supplemental oxygen

[b] Adjusted by body temperature and consciousness

[c] Adjusted by age, sex, heart rate, SaO_2, bilirubin and creatinine

[d] Adjusted by age, sex, systolic blood pressure, breath rate, SaO_2, consciousness, supplemental oxygen, bilirubin, platelet and initial PO_2

[e] Adjusted by NEWS, bilirubin, creatinine, platelet and initial PO_2

[f] Adjusted by sex, systolic blood pressure, breath rate, SaO_2, consciousness, supplemental oxygen, bilirubin, platelet and initial PO_2

[g] $P < 0.0001$

[h] $P < 0.001$

[i] $P < 0.05$

ICU, intensive care unit; PO_2, Partial pressure of Oxygen; PaO_{2Max}, highest value of PO_2 within 72 hours ; PaO_{2AVG}, average value of PO_2 within 72 hours; PaO_{2MED} , median value of PO_2 within 72 hours; AUC_{72}, area under the curve divided by elapsed time between ED arrival and the last result of PO_2 within 72 hours

Discussion

We assessed the association between hyperoxia during the first 72 h and the outcomes after the fifth day of ED arrival. In univariate analyses, all of the hyperoxia variables showed significant correlations with the 90-day in-hospital mortality rate

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(Table 2). After adjustment, only AUC_{72} was significantly associated with the 90-day in-hospital mortality rate (Table 3). AUC_{72} was significantly positively correlated with ICU transfer, respiratory failure, cardiovascular dysfunction, hepatic dysfunction, and renal dysfunction. PaO_{2MAX} was significantly associated with ICU transfer and cardiovascular dysfunction. PaO_{2MAX} and AUC_{72} were negatively associated with coagulation dysfunction.

Only AUC_{72} was significantly associated with 90-day in-hospital mortality in this study; the one-time hyperoxia parameters (PaO_{2MAX}, PaO_{2AVG}, and PaO_{2MED}) were not.[15,16] Because AUC_{72} is indicative of cumulative exposure to hyperoxia, it may reflect the degree of hyperoxia more accurately than the other variables.

The patients in this study were in a less-severe condition than those in previous studies. Our target population was patients who arrived at the ED but were not admitted to the ICU in the next 5 days. By contrast, previous studies involved only patients admitted to the ICU.[2,15,16] The median NEWS was 4 (IQR, 2–7) in this study; a NEWS of ≥ 5 is the accepted threshold for critical illness.[14,17] We also used a noninvasive method of oxygen delivery, unlike previous studies. Many patients in the ICU undergo mechanical ventilation. Mechanical ventilation delivers a larger dose of oxygen more accurately; therefore, the values of hyperoxia variables were lower than those in previous studies.[7-9] The one time hyperoxia variables in non-critically ill patients under less-severe hyperoxia are not enough to show statistical significance on mortality rate. Instead, ICU transfer was used as an indicator of an increase in clinical severity in this study. Therefore, AUC_{72} is more suitable than the one-time hyperoxia values for assessing mortality and complications in these patients.

The significant association between AUC_{72} and cardiovascular and hepatic dysfunction is consistent with Girardis *et al*. [9], which found that strict oxygen use reduces the rates of mortality, shock, and liver failure compared to conventional oxygen use. Because that previous study was conducted in the ICU, this is the first

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report of AUC_{72} as an indicator of complications in non-ICU patients.

The PaO_{2MAX} and AUC_{72} values were significantly negatively associated with coagulation dysfunction. The relationship between hyperoxia and coagulation dysfunction could be found in lung. Coagulation dysfunction, as determined by fibrin deposition, occurs in hyperoxia-induced acute lung injury,[18] but has not been investigated extensively. Thus, further studies should evaluate the association between coagulation dysfunction and hyperoxia.

The mechanisms of oxygen toxicity include increased production of reactive oxygen species (ROS), pulmonary toxicity, hemodynamic effects on the heart, and neurological effects. ROS lead to lipid peroxidation, protein oxidation, and DNA damage. Pulmonary toxicity can be divided into direct pulmonary toxicity and effects on pulmonary gas exchange. ROS-induced direct pulmonary toxicity is mediated by damage to the alveolar capillary barrier, and effects on gas exchange by intrapulmonary shunt. Hemodynamic effects on the heart include reductions in cardiac output, coronary blood flow, myocardial O_2 consumption and heart rate, as well as increased vascular resistance. Excessive oxygen levels disrupt the protective mechanisms of the neural system.[4,19,20]

However, it is unclear when oxygen toxicity occurs. The lung is first affected because of higher oxygen tension.[21] In an animal study, alveolar septal injury occurred following exposure to 60% O_2 for 14 days.[22] In another animal study, lung injury occurred following exposure to moderate hyperoxia and a large tidal volume for 2 h.[23] In humans, symptoms can occur 10 h after the initial exposure to hyperoxia,[24] although histological changes occur earlier. Helmerhost *et al*. [25] reported that exposure to high FiO_2 for 15 min alters systemic resistance in patients after coronary artery bypass grafting (CABG) surgery. In this study, exposure to hyperoxia during the first 72 h after admission affected the rates of mortality and complications. Therefore, physicians should be aware of the importance of exposure

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to hyperoxia during the early treatment period.

This retrospective study had several limitations. First, we could not rule out selection bias, as the study population was limited to patients who visited our ED and underwent blood gas analysis. Second, because the NEWS was calculated using the initial values in the ED rather than ICU-based severity scores, the assessment of severity may have been inaccurate; if so, this would introduce bias into the regression model. Third, this study was conducted in a single center; thus, a further multicenter randomized controlled study is warranted.

Despite its limitations, this study was novel because we evaluated the association between hyperoxia and outcomes in non-ICU patients. To the best of our knowledge, this is the first report that hyperoxia may be harmful in non-critical patients.

Conclusion

Hyperoxia during the first 3 days in ED patients was associated with in-hospital mortality and ICU transfer after the fifth day of ED arrival.

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Figure 1. The study patients

ED; emergency department, ICU; intensive care unit, AUC; area under the curve

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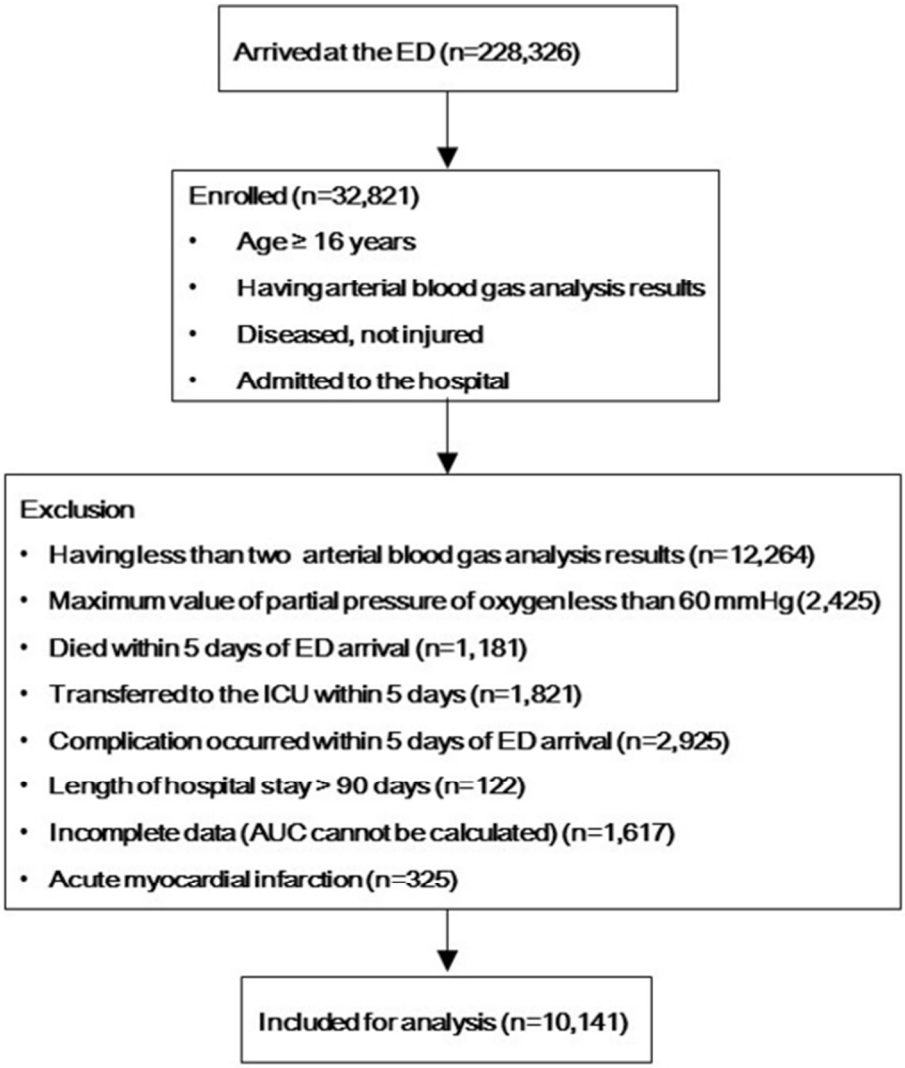

Figure 1. The study patients
ED; emergency department, ICU; intensive care unit, AUC; area under the curve

54x59mm (300 x 300 DPI)

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STROBE Statement—checklist of items that should be included in reports of observational studies

	Item No	Recommendation
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract → p.4
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found → p. 4
Introduction		
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported → p.6
Objectives	3	State specific objectives, including any prespecified hypotheses → p.6
Methods		
Study design	4	Present key elements of study design early in the paper → p.7
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection → p.7
Participants	6	(*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up *Case-control study*—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls→ p.7-8 *Cross-sectional study*—Give the eligibility criteria, and the sources and methods of selection of participants
		(*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed *Case-control study*—For matched studies, give matching criteria and the number of controls per case
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable → p.8
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group → p.8
Bias	9	Describe any efforts to address potential sources of bias→ p.17
Study size	10	Explain how the study size was arrived at → p.10
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why → p.10
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding → p.10
		(*b*) Describe any methods used to examine subgroups and interactions
		(*c*) Explain how missing data were addressed
		(*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed *Case-control study*—If applicable, explain how matching of cases and controls was addressed *Cross-sectional study*—If applicable, describe analytical methods taking account of sampling strategy
		(*e*) Describe any sensitivity analyses

Continued on next page

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Results		
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed → p.10
		(b) Give reasons for non-participation at each stage
		(c) Consider use of a flow diagram
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders → p.10
		(b) Indicate number of participants with missing data for each variable of interest → p.10
		(c) *Cohort study*—Summarise follow-up time (eg, average and total amount)
Outcome data	15*	*Cohort study*—Report numbers of outcome events or summary measures over time → p.11
		Case-control study—Report numbers in each exposure category, or summary measures of exposure
		Cross-sectional study—Report numbers of outcome events or summary measures
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included → p.11-12
		(*b*) Report category boundaries when continuous variables were categorized
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses → p.13
Discussion		
Key results	18	Summarise key results with reference to study objectives → p.15
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias → p.17
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence → p.16
Generalisability	21	Discuss the generalisability (external validity) of the study results → p.17
Other information		
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based → p.2

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

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Delayed effects of early hyperoxia in patients admitted to the general ward: retrospective cohort study

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Article title

Delayed effects of early hyperoxia in patients admitted to the general ward: retrospective cohort study

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Authors' contributions

Jin Hee Jeong: Dr. Jeong conceptualized and designed the study, analyzed the data, drafted the initial manuscript, critically reviewed the manuscript, approved the final manuscript as submitted, and agreed to be accountable for all aspects of the work.

Dong Hoon Kim: Dr. Kim conceptualized and designed the study, coordinated and supervised data collection, critically reviewed the manuscript, approved the final manuscript as submitted, and agreed to be accountable for all aspects of the work.

Tae Yun Kim: Dr. Kim conceptualized and designed the study, interpreted data, critically reviewed the manuscript, approved the final manuscript as submitted, and agreed to be accountable for all aspects of the work.

Changwoo Kang: Dr. Kang interpreted data, critically reviewed the manuscript, approved the final manuscript as submitted, and agreed to be accountable for all aspects of the work.

Soo Hoon Lee: Dr. Lee interpreted data, critically reviewed the manuscript, approved the final manuscript as submitted, and agreed to be accountable for all aspects of the work.

Sang Bong Lee: Dr. Lee interpreted data, critically reviewed the manuscript, approved

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Yong Joo Park: Dr. Park interpreted data, critically reviewed the manuscript, approved the final manuscript as submitted, and agreed to be accountable for all aspects of the work.

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Delayed effects of early hyperoxia in patients admitted to the general ward: retrospective cohort study

Abstract

Introduction

We evaluated the association between hyperoxia induced by a noninvasive oxygen supply method for 3 days after emergency department (ED) arrival and the clinical outcomes after the fifth day of ED arrival.

Methods

Consecutive ED patients ≥ 16 years of age with available arterial blood gas analysis results who were admitted to our hospital with disease (not injury) were enrolled from January 2010 to December 2016. The highest (PaO_{2MAX}), average (PaO_{2AVG}), and median (PaO_{2MED}) PaO_2 (arterial oxygen pressure) values within 72 h, and the area under the curve divided by the time elapsed between ED admittance and the last PaO_2 result (AUC_{72}), were used to assess hyperoxia. AUC_{72} was calculated using trapezoid rule. The primary outcome was the 90-day in-hospital mortality rate. The secondary outcomes were intensive care unit (ICU) transfer and respiratory failure after the fifth day of ED arrival, as well as new-onset cardiovascular, coagulation, hepatic, and renal dysfunction after the fifth day of ED arrival.

