Admission oxygen saturation and all-cause in-hospital mortality in acute myocardial infarction patients: data from the MIMIC-III database

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Background: Acute myocardial infarction (AMI) is mainly caused by a mismatch of blood oxygen supply and demand in the myocardium. However, several studies have suggested that excessively high or low arterial oxygen tension could have deleterious effects on the prognosis of AMI patients. Therefore, the relationship between blood oxygenation and clinical outcomes among AMI patients is unclear, and could be nonlinear. In the critical care setting, blood oxygen level is commonly measured continuously using pulse oximetry-derived oxygen saturation (SpO_2). The present study aimed to determine the association between admission SpO_2 levels and all-cause in-hospital mortality, and to elucidate the optimal SpO_2 range with real-world data.

Methods: Patients diagnosed with AMI on admission in the Medical Information Mart for Intensive Care III (MIMIC-III) database were included. A generalized additive model (GAM) with loess smoothing functions was used to determine and visualize the nonlinear relationship between admission SpO_2 levels within the first 24 hours after ICU admission and mortality. Moreover, the Cox regression model was constructed to confirm the association between SpO_2 and mortality.

Results: We included 1,846 patients who fulfilled our inclusion criteria, among whom 587 (31.80%) died during hospitalization. The GAM showed that the relationship between admission SpO_2 levels and all-cause in-hospital mortality among AMI patients was nonlinear, as a U-shaped curve was observed. In addition, the lowest mortality was observed for an SpO_2 range of 94–96%. Adjusted multivariable Cox regression analysis confirmed that the admission SpO_2 level of 94–96% was independently associated with decreased mortality compared to SpO_2 levels <94% [hazard ratio (HR) 1.352; 95% confidence interval (CI): 1.048–1.715; P=0.028] and >96% (HR 1.315; 95% CI: 1.018–1.658; P=0.030).

Conclusions: The relationship between admission SpO_2 levels and all-cause in-hospital mortality followed a U-shaped curve among patients with AMI. The optimal oxygen saturation range was identified as an SpO_2 range of 94–96%, which was independently associated with increased survival in a large and heterogeneous cohort of AMI patients.

Keywords: Acute myocardial infarction (AMI); blood oxygen saturation; hospital mortality; hyperoxemia; oxygen therapy

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Introduction

Acute myocardial infarction (AMI) is a leading cause of mortality worldwide, which accounts for nearly 1.8 million deaths annually, and 20% of all deaths in Europe (1,2). AMI mainly results from a mismatch of blood oxygen supply and demand in the myocardium that leads to ischemia and eventual cellular death (3). Therefore, supplemental oxygen to increase oxygen delivery to the ischemic myocardium has been routinely used in the treatment of AMI patients for over 100 years (4). However, excessively high oxygen tension might cause coronary vasoconstriction and increase the production of reactive oxygen species (ROS), potentially contributing to reperfusion injury (5,6). Hence, blood oxygenation and mortality among AMI patients could be nonlinear and have a U-shaped relation. However, few empirical studies directly support this theory. Considering the high incidence and poor prognosis of AMI, it is necessary to determine the relationship between blood oxygenation and mortality, and explore its impact on survival, which could help more precisely predict the prognosis of AMI patients, and improve the implementation of appropriate oxygen therapy.

In critically ill patients with cardiorespiratory compromise, the blood oxygen level is commonly measured continuously using pulse oximetry-derived oxygen saturation (SpO_2), which could provide an early warning of hypoxemia (7,8). Interestingly, a study showed that among AMI patients with normal peripheral oxygen saturations, low-normal oxygen saturation ($90\% \leq SpO_2 \leq 94\%$) was identified as an independent marker of poor prognosis compared to high-normal oxygen saturation ($95\% \leq SpO_2 \leq 100\%$) (9). However, the authors of that study classified SpO_2 in arbitrarily defined categories rather than as a continuous variable, and did not explore the nonlinear relationship between SpO_2 and clinical outcomes. Moreover, there are few guideline recommendations on the optimal oxygenation target specifically for AMI patients, and the available evidence to support such recommendations is limited (1,10).

In this study, we aimed to determine the nonlinear relationship between admission SpO_2 levels and all-cause in-hospital mortality among patients with AMI, and to derive an optimal range of oxygen saturation for clinical practice and future research.

We present the following article in accordance with the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) reporting checklist (available at http://dx.doi.org/10.21037/atm-20-2614).

Methods

Data source & ethical statement

All the relevant data were collected from the Medical Information Mart for Intensive Care-III (MIMIC-III) database. MIMIC-III is a freely accessible critical care database covering more than 50,000 hospital admissions comprised of 38,645 adults as well as 7,875 neonates admitted to surgical, trauma surgery, coronary, and cardiac surgery recovery intensive care units (ICUs) of Beth Israel Deaconess Medical Center (BIDMC) in Boston from 2001 to 2012 (11,12). The MIMIC-III database documents included charted events such as demographic data, vital signs, laboratory findings and blood gas analysis data, prognostic scoring systems, and survival data. International Classification of Diseases, Ninth Revision (ICD-9) codes were recorded by hospital staff on patient discharge. Physiologic readings from bedside monitors were validated and documented hourly by ICU nurses. We passed the "Protecting Human Research Participants" exam and obtained permission to access the dataset (authorization code: 33281932). The establishment of the MIMIC-III database was approved by the Institutional Review Boards (IRB) of the Massachusetts Institute of Technology (MIT, Cambridge, MA, USA) and BIDMC. Our study utilized the anonymous data available from this database; hence, the requirement for informed consent was waived. In summary, the study complied with the ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments.

