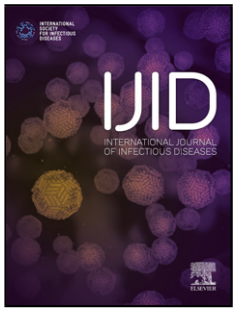

Oxygen metabolism markers as predictors of mortality in severe COVID-19

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Title: Oxygen metabolism markers as predictors of mortality in severe COVID-19.

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Highlights

- Hypoxemia determines mortality in COVID-19.
- Values of $ScvO_2$, VO_2 and O_2ER reflect the systemic oxygenation status in patients critically ill with COVID-19.
- $ScvO_2$ below 29%, VO_2 > 124.6 ml/min and O_2ER over 30.2% might be used as predictors of mortality in patients with COVID-19.
- Careful monitoring of oxygen metabolism markers is important in treatment modification in critically ill patients with COVID-19.

Summary

Objective: The aim of this paper was to find oxygen metabolism markers that could predict mortality in patients with severe COVID-19.

Methods: In a retrospective analysis we compared the medical records of patients with severe COVID-19 including 53 records of deceased patients and 50 records of survivors. The latter were selected from 222 records using a random number generator. For comparison, 28 individuals who considered themselves healthy and had no history of serious illness were also examined. Oxygen saturation in arterial blood (SaO_2) and in central venous blood ($ScvO_2$), arterial partial pressure of oxygen (PaO_2), respiratory index (PaO_2/FiO_2), oxygen delivery (DO_2), consumption (VO_2) and extraction (O_2ER) were compared in all participating individuals. Optimal cutoff point for oxygen parameters in prediction of death was performed using maximization of Youden Index in receiver operating characteristic (ROC) curve analysis.

Results: There were statistically significant differences between values of all studied oxygen metabolism markers in the survivors as compared to the deceased patients ($p<0.001$). $ScvO_2$, VO_2 and O_2ER (AUC 1.0) were the strongest predictors of mortality, while PaO_2 the lowest (0.81). $ScvO_2$ < 29%, VO_2 > 124.6 ml/min and O_2ER > 30.2% were found to be predictors of mortality in patients with COVID-19.

Conclusion: Values of $ScvO_2$, VO2 and O_2ER appear to be good predictors of mortality in critically ill patients with COVID-19.

Keywords: COVID-19; ARDS; oxygen metabolism; determinants of mortality; respiratory failure.

Introduction

Recently, the medical world has focused its attention on issues concerning diagnosing and treating COVID-19 [1]. The numbers who have been infected by and died from this disease are increasing daily. Due to the significant number of deaths, predicting the outcome of the disease remains essential and researchers are trying to find predictive markers of mortality for COVID-19 patients. A recent meta-analysis by Wenjie T. et al. focused on this issue [2]. The authors demonstrated that levels of cardiac troponin, C-reactive protein, interleukin-6, D-dimer, creatinine, alanine transferase and albumin can be used as mortality predictors for COVID-19. The authors of another meta-analysis considered the absolute values of lymphocytes, platelets, albumin, total bilirubin, urea, creatinine, myoglobin, cardiac troponin, C-reactive protein, and interleukin-6 as possible mortality predictors in COVID-19 [3]. We have not found any studies that investigate the possibility of using oxygen balance markers as predictors of mortality in patients with COVID-19. The most common indices used to estimate the severity of respiratory failure in patients with COVID-19 are arterial oxygen saturation (SaO_2), partial pressure of oxygen in arterial blood (PaO_2) and respiratory index PaO_2/FiO_2 [1]. Considering the high mortality rate in severe COVID-19 cases, there is an urgent need to identify patients at increased risk of death. Early intensification of treatment in this group is crucial. Oxygen metabolism markers might be used as predictors of mortality.

Objective: To find out if oxygen balance markers could be predictors of mortality in patients with COVID-19.

Methods

Study design

This is a retrospective observational study. We analysed the medical records of patients with a severe form of COVID-19 i.e. interstitial pneumonia with acute respiratory distress syndrome (ARDS) and acute respiratory insufficiency treated in Kyiv City Clinical Hospital №4 from February 2, 2020 to September 15, 2020. We used the Berlin definition as the criteria for ARDS [4].

