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

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ABSTRACT

Objective: To investigate the use of oxygen metabolism markers as predictors of mortality in patients with severe coronavirus disease 2019 (COVID-19).
Methods: A retrospective analysis was undertaken to compare the medical records of patients with severe COVID-19 (53 deceased patients and 50 survivors). The survivors were selected from 222 records using a random number generator. In addition, 28 individuals who considered themselves to be healthy and who had no history of serious illness were included in the study for comparison. Oxygen saturation in arterial blood, oxygen saturation in central venous blood ($ScvO_2$), arterial partial pressure of oxygen (PaO_2), respiratory index (PaO_2/fraction of inspired oxygen), oxygen delivery, oxygen consumption (VO_2) and oxygen extraction (O_2ER) were compared in all participants. The optimal cut-off point for each oxygen metabolism marker in the prediction of mortality was determined based on the maximum value of the Youden Index in receiver operating characteristic curve analysis.
Results: Significant differences in all studied oxygen metabolism markers were found between survivors compared with deceased patients ($p < 0.001$). $ScvO_2$, VO_2 and O_2ER [area under curve (AUC) 1.0] were the strongest predictors of mortality, and PaO_2 was the weakest predictor of mortality (AUC 0.81). $ScvO_2$ <29%, VO_2 >124.6 ml/min and O_2ER >30.2% were identified as predictors of mortality in patients with COVID-19.
Conclusion: $ScvO_2$, VO2 and O_2ER are good predictors of mortality in critically ill patients with COVID-19.

Introduction

Recently, the medical world has focused its attention on the diagnosis and treatment of coronavirus disease 2019 (COVID-19) (Coronavirus (COVID-19), 2020). The number of cases of COVID-10 and the number of associated deaths are increasing daily. Due to the significant number of deaths, prediction of the outcome of COVID-19 is essential, and there is a need to identify predictive markers of mortality for infected patients. This was the subject of a recent meta-analysis by Tian et al. (2020), who reported that levels of cardiac troponin, C-reactive protein (CRP), interleukin-6, D-dimer, creatinine, alanine transferase and albumin can be used to predict mortality in patients with COVID-19. In another meta-analysis, Henry et al. reported that the absolute values of lymphocytes, platelets, albumin, total bilirubin, urea, creatinine, myoglobin, cardiac troponin, CRP and interleukin-6 were potential predictors of mortality in patients with COVID-19 (Henry et al., 2020). As far as is known, no studies to date have investigated whether oxygen metabolism markers can be used to predict 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 the respiratory index [PaO_2/fraction of inspired oxygen (FiO_2)] (Coronavirus (COVID-19), 2020). Considering the high mortality rate in cases of severe COVID-19, there is an urgent need to identify those patients at increased risk of death. Early intensification of treatment in this group is crucial. This study investigated the use of oxygen metabolism markers as predictors of mortality in patients with severe COVID-19.

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Methods

Study design

This retrospective observational study analysed the medical records of patients with severe COVID-19 [i.e. interstitial pneumonia with acute respiratory distress syndrome (ARDS) and acute respiratory insufficiency] treated in Kiev City Clinical Hospital No. 4 between 2 February 2020 and 15 September 2020. ARDS was defined using the Berlin definition (Costa and Amato, 2013).

Selection of participants

The inclusion criteria used to select patients with COVID-19 were:

- severe acute respiratory syndrome coronavirus-2 infection confirmed by reverse transcription polymerase chain reaction;
- presence of diffuse, bilateral lung inflammation on computed tomography; and
- PaO2/FIO2 ratio <200.

The exclusion criteria for patients with COVID-19 were:

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

In total, 272 medical records that met the study criteria were identified through initial screening. Among these individuals, 53 patients (28 female, 52.8%) had died. The remaining 222 medical records were numbered using a random number generator (Costa and Amato, 2013), and 50 (23 female, 46%) patients were selected to represent survivors. In addition, 28 (10 female, 35.7%) individuals who considered themselves to be healthy, who had no history of serious illness, and who were awaiting ophthalmic surgery were included in the study for comparison.