Population selection

We included all ICU patients (aged >18 years) diagnosed with AMI using International Classification of Diseases (ICD)-9 diagnosis codes between 410.00 and 410.92 in the MIMIC-III database. Eligible patients had to have

typical symptoms suggestive of MI (defined as chest pain or dyspnea) for <6 hours and either ischemic changes on electrocardiography or elevated cardiac troponin on admission (above the locally defined decision limit for MI) based on the third universal definition of AMI (13). Patients were excluded meeting the following criteria: (I) who had multiple admissions other than the first admission; (II) who had a secondary diagnosis of cancer, anemia, fluid and electrolyte disorder, or peripheral vascular disease (PVD) on admission; (III) who were admitted to the ICU during pregnancy, childbirth, or puerperium; (IV) who were at risk of oxygen-induced hypercapnia [chronic obstructive pulmonary disease (COPD), asthma, or pneumonia] on admission; (V) who stayed in the ICU less than 24 hours; (VI) who had incomplete or unobtainable documented SpO_2 or other important medical data records.

Data extraction and data processing

The data were extracted from the database using structure query language (SQL) with PostgreSQL (version 9.4.6, www.postgresql.org). The code that supports the MIMIC-III documentation and website is publicly available, and contributions from the community of users are encouraged (https://github.com/MIT-LCP/mimic-website). The variables in this study included demographics, admission type, vital signs, comorbidities, laboratory parameters, scoring systems, and clinical outcomes. Demographic information included age, gender, ethnicity, insurance status, marital status, and body mass index (BMI). BMI was calculated as weight (kg) divided by height^2 (m^2), using the height and weight reported at the time of admission. Vital signs included body temperature (T), systolic blood pressure (SBP), diastolic blood pressure (DBP), mean blood pressure (MBP), heart rate (HR), respiratory rate (RR), and SpO_2. Vital signs were measured multiple times within the first 24 hours after ICU admission, and the average values were used in our analysis as a measure of the central tendency of patients' conditions. Comorbidities included congestive heart failure (CHF), hypertension, cardiac arrhythmia, cardiogenic shock, cardiac arrest, pulmonary circulation disorder, diabetes mellitus (DM), renal failure, liver disease, coagulopathy, stroke, obesity, and weight loss. Moreover, the Elixhauser comorbidity index (ECI) was calculated to comprehensively evaluate the impact of comorbidities (14). Laboratory parameters included white blood cell (WBC) count, hematocrit (HCT), hemoglobin (Hb), blood platelet (PLT) count, glucose, cardiac troponin t, blood urea nitrogen (BUN), creatinine, and PH. If patients received a laboratory test more than one time during their hospitalization, only the initial test results were included. Four scoring systems [the Glasgow Coma Scale (GCS), the Sequential Organ Failure Assessment (SOFA), the Systemic Inflammatory Response Syndrome (SIRS), and the Simplified Acute Physiology Score II (SAPS II)] were calculated within an hourly sliding 24-hour window, and the maximum was selected using the SQL code. For treatment information, oxygen therapy could refer to any oxygen supplementation methods such as face mask, non-invasive ventilation, or mechanical ventilation.

As extensive missing data might lead to bias, variables with over 30% missing values were not included in the subsequent analyses. Correspondingly, multivariate imputation (MI) was used for variables with less than 30% missing values (15,16).

The endpoint of our study was all-cause in-hospital mortality, which was defined as survival status at hospital discharge. Patients with missing survival outcome data were excluded from the final cohort.

Statistical analysis

Baseline characteristics of enrolled participants were presented and compared between survivors and non-survivors by using either Student *t*-test, Kruskal Wallis rank test, Pearson's χ^2 test, or Fisher's exact test as appropriate. Continuous variables were characterized as mean [standardized differences (SD) or median (interquartile range (IQR)], while categorical or ranked data were presented as count and proportion.

A generalized additive model (GAM) with loess smoothing functions was used to identify the nonlinear relationship between admission SpO_2 readings and in-hospital mortality. According to the results, an optimal oxygen saturation range was derived, and the study cohort was then divided into several subgroups with different SpO_2 levels for subsequent analyses.

We also used Cox proportional hazards models to confirm the associations between SpO_2 levels and mortality, with results expressed as hazard ratios (HRs) with 95% confidence intervals (CIs). A three-step Cox regression model was constructed based on different SpO_2 groups. Model I included only the SpO_2 data. In Model II, covariates were adjusted for age and gender. Model III further adjusted for covariates that were statistically significant (P<0.100) in the univariable Cox regression

model. We tested for detrimental effects of collinearity on the model using variance inflation factors (VIFs) (17). The Kaplan-Meier (KM) method was used to plot unadjusted survival curves, and the log-rank test was used to compare differences between groups. A series of sensitivity analyses were performed to further validate the robustness of our findings.

A two-tailed P value of less than 0.050 was considered to be statistically significant. All statistical analyses were performed using SPSS software (version 22.0; IBM Corporation, St. Louis, Missouri, USA) and R software (version.3.6.1; The R Project for Statistical Computing, TX, USA; http://www.r-project.org).

Results

Subject and variable characteristics

After application of the inclusion and exclusion criteria, the final study cohort consisted of 1,846 AMI patients, of whom 587 (31.80%) patients died during hospitalization. The detailed information on the enrollment and selection process was summarized in Table S1. In total, 42 variables were extracted from the MIMIC-III database, and 11 of them had missing values (Table S2).