Results

Among the 10,141 patients, the mortality rate was 5.8%. The adjusted odds ratios (ORs) of in-hospital mortality for PaO_{2MAX}, PaO_{2AVG}, PaO_{2MED}, and AUC_{72} were 0.79 (95% CI, 0.61–1.02; P = 0.0715), 0.92 (95% CI, 0.69–1.24; P = 0.5863), 0.82 (95% CI, 0.61–1.11; P = 0.2005), and 1.53 (95% CI, 1.25–1.88; P <0.0001). All of the hyperoxia variables showed significant positive correlations with ICU transfer after the fifth day of ED arrival (P < 0.05). AUC_{72} was positively correlated with respiratory failure, as well as cardiovascular, hepatic, and renal dysfunction (P < 0.05). PaO_{2MAX} was positively

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correlated with cardiovascular dysfunction. PaO_{2MAX} and AUC_{72} were negatively correlated with coagulation dysfunction ($P < 0.05$).

Conclusion

Hyperoxia during the first 3 days in patients outside the ICU is associated with in-hospital mortality and ICU transfer after the fifth day of ED arrival.

Keywords: Hyperoxia; Oxygen; Oxygen Inhalation Therapy

Strengths and limitation of this study

A retrospective observational cohort study of 10,141 consecutive patients visiting at the emergency department of a tertiary teaching hospital.

The relation between hyperoxia and clinical outcome was analyzed using various statistical measures: maximum, central tendency (average and median), and cumulative exposure in the patients who were admitted to general ward.

Impact of hyperoxia variables on clinical outcomes were adjusted for demographic, physiological, and biochemical parameters

Severity adjustment with the National Early Warning Score rather than ICU-based scores might lead to inaccurate results.

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Introduction

Supplemental oxygen is a fundamental therapy for hypoxic patients, and is frequently ordered in various clinical settings. Physicians tend to believe that oxygen is a safe and beneficial treatment option in non-hypoxic patients, and even in patients with hyperoxia.[1] Although some doctors thought the potential deleterious effect of hyperoxia, many patients were exposed to hyperoxia.[2-4] However, hyperoxia is positively correlated with poor outcomes.[5] Patients in the intensive care unit (ICU) with high arterial oxygen pressure (PaO_2) and a high fraction of inspired oxygen (FiO_2) have a higher mortality rate than normoxic patients.[6] Hyperoxia is associated with the in-hospital mortality rate of patients resuscitated from cardiac arrest.[7-11] In addition, hyperoxia is associated with poor outcomes in patients with stroke, spontaneous SAH, and traumatic brain injury. [10,12-14] A recent randomized clinical study and a before-after study reported better outcomes in normoxic compared to hyperoxic ICU patients.[15,16]

Despite the evidence that hyperoxia is harmful, therapeutic strategies that prevent hyperoxia cannot be translated to all the patients because related studies involved ICU patients or ventilator applied patients.[6,12,15,17] Many patients in the emergency department (ED) require supplemental oxygen, and some need mechanical ventilation and so are admitted to the ICU. However, in most ED patients, oxygen therapy is administered using a noninvasive method such as a facial mask or nasal prong; such patients are then admitted to the general ward.[18] The study for ED hyperoxia and clinical outcomes was limited. One study about ED hyperoxia were involved mechanically ventilated patients.[17] The other study in the ED reported that hyperoxia using facial mask was harmful in patients diagnosed with sepsis.[19] However, that study involved a small number of patients, a limited disease spectrum, and a single arterial blood gas analysis (ABGA) result. No studies have evaluated the associations between hyperoxia and mortality in patients admitted to the general ward.

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We hypothesized that hyperoxia induced by a noninvasive oxygen supply method during the early treatment period would have adverse effects somewhat later in patients admitted to the general ward.

We evaluated the association between hyperoxia during the first 3 days after ED arrival and clinical outcomes after the fifth day of ED arrival.

Method

Study design and setting

We conducted a single-center study at Gyeongsang National University Hospital, a tertiary teaching hospital located in the south-central region of the Republic of Korea, from January 2010 to December 2016. This study was approved by our Institutional Review Board. All patients admitted to the ED are enrolled in the National Emergency Department Information System (NEDIS). The NEDIS was developed in 2003 to establish a national database of ED patients.[20,21] The quality of the data are examined annually by the National Emergency Medical Center, a government-funded, national ED control agency. In our ED, triage nurses and attending physicians enter into the NEDIS the patients' data, including basic demographic and temporal parameters, physiologic parameters at ED arrival, symptoms, diagnosis, treatment details (including drugs and procedures), outcomes, and other information. The data are organized using the standard NEDIS registry format in the hospital electronic medical records (EMRs). The validity of all data are checked by function modules within the system before the data are saved.

Participants

All consecutive patients ≥ 16 years of age with available ABGA results in the ED who were admitted to the hospital with disease (not injury) during the study period were enrolled. We excluded patients with fewer than two partial pressure of oxygen (PaO_2)

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results within 72 h of ED arrival. We also excluded patients with a maximum value of PaO_2 within 72 h (PaO_{2MAX}) of < 60 mmHg because we wished to compare hyperoxic and normoxic patients. Because we intended to assess delayed effects of hyperoxia, we also excluded patients who died prior to day 5 after ED arrival and who showed complications in the first 5 days (ICU transfer and respiratory failure, as well as new-onset cardiovascular, hepatic, renal, and coagulation dysfunction).

The other exclusion criteria were transfer to other facilities after admission, discharge with no hope of recovery, left the hospital against medical advice, and a hospital stay duration > 90 days. Patients diagnosed with acute myocardial infarction were also excluded because supplemental oxygen is no longer recommended as a routine therapy in normoxic patients with acute myocardial infarction.[22]

Data collection

The data were extracted from the hospital EMR system. The demographic parameters recorded were age and sex. The physiological parameters were systolic blood pressure, heart rate, breathing rate, body temperature, arterial oxyhemoglobin saturation, and mental status (assessed as alert, verbal, pain, and unresponsive [AVPU]). We also extracted data from the Prehospital Record and List of Therapeutic Management sections of the EMR to determine whether a given patient had received supplemental oxygen therapy before ED arrival. All patients were applied oxygen during ED stay. The National Early Warning Score (NEWS) was calculated in each patient to access the severity of illness.[23] The PaO_2 results determined by arterial blood gas analysis within 72 h of ED arrival were collected. Temporal parameters between ED arrival and hospital discharge (dates of ED arrival, admission, ICU transfer, beginning of ventilator care, death, and discharge) and final outcome (discharge, transfer, death, or other) were also collected. Because we assessed complications of hyperoxia using the Sequential Organ Failure Assessment (SOFA)

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score components (cardiovascular, hepatic, renal, and coagulation dysfunction), we evaluated the platelet count, and serum creatinine and bilirubin levels, at ED arrival and after the fifth day of ED arrival, and determined whether a given patient received vasopressors. We also evaluated use of mechanical ventilation therapy after the fifth day of ED arrival to assess respiratory failure. Because the PaO_2/FIO_2 ratio could not be accurately calculated in the ED and general ward, respiratory failure was defined as the need for endotracheal intubation.

Hyperoxia variables

Among the hyperoxia metrics described by Helmerhorst *et al*. [24], the highest (PaO_{2MAX}), average (PaO_{2AVG}), and median (PaO_{2MED}) PaO_2 values within 72 h, and the area under the curve divided by the time elapsed between ED arrival and the last PaO_2 result (AUC_{72}) were used in this study. Using the PaO_{2MED} as the starting value (t = 0; ED arrival time) and the value at 72 h (t = 72), the AUC_{72} was calculated using the trapezoid rule. Because no definition of hyperoxia has been established, we used the following upper quintile values: 137 mmHg for PaO_{2MAX}, 105 mmHg for PaO_{2AVG}, 103 mmHg for PaO_{2MED}, and 174 mmHg for AUC_{72}.

Study outcome

The primary outcome was the 90-day in-hospital mortality rate. The secondary outcomes were ICU transfer and respiratory failure after the fifth day of ED arrival, and new-onset cardiovascular, coagulation, hepatic, and renal dysfunction (SOFA sub-score ≥ 2) after the fifth day of ED arrival.

Data analysis

Age was categorized into 16–39, 40–79, and ≥80 years. All continuous variables showed a skewed distribution, and are presented as medians with interquartile ranges

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(IQRs). The Mann-Whitney U-test was used to compare continuous variables, and Pearson's χ^2 test for categorical variables.

Univariate logistic regression was performed using demographic and physiological data and the NEWS, laboratory parameter values (platelet, creatinine, and bilirubin levels, and initial PaO_2), and hyperoxia variable values. The significant variables which showed $P < 0.01$ were used in multivariate logistic regression. Adjusted odds ratios (ORs) using these variables were calculated for each hyperoxia variable to assess their association with in-hospital mortality.

The secondary outcomes (ICU transfer, respiratory failure and new-onset cardiovascular, hepatic, renal, and coagulation dysfunction after the fifth day) were subjected to the same analyses as the primary outcome. The PaO_{2MAX}, PaO_{2AVG}, PaO_{2MED}, and AUC_{72} values were subjected to multivariate analyses.

All P-values were two-sided, and a P-value of < 0.05 was considered indicative of statistical significance. Analyses were performed using MedCalc version 17 (MedCalc Software BVBA, Ostend, Belgium) and Stata version 13 (StataCorp, LP, College Station, TX).

Patient and Public Involvement

The patients were not involved in research question and outcome.

The patients were not involved in the study design.

The patients were not involved in the recruitment to and conduct of this study.

The study results will not be disseminated to study participants.

This study is not a randomised controlled trials.

Patient advisers were not applicable in this study.

Results

Baseline

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Of the 228,326 patients who arrived at the ED during the study period, 32,821 met the inclusion criteria. After applying the exclusion criteria, 10,141 patients were eligible for analysis (Figure 1). Males accounted for 59.6% (6,040) of patients, and the median age of the study population was 69 (IQR 57–78) years old. The total number of ABGA sample was 37,908 and the mean number of ABGA samples was 3 (IQR 2–4) within within 72 h of ED arrival. The baseline characteristics of the patients are shown in Table 1.

Table 1. Baseline characteristics of patients

Characteristics	Total	Missing data, n (%)
Number of patients	10,141	
Age	69.0 (57.0 – 78.0)	0 (0)
Age category, n (%)		
16-39	786 (7.8)	0 (0)
40-79	7,434 (73.3)	0 (0)
≥80	1,921 (18.9)	0 (0)
Male, n (%)	6040 (59.6)	0 (0)
Physiologic variables		
Systolic blood pressure, mmHg	130 (110-150)	0 (0)
Heart rate, per minute	90 (78 - 108)	0 (0)
Breath rate, per minute	20 (20-22)	4 (0.0)
Body temperature, °C	36.7 (36.4 - 37.2)	10 (0.1)
SaO_2, %	96 (93 - 98)	230 (2.3)
Consciousness (alert), n (%)	9,076 (89.5)	0 (0)

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Supplemental oxygen, n (%)	4,012 (39.6)	0 (0)
NEWS	4 (1-7)	236 (2.3)
Initial laboratory results		
Platelet, $x10^3/mm^3$	220 (162-287)	56 (0.6)
Creatinine, mg/dl	0.87 (0.66-1.31)	61 (0.6)
Bilirubin, mg/dl	0.68 (0.43-1.10)	80 (0.8)
PO_2, mmHg	76 (59-96)	371 (3.7)
Hyperoxia variables results		
PaO_{2MAX}	99.0 (83.0 – 126.0)	0 (0)
PaO_{2AVG}	81.0 (68.9 – 99.0)	0 (0)
PaO_{2MED}	80.0 (67.5 – 97.5)	0 (0)
AUC_{72}	63.8 (23.2 – 153.2)	0 (0)
Mortality, n (%)	584 (5.8)	0 (0)

SaO_2, Oxyhemoglobin saturation; NEWS, National Early Warning Score; PO_2, Partial pressure of Oxygen; PaO_{2Max}, highest value of PO_2 within 72 hours ; PaO_{2AVG}, average value of PO_2 within 72 hours; PaO_{2MED} , median value of PO_2 within 72 hours; AUC_{72}, area under the curve divided by elapsed time between ED arrival and the last result of PO_2 within 72 hours

Data are medians (interquartile range) unless stated otherwise.

Primary outcome

The results of univariate regression analyses are shown in Table 2. Patient age, sex, and all physiologic variables were significant for 90 day in-hospital mortality. Regarding the initial values of the laboratory parameters, bilirubin and PaO_2 were significant for 90 day in-hospital mortality. The unadjusted ORs of PaO_{2MAX}, PaO_{2AVG}, PaO_{2MED}, and AUC_{72} were 0.64 (95% CI, 0.51–0.82; P = 0.0003), 0.57 (95% CI,

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0.45–0.74; P < 0.0001), 0.54 (95% CI, 0.42–0.69; P < 0.0001), and 1.59 (95% CI, 1.32–1.92); P < 0.0001), respectively.

Because the values of the NEWS components (systolic blood pressure, heart rate, breath rate, body temperature, SaO2, supplemental oxygen, and consciousness) had P-values of < 0.01 in univariate analyses, we subjected NEWS to multivariate regression analyses. The adjusted ORs of PaO_{2MAX}, PaO_{2AVG}, PaO_{2MED}, and AUC_{72} were 0.79 (95% CI, 0.61–1.02; P = 0.0715), 0.92 (95% CI, 0.69–1.24; P = 0.5863), 0.82 (95% CI, 0.61–1.11; P = 0.2005) and 1.53 (95% CI, 1.25–1.88; P < 0.0001), respectively (Table 3).