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

Measurement methods

Arterial blood was sampled from the radial artery and venous blood was sampled from the internal jugular vein during catheterization. In patients with COVID-19, sampling was performed immediately after admission to the intensive care unit. SaO_2, oxygen saturation in central venous blood ($ScvO_2$), PaO_2, PaO_2/FiO_2, oxygen delivery (DO_2), oxygen consumption (VO_2) and oxygen extraction (O_2ER) were compared in all participating individuals.

A BGA 101 gas analyser (Wondfo, Guangzhou, China) was used to measure PaO_2, SaO_2 and $ScvO_2$. The cardiac index was estimated using a portable non-invasive cardiometer (ICON; Cardiotronic, Inc., La Jolla, CA, USA).

DO_2 (ml/min) was calculated as:

$DO_2 = 1.34 \times SaO_2 \times CO \times Hb / 100$where 1.34 is Huffner's constant, Hb is the

blood haemoglobin concentration (g/l), SaO_2 is arterial oxygen saturation (%), CO is cardiac output (l/min), and 100 is the unit conversion index.

VO_2 (ml/min) was calculated as the difference between arterial and venous oxygen transport (Marino, 2013):

$VO_2 = CO \times Hb \times 1.34 \times (SaO_2 - ScvO_2) /100$where CO is

cardiac output (l/min); Hb is haemoglobin concentration (g/l); 1.34 is Huffner's constant; SaO_2 and $ScvO_2$ are oxygen saturation in arterial blood and oxygen saturation in central venous blood, respectively (%); and 100 is the unit conversion index.

FiO_2 was calculated as:

$FiO_2\% = 20 + (4 \times O_2$ l/min)w

here O_2 is the oxygen supply speed.

O_2ER was calculated as (Marino, 2013):

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

Statistical analysis

Statistical analysis was undertaken using Statistica Version 13.1 (TIBCO Software Inc., Palo Alto, CA, USA). Non-parametric statistics were used to compare categorical variables between the study groups. Demographics and laboratory results for the three groups (healthy patients, survivors and patients who died due to COVID-19) were compared using the post-hoc Kruskal–Wallis test. The optimal cut-off point for each oxygen metabolism marker for predicting mortality was determined based on the maximum value of the Youden Index in receiver operating characteristic curve (ROC) curve analysis. For all statistical tests, $p < 0.05$ was considered to indicate significance.

Results

This study found that patients with COVID-19 had a significantly higher temperature, and CRP, procalcitonin and creatinine levels ($p < 0.001$) compared with healthy subjects (Table 1).

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

	Healthy subjects, n = 28	COVID-19 survivors, n = 50	COVID-19 deceased patients, n = 53	p-value for correlation between examined groups		
				Healthy vs survivors	Healthy vs deceased	Survivors vs deceased
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 blood pressure, mean (SD), mmHg	133 (14)	132 (15)	133 (14)	0.93		
Diastolic blood pressure, mean (SD), mmHg	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
C-reactive protein, mean (SD), mg/l	3.80 (0.63)	47.64 (12.83)	43.94 (13.78)	<0.001	<0.001	0.68
Procalcitonin, mean (SD) (ng/ml)	0.19 (0.03)	1.28 (0.45)	1.19 (0.39)	<0.001	<0.001	1.0

COVID-19, coronavirus disease 2019; SD, standard deviation.

Table 2
Values of oxygen metabolism markers in study patients.

	Healthy individuals, n = 28	COVID-19 survivors, n = 50	COVID-19 deceased patients, n = 53	p-value for correlation between examined groups		
				Healthy vs survivors	Healthy vs deceased	Survivors vs deceased
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

COVID-19, coronavirus disease 2019; SaO_2, oxygen saturation in arterial blood; SD, standard deviation; $ScvO_2$, oxygen saturation in central venous blood; PaO_2, arterial partial pressure of oxygen; FiO_2, fraction of inspired oxygen; PaO_2/FiO_2, respiratory index; DO_2, oxygen delivery; VO_2, oxygen consumption; O_2ER, oxygen extraction.