The comparison of baseline characteristic between survivors and non-survivors was summarized in *Table 1*. Notably, patients of the non-survivor group were much older than those of the survivor group [75.00 (64.50–83.00) *vs.* 65.00 (56.00–77.00); P<0.001], while more patients in the survivor group had higher BMI compared to those in the non-survivor group [27.67 (24.37–30.99) *vs.* 26.44 (23.05–30.15); P<0.001]. As for the comorbidities, patients who died during hospitalization had higher incidence of CHF (56.90% *vs.* 37.41%; P<0.001), cardiac arrhythmias (56.22% *vs.* 45.04%; P<0.001), stroke (13.63% *vs.* 5.48%; P<0.001), cardiogenic shock (32.54% *vs.* 7.15%), cardiac arrest (15.50% *vs.* 3.73%), renal failure (20.44% *vs.* 9.93%; P<0.001), liver disease (7.33% *vs.* 2.86%; P<0.001), and coagulopathy (11.41% *vs.* 6.67%; P<0.001). With regard to the vital signs, HR [84.71 (73.81–95.79) *vs.* 80.63 (71.05–89.94); P<0.001] and RR [18.89 (16.83–21.70) *vs.* 17.96 (16.09–20.05); P<0.001] were significantly higher in the non-survivor group, while the SBP [108.67 (98.94–119.78) *vs.* 112.30 (103.45–121.78); P<0.001], DBP [56.79 (50.14–63.94) *vs.* 60.40 (54.68–67.65); P<0.001], MBP [74.09 (68.00–81.36) *vs.* 77.52 (71.88–83.88); P<0.001], PLT [231.00 (179.00–288.50) *vs.* 238.00 (185.00–305.08); P=0.049] as well as PH [7.35 (7.30–7.39) *vs.* 7.37 (7.32–7.43); P=0.039] were lower than those from the survivor group. No difference was observed in admission SpO_2 level between the two cohorts [95.57 (94.30–96.63) *vs.* 95.82 (94.98–96.79); P=0.621].

Relationship between oxygen saturation and all-cause in-hospital mortality

The relationship between admission SpO_2 level and all-cause in-hospital mortality was nonlinear, and a U-shaped curve was observed, as shown in *Figure 1*. While low SpO_2 correlated more strongly with mortality, high SpO_2 was also associated with increased mortality. Informed by the flattest part of the U-shape in *Figure 1*, we chose an SpO_2 range of 94–96% as the optimal oxygen saturation range, and then divided the study cohort into three groups with different SpO_2 levels: Group 1 (94% ≤SpO_2 ≤96%), Group 2 (SpO_2 <94%), and Group 3 (96%< SpO_2 ≤100%).

Survival analysis

The unadjusted survival curve for patients with different SpO_2 groups is shown in a Kaplan-Meier plot in *Figure 2* (log-rank test: P<0.001). We used Cox regression models to determine the association between the different SpO_2 groups and hospital mortality among patients with AMI. Group 1 (94%≤ SpO_2 ≤96%) was always considered as the reference group. Model I showed that Group 1 (94%≤ SpO_2 ≤96%) was associated with decreased risk of all-cause mortality compared to Group 2 (HR =1.783; 95% CI: 1.433–2.217; P<0.001) and Group 3 (HR =1.495; 95% CI: 1.245–1.796; P<0.001) (*Table 2*). After adjustment for age and gender, Model II showed similar results (Group 2: HR =1.859; 95% CI: 1.494–2.313; P<0.001; Group 3: HR =1.485; 95% CI: 1.237–1.784; P<0.001) (*Table 2*). The univariable Cox regression analysis suggested that age, gender, marital status, admission type, DBP, MBP, RR, T, cardiogenic shock, cardiac arrest, renal failure, coagulopathy, weight loss, SOFA, SAPS II, percutaneous coronary intervention (PCI), ICU length of stay (LOS), and SpO_2 level were potential prognostic factors for mortality in Table S3 (all P<0.100), which were then entered into the multivariable Cox regression model (Model III). Additionally, VIFs did not show any possibility of collinearity between SpO_2 and the other variables in Model III (maximum VIF of 4.2, which is below the threshold of concern, VIF <5). Model III demonstrated that age

Table 1 Baseline characteristics between survivors and non-survivors

Characteristics	Total (n=1,846)	Survivors (n=1,259)	Non-survivors (n=587)	P value
Demographics				
Age, years	68.00 (58.00–79.00)	65.00 (56.00–77.00)	75.00 (64.50–83.00)	<0.001
Gender, male	1,193 (64.63%)	865 (68.71%)	328 (55.88%)	<0.001
Ethnicity, white	1,176 (63.71%)	800 (63.54%)	376 (64.05%)	0.831
Marital status				<0.001
Married	1,012 (54.82%)	736 (58.46%)	276 (47.02%)	
Single	303 (16.41%)	202 (16.04%)	101 (17.21%)	
Others	531 (28.76%)	321 (25.50%)	210 (35.78%)	
BMI, kg/m^2	27.34 (23.84–30.75)	27.67 (24.37–30.99)	26.44 (23.05–30.15)	<0.001
Admission type				0.023
Emergency	1,652 (89.49%)	1,110 (88.17%)	542 (92.33%)	
Elective	76 (4.12%)	57 (4.53%)	19 (3.24%)	
Urgent	118 (6.39%)	92 (7.31%)	26 (4.43%)	
Vital signs				
HR, beats/min	82.13 (72.07–91.51)	80.63 (71.05–89.94)	84.71 (73.81–95.79)	<0.001
SBP, mmHg	111.00 (102.33–121.09)	112.30 (103.45–121.78)	108.67 (98.94–119.78)	<0.001
DBP, mmHg	59.41 (53.38–66.53)	60.40 (54.68–67.65)	56.79 (50.14–63.94)	<0.001
MBP, mmHg	76.53 (70.78–83.17)	77.52 (71.88–83.88)	74.09 (68.00–81.36)	<0.001
RR, beats/min	18.18 (16.26–20.62)	17.96 (16.09–20.05)	18.89 (16.83–21.70)	<0.001
T, ℃	36.81 (36.48–37.17)	36.83 (36.54–37.15)	36.75 (36.39–37.20)	0.050
SpO_2, %	95.64 (94.25–96.70)	95.57 (94.30–96.63)	95.82 (94.98–96.79)	0.621
Comorbidities				
Congestive heart failure	805 (43.61%)	471 (37.41%)	334 (56.90%)	<0.001
Hypertension	1,064 (57.64%)	754 (59.89%)	310 (52.81%)	0.004
Cardiac arrhythmias	897 (48.59%)	567 (45.04%)	330 (56.22%)	<0.001
Cardiogenic shock	281 (15.22%)	90 (7.15%)	191 (32.54%)	<0.001
Cardiac arrest	138 (7.48%)	47 (3.73%)	91 (15.50%)	<0.001
Pulmonary circulation disorder	120 (6.50%)	78 (6.20%)	42 (7.16%)	0.436
Diabetes	412 (22.32%)	284 (22.56%)	128 (21.81%)	0.718
Stroke	149 (8.07%)	69 (5.48%)	80 (13.63%)	<0.001
Renal failure	245 (13.27%)	125 (9.93%)	120 (20.44%)	<0.001
Liver disease	79 (4.28%)	36 (2.86%)	43 (7.33%)	<0.001
Coagulopathy	151 (8.18%)	84 (6.67%)	67 (11.41%)	<0.001
Obesity	66 (3.58%)	54 (4.29%)	12 (2.04%)	0.016
Weight loss	33 (1.79%)	18 (1.43%)	15 (2.56%)	0.089
Elixhauser comorbidity index	3.00 (0.00–11.00)	0.00 (0.00–8.00)	9.00 (0.00–17.00)	<0.001