Table 2. Univariate analysis of independent variables for 90 day in-hospital mortality

Variable	Odds ratio	P
Age 40 - 79	2.63 (1.63 - 4.24)	0.0001
Age ≥ 80	3.20 (1.94 - 5.27)	<0.0001
Female	0.54 (0.45 - 0.65)	<0.0001
Systolic blood pressure	0.99 (0.99 - 0.99)	<0.0001
Heart rate	1.01 (1.01 - 1.02)	<0.0001
breathing rate	1.07 (1.05 - 1.09)	<0.0001
Body temperature	0.90 (0.83 - 0.98)	0.0143
SaO_2	0.96 (0.96 - 0.97)	<0.0001
Consciousness (non-alert)	1.96 (1.57 - 2.45)	<0.0001
Supplemental oxygen	1.97 (1.66 - 2.33)	<0.0001
NEWS	1.14 (1.11 - 1.16)	<0.0001
Platelet	1.00 (1.00 - 1.00)	0.0659
Creatinine	0.97 (0.93 - 1.01)	0.1875
Bilirubin	1.15 (1.12 - 1.17)	<0.0001

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Initial PO_2	0.99 (0.99 - 1.00)	0.0005
PaO_{2MAX}	0.64 (0.51 - 0.82)	0.0003
PaO_{2AVG}	0.57 (0.45 - 0.74)	<0.0001
PaO_{2MED}	0.54 (0.42 - 0.69)	<0.0001
AUC_{72}	1.59 (1.32 – 1.92)	<0.0001

SaO_2, Oxyhemoglobin saturation; NEWS, National Early Warning Score; PO_2, Partial pressure of Oxygen; PaO_{2Max}, highest value of PO_2 within 72 hours ; PaO_{2AVG}, average value of PO_2 within 72 hours; PaO_{2MED} , median value of PO_2 within 72 hours; AUC_{72}, area under the curve divided by elapsed time between ED arrival and the last result of PO_2 within 72 hours

Table 3. Mortality and adjusted odds ratios for 90 day in-hospital mortality according to hyperoxia variables

Variable	Patients, n (%)	Deaths, n (%)	Odds ratio [a]	P
PaO_{2MAX}	10,141			
Fourth quintile (<137 mmHg)	8,081 (79.7)	500 (6.2)	1	
Upper quintile (≥137 mmHg)	2,060 (20.3)	84 (4.1)	0.79 (0.61 – 1.02)	0.0715
PaO_{2AVG}				
Fourth quintile (<105 mmHg)	8,140 (80.3)	510 (6.3)		
Upper quintile (≥105 mmHg)	2,001 (19.7)	74 (3.7)	0.92 (0.69 - 1.24)	0.5863
PaO_{2MED}				
Fourth quintile (<103mmHg)	8,111 (80.0)	513 (6.3)		
Upper quintile (≥103 mmHg)	2,030 (20.0)	71 (3.5)	0.82	0.2005

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			(0.61 - 1.11)	
AUC_{72}				
Fourth quintile (<174 mmHg)	8,124 (80.1)	422 (5.2)		
Upper quintile (≥174 mmHg)	2,017 (19.9)	162 (8.0)	1.53 (1.25 - 1.88)	<0.0001

[a] Adjusted for age, sex, NEWS, initial bilirubin and initial

PO_2, Partial pressure of Oxygen; PaO_{2Max}, highest value of PO_2 within 72 hours ; PaO_{2AVG}, average value of PO_2 within 72 hours; PaO_{2MED} , median value of PO_2 within 72 hours; AUC_{72}, area under the curve divided by elapsed time between ED arrival and the last result of PO_2 within 72 hours

Secondary outcomes

All of the hyperoxia variables were significantly positively correlated with ICU transfer after the fifth day of ED arrival (Table 4). Among the hyperoxia variables, AUC_{72} had the highest OR for ICU transfer (4.03; 95% CI, 3.25–5.01; P < 0.0001). AUC_{72} was positively correlated with respiratory failure as well as cardiovascular, hepatic, and renal dysfunction. PaO_{2MAX} was positively correlated with cardiovascular dysfunction. PaO_{2MAX} and AUC_{72} were negatively correlated with coagulation dysfunction (0.64; 95% CI, 0.43–0.94; P = 0.022 and 0.67; 95% CI, 0.48–0.92; P = 0.015).

Table 4. Hyperoxia variables and adjusted odds ratio (95% CI) for secondary outcomes

Variable	ICU transfer [a]	Respiratory failure [b]	Cardiovascular dysfunction [c]	Hepatic dysfunction [d]	Renal dysfunction [e]	Coagulation dysfunction [f]
	358 (3.5)	68 (0.7)	386 (3.8)	678 (8.7)	983 (12.6)	408 (5.0)

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PaO_{2MAX}	2.81 [g] (2.26 - 3.50)	1.45 (0.85 - 2.47)	1.39 [i] (1.09 - 1.78)	0.99 (0.74 - 1.33)	0.95 (0.72 - 1.26)	0.64 [i] (0.43 – 0.94)
PaO_{2AVG}	2.04 [g] (1.61 - 2.57)	1.13 (0.63 - 2.01)	1.13 (0.87 - 1.47)	0.96 (0.70 - 1.34)	1.13 (0.84 - 1.53)	1.08 (0.74 - 1.59
PaO_{2MED}	1.51 [h] (1.18 – 1.94)	0.66 (0.34 - 1.30)	1.02 (0.78 - 1.33)	1.02 (0.74 - 1.40)	0.97 (0.72 - 1.31)	1.17 (0.81 – 1.69)
AUC_{72}	4.03 [g] (3.25 – 5.01)	2.40 [h] (1.46 – 3.95)	1.63 [h] (1.29 – 2.07)	1.53 [i] (1.18 - 1.97)	1.33 [i] (1.05 - 1.68)	0.67 [i] (0.48 – 0.92)

[a] Adjusted for systolic blood pressure, heart rate, body temperature, consciousness and supplemental oxygen

[b] Adjusted for body temperature and consciousness

[c] Adjusted for age, sex, heart rate, SaO_2, bilirubin and creatinine

[d] Adjusted for age, sex, systolic blood pressure, breath rate, SaO_2, consciousness, supplemental oxygen, bilirubin, platelet and initial PO_2

[e] Adjusted for NEWS, bilirubin, creatinine, platelet and initial PO_2

[f] Adjusted for sex, systolic blood pressure, breath rate, SaO_2, consciousness, supplemental oxygen, bilirubin, platelet and initial PO_2

[g] $P < 0.0001$

[h] $P < 0.001$

[i] $P < 0.05$

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ICU, intensive care unit; PO_2, Partial pressure of Oxygen; PaO_{2Max}, highest value of PO_2 within 72 hours ; PaO_{2AVG}, average value of PO_2 within 72 hours; PaO_{2MED} , median value of PO_2 within 72 hours; AUC_{72}, area under the curve divided by elapsed time between ED arrival and the last result of PO_2 within 72 hours

Discussion

We assessed the association between hyperoxia during the first 72 h and the outcomes after the fifth day of ED arrival. In univariate analyses, all of the hyperoxia variables showed significant correlations with the 90-day in-hospital mortality rate (Table 2). After adjustment, only AUC_{72} was significantly associated with the 90-day in-hospital mortality rate (Table 3). AUC_{72} was significantly positively correlated with ICU transfer, respiratory failure, cardiovascular dysfunction, hepatic dysfunction, and renal dysfunction. PaO_{2MAX} was significantly associated with ICU transfer and cardiovascular dysfunction. PaO_{2MAX} and AUC_{72} were negatively associated with coagulation dysfunction.

Only AUC_{72} was significantly associated with 90-day in-hospital mortality in this study; the one-time hyperoxia parameters (PaO_{2MAX}, PaO_{2AVG}, and PaO_{2MED}) were not.[24,25] Because AUC_{72} is indicative of cumulative exposure to hyperoxia, it may reflect the degree of hyperoxia more accurately than the other variables.

The patients in this study were in a less-severe condition than those in previous studies. Our target population was patients who arrived at the ED but were not admitted to the ICU in the next 5 days. By contrast, previous studies involved only patients admitted to the ICU.[6,24,25] The median NEWS was 4 (IQR, 2–7) in this study; a NEWS of ≥ 5 is the accepted threshold for critical illness.[23,26] We also used a noninvasive method of oxygen administration, unlike previous studies. Many

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patients in the ICU undergo mechanical ventilation. Mechanical ventilation delivers a larger dose of oxygen more accurately. If the patient needed higher concentrations of oxygen, the patients were applied the mechanical ventilation and were excluded from this study. We believe that this exclusion lead to lower values of hyperoxia variable in this study than those in previous studies.[13-15] The one time hyperoxia variables in non-critically ill patients under less-severe hyperoxia might not be enough to show statistical significance on mortality rate. Instead, ICU transfer was used as an indicator of an increase in clinical severity in this study. Therefore, AUC_{72} is more suitable than the one-time hyperoxia values for assessing mortality and complications in these patients.

The significant association between AUC_{72} and cardiovascular and hepatic dysfunction is consistent with Girardis *et al*. [15], which found that strict oxygen use reduces the rates of mortality, shock, and liver failure compared to conventional oxygen use. Because that previous study was conducted in the ICU, this is the first report of AUC_{72} as an indicator of complications in non-ICU patients.

The PaO_{2MAX} and AUC_{72} values were associated with greater coagulation dysfunction. Coagulation dysfunction in the lung was mentioned in previous study. Coagulation dysfunction, as determined by fibrin deposition, occurs in hyperoxia-induced acute lung injury,[27] but has not been investigated extensively. Thus, further studies should evaluate the association between coagulation dysfunction and hyperoxia.

Hyperoxia toxicity caused through production of reactive oxygen species (ROS), pulmonary toxicity, hemodynamic alterations, and neurological damage. ROS lead to lipid peroxidation, protein oxidation, DNA damage and direct pulmonary damage mediated by damage to the alveolar capillary barrier. Other pulmonary toxicity is impairment of pulmonary gas exchange by adsorption atelectasis. Hemodynamic alterations include reductions in cardiac output, coronary blood flow,

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myocardial O2 consumption and heart rate, as well as increased vascular resistance. Neurological damage is caused by excessive oxygen levels, which disrupt the protective mechanisms of the neural system under hyperbaric oxygen situation.[8,10,27-30]

However, it is unclear that the amount of oxygen exposure time and concentration necessary for toxicity to occur. The lung is first affected because of higher oxygen tension.[31] In an animal study of baboons, alveolar septal injury occurred following exposure to 60% O_2 for 14 days.[32] In another animal study of rabbits, lung injury occurred following exposure to moderate hyperoxia and a large tidal volume for 2 h.[33] In humans, symptoms can occur 10 h after the initial exposure to hyperoxia,[34] although histological changes occur earlier. Helmerhost *et al*. [35] reported that exposure to high FiO_2 for 15 min alters systemic vascular resistance in patients after coronary artery bypass grafting (CABG) surgery. In this study, exposure to hyperoxia during the first 72 h after admission affected the rates of mortality and ICU transfer. Therefore, physicians should be aware of the importance of exposure to hyperoxia during the early treatment period.

The present study had several limitations. First, we could not rule out selection bias, as the study population was limited to patients who visited our ED and underwent blood gas analysis. Second, because the NEWS was calculated using the initial values in the ED rather than ICU-based severity scores, the assessment of severity may have been inaccurate; if so, this would introduce bias into the regression model. Third, this study was conducted in a single center; thus, a further multicenter randomized controlled study is warranted. Fourth, this is a retrospective study, therefore although statistical associations were identified, this is by no means indicative of causation.

Despite its limitations, this study was novel because we evaluated the association between hyperoxia and outcomes in non-critical patients at ED.

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Conclusion

Hyperoxia during the first 3 days in ED patients was associated with higher in-hospital mortality and ICU transfer after the fifth day of ED arrival.

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Figure 1. The study patients

ED; emergency department, ICU; intensive care unit, AUC; area under the curve

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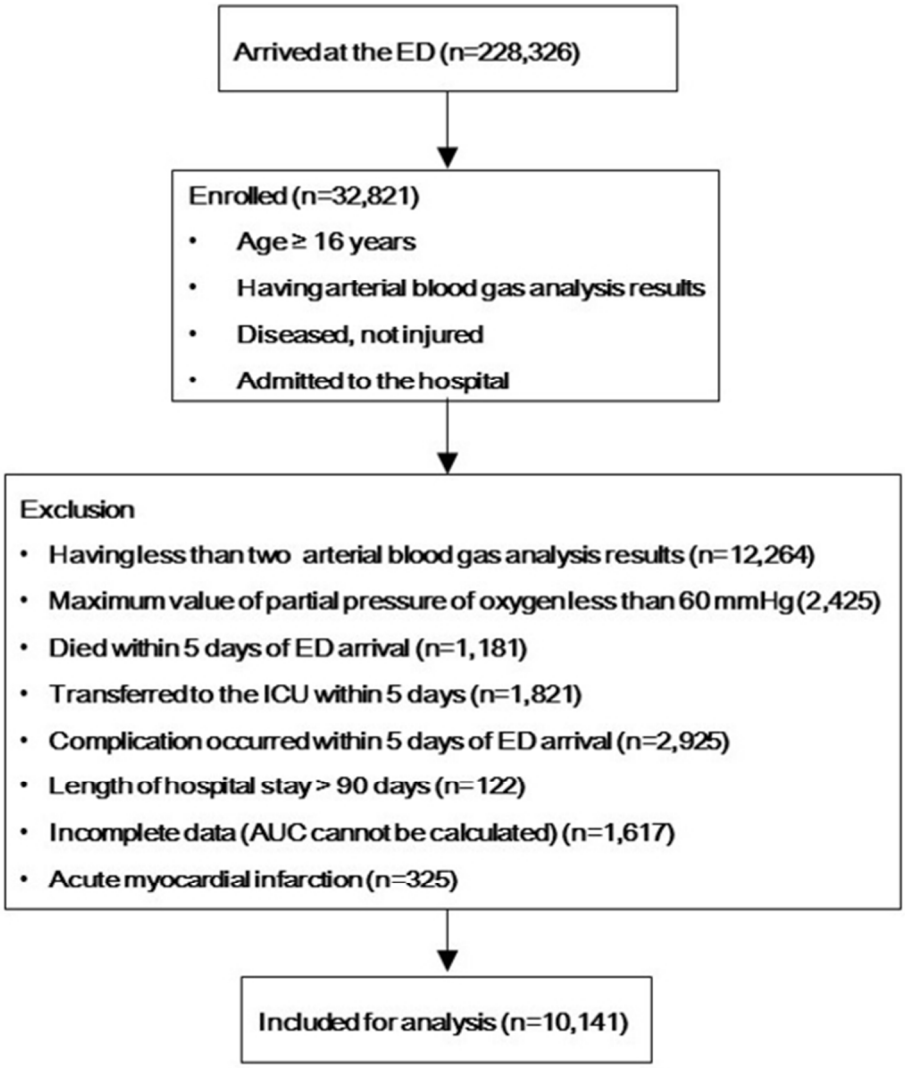