Oxygen metabolism indices in patients with COVID-19 differed significantly from those in healthy subjects, and also between patients with COVID-19 who survived and those who died (Table 2). All patients with COVID-19 had significant oxygen metabolism disorders which were manifested by substantial decreases in SaO_2, PaO_2, PaO_2/FiO_2 and DO_2. SaO_2 in survivors and deceased patients was 2.16 and 2.42 times lower, respectively, compared with healthy subjects, and 1.12 times lower in deceased patients compared with survivors (4.88% lower). Similarly, PaO_2 in survivors and deceased patients was 2.97 and 3.22 times lower, respectively, compared with healthy subjects, and 1.08 times lower in deceased patients compared with survivors (2.5 mm lower). DO_2 in survivors and deceased patients was 2.15 and 2.41 times lower, respectively, compared with healthy subjects, and 1.12 times lower in deceased patients compared with survivors (46.44 ml/min lower). PaO_2/FiO_2 in survivors and deceased patients was 3.13 and 3.39 times lower, respectively, compared with healthy subjects, and 1.08 times lower in deceased patients compared with survivors (11.59 mmHg lower).

Analysis was also conducted for $ScvO_2$, VO_2 and O_2ER. $ScvO_2$ in survivors and deceased patients was 1.99 and 3.68 times lower, respectively, compared with healthy subjects. $ScvO_2$ in survivors was 1.85 times higher compared with deceased patients (15.24 mmHg higher). VO_2 in deceased patients was 1.84 times higher compared with survivors (93.84 ml/min higher). Similarly, O_2ER in deceased patients was 1.76 times higher compared with healthy subjects, and 2.07 times higher compared with survivors. O_2ER in deceased patients was 1.76 times higher compared with survivors (28.38% higher).

All of the differences reported 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). The analysis revealed that all parameters had prognostic value, with $ScvO_2$, VO_2 and O_2ER [area under curve (AUC) 1.0] being the strongest predictors of mortality, and PaO_2 being the weakest predictor of mortality (AUC 0.81).

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

	Cut-off point	AUC	95% CI	p-value	Youden Index

AUC, area under curve; CI, confidence interval; SaO_2, oxygen saturation in arterial blood; $ScvO_2$, oxygen saturation in central venous blood; PaO_2, arterial partial pressure of oxygen; FiO_2, fraction of inspired oxygen; PaO_2/FiO_2, respiratory index; DO_2, oxygen delivery; VO_2, oxygen consumption; O_2ER, oxygen extraction.

Discussion

A limited number of studies on hypoxia have been undertaken in patients with COVID-19. 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 (Coronavirus (COVID-19), 2020). Li et al. (2020) studied the pathogenesis of COVID-19, and stated that a severe form of the disease progresses into sepsis and ARDS, and consequently into severe hypoxia. The latter is the leading cause of death in these patients. Xie et al. (2020) suggested that hypoxaemia in COVID-19 is predictive of 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 Xie et al. (2020).

$ScvO_2$ 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% (van Beest et al., 2011). A decrease below 70% is evidence of tissue hypoperfusion (Walley, 2011). A decrease in $ScvO_2$ can be caused by tissue hypoperfusion, arterial desaturation or a decline in haemoglobin concentration. In critical conditions, dynamic changes in $ScvO_2$ are more significant than changes in SaO_2 (Jones et al., 2010; Smetkin and Kirov, 2018).

$ScvO_2$ 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 O_2ER in response to reduced DO_2 (Nebout and Pirracchio, 2012). In patients with respiratory insufficiency, $ScvO_2$ is one of the oxygen metabolism markers used to set the parameters for mechanical ventilation and other respiratory treatment (Peyrony et al., 2019). A study conducted in a multidisciplinary intensive care unit showed that mortality in patients with $ScvO_2$ <60% was 1.7 times higher compared with patients with higher $ScvO_2$ values. Treatment attempts only resulted in a slight increase in $ScvO_2$, and did not affect the fatal outcome (Salem et al., 2019). Similar clinical findings were observed in the present study in deceased patients. Mean $ScvO_2$ values in deceased patients were two times lower compared with survivors, and more than three and half times lower compared with healthy subjects (Table 2). Therefore, $ScvO_2$ <29% appears to be predictive of mortality in patients with severe COVID-19 (Table 3). This parameter is particularly useful as it can be measured quickly and easily in all patients.