Table 1 (*continued*)

Table 1 (*continued*)

Characteristics	Total (n=1,846)	Survivors (n=1,259)	Non-survivors (n=587)	P value
Laboratory parameters				
WBC, 10^9/L	11.60 (8.70–15.02)	11.77 (8.70–15.10)	11.20 (8.80–14.98)	0.219
Hb, g/dL	12.50 (11.00-14.10)	12.43 (10.93–14.10)	12.60 (11.00–14.10)	0.778
HCT, %	36.01 (6.28)	36.00 (6.31)	36.05 (6.23)	0.857
PLT, 10^9/L	236.00 (183.00–301.00)	238.00 (185.00–305.08)	231.00 (179.00–288.50)	0.049
Troponin t, ng/mL	1.26 (0.06–4.73)	1.31 (0.07–4.66)	1.10 (0.03–4.84)	0.420
BUN, mg/dL	22.00 (15.00–34.21)	22.00 (15.00–34.65)	22.00 (15.00–34.00)	0.376
Glucose, mg/dL	141.00 (110.00–198.32)	142.00 (109.56–199.50)	137.23 (111.00–197.50)	0.631
Creatinine, mEq/L	1.00 (0.80–1.50)	1.10 (0.80–1.50)	1.00 (0.80–1.50)	0.365
PH	7.36 (7.32–7.42)	7.37 (7.32–7.43)	7.35 (7.30–7.39)	0.039
Scoring system				
SOFA	3.00 (1.00–6.00)	2.00 (1.00–5.00)	5.00 (2.00–8.00)	<0.001
SAPS II	33.00 (25.00–44.00)	30.00 (23.00–39.00)	42.00 (32.50–53.00)	<0.001
SIRS	3.00 (2.00–4.00)	3.00 (2.00–3.00)	3.00 (2.00–4.00)	<0.001
GCS	15.00 (15.00–15.00)	15.00 (15.00–15.00)	15.00 (14.00–15.00)	<0.001
Treatment information				
PCI	1,199 (64.95%)	917 (72.84%)	282 (48.04%)	<0.001
CABG	59 (3.20%)	40 (3.18%)	19 (3.24%)	0.076
Oxygen therapy	949 (51.41%)	663 (52.66%)	286 (48.72%)	0.115
Renal replacement treatment	118 (6.39%)	40 (3.18%)	78 (13.29%)	<0.001
ICU LOS, days	2.64 (1.63–4.96)	2.33 (1.52–4.08)	3.30 (1.96–7.31)	<0.001

Values are n (%), mean ± SD, or median (interquartile range). BMI, body mass index; HR, heart rate; SBP, systolic blood pressure; MBP, mean blood pressure; DBP, diastolic blood pressure; RR, respiratory rate; T, temperature; WBC, white blood cell; Hb, hemoglobin; HCT, hematocrit; PLT, platelet; BUN, blood urea nitrogen; SOFA, Sequential Organ Failure Assessment; SAPS, Systemic Inflammatory Response Syndrome; SIRS, Systemic Inflammatory Response Syndrome; GCS, Glasgow Coma Scale; PCI, percutaneous coronary intervention; CABG, coronary artery bypass grafting; LOS, length of stay.

(HR =1.012; 95% CI: 1.002–1.018; P=0.001), DBP (HR =0.954; 95% CI: 0.933–0.981; P=0.003), admission type (HR =0.511; 95% CI: 0.288–0.889; P=0.041; HR =0.581; 95% CI: 0.372–0.902; P=0.017), RR (HR =1.052; 95% CI: 1.030–1.082; P<0.001), cardiogenic shock (HR =1.711; 95% CI: 1.425–2.117; P<0.001), cardiac arrest (HR =2.048; 95% CI: 1.674–2.432; P<0.001), SOFA (HR =1.044; 95% CI: 1.001–1.087; P=0.040), SAPS II (HR =1.011; 95% CI: 1.000–1.021; P=0.018), PCI (HR =0.722; 95% CI: 0.502–0.789; P<0.001), and SpO_2 level (Group 2: HR =1.352; 95% CI: 1.048–1.715; P=0.028; Group 3: HR =1.315; 95% CI: 1.018–1.658; P=0.030) were all independent prognostic factors for predicting hospital mortality in patients with AMI (*Tables 2*, Table S3).