Figure 1. The study patients
ED; emergency department, ICU; intensive care unit, AUC; area under the curve

54x59mm (300 x 300 DPI)

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STROBE Statement—checklist of items that should be included in reports of observational studies

	Item No	Recommendation
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract → p.4
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found → p. 4
Introduction		
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported → p.6
Objectives	3	State specific objectives, including any prespecified hypotheses → p.7
Methods		
Study design	4	Present key elements of study design early in the paper → p.7
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection → p.7
Participants	6	(*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up *Case-control study*—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls→ p.7-8 *Cross-sectional study*—Give the eligibility criteria, and the sources and methods of selection of participants
		(*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed *Case-control study*—For matched studies, give matching criteria and the number of controls per case
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable → p.9
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group → p.9
Bias	9	Describe any efforts to address potential sources of bias→ p.19
Study size	10	Explain how the study size was arrived at → p.10
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why → p.9-10
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding → p.9-10
		(*b*) Describe any methods used to examine subgroups and interactions
		(*c*) Explain how missing data were addressed
		(*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed *Case-control study*—If applicable, explain how matching of cases and controls was addressed *Cross-sectional study*—If applicable, describe analytical methods taking account of sampling strategy
		(*e*) Describe any sensitivity analyses

Continued on next page

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Results		
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed → p.10
		(b) Give reasons for non-participation at each stage
		(c) Consider use of a flow diagram
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders → p.10-11
		(b) Indicate number of participants with missing data for each variable of interest → p.10-11
		(c) *Cohort study*—Summarise follow-up time (eg, average and total amount)
Outcome data	15*	*Cohort study*—Report numbers of outcome events or summary measures over time → p.12
		Case-control study—Report numbers in each exposure category, or summary measures of exposure
		Cross-sectional study—Report numbers of outcome events or summary measures
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included → p.13
		(*b*) Report category boundaries when continuous variables were categorized
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses → p.14-16
Discussion		
Key results	18	Summarise key results with reference to study objectives → p.17
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias → p.19
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence → p.18-19
Generalisability	21	Discuss the generalisability (external validity) of the study results → p.19
Other information		
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based → p.2

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

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Delayed effects of early hyperoxaemia in patients admitted to general wards: an observational cohort study in South Korea

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Article title

Delayed effects of early hyperoxaemia in patients admitted to general wards: an observational cohort study in South Korea

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Authors' contributions

Jin Hee Jeong: Dr. Jeong conceptualized and designed the study, analyzed the data, drafted the initial manuscript, critically reviewed the manuscript, approved the final manuscript as submitted, and agreed to be accountable for all aspects of the work.

Dong Hoon Kim: Dr. Kim conceptualized and designed the study, coordinated and supervised data collection, critically reviewed the manuscript, approved the final manuscript as submitted, and agreed to be accountable for all aspects of the work.

Tae Yun Kim: Dr. Kim conceptualized and designed the study, interpreted data, critically reviewed the manuscript, approved the final manuscript as submitted, and agreed to be accountable for all aspects of the work.

Changwoo Kang: Dr. Kang interpreted data, critically reviewed the manuscript, approved the final manuscript as submitted, and agreed to be accountable for all aspects of the work.

Soo Hoon Lee: Dr. Lee interpreted data, critically reviewed the manuscript, approved the final manuscript as submitted, and agreed to be accountable for all aspects of the work.

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Delayed effects of early hyperoxaemia in patients admitted to general wards: an observational cohort study in South Korea

Abstract

Objectives

We evaluated the association between hyperoxaemia induced by a non-invasive oxygen supply for 3 days after emergency department (ED) arrival and the clinical outcomes at day 5 after ED arrival.

Design

Observational study

Setting and patients

Consecutive ED patients ≥ 16 years of age with available arterial blood gas analysis results who were admitted to our hospital were enrolled from January 2010 to December 2016.

Interventions

The highest (PaO_{2MAX}), average (PaO_{2AVG}), and median (PaO_{2MED}) PaO_2 (arterial oxygen pressure) values within 72 h, and the area under the curve divided by the time elapsed between ED admittance and the last PaO_2 result (AUC_{72}), were used to assess hyperoxaemia. The AUC_{72} values were calculated using the trapezoid rule.

Outcomes

The primary outcome was the 90-day in-hospital mortality rate. The secondary outcomes were intensive care unit (ICU) transfer and respiratory failure at day 5 after ED arrival, as well as new-onset cardiovascular, coagulation, hepatic, and renal dysfunction at day 5 after ED arrival.

Results

Among the 10,141 patients, the mortality rate was 5.8%. The adjusted odds ratios (ORs) of in-hospital mortality for PaO_{2MAX}, PaO_{2AVG}, PaO_{2MED}, and AUC_{72} were 0.79

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(95% CI, 0.61–1.02; P = 0.0715), 0.92 (95% CI, 0.69–1.24; P = 0.5863), 0.82 (95% CI, 0.61–1.11; P = 0.2005), and 1.53 (95% CI, 1.25–1.88; P <0.0001). All of the hyperaemic variables showed significant positive correlations with ICU transfer at day 5 after ED arrival (P < 0.05). AUC_{72} was positively correlated with respiratory failure, as well as cardiovascular, hepatic, and renal dysfunction (P < 0.05). PaO_{2MAX} was positively correlated with cardiovascular dysfunction. PaO_{2MAX} and AUC_{72} were negatively correlated with coagulation dysfunction (P < 0.05).

Conclusions

Hyperoxaemia during the first 3 days in patients outside the ICU is associated with in-hospital mortality and ICU transfer at day 5 after arrival at the ED.

Keywords: Hyperoxaemia; oxygen; oxygen inhalation therapy; Hyperoxia

Strengths and limitations of this study

An observational cohort study of 10,141 consecutive patients visiting at the emergency department of a tertiary teaching hospital.

The relation between hyperoxaemia and clinical outcome was analyzed using various statistical measures: maximum, central tendency (average and median), and cumulative exposure in the patients who were admitted to general ward.

Impact of hyperoxaemia variables on clinical outcomes were adjusted for demographic, physiological, and biochemical parameters

Severity adjustment with the National Early Warning Score rather than ICU-based scores might lead to inaccurate results.

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Introduction

Supplemental oxygen is always required by hypoxic patients and is frequently given in various clinical settings. Physicians tend to believe that oxygen is safe and beneficial for both non-hypoxaemic and hyperoxaemic patients.[1] However, hyperoxaemic is associated with poor clinical outcomes.[2] Patients in intensive care units (ICUs) exhibiting high arterial oxygen pressure (PaO_2) and high fraction of inspired oxygen (FiO_2) experience more mortality than normoxic patients.[3] Hyperoxaemia is associated with higher in-hospital mortality rates than normoxaemia in patients resuscitated from cardiac arrest.[4–8] In addition, hyperoxaemia is associated with poor outcomes in patients with stroke, spontaneous SAH, and traumatic brain injury.[7,9–11] A recent randomised clinical study and a before-and-after study reported better outcomes in normoxic than hyperoxic ICU patients.[12,13]

Despite the evidence that hyperoxaemia is harmful, therapeutic strategies that prevent hyperoxaemia cannot be translated to all patients because the few relevant studies involved patients in ICUs or ventilator-assisted patients.[3, 9, 12, 14] A certain proportion of emergency department (ED) patients require supplemental oxygen. Of these, some require mechanical ventilation and thus ICU admission. However, others receive supplemental oxygen noninvasively via a facial mask or nasal prong, and are admitted to general wards.[15] Only a few studies have explored the effects of hyperoxaemia on the clinical outcomes of ED patients. One study involved mechanically ventilated patients.[14] Another study found that hyperoxaemia in ED patients induced by facial masks was harmful in those diagnosed with sepsis.[16] However, that study involved a small number of patients, a limited disease spectrum, and a single arterial blood gas (ABG) analysis result. No studies have evaluated the associations between hyperoxaemia and mortality in patients admitted to general wards. We hypothesised that hyperoxaemia induced by a non-invasive oxygen supply during the early treatment period would have adverse effects somewhat later in

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patients admitted to the general ward.

We evaluated the association between hyperoxaemia during the first 3 days after ED arrival and clinical outcomes day 5 after ED arrival.

Method

Study design and setting

We conducted a single-centre study at Gyeongsang National University Hospital, a tertiary teaching hospital located in the south-central region of the Republic of Korea, from January 2010 to December 2016. This study was approved by our Institutional Review Board. All patients admitted to the ED are enrolled in the National Emergency Department Information System (NEDIS). The NEDIS was developed in 2003 to establish a national database of ED patients.[17, 18] The quality of the data are examined annually by the National Emergency Medical Center, a government-funded, national ED control agency. In our ED, triage nurses and attending physicians enter into the NEDIS the patients' data, including basic demographic and temporal parameters, physiologic parameters at ED arrival, symptoms, diagnosis, treatment details (including drugs and procedures), outcomes, and other information. The data are organised using the standard NEDIS registry format in the hospital electronic medical records (EMRs). The validity of all data are checked by function modules within the system before the data are saved.

Participants

All consecutive patients ≥ 16 years of age with available ED ABG data who were admitted to the hospital with disease (not injury) during the study period were enrolled. We excluded patients with fewer than two arterial partial pressure of oxygen (PaO_2) results within 72 h of ED arrival. We also excluded patients with a maximum value of PaO_2 within 72 h (PaO_{2MAX}) of < 60 mmHg because we wished to compare hyperoxic

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and normoxic patients. Because we intended to assess delayed effects of hyperoxaemia, we also excluded patients who died prior to day 5 after ED arrival and who showed complications in the first 5 days (ICU transfer and respiratory failure, as well as new-onset cardiovascular, hepatic, renal, and coagulation dysfunction).

The other exclusion criteria were transfer to other facilities after admission, discharge with no hope of recovery, left the hospital against medical advice, and a hospital stay duration > 90 days. Patients diagnosed with acute myocardial infarction were also excluded because supplemental oxygen is no longer recommended as a routine therapy in normoxic patients with acute myocardial infarction.[19]

Data collection

The data were extracted from the hospital EMR system. The demographic parameters recorded were age and sex. The physiological parameters were systolic blood pressure, heart rate, breathing rate, body temperature, arterial oxyhaemoglobin saturation, and mental status (assessed as alert, verbal, pain, and unresponsive [AVPU]). We also extracted data from the Prehospital Record and List of Therapeutic Management sections of the EMR to determine whether a given patient had received supplemental oxygen therapy before ED arrival. All patients were given oxygen during their ED stays. The National Early Warning Score (NEWS) was calculated in each patient to access the severity of illness.[20] The PaO_2 results determined by ABG analysis within 72 h of ED arrival were collected. Temporal parameters between ED arrival and hospital discharge (dates of ED arrival, admission, ICU transfer, beginning of ventilator care, death, and discharge) and final outcome (discharge, transfer, death, or other) were also collected. Because we assessed complications of hyperoxaemia using the Sequential Organ Failure Assessment (SOFA) score components (cardiovascular, hepatic, renal, and coagulation dysfunction), we evaluated the platelet count, and serum creatinine and bilirubin levels, at ED arrival and at day 5

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after ED arrival, and determined whether a given patient received vasopressors. We also evaluated use of mechanical ventilation therapy at day 5 after ED arrival to assess respiratory failure. Because the PaO_2/FIO_2 ratio could not be accurately calculated in the ED and general ward, respiratory failure was defined as the need for endotracheal intubation.

Hyperaemic variables

Among the hyperaemic metrics described by Helmerhorst *et al*. [21], the highest (PaO_{2MAX}), average (PaO_{2AVG}), and median (PaO_{2MED}) PaO_2 values within 72 h, and the area under the curve divided by the time elapsed between ED arrival and the last PaO_2 result (AUC_{72}) were used in this study. Using the PaO_{2MED} as the starting value (t = 0; ED arrival time) and the value at 72 h (t = 72), the AUC_{72} was calculated using the trapezoid rule. Because no definition of hyperoxaemia has been established, we used the following upper quintile values: 137 mmHg for PaO_{2MAX}, 105 mmHg for PaO_{2AVG}, 103 mmHg for PaO_{2MED}, and 174 mmHg for AUC_{72}.

Study outcome

The primary outcome was the 90-day in-hospital mortality rate. The secondary outcomes were ICU transfer and respiratory failure at day 5 after ED arrival, and new-onset cardiovascular, coagulation, hepatic, and renal dysfunction (SOFA sub-score ≥ 2) at day 5 after ED arrival.

Data analysis

Age was categorised as 16–39, 40–79, or ≥ 80 years. All continuous variables showed a skewed distribution, and are presented as medians with interquartile ranges (IQRs). The Mann-Whitney U test was used to compare continuous variables, and Pearson's χ^2 test for categorical variables.

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Univariate logistic regression was performed using demographic and physiological data and the NEWS, laboratory parameter values (platelet, creatinine, and bilirubin levels, and initial PaO_2), and hyperaemic variables. Variables that were significantly (P<0.01) associated with the outcome in univariate analyses were used in the multivariate logistic regression model. The adjusted odds ratios (ORs) of these variables were calculated for each hyperaemic parameter to assess their association with in-hospital mortality.