DO_2 is another marker of life support mechanism, and DO_2 disorders are crucial factors determining mortality in intensive care units (Pappachan et al., 2019). This is consistent with the present findings. In this study, DO_2 was substantially lower in patients with COVID-19 compared with healthy subjects, and the values in deceased patients were significantly lower compared

with survivors (Table 2). A considerable decrease in DO_2 in both COVID-19 groups should be referred to as ARDS, the leading pathology in the study population (Pappachan et al., 2019). Pathology in DO_2 is particularly 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 approximately 25% of the delivered O_2 (Walton and Hansen, 2018) (i.e. approximately 220–250 ml O_2/min). In critical conditions, VO_2 is considerably greater. An increase in body temperature by just 1 °C increases VO_2 by 10%. VO_2 is 1.5–2.0 times higher in patients with chills, and 2.0–2.5 times higher in patients with sepsis (Muzdubayeva, 2016).

DO_2/VO_2 balance is achieved by metabolic autoregulation of cells, resulting in enhanced O_2ER when DO_2 is markedly reduced (Nevares et al., 2017). 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 the COVID-19 patients in the present study, as the decrease in DO_2 also reduced VO_2. However, VO_2 in deceased patients was nearly twice as high compared with survivors (Table 2). This was likely related to an oxygen debt resulting from critical tissue hypoxia (Navalta et al., 2018). This is known as the 'oxygen paradox', where energy exchange disorders begin before DO_2 is reduced to a critical level (i.e. when VO_2 is proportional to supply), and can happen before the occurrence of an oxygen debt (Moen and Stuhr, 2012).

Hypoxia in patients with severe COVID-19 is determined not only by the DO_2/VO_2 ratio but also by hypoxaemic processes at subcellular, cellular, tissue and organ levels (Bhatraju et al., 2020). It is difficult to explain the higher VO_2 values in deceased patients compared with survivors. Physiologically, VO_2 depends on tissue needs alone, not on DO_2, as DO_2 exceeds tissue demands. In certain clinical circumstances, VO_2 increases in direct proportion to DO_2 (Place et al., 2017). This is known as 'pathological dependence of VO_2 on DO_2'. Clinical observations have confirmed this pathology in patients with sepsis, where microcirculation disorders occur and VO_2 may increase; this is an extremely unfavourable sign (Dietz et al., 2019; Kirov, 2014). The present findings were similar. In survivors, the decrease in DO_2 was followed by a proportional decrease in VO_2. This was not observed in deceased patients, in whom a substantial decrease in DO_2 was accompanied by a relatively small decrease in VO_2. The abnormalities observed in O_2ER mirror tissue hypoxia. This results in multiple organ dysfunction. Xie et al. reported that therapeutic attempts to reduce VO_2 are key factors in the successful treatment of patients with COVID-19 (Xie et al., 2020). Increased VO_2 was the cause of increased hypoxia in deceased patients in the present study.

Evaluation of the imbalance between DO_2 and VO_2 can be crucial for tailoring therapy in patients with severe COVID-19, as it enables early identification and assessment of the severity of global body dysoxia. The body launches several compensatory mechanisms in response to the imbalance between DO_2 and VO_2, including increased cardiac output, increased O_2ER, and redistribution of blood flow to organs and tissues with the highest oxygen demands (Chu et al., 2018). VO_2 depends on oxidative phosphorylation activity and functional activity of the tissue at a given time. This process is characterized by O_2ER (Li et al., 2020). At rest, O_2ER is 20–30%. It is believed that one of the reasons for an increase in O_2ER from blood is the disturbance of microcirculation in the tissues (Li et al., 2019). In the present study, O_2ER values in healthy subjects and survivors, although significantly different, were close to normal ranges, but were almost twice as high in deceased patients compared with healthy subjects (Table 2). In the authors' 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 VO_2, but it was not possible to confirm this in the present study. 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 oxygen metabolism allows identification of patients with severe COVID-19. $ScvO_2$ <29%, VO_2 <125 ml/min and O_2ER >30% appear to be good predictors of mortality. In patients with severe COVID-19, markers of internal respiration seem to be better predictors of mortality than markers of external respiration. Further clinical studies are needed for better elucidation of these findings.