Sensitivity analyses

A series of sensitivity analyses were performed to validate the robustness of our findings. First, we excluded 11 patients with hypoxemia (SpO_2 <90%) and found Group 1 (94% ≤ SpO_2 ≤96%) was an independent prognostic predictor even among patients without hypoxemia (Table S4). Second, we used the original data for analysis without using the MI method, and 1,049 patients remained in the final cohort. After adjustment for covariates in Model III, Group 1 (94%≤ SpO_2 ≤96%) was not independently associated with hospital

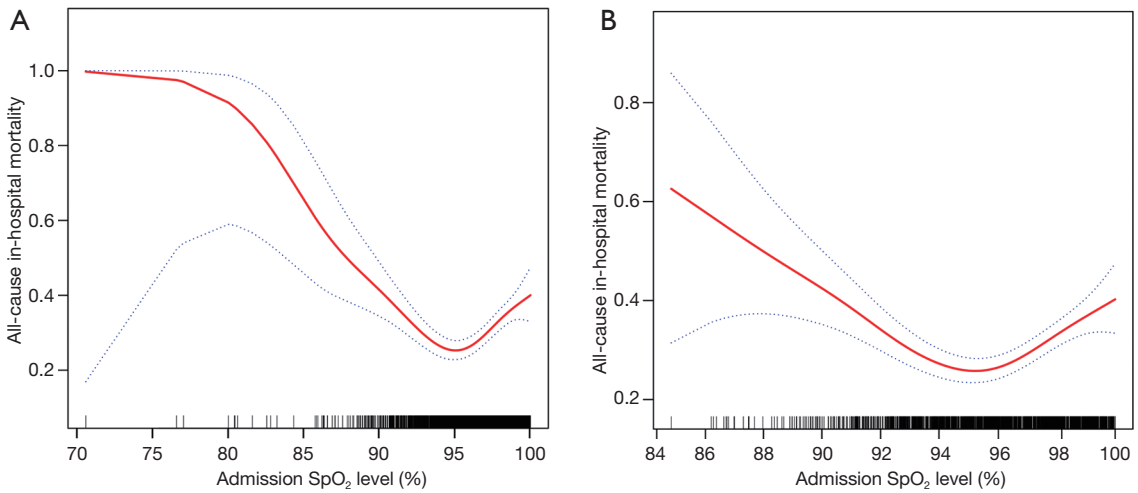

Figure 1 Relationship between admission SpO_2 levels and mortality. (A) Showed the relationship between admission SpO_2 levels and all-cause in-hospital mortality in AMI patients by using a generalized additive model and (B) showed the U-shaped part of *Figure 1A*. Solid red line represents the smooth curve fit between variables. Dotted blue lines represent the 95% of confidence interval from the fit. AMI, acute myocardial infarction; SpO_2, pulse oximetry-derived oxygen saturation.

mortality when compared to Group 3 (96%< SpO_2 ≤100%), which might have resulted from the reduction in the number of participants (Table S5). In addition, as shown in *Table 3*, the association between SpO_2 and hospital mortality was similar for most strata except for some subgroups with small sample sizes. Among these strata, we observed that the SpO_2 range of 94–96% had significantly lower mortality in patients with age <65 years, age ≥65 years, male, female, married status, BMI <27 kg/m^2, BMI ≥27 kg/m^2, admission type (Emergency), HR <82 beats/min, HR ≥82 beats/min, SBP <110 mmHg, SBP ≥110 mmHg, DBP <60 mmHg, MBP <75 mmHg, MBP ≥75 mmHg, RR ≥18 beats/min, CHF, hypertension, cardiac arrhythmias, diabetes, SOFA ≥3, SAPS II ≥33, and oxygen therapy.

Discussion

In the current study, our analyses demonstrated a U-shaped relationship between early admission SpO_2 readings and all-cause in-hospital mortality among patients with AMI. In addition, the multivariable Cox regression analysis identified SpO_2 as an independent prognostic predictor of clinical outcomes during hospitalization. Moreover, our study also showed the lowest mortality for an SpO_2 range of 94–96%, which could become the optimal oxygen saturation targets and benefit oxygen therapy among AMI patients. To our knowledge, this study was the first to explore the nonlinear relationship of admission SpO_2 level and all-cause in-hospital mortality among AMI patients.

Pulse oximetry is a ubiquitously used monitoring technique for patients in ICUs (7). Using a spectrophotometric methodology, pulse oximetry measures oxygen saturation by illuminating the skin and measuring changes in light absorption of oxygenated and deoxygenated blood using two light wavelengths: 660 and 940 nm (7,18,19). The ratio of absorbance at these two wavelengths is calibrated against direct measurements of arterial oxygen saturation (SaO_2) to calculate the pulse oximeter's measure of arterial saturation. SpO_2 provides pragmatic advantages over the arterial partial pressure of oxygen (PaO_2) and SaO_2, including the ability to inexpensively, noninvasively and repeatedly measure blood oxygenation (20). Additionally, SpO_2 is also clinically more relevant as adjustments of inspired oxygen, and ventilator settings are based on SpO_2 changes rather than on intermittent arterial blood gas assays. Therefore, it is common practice to use SpO_2 as a surrogate for SaO_2. The agreement between SpO_2 and SaO_2 is sufficient to use them interchangeably (mean difference 1 ±2%), and the specificity of the latest generation devices to detect hypoxemia is >95% (21). Furthermore, using SpO_2 to titrate supplemental oxygen is superior to fixed inspired oxygen fractions, which risk over-oxygenation in patients with narrow alveolar arterial oxygen gradients, and under-oxygenation in those with broad gradients. However, due