Selection of participants:

Inclusion criteria for patients with COVID-19:

- SARS-CoV-2 infection confirmed by RT-PCR;
- presence of diffuse, bilateral lung inflammation on a CT scan;
- PaO_2/FIO_2 ratio <200;

Exclusion criteria for patients with COVID-19:

- the presence of comorbidities that could have caused death: cardiogenic pulmonary oedema, advanced chronic pulmonary disease, active malignancy, pulmonary embolism, diabetic ketoacidosis, advanced chronic kidney diseases, pregnancy, brain stroke and myocardial infarction.
- participation in other clinical studies.

Through initial screening, we selected 272 medical records matching the study criteria. Among these individuals, 53 patients (28 female, 52.8%) died (group 3). The remaining 222 medical records were then numbered using a random number generator [4], and 50 medical histories (23

female, 46%) were selected to be a control sample (group 2). For comparison, 28 (10 female, 35.7%) individuals who considered themselves healthy, had no history of serious illness and were awaiting ophthalmic surgery were included in the study (group 1).

The overview of basic data for the study population is presented in Table 1.

Measurement methods

Arterial blood was sampled from the radial artery and the venous blood from the internal jugular vein during catheterization procedure. In COVID-19 patients, sampling was performed immediately after admission to the ICU. Oxygen saturation in arterial blood (SaO_2) and in central venous blood ($ScvO_2$), arterial partial pressure of oxygen (PaO_2), respiratory index (PaO_2/FiO_2) and oxygen delivery (DO_2), consumption (VO_2) and extraction (O_2ER) were compared in all participating individuals.

For PaO_2, SaO_2, and $ScvO_2$ measurements, BGA 101 gas analyzer, Wondfo, China was used. The cardiac index was estimated using a Portable Noninvasive Cardiometer ICON™ from Cardiotronic, Inc.

The formula used to calculate the delivery of O_2 to tissues was:

$DO_2 = 1.34 \times SaO_2 \times CO \times Hb / 100$,

where DO_2 - delivery of O_2 with arterial blood (ml/min); 1.34 - Huffner's constant; Hb - blood haemoglobin concentration (g/l); SaO_2 - arterial oxygen saturation (%); CO - cardiac output (l/min); 100 - unit conversion index.

Oxygen consumption was calculated as the difference between arterial and venous O_2 transport [5]:

$VO_2 = CO \times Hb \times 1.34 \times (SaO_2 – ScvO_2) /100$,

where VO_2 - oxygen consumption (ml/min); CO - cardiac output (l/min); Hb - haemoglobin concentration (g/l); 1.34 – Huffner's constant; SaO_2 and $ScvO_2$ - arterial oxygen saturation and $ScvO_2$, respectively (%); 100 - unit conversion index.

The formula used to determine the fraction of inspired oxygen - FiO_2:

$FiO_2\% = 20 + (4 \times O_2$ l/min), where O_2 is the oxygen supply speed.

The oxygen extraction ratio (O_2ER) was also calculated using the following formula [5]:

$O_2ER = VO_2 / DO_2 \times 100\%$.

Statistical analysis: Statistical analysis was performed using Statistica version 13.1 (TIBCO Software Inc., 2017). Nonparametric statistics was used to compare categorical variables between the study groups. Comparison of the healthy, survivors and deceased groups' demographics and laboratory results, was conducted with the Kruskal-Wallis test with the post-hoc test. The optimal cut-off point for oxygen metabolism markers for predicting death was established by maximising the Youden Index in a receiver operating characteristic (ROC) curve analysis. For all statistical tests, the P-value <0.05 was considered significant.

Results

The study revealed significantly higher temperature, C-reactive protein (CRP), procalcytonin (PCT) and creatinine concentration ($p<0.001$) in COVID-19 patients compared to healthy ones (Table 1).

Oxygen metabolism indices in patients with COVID-19 differed significantly from those in healthy people, but also between those who survived and died (Table 2). All patients with COVID-19 had significant oxygen metabolism disorders which were manifested by a substantial decrease in SaO_2, PaO_2, PaO_2/FiO_2 and DO_2. Thus, SaO_2 in the survivors and deceased patients was significantly decreased by factors of 2.16 and 2.42 respectively, as compared to the healthy

individuals, in turn in the deceased patients of 1.12 compared to the survivors (less by 4.88%). Similarly, PaO_2 in those patients decreased by factors of 2.97 and 3.22 respectively, in the deceased 1.08 compared to the survivors (less by 2.5 mm). In the two COVID-19 groups DO_2 was significantly lower as compared to healthy individuals (2.15 times in the survivors and 2.41 in the deceased) and lower in the deceased than in the survivors 1.12 times (less by 46.44 ml/min). Analogically PaO_2/FiO_2 decreased 3.13 times in the survivors and 3.39 in the deceased in comparison to the controls, 1.08 times in the deceased in comparison to survivors (less by 11.59 mm Hg).