The secondary outcomes (ICU transfer, respiratory failure and new-onset cardiovascular, hepatic, renal, and coagulation dysfunction at day 5) were subjected to the same analyses as the primary outcome. The PaO_{2MAX}, PaO_{2AVG}, PaO_{2MED}, and AUC_{72} values were subjected to multivariate analyses.

All P-values were two-sided, and a P-value of < 0.05 was considered indicative of statistical significance. Analyses were performed using MedCalc version 17 (MedCalc Software BVBA, Ostend, Belgium) and Stata version 13 (StataCorp, LP, College Station, TX).

Patient and Public Involvement

The patients were not involved in research question and outcome.

The patients were not involved in the study design.

The patients were not involved in the recruitment to and conduct of this study.

The study results will not be disseminated to study participants.

This study is not a randomised controlled trial.

Patient advisers were applicable in this study.

Results

Baseline

Of the 228,326 patients who arrived at the ED during the study period, 32,821 met the

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inclusion criteria. After applying the exclusion criteria, 10,141 patients were eligible for analysis (Figure 1). Males accounted for 59.6% (6,040) of patients, and the median age of the study population was 69 (IQR: 57–78) years old. The total number of ABG samples was 37,908 and the mean number of ABG samples per patient was 3 (IQR 2–4) within 72 h of ED arrival. The baseline characteristics of the patients are shown in Table 1.

Table 1. Baseline characteristics of patients

Characteristics	Total	Missing data, n (%)
Number of patients	10,141	
Age	69.0 (57.0 – 78.0)	0 (0)
Age category, n (%)		
16-39	786 (7.8)	0 (0)
40-79	7,434 (73.3)	0 (0)
≥80	1,921 (18.9)	0 (0)
Male, n (%)	6040 (59.6)	0 (0)
Physiologic variables		
Systolic blood pressure, mmHg	130 (110-150)	0 (0)
Heart rate, per minute	90 (78 - 108)	0 (0)
Breath rate, per minute	20 (20-22)	4 (0.0)
Body temperature, °C	36.7 (36.4 - 37.2)	10 (0.1)
SaO_2, %	96 (93 - 98)	230 (2.3)
Consciousness (alert), n (%)	9,076 (89.5)	0 (0)
Supplemental oxygen, n	4,012 (39.6)	0 (0)

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(%)		
NEWS	4 (1-7)	236 (2.3)
Initial laboratory results		
Platelet, $x10^3/mm^3$	220 (162-287)	56 (0.6)
Creatinine, mg/dl	0.87 (0.66-1.31)	61 (0.6)
Bilirubin, mg/dl	0.68 (0.43-1.10)	80 (0.8)
PO_2, mmHg	76 (59-96)	371 (3.7)
hyperoxaemia variables results		
PaO_{2MAX}	99.0 (83.0 – 126.0)	0 (0)
PaO_{2AVG}	81.0 (68.9 – 99.0)	0 (0)
PaO_{2MED}	80.0 (67.5 – 97.5)	0 (0)
AUC_{72}	63.8 (23.2 – 153.2)	0 (0)
Mortality, n (%)	584 (5.8)	0 (0)

SaO_2, Oxyhemoglobin saturation; NEWS, National Early Warning Score; PO_2, Partial pressure of Oxygen; PaO_{2Max}, highest value of PO_2 within 72 hours ; PaO_{2AVG}, average value of PO_2 within 72 hours; PaO_{2MED} , median value of PO_2 within 72 hours; AUC_{72}, area under the curve divided by elapsed time between ED arrival and the last result of PO_2 within 72 hours

Data are medians (interquartile range) unless stated otherwise.

Primary outcome

The results of univariate regression analyses are shown in Table 2. Patient age, sex, and all physiologic variables were significantly associated with 90-day in-hospital mortality. Regarding the initial values of the laboratory parameters, bilirubin and PaO_2 were significantly associated with 90-day in-hospital mortality. The unadjusted ORs of PaO_{2MAX}, PaO_{2AVG}, PaO_{2MED}, and AUC_{72} were 0.64 (95% CI, 0.51–0.82; P = 0.0003), 0.57 (95% CI, 0.45–0.74; P < 0.0001), 0.54 (95% CI, 0.42–0.69; P < 0.0001), and 1.59

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(95% CI, 1.32–1.92); P < 0.0001), respectively.

Because the values of the NEWS components (systolic blood pressure, heart rate, breath rate, body temperature, SaO2, supplemental oxygen, and consciousness) had P-values of < 0.01 in univariate analyses, we subjected NEWS to multivariate regression analyses. The adjusted ORs of PaO_{2MAX}, PaO_{2AVG}, PaO_{2MED}, and AUC_{72} were 0.79 (95% CI, 0.61–1.02; P = 0.0715), 0.92 (95% CI, 0.69–1.24; P = 0.5863), 0.82 (95% CI, 0.61–1.11; P = 0.2005) and 1.53 (95% CI, 1.25–1.88; P < 0.0001), respectively (Table 3).

Table 2. Univariate analysis of independent variables for 90 day in-hospital mortality

Variable	Odds ratio	P
Age 40 - 79	2.63 (1.63 - 4.24)	0.0001
Age ≥ 80	3.20 (1.94 - 5.27)	<0.0001
Female	0.54 (0.45 - 0.65)	<0.0001
Systolic blood pressure	0.99 (0.99 - 0.99)	<0.0001
Heart rate	1.01 (1.01 - 1.02)	<0.0001
breathing rate	1.07 (1.05 - 1.09)	<0.0001
Body temperature	0.90 (0.83 - 0.98)	0.0143
SaO_2	0.96 (0.96 - 0.97)	<0.0001
Consciousness (non-alert)	1.96 (1.57 - 2.45)	<0.0001
Supplemental oxygen	1.97 (1.66 - 2.33)	<0.0001
NEWS	1.14 (1.11 - 1.16)	<0.0001
Platelet	1.00 (1.00 - 1.00)	0.0659
Creatinine	0.97 (0.93 - 1.01)	0.1875
Bilirubin	1.15 (1.12 - 1.17)	<0.0001

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Initial PO_2	0.99 (0.99 - 1.00)	0.0005
PaO_{2MAX}	0.64 (0.51 - 0.82)	0.0003
PaO_{2AVG}	0.57 (0.45 - 0.74)	<0.0001
PaO_{2MED}	0.54 (0.42 - 0.69)	<0.0001
AUC_{72}	1.59 (1.32 – 1.92)	<0.0001

SaO_2, Oxyhemoglobin saturation; NEWS, National Early Warning Score; PO_2, Partial pressure of Oxygen; PaO_{2Max}, highest value of PO_2 within 72 hours ; PaO_{2AVG}, average value of PO_2 within 72 hours; PaO_{2MED} , median value of PO_2 within 72 hours; AUC_{72}, area under the curve divided by elapsed time between ED arrival and the last result of PO_2 within 72 hours

Table 3. Mortality and adjusted odds ratios for 90 day in-hospital mortality according to hyperoxaemia variables

Variable	Patients, n (%)	Deaths, n (%)	Odds ratio [a]	P
PaO_{2MAX}	10,141			
Fourth quintile (<137 mmHg)	8,081 (79.7)	500 (6.2)	1	
Upper quintile (≥137 mmHg)	2,060 (20.3)	84 (4.1)	0.79 (0.61 – 1.02)	0.0715
PaO_{2AVG}				
Fourth quintile (<105 mmHg)	8,140 (80.3)	510 (6.3)		
Upper quintile (≥105 mmHg)	2,001 (19.7)	74 (3.7)	0.92 (0.69 - 1.24)	0.5863
PaO_{2MED}				
Fourth quintile (<103mmHg)	8,111 (80.0)	513 (6.3)		
Upper quintile (≥103 mmHg)	2,030 (20.0)	71 (3.5)	0.82	0.2005

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			(0.61 - 1.11)	
AUC_{72}				
Fourth quintile (<174 mmHg)	8,124 (80.1)	422 (5.2)		
Upper quintile (≥174 mmHg)	2,017 (19.9)	162 (8.0)	1.53 (1.25 - 1.88)	<0.0001

[a] Adjusted for age, sex, NEWS, initial bilirubin and initial

PO_2, Partial pressure of Oxygen; PaO_{2Max}, highest value of PO_2 within 72 hours ; PaO_{2AVG}, average value of PO_2 within 72 hours; PaO_{2MED} , median value of PO_2 within 72 hours; AUC_{72}, area under the curve divided by elapsed time between ED arrival and the last result of PO_2 within 72 hours

Secondary outcomes

All of the hyperaemic variables were significantly positively correlated with ICU transfer at day 5 after ED arrival (Table 4). Among the hyperaemic variables, AUC_{72} had the highest OR for ICU transfer (4.03; 95% CI, 3.25–5.01; P < 0.0001). AUC_{72} was positively correlated with respiratory failure as well as cardiovascular, hepatic, and renal dysfunction. PaO_{2MAX} was positively correlated with cardiovascular dysfunction. PaO_{2MAX} and AUC_{72} were negatively correlated with coagulation dysfunction (0.64; 95% CI, 0.43–0.94; P = 0.022 and 0.67; 95% CI, 0.48–0.92; P = 0.015).

Table 4. hyperoxaemia variables and adjusted odds ratio (95% CI) for secondary outcomes

Variable	ICU transfer [a]	Respiratory failure [b]	Cardiovascular dysfunction [c]	Hepatic dysfunction [d]	Renal dysfunction [e]	Coagulation dysfunction [f]
	358 (3.5)	68 (0.7)	386 (3.8)	678 (8.7)	983 (12.6)	408 (5.0)

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PaO_{2MAX}	2.81 [g] (2.26 - 3.50)	1.45 (0.85 - 2.47)	1.39 [i] (1.09 - 1.78)	0.99 (0.74 - 1.33)	0.95 (0.72 - 1.26)	0.64 [i] (0.43 – 0.94)
PaO_{2AVG}	2.04 [g] (1.61 - 2.57)	1.13 (0.63 - 2.01)	1.13 (0.87 - 1.47)	0.96 (0.70 - 1.34)	1.13 (0.84 - 1.53)	1.08 (0.74 - 1.59
PaO_{2MED}	1.51 [h] (1.18 – 1.94)	0.66 (0.34 - 1.30)	1.02 (0.78 - 1.33)	1.02 (0.74 - 1.40)	0.97 (0.72 - 1.31)	1.17 (0.81 – 1.69)
AUC_{72}	4.03 [g] (3.25 – 5.01)	2.40 [h] (1.46 – 3.95)	1.63 [h] (1.29 – 2.07)	1.53 [i] (1.18 - 1.97)	1.33 [i] (1.05 - 1.68)	0.67 [i] (0.48 – 0.92)

[a] Adjusted for systolic blood pressure, heart rate, body temperature, consciousness and supplemental oxygen

[b] Adjusted for body temperature and consciousness

[c] Adjusted for age, sex, heart rate, SaO_2, bilirubin and creatinine

[d] Adjusted for age, sex, systolic blood pressure, breath rate, SaO_2, consciousness, supplemental oxygen, bilirubin, platelet and initial PO_2

[e] Adjusted for NEWS, bilirubin, creatinine, platelet and initial PO_2

[f] Adjusted for sex, systolic blood pressure, breath rate, SaO_2, consciousness, supplemental oxygen, bilirubin, platelet and initial PO_2

[g] $P < 0.0001$

[h] $P < 0.001$

[i] $P < 0.05$

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ICU, intensive care unit; PO_2, Partial pressure of Oxygen; PaO_{2Max}, highest value of PO_2 within 72 hours ; PaO_{2AVG}, average value of PO_2 within 72 hours; PaO_{2MED} , median value of PO_2 within 72 hours; AUC_{72}, area under the curve divided by elapsed time between ED arrival and the last result of PO_2 within 72 hours

Discussion

We assessed the association between hyperoxaemia during the first 72 h and the outcomes at day 5 after ED arrival. In univariate analyses, all of the hyperaemic variables showed significant correlations with the 90-day in-hospital mortality rate (Table 2). After adjustment, only AUC_{72} was significantly associated with the 90-day in-hospital mortality rate (Table 3). AUC_{72} was significantly positively correlated with ICU transfer, respiratory failure, cardiovascular dysfunction, hepatic dysfunction, and renal dysfunction. PaO_{2MAX} was significantly associated with ICU transfer and cardiovascular dysfunction. PaO_{2MAX} and AUC_{72} were negatively associated with coagulation dysfunction.

Only AUC_{72} was significantly associated with 90-day in-hospital mortality in this study; the one-time hyperaemic parameters (PaO_{2MAX}, PaO_{2AVG}, and PaO_{2MED}) were not.[21,22] Because AUC_{72} is indicative of cumulative exposure to hyperoxaemia, it may reflect the degree of hyperoxaemia more accurately than the other variables.

The patients in this study were in a less-severe condition than those in previous studies. Our target population was patients who arrived at the ED but were not admitted to the ICU in the next 5 days. By contrast, previous studies involved only patients admitted to the ICU.[3,21,22] The median NEWS was 4 (IQR: 2–7) we considered that a NEWS ≥ 5 reflected critical illness.[20, 23] We also used a non-invasive method of oxygen administration, unlike previous studies. Many patients in the ICU undergo mechanical ventilation. Mechanical ventilation may deliver a larger

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dose of oxygen in a more accurate manner. Patients who required higher oxygen levels, and those who were mechanically ventilated because of altered mentality or muscle weakness, were excluded from this study. We believe that this exclusion leads to a lower incidence of hyperoxaemia in this study than in previous studies.[10–12] The single time exposure in non-critically ill patients under less severe hyperoxaemia conditions may not be as harmful and may therefore fail to show statistical significance on mortality rate. Instead, ICU transfer was used as an indicator of an increase in clinical severity in this study. Therefore, AUC_{72} is more suitable than the one-time hyperaemic parameters for assessing mortality and complications in these patients.