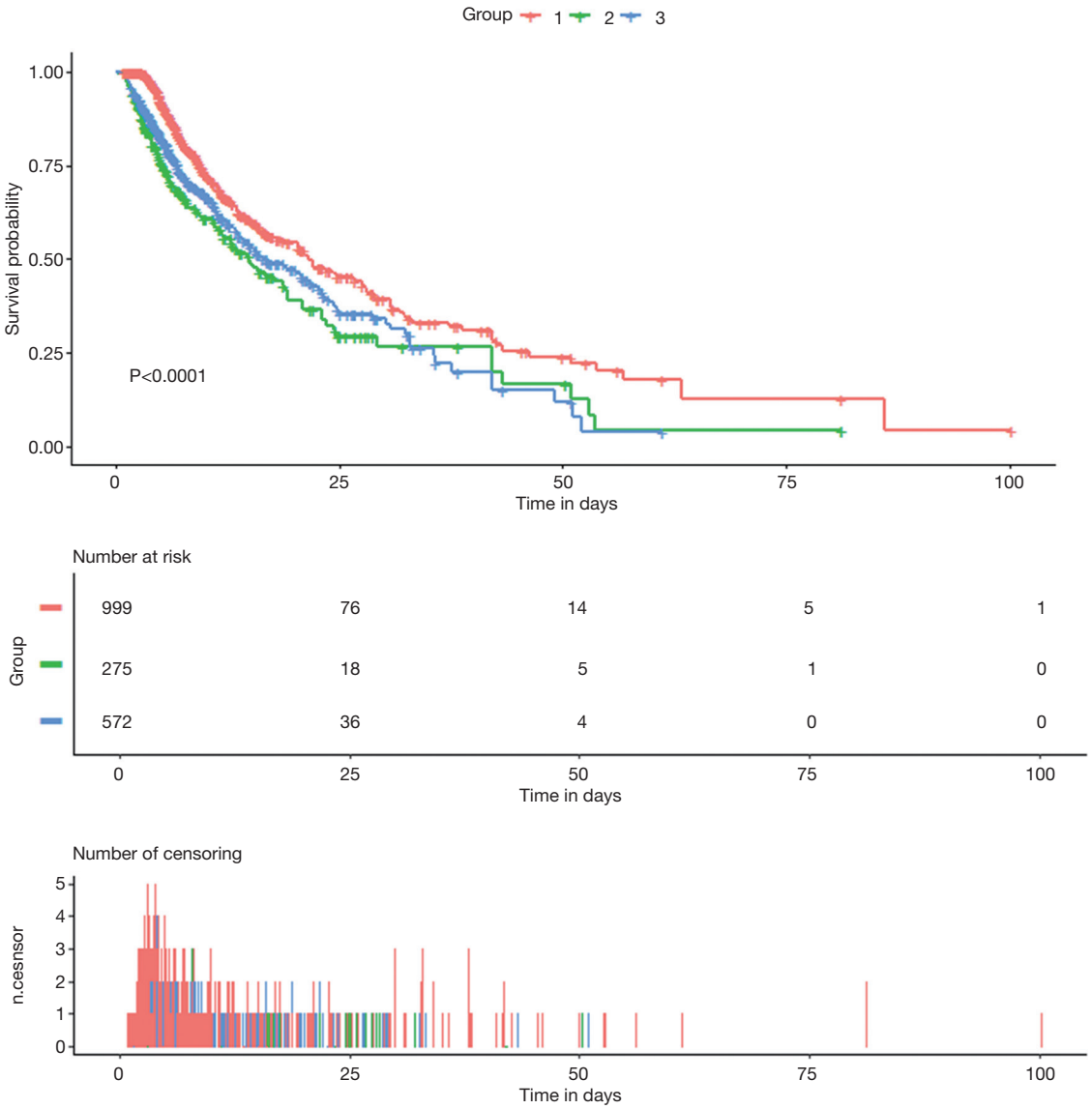

Figure 2 Kaplan-Meier plot for AMI patients with different SpO_2 levels. Group 1 represents 94%≤ SpO_2 ≤96%. Group 2 represents SpO_2 <94%. Group 3 represents 96%< SpO_2 ≤100%. AMI, acute myocardial infarction; SpO_2, pulse oximetry-derived oxygen saturation.

Table 2 Relationship between SpO_2 levels and all-cause in-hospital mortality in different Cox regression models

Variables	Model I		Model II		Model III	
	HR (95% CI)	P value	HR (95% CI)	P value	HR (95% CI)	P value
SpO_2 groups						
Group 1 (94%≤ SpO_2 ≤96%)	Ref		Ref		Ref	
Group 2 (SpO_2 <94%)	1.783 (1.433, 2.217)	<0.001	1.859 (1.494, 2.313)	<0.001	1.352 (1.048, 1.715)	0.028
Group 3 (96%< SpO_2 ≤100%)	1.495 (1.245, 1.796)	<0.001	1.485 (1.237, 1.784)	<0.001	1.315 (1.018, 1.658)	0.030

HR, hazard ratio; CI, confidence interval; ref, reference.

Table 3 Subgroup analysis of the relationship between SpO_2 levels and all-cause in-hospital mortality

Characteristics	N	Group 1 (Ref)	Group 2		Group 3	
			HR (95% CI)	P value	HR (95% CI)	P value
Age, years						
<65	745	Ref	1.972 (1.265, 3.075)	0.003	2.020 (1.395, 2.926)	<0.001
≥65	1,101	Ref	1.779 (1.383, 2.287)	<0.001	1.358 (1.099, 1.678)	0.005
Gender						
Male	1,193	Ref	1.434 (1.065, 1.931)	0.018	1.358 (1.065, 1.733)	0.014
Female	653	Ref	2.445 (1.764, 3.387)	<0.001	1.696 (1.280, 2.246)	<0.001
Marital status						
Married	1,012	Ref	2.141 (1.575, 2.911)	<0.001	1.649 (1.253, 2.169)	<0.001
Single	303	Ref	1.407 (0.800, 2.477)	0.236	1.369 (0.889, 2.107)	0.154
Others	531	Ref	1.540 (1.057, 2.244)	0.025	1.355 (1.001, 1.834)	0.049
BMI, kg/m^2						
<27	948	Ref	1.808 (1.352, 2.418)	<0.001	1.457 (1.144, 1.855)	0.002
≥27	898	Ref	1.699 (1.220, 2.365)	0.002	1.508 (1.136, 2.001)	0.004
Admission type						
Emergency	1,652	Ref	1.796 (1.430, 2.256)	<0.001	1.529 (1.265, 1.849)	<0.001
Elective	76	Ref	1.022 (0.312, 3.349)	0.971	0.758 (0.232, 2.476)	0.647
Urgent	118	Ref	3.064 (1.107, 8.479)	0.031	1.282 (0.505, 3.255)	0.602
HR, beats/min						
<82	905	Ref	1.708 (1.202, 2.427)	0.003	1.485 (1.129, 1.954)	0.005
≥82	941	Ref	1.872 (1.412, 2.481)	<0.001	1.500 (1.172, 1.919)	0.001
SBP, mmHg						
<110	838	Ref	2.042 (1.517, 2.748)	<0.001	1.533 (1.181, 1.988)	0.001
≥110	1,008	Ref	1.506 (1.081, 2.098)	0.015	1.459 (1.126, 1.890)	0.004
DBP, mmHg						
<60	929	Ref	2.159 (1.630, 2.860)	<0.001	1.550 (1.225, 1.961)	<0.001
≥60	917	Ref	1.365 (0.956, 1.949)	0.087	1.363 (1.015, 1.831)	0.040
MBP, mmHg						
<75	755	Ref	1.851 (1.378, 2.488)	<0.001	1.512 (1.167, 1.957)	0.002
≥75	1,091	Ref	1.601 (1.149, 2.230)	0.005	1.436 (1.106, 1.864)	0.007
RR, beats/min						
<18	744	Ref	2.042 (1.308, 3.187)	0.002	1.251 (0.920, 1.700)	0.153
≥18	1,102	Ref	1.668 (1.297, 2.146)	<0.001	1.845 (1.465, 2.324)	<0.001
Congestive heart failure						
No	1,041	Ref	2.549 (1.827, 3.556)	<0.001	1.679 (1.267, 2.225)	<0.001
Yes	805	Ref	1.392 (1.040, 1.863)	0.026	1.388 (1.088, 1.771)	0.008