Such analysis was also conducted with regards to $ScvO_2$, oxygen consumption (VO_2) and oxygen extraction rate (O_2ER). $ScvO_2$ decreased by a factor of 1.99 in the survived patients and by a factor of 3.68 in the deceased patients as compared to healthy individuals. It is noteworthy that $ScvO_2$ was 1.85 times higher in the survivors as compared to the deceased patients (less by 15.24 mm Hg). In the deceased patients VO_2 was 1.84 times higher than in the survivors (93,84 ml/min more). Similarly with the oxygen extraction ratio (O_2ER) - in the deceased patients the index increased by a factor of 1.76 in comparison with the healthy individuals, and by a factor of 2.07 in comparison with the survivors. In the deceased patients the index was 1.76 higher than in the survivors (28.38% more).

All the differences discussed above were statistically significant ($p<0.001$).

A discrimination model was established to determine the values of oxygen metabolism markers for predicting mortality. ROC analysis was used to calculate the cut-off points (Table 3). Despite the analysis revealed the prognostic value of all parameters, $ScvO_2$, VO_2 and O_2ER (AUC 1.0) were the strongest predictors, while PaO_2 the lowest (0.81).

Discussion

There is a limited number of studies on hypoxia in COVID-19. Typical indicators: SaO_2, PaO_2, and PaO_2/FiO_2 are most often used to characterize the degree of respiratory insufficiency in

patients with COVID-19 [1], which also confirms our study. Li HC. et al. [6] studied the pathogenesis of COVID-19 and stated that a severe form of the disease progresses into sepsis and acute respiratory distress syndrome, and consequently into severe hypoxia. The latter is the leading cause of death in these patients. Xie J. et al. [7] suggest that hypoxemia in COVID-19 predicts mortality. In their opinion, careful monitoring of oxygenation helps in the clinical management of patients with severe COVID-19, especially if limited intensive care resources are available [7].

$ScvO_2$ measurements provide insight into the balance between oxygen supply and tissue oxygen demand. Physiologically, $ScvO_2$ is in the range of 65-75% and usually exceeds 70% [8]. A decrease below 70% is evidence of tissue hypoperfusion [9]. A decrease in $ScvO_2$ can be caused by tissue hypoperfusion, arterial desaturation, and a decline in haemoglobin concentration. Some authors point out that in critical conditions the dynamic changes in $ScvO_2$ values are more significant than those in SaO_2 [10, 11].

$ScvO_2$ values can differ considerably in various clinical situations. Patients with chronic heart failure may have $ScvO_2$ as low as 65% without signs of tissue hypoxia due to a compensatory increase in oxygen extraction in response to reduced oxygen delivery [12]. In patients with respiratory insufficiency, $ScvO_2$ is one of the oxygen balance markers used to set parameters of mechanical ventilation and other respiratory treatment [13]. A study conducted in the multidisciplinary intensive care unit showed that mortality in patients with $ScvO_2$ below 60% was 1.7 times higher as compared to patients with higher values of this marker. Treatment attempts only resulted in a slight increase in $ScvO_2$ which, however, did not affect the fatal outcome [14]. Similar clinical findings were observed in our deceased patients with COVID-19. The mean values of $ScvO_2$ in the deceased were two times lower than in the survivors and over three and half times lower than in the controls (Table 2). Therefore, $ScvO_2 < 29\%$ appears to be a good variable predicting mortality in severe COVID-19 cases (Table 3). This parameter is especially useful, as it can be easily and quickly identified in each patient.