The significant association between AUC_{72} and cardiovascular and hepatic dysfunction is consistent with Girardis *et al*. [12], which found that strict oxygen use reduces the rates of mortality, shock, and liver failure compared to conventional oxygen use. Because that previous study was conducted in the ICU, this is the first report of AUC_{72} as an indicator of complications in non-ICU patients.

The PaO_{2MAX} and AUC_{72} values were associated with greater coagulation dysfunction. A previous study showed that coagulation dysfunction, as determined by fibrin desposition occurs in patients with hyperoxaemia-induced acute lung injury,[24] but has not been investigated extensively. Thus, further studies should evaluate the association between coagulation dysfunction and hyperoxaemia.

hyperoxaemia toxicity caused through production of reactive oxygen species (ROS), pulmonary toxicity, hemodynamic alterations, and neurological damage. ROS lead to lipid peroxidation, protein oxidation, DNA damage and direct pulmonary damage mediated by damage to the alveolar capillary barrier. Another pulmonary complication includes impairment of pulmonary gas exchange by adsorption atelectasis. Hemodynamic alterations include reductions in cardiac output, coronary blood flow, myocardial O2 consumption and heart rate, as well as increased vascular resistance. Neurological damage is caused by excessive oxygen levels, which disrupt

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the protective mechanisms of the neural system under hyperbaric oxygen situation.[5, 7, 24–27]

However, it is unclear from which exposure duration and oxygen concentrations are necessary for toxicity to occur. The lung is first affected because of higher oxygen tension.[28] In a study on baboons, alveolar septal injury occurred following exposure to 60% O_2 for 14 days.[29] In rabbits, lung injury developed following exposure to moderate hyperoxaemia at a large tidal volume for 2 h.[30] In humans, symptoms can occur at 10 h after initial exposure to hyperoxaemia,[31] although histological changes are apparent earlier. Helmerhorst *et al*.[32] reported that exposure to a high FiO_2 for 15 min affected the systemic vascular resistance of patients who had undergone coronary artery bypass grafting (CABG) surgery. Thus, physiological changes onset within minutes or hours after exposure to hyperoxaemia. We found that clinical outcomes (mortality and ICU transfer) were affected during the first 72 h of exposure to hyperoxaemia. Therefore, physicians should be aware of the potential risks of early hyperoxaemia.

The present study had several limitations. First, we could not rule out selection bias, as the study population was limited to patients who visited our ED and underwent blood gas analysis. Second, because the NEWS was calculated using the initial values in the ED rather than ICU-based severity scores, the assessment of severity may have been inaccurate; if so, this would introduce bias into the regression model. Third, this study was conducted in a single centre; thus, a further multicentre randomised controlled study is warranted. Fourth, we excluded the patients with poor outcomes prior to day 5 after ED arrival because there are not knowledge about the onset time of clinical outcome following hyperoxaemia. Further prospective randomized study is needed about those patients. Fifth, this was an observational cohort study; although statistical associations were evident, causation cannot be inferred. Some relevant factors may not have been measured.

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Despite its limitations, this study was novel because we evaluated the association between hyperoxaemia and outcomes in non-critically ill patients presenting to the ED.

Conclusion

Hyperoxaemia during the first 3 days in ED patients was associated with higher in-hospital mortality and more common ICU transfer at day 5 after ED arrival.

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Figure 1. The study patients.

ED; emergency department, ICU; intensive care unit, AUC; area under the curve.

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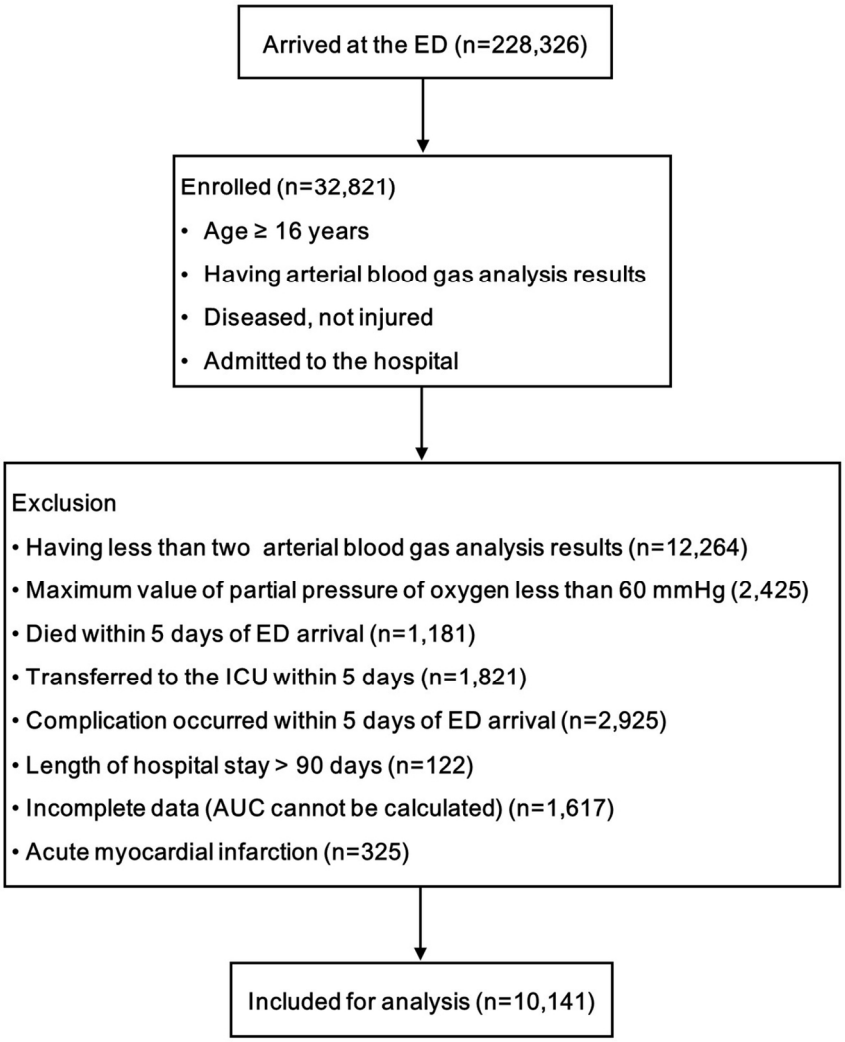

Figure 1. The study patients.
ED; emergency department, ICU; intensive care unit, AUC; area under the curve.

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STROBE Statement—checklist of items that should be included in reports of observational studies

	Item No	Recommendation
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract → p.4
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found → p. 4
Introduction		
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported → p.6
Objectives	3	State specific objectives, including any prespecified hypotheses → p.7
Methods		
Study design	4	Present key elements of study design early in the paper → p.7
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection → p.7
Participants	6	(*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up *Case-control study*—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls→ p.7-8 *Cross-sectional study*—Give the eligibility criteria, and the sources and methods of selection of participants
		(*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed *Case-control study*—For matched studies, give matching criteria and the number of controls per case
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable → p.9
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group → p.9
Bias	9	Describe any efforts to address potential sources of bias→ p.19
Study size	10	Explain how the study size was arrived at → p.10-11
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why → p.9-10
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding → p.9-10
		(*b*) Describe any methods used to examine subgroups and interactions
		(*c*) Explain how missing data were addressed
		(*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed *Case-control study*—If applicable, explain how matching of cases and controls was addressed *Cross-sectional study*—If applicable, describe analytical methods taking account of sampling strategy
		(*e*) Describe any sensitivity analyses

Continued on next page

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Results		
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed → p.10-11
		(b) Give reasons for non-participation at each stage
		(c) Consider use of a flow diagram
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders → p.10-11
		(b) Indicate number of participants with missing data for each variable of interest → p.10-11
		(c) *Cohort study*—Summarise follow-up time (eg, average and total amount)
Outcome data	15*	*Cohort study*—Report numbers of outcome events or summary measures over time
		Case-control study—Report numbers in each exposure category, or summary measures of exposure → p.12-13
		Cross-sectional study—Report numbers of outcome events or summary measures
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included → p.12-13
		(*b*) Report category boundaries when continuous variables were categorized
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses → p.14-16
Discussion		
Key results	18	Summarise key results with reference to study objectives → p.17
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias → p.19
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence → p.18-19
Generalisability	21	Discuss the generalisability (external validity) of the study results → p.19
Other information		
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based → p.2

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

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The harmful effects of early hyperoxaemia in patients admitted to general wards: an observational cohort study in South Korea

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The harmful effects of early hyperoxaemia in patients admitted to general wards: an observational cohort study in South Korea

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Authors' contributions

Jin Hee Jeong: Dr. Jeong conceptualized and designed the study, analyzed the data, drafted the initial manuscript, critically reviewed the manuscript, approved the final manuscript as submitted, and agreed to be accountable for all aspects of the work.

Dong Hoon Kim: Dr. Kim conceptualized and designed the study, coordinated and supervised data collection, critically reviewed the manuscript, approved the final manuscript as submitted, and agreed to be accountable for all aspects of the work.

Tae Yun Kim: Dr. Kim conceptualized and designed the study, interpreted data, critically reviewed the manuscript, approved the final manuscript as submitted, and agreed to be accountable for all aspects of the work.

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The harmful effects of early hyperoxaemia in patients admitted to general wards: an observational cohort study in South Korea

Abstract

Objectives

We evaluated the association between hyperoxaemia induced by a non-invasive oxygen supply for 3 days after emergency department (ED) arrival and the clinical outcomes at day 5 after ED arrival.

Design

Observational cohort study

Setting and patients

Consecutive ED patients ≥ 16 years of age with available arterial blood gas analysis results who were admitted to our hospital were enrolled from January 2010 to December 2016.

Interventions

The highest (PaO_{2MAX}), average (PaO_{2AVG}), and median (PaO_{2MED}) PaO_2 (arterial oxygen pressure) values within 72 h, and the area under the curve divided by the time elapsed between ED admittance and the last PaO_2 result (AUC_{72}), were used to assess hyperoxaemia. The AUC_{72} values were calculated using the trapezoid rule.

Outcomes

The primary outcome was the 90-day in-hospital mortality rate. The secondary outcomes were intensive care unit (ICU) transfer and respiratory failure at day 5 after ED arrival, as well as new-onset cardiovascular, coagulation, hepatic, and renal dysfunction at day 5 after ED arrival.

Results

Among the 10,141 patients, the mortality rate was 5.8%. The adjusted odds ratios (ORs) of in-hospital mortality for PaO_{2MAX}, PaO_{2AVG}, PaO_{2MED}, and AUC_{72} were 0.79

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(95% CI, 0.61–1.02; P = 0.0715), 0.92 (95% CI, 0.69–1.24; P = 0.5863), 0.82 (95% CI, 0.61–1.11; P = 0.2005), and 1.53 (95% CI, 1.25–1.88; P <0.0001). All of the hyperoxaemia variables showed significant positive correlations with ICU transfer at day 5 after ED arrival (P < 0.05). AUC_{72} was positively correlated with respiratory failure, as well as cardiovascular, hepatic, and renal dysfunction (P < 0.05). PaO_{2MAX} was positively correlated with cardiovascular dysfunction. PaO_{2MAX} and AUC_{72} were negatively correlated with coagulation dysfunction (P < 0.05).

Conclusions

Hyperoxaemia during the first 3 days in patients outside the ICU is associated with in-hospital mortality and ICU transfer at day 5 after arrival at the ED.

Keywords: Hyperoxaemia; oxygen; oxygen inhalation therapy; hyperoxia

Strengths and limitations of this study

An observational cohort study of 10,141 consecutive patients visiting the emergency department of a tertiary teaching hospital.

The relationship between hyperoxaemia and clinical outcomes was analyzed using various statistical measures: maximum, central tendency (average and median), and cumulative exposure in those patients who were admitted to a general ward.

The impact of hyperoxaemia variables on clinical outcomes was adjusted for demographic, physiological, and biochemical values.

Severity adjustment with the National Early Warning Score rather than ICU-based scores might lead to inaccurate results.

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Introduction

Supplemental oxygen is frequently required by hypoxaemic patients and is frequently given in various clinical settings. Physicians tend to believe that oxygen is safe and beneficial for both non-hypoxaemic and hyperoxaemic patients.[1] However, hyperoxaemia is associated with poor clinical outcomes.[2] Patients in intensive care units (ICUs) exhibiting high arterial oxygen partial pressure (PaO_2) and a high fraction of inspired oxygen (FiO_2) experience more mortality than normoxaemic patients.[3] Hyperoxaemia is associated with higher in-hospital mortality rates than normoxaemia in patients resuscitated from cardiac arrest.[4–8] In addition, hyperoxaemia is associated with poor outcomes in patients with stroke, spontaneous subarachnoid haemorrhage, and traumatic brain injury.[7,9–11] A recent randomised controlled trial and a before-and-after study reported better outcomes in normoxaemic than hyperoxaemic ICU patients.[12,13]

Despite the evidence that hyperoxaemia is harmful, therapeutic strategies that prevent hyperoxaemia cannot be translated to all patients because the few relevant studies involved patients in ICUs or ventilator-assisted patients.[3, 9, 12, 14] A certain proportion of emergency department (ED) patients require supplemental oxygen. Of these, some require mechanical ventilation and thus ICU admission. However, others receive supplemental oxygen noninvasively via a facial mask or nasal prong and are admitted to general wards.[15] Only a few studies have explored the effects of hyperoxaemia on the clinical outcomes of ED patients. One study involved mechanically ventilated patients.[14] Another study found that hyperoxaemia in ED patients induced by facial masks was harmful in those diagnosed with sepsis.[16] However, that study involved a small number of patients, a limited disease spectrum, and a single arterial blood gas (ABG) analysis result. No studies have evaluated the associations between hyperoxaemia and mortality in patients admitted to general wards. We hypothesised that hyperoxaemia induced by a non-invasive oxygen supply

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during the early treatment period would have adverse effects somewhat later in patients admitted to the general ward.