Table 3 (*continued*)

Table 3 (*continued*)

Characteristics	N	Group 1 (Ref)	Group 2		Group 3	
			HR (95% CI)	P value	HR (95% CI)	P value
Hypertension						
No	782	Ref	1.580 (1.144, 2.183)	0.006	1.350 (1.036, 1.759)	0.026
Yes	1,064	Ref	1.954 (1.451, 2.631)	<0.001	1.626 (1.262, 2.096)	<0.001
Cardiac arrhythmias						
No	949	Ref	1.633 (1.155, 2.309)	0.006	1.633 (1.242, 2.146)	<0.001
Yes	897	Ref	1.878 (1.417, 2.490)	<0.001	1.397 (1.092, 1.789)	0.008
Pulmonary circulation disorder						
No	1,726	Ref	1.809 (1.439, 2.273)	<0.001	1.472 (1.218, 1.778)	<0.001
Yes	120	Ref	1.434 (0.678, 3.035)	0.346	1.630 (0.777, 3.423)	0.197
Diabetes						
No	1,434	Ref	1.696 (1.327, 2.168)	<0.001	1.491 (1.211, 1.835)	<0.001
Yes	412	Ref	2.254 (1.397, 3.635)	0.001	1.531 (1.039, 2.255)	0.031
Stroke						
No	1,697	Ref	1.779 (1.409, 2.245)	<0.001	1.446 (1.186, 1.761)	<0.001
Yes	149	Ref	1.665 (0.882, 3.141)	0.116	1.739 (1.042, 2.904)	0.034
Renal failure						
No	1,601	Ref	1.998 (1.574, 2.536)	<0.001	1.428 (1.161, 1.757)	<0.001
Yes	245	Ref	0.996 (0.569, 1.743)	0.989	1.891 (1.275, 2.804)	0.002
Liver disease						
No	1,767	Ref	1.759 (1.401, 2.210)	<0.001	1.459 (1.207, 1.764)	<0.001
Yes	79	Ref	1.758 (0.803, 3.851)	0.158	1.988 (0.979, 4.036)	0.057
Coagulopathy						
No	1,695	Ref	1.834 (1.450, 2.320)	<0.001	1.508 (1.242, 1.831)	<0.001
Yes	151	Ref	1.844 (0.998, 3.407)	0.051	1.546 (0.879, 2.721)	0.131
Obesity						
No	1,780	Ref	1.838 (1.473, 2.293)	<0.001	1.480 (1.230, 1.780)	<0.001
Yes	66	Ref	1.089 (0.216, 5.503)	0.918	2.256 (0.506, 10.057)	0.286
Weight loss						
No	1,813	Ref	1.744 (1.397, 2.177)	<0.001	1.442 (1.198, 1.736)	<0.001
Yes	33	Ref	3.520 (0.849, 14.592)	0.083	4.677 (1.268, 17.259)	0.021
SOFA						
<3	792	Ref	1.956 (1.289, 2.968)	0.002	1.361 (0.934, 1.983)	0.108
≥3	1,054	Ref	1.679 (1.299, 2.170)	<0.001	1.516 (1.228, 1.872)	<0.001

Table 3 (*continued*)

Table 3 (*continued*)

Characteristics	N	Group 1 (Ref)	Group 2		Group 3	
			HR (95% CI)	P value	HR (95% CI)	P value
SAPS II						
<33	885	Ref	1.401 (0.922, 2.128)	0.114	1.213 (0.827, 1.781)	0.323
≥33	961	Ref	1.992 (1.541, 2.575)	<0.001	1.555 (1.259, 1.922)	<0.001
Oxygen therapy						
No	897	Ref	2.442 (1.781, 3.350)	<0.001	1.905 (1.471, 2.468)	<0.001
Yes	949	Ref	1.343 (0.104, 1.823)	0.048	1.194 (0.108, 1.570)	0.050
Renal replacement treatment						
No	1,728	Ref	2.051 (1.626, 2.587)	<0.001	1.456 (1.195, 1.773)	<0.001
Yes	118	Ref	0.739 (0.383, 1.427)	0.368	1.864 (1.137, 3.057)	0.014

Covariates were adjusted as in Model I. N, number; BMI, body mass index; SBP, systolic blood pressure; MBP, mean blood pressure; DBP, diastolic blood pressure; RR, respiratory rate; SOFA, Sequential Organ Failure Assessment; SAPS, Systemic Inflammatory Response Syndrome; HR, hazard ratio; CI, confidence interval; ref, reference.

to the sigmoidal shape of the oxyhemoglobin dissociation curve, SpO_2 may not detect hyperoxemia in patients with high PaO_2 levels (7). However, for the SpO_2 range of 94–96%, the correlation between SpO_2 and PaO_2 would be fair, with little risk of underestimation of either hypoxemia or hyperoxemia (22,23).