Oxygen delivery is another marker of life support mechanism and DO_2 disorders are crucial factors determining mortality in ICUs [15]. This is consistent with our findings. In our COVID-19 patients, DO_2 was substantially lower than in the controls and the values in the deceased are significantly lower as compared to the survivors (Table 2). A considerable DO_2 decrease in both COVID-19 groups should be referred to ARDS, the leading pathology in the study population [15]. Pathology in DO_2 is especially important in critically ill patients i.e. when oxygen metabolism in the tissues is disturbed. Under normal conditions, VO_2 does not depend on DO_2. In healthy adults at rest the body uses only about 25% of the delivered O_2 [16], i.e. about 220-250 ml of O_2 per minute. In critical conditions, oxygen consumption is considerably greater. A rise in body temperature by just 1^o Celsius increases oxygen consumption by 10%. In the case of chills, it increases 1.5-2.0 times and in patients with sepsis - 2.0-2.5 times [17].

Oxygen delivery/consumption balance is provided by metabolic autoregulation of cells resulting in enhanced oxygen extraction when DO_2 is markedly reduced [18]. This mechanism has its limits and can fail in critical conditions i.e. when critically reduced DO_2 influences VO_2. This was observed in our COVID-19 groups, as the decrease in DO_2 also reduced VO_2. However, VO_2 in the deceased was nearly twice as high as in the survivors (Table 2). Most likely this was related to an oxygen debt resulting from critical tissue hypoxia [19]. This is known as the so-called oxygen paradox: energy exchange disorders begin before DO_2 is reduced to a critical level i.e. when consumption is proportional to the supply. That can happen even before oxygen debt occurs [20].

Hypoxia in patients with severe COVID-19 is determined not only by oxygen delivery/consumption ratio but also by the complex of hypoxemic processes at subcellular, cellular, tissue, and organ levels [21]. It is difficult to explain the increase in oxygen consumption in the deceased as compared to the survivors. Physiologically, VO_2 depends on the tissue needs only, and not on DO_2, as the delivery exceeds tissue demands. In certain clinical circumstances oxygen consumption increases in direct proportion to the delivery [22]. This is known as pathological dependence of oxygen consumption on oxygen delivery. Clinical observations

confirmed this pathology in patients with sepsis, where microcirculation disorders occur, oxygen consumption may increase, which is an extremely unfavourable sign [23, 24]. Our findings were similar. In the survivors, the decrease in DO_2 was followed by a proportional decrease in VO_2. This was not observed in the deceased group where a substantial decrease in DO_2 was accompanied by small relatively small reduction in VO_2. The abnormalities observed in oxygen extraction mirror tissue hypoxia. This results in multiple organ dysfunctions. Xie. J. et al. believe that therapeutic attempts aimed at reducing oxygen consumption are key factors in the successful treatment of patients with COVID-19 [7]. In our deceased patients, increased oxygen consumption was the cause of increased hypoxia.

The evaluation of the imbalance between DO_2 and VO_2 can be crucial for tailoring the therapy in severe COVID-19 patients, as it enables early identification and assessment of the severity of global body dysoxia. In response to the imbalance between DO_2 and VO_2 the body launches several compensatory mechanisms, which include increased cardiac output, increased O_2ER, and the redistribution of blood flow to the organs and tissues where oxygen demand is the greatest [25]. VO_2 depends on oxidative phosphorylation activity and the functional activity of the tissue at a given time. This process is characterized by O_2ER [6]. At rest, the extraction index is 20-30%. It is believed that one of the reasons of an increase in oxygen extraction from the blood is the disturbance of microcirculation in the tissues [26]. In our study, O_2ER values in the controls and in the survivors, although significantly different, were close to the normal ranges, while in the deceased it was almost twice as high compared to the control group (Table 2). In our opinion, $O_2ER > 30\%$ can be considered a good predictor of mortality in patients with COVID-19 (Table 3). The increase in O_2ER likely results from increased oxygen consumption by the tissues but we were not able to confirm this. The explanation of this pathology may be of critical importance for understanding the cellular pathomechanisms in severe COVID-19. Further clinical trials are needed to clarify this phenomenon.

Conclusions:

Monitoring of oxygen metabolism allows to identify the critically ill COVID-19 patients. $ScvO_2$ < 29%, VO_2 <125 ml/min and O_2ER > 30% appear to be good predictors of mortality in critically ill patients with COVID-19. In those patients, markers of internal respiration seem to predict mortality better than markers of the external one. Further clinical studies are needed for the better elucidation of those findings.