We evaluated the association between hyperoxaemia during the first 3 days after ED arrival and clinical outcomes day 5 after ED arrival.

Method

Study design and setting

We conducted a single-centre study at Gyeongsang National University Hospital, a tertiary teaching hospital located in the south-central region of the Republic of Korea, from January 2010 to December 2016. This study was approved by our Institutional Review Board. All patients admitted to the ED are enrolled in the National Emergency Department Information System (NEDIS). The NEDIS was developed in 2003 to establish a national database of ED patients.[17, 18] The quality of the data were examined annually by the National Emergency Medical Centre, a government-funded, national ED control agency. In our ED, triage nurses and attending physicians entered patients' data into the NEDIS, including basic demographic and time values, physiological values at ED arrival, symptoms, diagnosis, treatment details (including drugs and procedures), outcomes, and other information. The data were organised using the standard NEDIS registry format in the hospital electronic medical records (EMRs). The validity of all data was checked by function modules within the system before the data are saved.

Participants

All consecutive patients ≥ 16 years of age with available ED ABG data who were admitted to the hospital with disease (not injury) during the study period were enrolled. We excluded patients with fewer than two PaO_2 results within 72 h of ED arrival. We also excluded patients with a maximum value of PaO_2 within 72 h (PaO_{2MAX}) of < 60

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mmHg because we wished to compare hyperoxaemic and normoxaemic patients. Because we intended to assess delayed effects of hyperoxaemia, we also excluded patients who died prior to day 5 after ED arrival and who showed complications in the first 5 days (ICU transfer and respiratory failure, as well as new-onset cardiovascular, hepatic, renal, and coagulation dysfunction).

The other exclusion criteria were transfer to other facilities after admission, discharge with no hope of recovery, and left the hospital against medical advice. Patients with a hospital stay > 90 days were excluded since their long stay may, potentially, be due to secondary problems. Moreover, we assumed that patients who were hospitalised > 90 days would be free from the effects of early hyperoxaemia since there has been no study on how long the delayed effects of early hyperoxaemia last. Patients diagnosed with acute myocardial infarction were also excluded because supplemental oxygen is no longer recommended as a routine therapy in normoxaemic patients with acute myocardial infarction.[19]

Data collection

The data were extracted from the hospital EMR system. The demographic values recorded were age and sex. The physiological values were systolic blood pressure, heart rate, breathing rate, body temperature, arterial oxyhaemoglobin saturation, and mental status (assessed as alert, verbal, pain, and unresponsive [AVPU]). We also extracted data from the Prehospital Record and List of Therapeutic Management sections of the EMR to determine whether a given patient had received supplemental oxygen therapy before ED arrival. All patients were given oxygen during their ED stays. The National Early Warning Score (NEWS) was calculated in each patient to access the severity of illness.[20] The PaO_2 results determined by ABG analysis within 72 h of ED arrival were collected. Time values between ED arrival and hospital discharge (dates of ED arrival, admission, ICU transfer, beginning of ventilator care, death, and

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discharge) and final outcome (discharge, transfer, death, or other) were also collected. Because we assessed complications of hyperoxaemia using the Sequential Organ Failure Assessment (SOFA) score components (cardiovascular, hepatic, renal, and coagulation dysfunction), we evaluated the platelet count, and serum creatinine and bilirubin levels, at ED arrival and at day 5 after ED arrival, and determined whether a given patient received vasopressors. We also evaluated the use of mechanical ventilation therapy at day 5 after ED arrival to assess respiratory failure. Because the PaO_2/FIO_2 ratio could not be accurately calculated in the ED and general ward, respiratory failure was defined as the need for endotracheal intubation.

Hyperoxaemic variables

Among the hyperoxaemia metrics described by Helmerhorst *et al*. [21], the highest (PaO_{2MAX}), average (PaO_{2AVG}), and median (PaO_{2MED}) PaO_2 values within 72 h, and the area under the curve divided by the time elapsed between ED arrival and the last PaO_2 result (AUC_{72}) were used in this study. Using the PaO_{2MED} as the starting value (t = 0; ED arrival time) and the value at 72 h (t = 72), the AUC_{72} was calculated using the trapezoid rule. Because no definition of hyperoxaemia has been established, we used the following upper quintile values: 137 mmHg for PaO_{2MAX}, 105 mmHg for PaO_{2AVG}, 103 mmHg for PaO_{2MED}, and 174 mmHg for AUC_{72}.

Study outcome

The primary outcome was the 90-day in-hospital mortality rate. The secondary outcomes were ICU transfer and respiratory failure at day 5 after ED arrival, and new-onset cardiovascular, coagulation, hepatic, and renal dysfunction (SOFA sub-score ≥ 2) at day 5 after ED arrival.

Data analysis

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Age was categorised as 16–39, 40–79, or ≥ 80 years. All continuous variables showed a skewed distribution, and are presented as medians with interquartile ranges (IQRs). The Mann-Whitney U test was used to compare continuous variables, and Pearson's χ^2 test for categorical variables.

Univariate logistic regression was performed using demographic and physiological data and the NEWS, laboratory values (platelet, creatinine, and bilirubin levels, and initial PaO_2), and hyperoxaemia variables. Variables that were significantly ($P<0.01$) associated with the outcome in univariate analyses were used in the multivariate logistic regression model. The adjusted odds ratios (ORs) of these variables were calculated for each hyperoxaemia value to assess their association with in-hospital mortality.

The secondary outcomes (ICU transfer, respiratory failure and new-onset cardiovascular, hepatic, renal, and coagulation dysfunction at day 5) were subjected to the same analyses as the primary outcome. The PaO_{2MAX}, PaO_{2AVG}, PaO_{2MED}, and AUC_{72} values were subjected to multivariate analyses.

All P-values were two-sided, and a P-value of < 0.05 was considered indicative of statistical significance. Analyses were performed using MedCalc version 17 (MedCalc Software BVBA, Ostend, Belgium) and Stata version 13 (StataCorp, LP, College Station, TX).

Patient and Public Involvement

No patients were involved in the research question and outcome.

No patients were involved in recruitment to this study.

The study results will not be disseminated to study participants.

This study is not a randomised controlled trial.

No patients were involved in the study design or conduct of the study.

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Results

Baseline

Of the 228,326 patients who arrived at the ED during the study period, 32,821 met the inclusion criteria. After applying the exclusion criteria, 10,141 patients were eligible for analysis (Figure 1). Males accounted for 59.6% (6,040) of patients, and the median age of the study population was 69 (IQR: 57–78) years old. The total number of ABG samples was 37,908 and the mean number of ABG samples per patient was three (IQR 2–4) within 72 h of ED arrival. The baseline characteristics of the patients are shown in Table 1.

Table 1. Baseline characteristics of the patients

Characteristics	Total	Missing data, n (%)
Number of patients	10,141	
Age, yr	69.0 (57.0–78.0)	0 (0)
Age category, n (%)		
16–39	786 (7.8)	0 (0)
40–79	7,434 (73.3)	0 (0)
≥ 80	1,921 (18.9)	0 (0)
Male, n (%)	6,040 (59.6)	0 (0)
Physiological variables		
Systolic blood pressure, mmHg	130 (110–150)	0 (0)
Heart rate, beats/min	90 (78–108)	0 (0)
Breath rate, breaths/min	20 (20–22)	4 (0.0)
Body temperature, °C	36.7 (36.4–37.2)	10 (0.1)
SaO_2, %	96 (93–98)	230 (2.3)

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Consciousness (alert), n (%)	9,076 (89.5)	0 (0)
Supplemental oxygen, n (%)	4,012 (39.6)	0 (0)
NEWS	4 (1–7)	236 (2.3)
Initial laboratory results		
Platelet, $\times 10^3/mm^3$	220 (162–287)	56 (0.6)
Creatinine, mg/dl	0.87 (0.66–1.31)	61 (0.6)
Bilirubin, mg/dl	0.68 (0.43–1.10)	80 (0.8)
PO_2, mmHg	76 (59–96)	371 (3.7)
Hyperoxaemia variables results		
PaO_{2MAX}	99.0 (83.0–126.0)	0 (0)
PaO_{2AVG}	81.0 (68.9–99.0)	0 (0)
PaO_{2MED}	80.0 (67.5–97.5)	0 (0)
AUC_{72}	63.8 (23.2–153.2)	0 (0)
Mortality, n (%)	584 (5.8)	0 (0)

SaO_2, oxyhaemoglobin saturation; NEWS, National Early Warning Score; PO_2, partial pressure of oxygen; PaO_{2Max}, highest value of PO_2 within 72 hours ; PaO_{2AVG}, average value of PO_2 within 72 hours; PaO_{2MED} , median value of PO_2 within 72 hours; AUC_{72}, area under the curve divided by elapsed time between ED arrival and the last result of PO_2 within 72 hours.

Data are medians (interquartile range) unless otherwise stated.

Primary outcome

The results of univariate regression analyses are shown in Table 2. Patient age, sex, and all physiological variables such as systolic blood pressure, heart rate, breathing rate, body temperature, arterial oxyhaemoglobin saturation, and mental status were

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significantly associated with 90-day in-hospital mortality. Regarding the initial values of the laboratory values, bilirubin and PaO_2 were significantly associated with 90-day in-hospital mortality. The unadjusted ORs of PaO_{2MAX}, PaO_{2AVG}, PaO_{2MED}, and AUC_{72} were 0.64 (95% CI, 0.51–0.82; P = 0.0003), 0.57 (95% CI, 0.45–0.74; P < 0.0001), 0.54 (95% CI, 0.42–0.69; P < 0.0001), and 1.59 (95% CI, 1.32–1.92); P < 0.0001), respectively.

Because the values of the NEWS components (systolic blood pressure, heart rate, breath rate, body temperature, SaO2, supplemental oxygen, and consciousness) had P-values of < 0.01 in univariate analyses, we subjected NEWS to multivariate regression analyses. The adjusted ORs of PaO_{2MAX}, PaO_{2AVG}, PaO_{2MED}, and AUC_{72} were 0.79 (95% CI, 0.61–1.02; P = 0.0715), 0.92 (95% CI, 0.69–1.24; P = 0.5863), 0.82 (95% CI, 0.61–1.11; P = 0.2005) and 1.53 (95% CI, 1.25–1.88; P < 0.0001), respectively (Table 3).

Table 2. Univariate analysis of independent variables for 90-day in-hospital mortality

Variable	Odds ratio	P
Age 40–79 yr	2.63 (1.63–4.24)	0.0001
Age ≥ 80 yr	3.20 (1.94–5.27)	< 0.0001
Female	0.54 (0.45–0.65)	< 0.0001
Systolic blood pressure	0.99 (0.99–0.99)	< 0.0001
Heart rate	1.01 (1.01–1.02)	< 0.0001
Breathing rate	1.07 (1.05–1.09)	< 0.0001
Body temperature	0.90 (0.83–0.98)	0.0143
SaO_2	0.96 (0.96–0.97)	< 0.0001
Consciousness (non-alert)	1.96 (1.57–2.45)	< 0.0001

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Supplemental oxygen	1.97 (1.66–2.33)	< 0.0001
NEWS	1.14 (1.11–1.16)	< 0.0001
Platelet	1.00 (1.00–1.00)	0.0659
Creatinine	0.97 (0.93–1.01)	0.1875
Bilirubin	1.15 (1.12–1.17)	< 0.0001
Initial PO_2	0.99 (0.99–1.00)	0.0005
PaO_{2MAX}	0.64 (0.51–0.82)	0.0003
PaO_{2AVG}	0.57 (0.45–0.74)	< 0.0001
PaO_{2MED}	0.54 (0.42–0.69)	< 0.0001
AUC_{72}	1.59 (1.32–1.92)	< 0.0001

SaO_2, oxyhaemoglobin saturation; NEWS, National Early Warning Score; PO_2, partial pressure of oxygen; PaO_{2Max}, highest value of PO_2 within 72 hours ; PaO_{2AVG}, average value of PO_2 within 72 hours; PaO_{2MED} , median value of PO_2 within 72 hours; AUC_{72}, area under the curve divided by elapsed time between ED arrival and the last result of PO_2 within 72 hours.

Table 3. Mortality and adjusted odds ratios for 90-day in-hospital mortality according to hyperoxaemia variables

Variable	Patients, n (%)	Deaths, n (%)	Odds ratio [a]	P
PaO_{2MAX}	10,141			
Fourth quintile (< 137 mmHg)	8,081 (79.7)	500 (6.2)	1	
Upper quintile (≥ 137 mmHg)	2,060 (20.3)	84 (4.1)	0.79 (0.61–1.02)	0.0715
PaO_{2AVG}				
Fourth quintile (< 105 mmHg)	8,140 (80.3)	510 (6.3)		
Upper quintile (≥ 105 mmHg)	2,001 (19.7)	74 (3.7)	0.92	0.5863

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			(0.69–1.24)	
PaO_{2MED}				
Fourth quintile (< 103mmHg)	8,111 (80.0)	513 (6.3)		
Upper quintile (≥ 103 mmHg)	2,030 (20.0)	71 (3.5)	0.82 (0.61–1.11)	0.2005
AUC_{72}				
Fourth quintile (< 174 mmHg)	8,124 (80.1)	422 (5.2)		
Upper quintile (≥ 174 mmHg)	2,017 (19.9)	162 (8.0)	1.53 (1.25–1.88)	< 0.0001

[a] Adjusted for age, sex, NEWS, initial bilirubin and initial PO_2, partial pressure of oxygen; PaO_{2Max}, highest value of PO_2 within 72 hours ; PaO_{2AVG}, average value of PO_2 within 72 hours; PaO_{2MED} , median value of PO_2 within 72 hours; AUC_{72}, area under the curve divided by elapsed time between ED arrival and the last result of PO_2 within 72 hours.