All patients with AMI should undergo an early assessment of short-term risk. Several risk scores such as the Global Registry of Acute Coronary Events (GRACE) risk score have been developed, based on readily identifiable parameters in the acute phase (24,25). Blood oxygen saturation has been used as a useful prognostic predictor in many diseases (26-29). However, few studies have investigated the prognostic value of SpO_2 levels among AMI patients. In the present study, the assessment of early SpO_2 readings within the first 24 hours after patients' admission could serve as a preliminary prognostic marker for short-term mortality even among normoxic patients, which could help distinguish low-risk and high-risk AMI cohort and tailor individualized treatment. Similar to our results, James *et al.* (9) found that the SpO_2 range of 90–94% was associated with poor clinical outcomes compared to the SpO_2 range of 95–100% among patients with confirmed MI. However, considering the U-shaped relationship between SpO_2 and mortality, perhaps three, rather than two, SpO_2 groups are required to explore the effect of SpO_2 on patients' prognoses. In addition, our study showed that two scoring systems (SOFA and SAPS II) provided potentially valuable prognostic information on clinical outcomes when applied to patients with AMI. Huang *et al.* found that the SOFA score and the GRACE score provided better discrimination for long-term mortality than did the thrombolysis in myocardial infarction (TIMI) score (30). Different from their results, we mainly focused on the prognostic value of the SOFA to predict short-term mortality. No previous study has reported the prognostic ability of the SAPS II score in AMI patients, and further investigation is required to confirm our findings.

Although oxygen therapy is a standard medical practice during AMI, there is no clear oxygen therapy guideline for AMI patients, which might be attributed to the lack of evidence on the optimal oxygenation target. Our study showed the lowest mortality at a SpO_2 range within 94–96%. In healthy adults aged older than 70 years, and who are non-smokers, the mean (SD) SpO_2 is approximately 95% (1.5%), and healthy adults without obstructive sleep apnea have a mean minimum SpO_2 of 90% during sleep (31,32). Therefore, a target SpO_2 lower limit of 94% is below the expected SpO_2 of almost all healthy older adults who are awake, and above the mean minimum SpO_2 when asleep. Furthermore, a previous study showed that the prevalence of hyperoxemia appeared to be negligible as long as the upper limit of SpO_2 did not exceed 96% among critically ill patients (23). In addition, our results were

similar to the British Thoracic Society (BTS) guideline recommended oxygen saturation target of 94–98% and the Australia and New Zealand Thoracic Society guideline recommended target of 92–96% except for in patients associated with chronic respiratory failure (33,34). Another RCT in ICU patients suggested that a conservative protocol (maintaining SpO_2 between 94% and 98%) for oxygen therapy compared with conventional therapy (maintaining SpO_2 between 97% and 100%) resulted in lower ICU and in-hospital mortality, which was consistent with our study (35). As pulse oximetry is widespread and affordable, implementation of the 94–96% target would be feasible, even in resource-limited environments.

Previously, at least six randomized controlled trials (RCTs) investigated the effect of administration of supplemental oxygen during AMI and concluded that oxygen therapy did not benefit patients with baseline normal peripheral oxygen saturations levels ≥90% (36-41). In addition, among critically ill patients, several studies suggested overuse of oxygen therapy is prevalent and is associated with adverse outcomes, including longer duration of mechanical ventilation and longer hospitalization (42,43). However, these studies mainly focused on the comparison of clinical effect between routine oxygen therapy and ambient air, and did not explore the relationship between admission oxygen saturation and mortality. Similar to their findings, the univariable Cox analysis showed that oxygen therapy was not associated with mortality in our study. In addition, our subgroups analyses showed targeting SpO_2 between 94% and 96% might optimize survival for patients with or without oxygen therapy. Additionally, in the AVOID trial, Stub *et al.* (38) randomized 441 patients with pre-hospital ST-elevation AMI to receive air or oxygen (8 L/min via mask) until discharge, and concluded that oxygen therapy may aggravate myocardial injury and was associated with increased myocardial infarct size (55% larger) assessed at six months. At the end of treatment, SpO_2 significantly differed between the oxygen group [100% (IQR, 99–100%)] and the ambient air group [98% (IQR, 96–99%); $P<0.001$], which suggested that the SpO_2 in the ambient air group might be closer to the optimal SpO_2 range we identified. Moreover, in prior randomized trials of oxygen therapy, the treatment group cut-off values for SpO_2 were essentially arbitrary. Our study could provide a firmer basis for the selection of SpO_2 targets within treatment groups for future research. Furthermore, while designing trials in this complex area, the method of oxygen delivery, levels, and duration of therapy should also be considered.

Several limitations of our study should be noted. Firstly, this study was a single-center retrospective observational study, and selection bias was inevitable. Thus, prospective cohorts are needed for further validation. Secondly, there were several potential confounding variables that we were unable to assess due to severe data missing conditions and other reasons. However, some of the excluded variables might have predictive value for clinical outcomes. Given that, external validation was required to test its utility. Finally, our study only focused on the in-hospital mortality of patients with AMI, while other outcomes, such as long-term mortality and late prognosis, were also important and deserved further investigation.

Conclusions

In a large and heterogeneous group of AMI patients, the relationship between admission SpO_2 levels and in-hospital all-cause mortality followed a "U" shaped curve. The lowest mortality was observed for an SpO_2 range of 94–96%, and this finding could benefit future clinical trials of oxygen therapy.

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Footnote

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org/10.21037/atm-20-2614). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The establishment of the Medical Information Mart for Intensive Care III (MIMIC-III) database is approved by the Institutional Review Boards (IRB) of the Massachusetts Institute of Technology (MIT, Cambridge, MA, USA) and the Beth Israel Deaconess Medical Center (BIDMC). Our study utilized the anonymous data available from this database, and hence the requirement for informed consent was waived. In summary, the study complied with the ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments.

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