Conflict of Interest

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

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Ethical Approval

The study was conducted under the ethical principles of the Declaration of Helsinki. The study was approved by the Bioethics Committee of the Kiev City Clinical Hospital No. 4 [Decision No. 64, dated July 2, 2020]. Informed consent was only obtained for the control group of healthy patients. Since the study of the other patients was of a retrospective nature, informed consent for the study was not required under Ukrainian law.

Declaration of interests

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

References

1. Coronavirus Disease 2019 (COVID-19) Treatment Guidelines Get the latest public health information from CDC: https://www.coronavirus.gov (accessed August 7, 2020).
2. Wenjie T, Wanlin J, Jie Y. Predictors of mortality in hospitalized COVID- 19 patients: A systematic review and meta- analysis. J Med Virol 2020.
3. Henry BM, de Oliveira MH, Benoit S. Hematologic, biochemical and immune biomarker abnormalities associated with severe illness and mortality in coronavirus disease 2019 (COVID- 19): a meta- analysis. Clin Chem Lab Med 2020;58:1021-8.
4. Costa EL, Amato MB. The new definition for acute lung injury and acute respiratory distress syndrome: is there room for improvement? Curr Opin Crit Care 2013;19:16-23.
5. Marino Paul. The ICU Book. Fourth, North American Edition. Marinos. 2013.
6. Li HC, Ma J, Zhang H. Thoughts and practice on the treatment of severe and critical new coronavirus pneumonia. Zhonghua Jie He He Hu Xi Za Zhi 2020;43:396-400.
7. Xie J, Covassin N, Fan Z, et al. Association Between Hypoxemia and Mortality in Patients With COVID-19. Mayo Clin Proc 2020;95:1138-47.
8. van Beest P, Wietasch G, Scheeren T. Clinical review: use of venous oxygen saturations as a goal – a yet unfinished puzzle. Crit Care 2011;15:232.
9. Walley KR. Use of central venous oxygen saturation to guide therapy. Am J Respir Crit Care Med 2011;184:514-20.
10. Jones AE, Shapiro NI, Trzeciak S. Emergency Medicine Shock Research Network (EMShockNet) Investigators. Lactate clearance vs central venous oxygen saturation as goals of early sepsis therapy: a randomized clinical trial. JAMA. 2010;303:739-46.

11. Smetkin AA, Kirov MJ. Venous oxygen saturation monitoring in anesthesiology and intensive care. General Reanimatology 2018;4:86-96.
12. Nebout S, Pirracchio R. Should We Monitor ScVO2 in Critically Ill Patients? Cardiol Res Pract. 2012;2012:370697.
13. Peyrony O, Dumas G, Legay L. Central venous oxygen saturation is not predictive of early complications in cancer patients presenting to the emergency department. Intern Emerg Med 2019;14:281-9.
14. Salem G, Abbas NI, Zakaria AY. Central venous oxygen saturation/lactate ratio: a novel predictor of outcome following emergency open laparotomy. Eur J Trauma Emerg Surg. 2019.
15. Pappachan LG, Williams A, Sebastian T, Korula G, Singh G. Changes in central venous oxygen saturation, lactates, and ST segment changes in a V lead ECG with changes in hemoglobin in neurosurgical patients undergoing craniotomy and tumor excision: A prospective observational study. J Anaesthesiol Clin Pharmacol 2019;35:99-105.
16. Walton R, Hansen BD. Venous Oxygen Saturation in Critical Illness. J Vet Emerg Crit Care (San Antonio) 2018;28:387-97.
17. Muzdubayeva B. Hemodynamic monitoring in sepsis. Vestnik Kaz. NMU 2016;2:15-25.
18. Nevares I, Martínez-Martínez V, Martínez-Gil A, Martín R, Laurie VF, Del Álamo-Sanza M. On-line monitoring of oxygen as a method to qualify the oxygen consumption rate of wines. Food Chem 2017;229:588-96.
19. Navalta JW, Tanner EA, Bodell NG. Acute Normobaric Hypoxia Exposure and Excess Post-Exercise Oxygen Consumption. Aerosp Med Hum Perform 2018;89:1031-5.
20. Moen I, Stuhr LE. Hyperbaric oxygen therapy and cancer--a review. Target Oncol 2012;7:233-42.
21. Bhatraju PK, Ghassemieh BJ, Nichols M. Covid-19 in Critically Ill Patients in the Seattle Region - Case Series. N Engl J Med 2020;382:2012-22.