Secondary outcomes

All of the hyperoxaemia variables were significantly positively correlated with ICU transfer at day 5 after ED arrival (Table 4). Among the hyperoxaemia variables, AUC_{72} had the highest OR for ICU transfer (4.03; 95% CI, 3.25–5.01; P < 0.0001). AUC_{72} was positively correlated with respiratory failure as well as cardiovascular, hepatic, and renal dysfunction. PaO_{2MAX} was positively correlated with cardiovascular dysfunction. PaO_{2MAX} and AUC_{72} were negatively correlated with coagulation dysfunction (0.64; 95% CI, 0.43–0.94; P = 0.022 and 0.67; 95% CI, 0.48–0.92; P = 0.015).

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Table 4. Hyperoxaemia variables and adjusted odds ratios (95% CI) for secondary outcomes

Variable	ICU transfer [a]	Respiratory failure [b]	Cardiovascular dysfunction [c]	Hepatic dysfunction [d]	Renal dysfunction [e]	Coagulation dysfunction [f]
	358 (3.5)	68 (0.7)	386 (3.8)	678 (8.7)	983 (12.6)	408 (5.0)
PaO_{2MAX}	2.81 [g] (2.26–3.50)	1.45 (0.85–2.47)	1.39 [i] (1.09–1.78)	0.99 (0.74–1.33)	0.95 (0.72–1.26)	0.64 [i] (0.43–0.94)
PaO_{2AVG}	2.04 [g] (1.61–2.57)	1.13 (0.63–2.01)	1.13 (0.87–1.47)	0.96 (0.70–1.34)	1.13 (0.84–1.53)	1.08 (0.74–1.59
PaO_{2MED}	1.51 [h] (1.18–1.94)	0.66 (0.34–1.30)	1.02 (0.78–1.33)	1.02 (0.74–1.40)	0.97 (0.72–1.31)	1.17 (0.81–1.69)
AUC_{72}	4.03 [g] (3.25–5.01)	2.40 [h] (1.46–3.95)	1.63 [h] (1.29–2.07)	1.53 [i] (1.18–1.97)	1.33 [i] (1.05–1.68)	0.67 [i] (0.48–0.92)

[a] Adjusted for systolic blood pressure, heart rate, body temperature, consciousness and supplemental oxygen

[b] Adjusted for body temperature and consciousness

[c] Adjusted for age, sex,

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heart rate, SaO_2, bilirubin and creatinine

[d] Adjusted for age, sex, systolic blood pressure, breath rate, SaO_2, consciousness, supplemental oxygen, bilirubin, platelet and initial PO_2

[e] Adjusted for NEWS, bilirubin, creatinine, platelet and initial PO_2

[f] Adjusted for sex, systolic blood pressure, breath rate, SaO_2, consciousness, supplemental oxygen, bilirubin, platelet and initial PO_2

[g] $P < 0.0001$

[h] $P < 0.001$

[i] $P < 0.05$

ICU, intensive care unit; PO_2, partial pressure of oxygen; PaO_{2Max}, highest value of PO_2 within 72 hours ; PaO_{2AVG}, average value of PO_2 within 72 hours; PaO_{2MED} , median value of PO_2 within 72 hours; AUC_{72}, area under the curve divided by elapsed time between ED arrival and the last result of PO_2 within 72 hours.

Discussion

We assessed the association between hyperoxaemia during the first 72 h and the outcomes at day 5 after ED arrival. In univariate analyses, all of the hyperoxaemia variables showed significant correlations with the 90-day in-hospital mortality rate (Table 2). After adjustment, only AUC_{72} was significantly associated with the 90-day in-hospital mortality rate (Table 3). AUC_{72} was significantly positively correlated with ICU transfer, respiratory failure, cardiovascular dysfunction, hepatic dysfunction, and renal dysfunction. PaO_{2MAX} was significantly associated with ICU transfer and cardiovascular dysfunction. PaO_{2MAX} and AUC_{72} were negatively associated with coagulation dysfunction.

Only AUC_{72} was significantly associated with 90-day in-hospital mortality in this study; the one-time hyperoxaemia values (PaO_{2MAX}, PaO_{2AVG}, and PaO_{2MED}) were

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not.[21,22] Because AUC_{72} is indicative of cumulative exposure to hyperoxaemia, it may reflect the degree of hyperoxaemia more accurately than the other variables.

The patients in this study were in a less-severe condition than those in previous studies. Our target population was patients who arrived at the ED but were not admitted to the ICU in the next 5 days. By contrast, previous studies involved only patients admitted to the ICU.[3,21,22] The median NEWS was 4 (IQR: 2–7) we considered that a NEWS ≥ 5 reflected critical illness.[20, 23] We also used a non-invasive method of oxygen administration, unlike previous studies. Many patients in the ICU undergo mechanical ventilation. Mechanical ventilation may deliver a larger dose of oxygen in a more accurate manner. Patients who required higher oxygen levels, and those who were mechanically ventilated because of altered mentality or muscle weakness, were excluded from this study. We believe that this exclusion leads to a lower incidence of hyperoxaemia in this study than in previous studies.[10–12] The single time exposure in non-critically ill patients under less severe hyperoxaemic conditions may not be as harmful and may therefore fail to show statistical significance in terms of the mortality rate. Instead, ICU transfer was used as an indicator of an increase in clinical severity in this study. Therefore, AUC_{72} is more suitable than the one-time hyperoxaemia values for assessing mortality and complications in these patients.

The significant association between AUC_{72} and cardiovascular and hepatic dysfunction is consistent with Girardis *et al*. [12], which found that strict oxygen use reduces the rates of mortality, shock, and liver failure compared to conventional oxygen use. Because that previous study was conducted in the ICU, this is the first report of AUC_{72} as an indicator of complications in non-ICU patients.

The PaO_{2MAX} and AUC_{72} values were associated with greater coagulation dysfunction. A previous study showed that coagulation dysfunction, as determined by fibrin deposition, occurs in patients with hyperoxaemia-induced acute lung injury,[24]

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but has not been investigated extensively. Thus, further studies should evaluate the association between coagulation dysfunction and hyperoxaemia.

Hyperoxaemia toxicity is caused by the production of reactive oxygen species (ROS), pulmonary toxicity, haemodynamic alterations, and neurological damage. ROS lead to lipid peroxidation, protein oxidation, DNA damage and direct pulmonary damage mediated by damage to the alveolar capillary barrier. Another pulmonary complication includes pulmonary gas exchange impairment by adsorption atelectasis. Haemodynamic alterations include reductions in cardiac output, coronary blood flow, myocardial O2 consumption and heart rate, as well as increased vascular resistance. Neurological damage is caused by excessive oxygen levels, which disrupt the protective mechanisms of the neural system under hyperbaric oxygen conditions.[5, 7, 24–27]

However, it is unclear from which oxygen concentrations and after which exposure time toxicity may occur. The lung is first affected because of higher oxygen tension.[28] In a study on baboons, alveolar septal injury occurred following exposure to 60% O_2 for 14 days.[29] In rabbits, lung injury developed following exposure to moderate hyperoxaemia at a large tidal volume for 2 h.[30] In humans, symptoms can occur at 10 h after initial exposure to hyperoxaemia,[31] although histological changes are apparent earlier. Helmerhorst *et al*.[32] reported that exposure to a high FiO_2 for 15 min affected the systemic vascular resistance of patients who had undergone coronary artery bypass grafting (CABG) surgery. Thus, physiological changes onset within minutes or hours after exposure to hyperoxaemia. We found that clinical outcomes (mortality and ICU transfer) were affected during the first 72 h of exposure to hyperoxaemia. Therefore, physicians should be aware of the potential risks of early hyperoxaemia.

The present study had several limitations. First, we could not rule out selection bias, as the study population was limited to patients who visited our ED and underwent

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blood gas analysis. Second, because the NEWS was calculated using the initial values in the ED rather than ICU-based severity scores, the assessment of severity may have been inaccurate; if so, this would introduce bias into the regression model. Third, this study was conducted in a single centre; thus, a further multicentre randomised controlled study is warranted. Fourth, we excluded the patients with poor outcomes prior to day 5 after ED arrival because there is no compelling evidence about the onset time of clinical outcome following hyperoxaemia. A further prospective randomised study is needed with regard to these patients. Fifth, this was an observational cohort study; although statistical associations were evident, causation cannot be inferred. Some relevant factors may not have been measured.

Despite its limitations, this study was novel because we evaluated the association between hyperoxaemia and outcomes in non-critically ill patients presenting to the ED.

Conclusion

Hyperoxaemia during the first 3 days in ED patients was associated with higher in-hospital mortality and more common ICU transfer at day 5 after ED arrival.

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Figure 1. The study patients.

ED; emergency department, ICU; intensive care unit, AUC; area under the curve.

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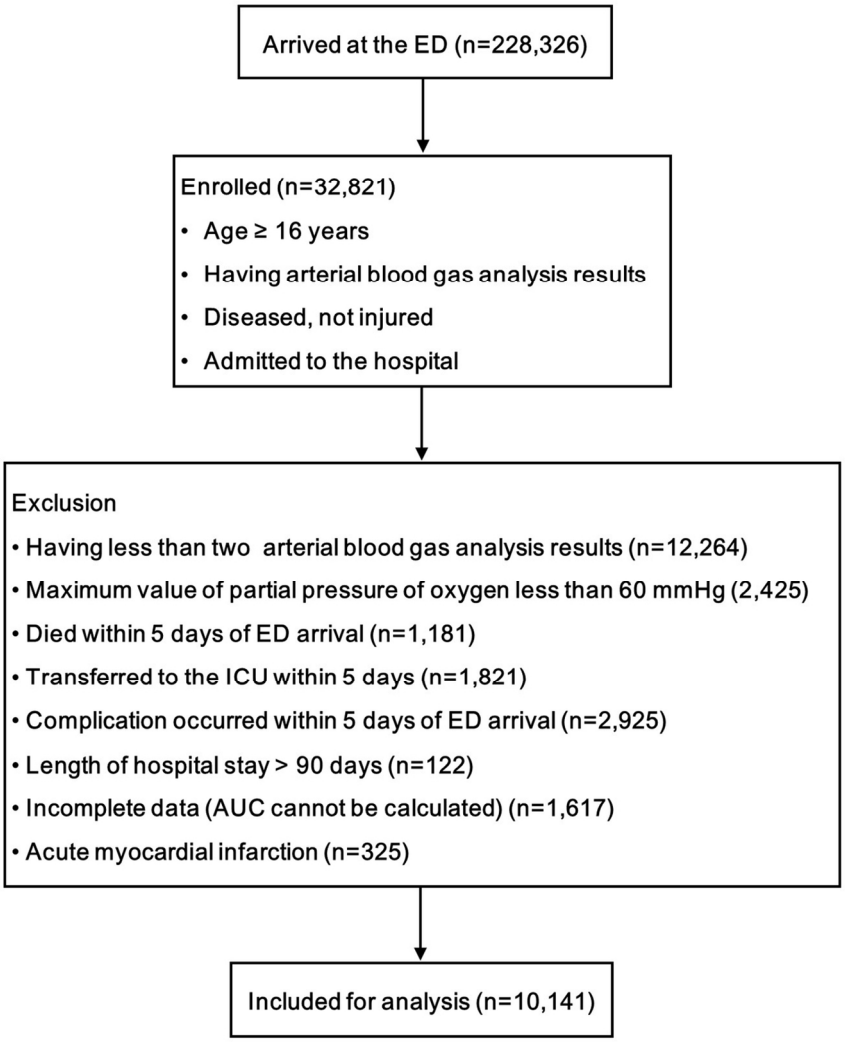

Figure 1. The study patients.
ED; emergency department, ICU; intensive care unit, AUC; area under the curve.

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STROBE Statement—checklist of items that should be included in reports of observational studies

	Item No	Recommendation
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract → p.4
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found → p. 4
Introduction		
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported → p.6
Objectives	3	State specific objectives, including any prespecified hypotheses → p.7
Methods		
Study design	4	Present key elements of study design early in the paper → p.7
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection → p.7
Participants	6	(*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up *Case-control study*—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls→ p.7-8 *Cross-sectional study*—Give the eligibility criteria, and the sources and methods of selection of participants
		(*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed *Case-control study*—For matched studies, give matching criteria and the number of controls per case
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable → p.9
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group → p.8-9
Bias	9	Describe any efforts to address potential sources of bias→ p.19-20
Study size	10	Explain how the study size was arrived at → p.10-11
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why → p.9-10
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding → p.9-10
		(*b*) Describe any methods used to examine subgroups and interactions
		(*c*) Explain how missing data were addressed
		(*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed *Case-control study*—If applicable, explain how matching of cases and controls was addressed *Cross-sectional study*—If applicable, describe analytical methods taking account of sampling strategy
		(*e*) Describe any sensitivity analyses

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Results		
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed → p.11
		(b) Give reasons for non-participation at each stage
		(c) Consider use of a flow diagram
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders → p.11
		(b) Indicate number of participants with missing data for each variable of interest → p.11
		(c) *Cohort study*—Summarise follow-up time (eg, average and total amount)
Outcome data	15*	*Cohort study*—Report numbers of outcome events or summary measures over time
		Case-control study—Report numbers in each exposure category, or summary measures of exposure → p.12-13
		Cross-sectional study—Report numbers of outcome events or summary measures
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included → p.12-13
		(*b*) Report category boundaries when continuous variables were categorized
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses → p.15-17
Discussion		
Key results	18	Summarise key results with reference to study objectives → p.17
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias → p.19-20
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence → p.18-20
Generalisability	21	Discuss the generalisability (external validity) of the study results → p.20
Other information		
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based → p.2

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

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