Conflict of interest

None declared.

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Ethical approval

This study was conducted in accordance with the ethical principles of the Declaration of Helsinki. The study was approved by the Bioethics Committee of Kiev City Clinical Hospital No. 4 (Decision No. 64, 2 July 2020). Informed consent was obtained for the control group of healthy subjects. As the study of the patients with COVID-19 was of a retrospective nature, their informed consent was not required under Ukrainian law.

References

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.

Chu DK, Kim LH, Young PJ, Zamiri N, Almenawer SA, Jaeschke R, 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.

Coronavirus (COVID-19). 2020 Available at: https://www.coronavirus.gov. (Accessed 7 August 2020).

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.

Dietz LJ, Venkatasubramani AV, Müller-Eigner A, Hrabe de Angelis M, Imhof A, Becker L, et al. Measuring and interpreting oxygen consumption rates in whole fly head segments. J Vis Exp 2019;143:e58601, doi:http://dx.doi.org/10.3791/58601.

Henry BM, de Oliveira MH, Benoit S, Plebani M, Lippi G. 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.

Jones AE, Shapiro NI, Trzeciak S, Pusateri AE, Arnold RC, Rizzuto M, et al. 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.

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

Li B, Esipova T, Sencan I, Kılıç K, Fu B, Desjardins M, et al. More homogeneous capillary flow and oxygenation in deeper cortical layers correlate with increased oxygen extraction. Elife 2019;8:e42299.

Li HC, Ma J, Zhang H, Cheng Y, Wang X, Hu ZW, et al. 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.
Marino P. The ICU book. Fourth edition London: Lippincott Williams and Wilkins; 2013.
Moen I, Stuhr LE. Hyperbaric oxygen therapy and cancer – a review. Target Oncol 2012;7:233–42.
Muzdubayeva B. Hemodynamic monitoring in sepsis. Vestnik Kaz NMU 2016;2:15–25.
Navalta JW, Tanner EA, Bodell NG. Acute normobaric hypoxia exposure and excess post-exercise oxygen consumption. Aerosp Med Hum Perform 2018;89:1031–5.
Nebout S, Pirracchio R. Should we monitor $ScVO_2$ in critically ill patients?. Cardiol Res Pract 2012;2012:370697.
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.
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.
Peyrony O, Dumas G, Legay L, Principe A, Franchitti J, Simonetta M, et al. 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.
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.
Salem G, Abbas NI, Zakaria AY, Radwan WA. Central venous oxygen saturation/lactate ratio: a novel predictor of outcome following emergency open laparotomy. Eur J Trauma Emerg Surg 2019;, doi:http://dx.doi.org/10.1007/s00068-019-01188-0 Epub ahead of print. PMID: 31317201.
Smetkin AA, Kirov MJ. Venous oxygen saturation monitoring in anesthesiology and intensive care. Gen Reanimatol 2018;4:86–96.
van Beest P, Wietasch G, Scheeren T, Spronk P, Kuiper M. Clinical review: use of venous oxygen saturations as a goal – a yet unfinished puzzle. Crit Care 2011;15:232.
Tian W, Jiang W, Yao J, Nicholson CJ, Li RH, Sigurslid HH, et al. Predictors of mortality in hospitalized COVID-19 patients: a systematic review and meta-analysis. J Med Virol 2020;92:1875–83.
Walley KR. Use of central venous oxygen saturation to guide therapy. Am J Respir Crit Care Med 2011;184:514–20.
Walton R, Hansen BD. Venous oxygen saturation in critical illness. J Vet Emerg Crit Care (San Antonio) 2018;28:387–97.
Xie J, Covassin N, Fan Z, Singh P, Gao W, Li G, et al. Association between hypoxemia and mortality in patients with COVID-19. Mayo Clin Proc 2020;95:1138–47.