22. Place TL, Domann FE, Case AJ. Limitations of oxygen delivery to cells in culture: An underappreciated problem in basic and translational research. Free Radic Biol Med 2017;113:311-22.

23. Dietz LJ, Venkatasubramani AV, Müller-Eigner A, et al. Measuring and Interpreting Oxygen Consumption Rates in Whole Fly Head Segments. J Vis Exp 2019;(143).

24. Kirov MY. Venous saturation. Oximetry in anesthesiology and resuscitation. 2014. http://oximetry.rf/metody/30-venoznaya-saturatsiya (accessed August 7, 2020).

25. Chu DK, Kim LH, Youn g PJ, et al. Mortality and morbidity in acutely ill adults treated with liberal versus conservative oxygen therapy (IOTA): a systematic review and meta-analysis. Lancet 2018;391:1693-705.

26. Li B, Esipova T, Sencan I. More homogeneous capillary flow and oxygenation in deeper cortical layers correlate with increased oxygen extraction. Elife 2019;8:e42299.

Table 1. Baseline parameters and laboratory test results of the study patients.

	Healthy controls, n=28 (group 1)	COVID-19 survivors, n=50 (group 2)	COVID-19 deceased, n=53 (group 3)	P value for the correlation between examined groups		
				1 v 2	1 v 3	2 v 3
Age, years, mean (SD), range	66.3 (4.3) 55-77	70.5 (4.2) 61-80	67.8 (4.0), 59-78	<0.001	0.29	<0.001
Temperature, mean (SD), °C	36.5 (0.1)	38.0 (0.2)	38.0 (0.2)	<0.001	<0.001	1.0
Systolic BP, mean (SD), mm Hg	133 (14)	132 (15)	133 (14)	0.93		
Diastolic BP, mean (SD), mm Hg	83 (9)	82 (9)	83 (9)	0.90		
Creatinine, mean (SD), mmol/l	0.09 (0.02)	0.11 (0.02)	0.13 (0.11)	<0.001	<0.001	0.99
CRP, mean (SD), mg/l	3.80 (0.63)	47.64 (12.83)	43.94 (13.78)	<0.001	<0.001	0.68
PCT, mean (SD) (ng/ml)	0.19 (0.03)	1.28 (0.45)	1.19 (0.39)	<0.001	<0.001	1.0

Table 2. Values of oxygen metabolism markers in examined patients.

	Healthy individuals, n=28 (group 1)	COVID-19 survivors, n=50 (group 2)	COVID-19 deceased patients, n=53 (group 3)	P value for the correlation between examined groups		
				1 v 2	1 v 3	2 v 3
SaO_2, mean (SD), %	97.07 (0.98)	44.90 (2.06)	40.02 (3.03)	<0.001	<0.001	<0.001
$ScvO_2$, mean (SD), %	66.07 (3.05)	33.18 (1.93)	17.94 (1.64)	<0.001	<0.001	<0.001
PaO_2, mean (SD), mm Hg	95.36 (3.15)	32.14 (1.70)	29.64 (1.99)	<0.001	<0.001	<0.001
PaO_2/FiO_2, mean (SD), mm Hg	475.71 (16.03)	152.12 (3.73)	140.53 (5.49)	<0.001	<0.001	<0.001
DO_2, mean (SD), ml/min	905.90 (39.39)	421.99 (18.95)	375.55 (23.87)	<0.001	<0.001	<0.001
VO_2, mean (SD), ml/min	281.75 (11.29)	112.18 (4.95)	206.02 (15.31)	<0.001	<0.001	<0.001
O_2ER, mean (SD), %	31.16 (1.88)	26.51 (1.49)	54.89 (1.53)	<0.001	<0.001	<0.001

Table 3. Performance of oxygen metabolism markers for predicting death using logistic regression analysis.

	Cut-off point	AUC	95% CI	P value	Index Youden
SaO2, %	43	0.94	0.90-0.98	<0.001	0.75
$ScvO_2$, %	29	1	1	<0.001	1.0
PaO_2, mm Hg	31.6	0.81	0.73-0.89	<0.001	0.43
PaO_2/FiO_2, mm Hg	144.5	0.96	0.93-0.99	<0.001	0.79
DO_2, ml/min	401	0.95	0.92-0.99	<0.001	0.83
VO_2, ml/min	124.6	1	1	<0.001	1.0
O_2ER, %	30.2	1	1	<0.001	1.0