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



Oleksandr V. Oliynyk<sup>a,b</sup>, Marta Rorat<sup>c,d,\*</sup>, Wojciech Barg<sup>e</sup>

<sup>a</sup> Department of Anaesthesiology and Intensive Care, Bogomolets National Medical University, Kiev, Ukraine

<sup>b</sup> Department of Emergency Medicine, High Education State School named by Pope John Paul II, Biala Podlaska, Poland

<sup>c</sup> Infectious Diseases Ward, J. Gromkowski Regional Specialist Hospital, Wroclaw, Poland

<sup>d</sup> Department of Forensic Medicine, Wroclaw Medical University, Wroclaw, Poland

<sup>e</sup> Department of Internal Medicine, Pneumology and Allergology, Wroclaw Medical University, Wroclaw, Poland

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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<sub>2</sub>), arterial partial pressure of oxygen (PaO<sub>2</sub>), respiratory index (PaO<sub>2</sub>/fraction of inspired oxygen), oxygen delivery, oxygen consumption (VO<sub>2</sub>) and oxygen extraction (O<sub>2</sub>ER) 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<sub>2</sub>, VO<sub>2</sub> and O<sub>2</sub>ER [area under curve (AUC) 1.0] were the strongest predictors of mortality, and PaO<sub>2</sub> was the weakest predictor of mortality (AUC 0.81). ScvO<sub>2</sub> <29%, VO<sub>2</sub> >124.6 ml/min and O<sub>2</sub>ER >30.2% were identified as predictors of mortality in patients with COVID-19.

**Conclusion:** ScvO<sub>2</sub>, VO<sub>2</sub> and O<sub>2</sub>ER are good predictors of mortality in critically ill patients with COVID-19.

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### 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-19 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<sub>2</sub>), partial pressure of oxygen in arterial blood (PaO<sub>2</sub>) and the respiratory index [PaO<sub>2</sub>/fraction of inspired oxygen (FiO<sub>2</sub>)] (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.

\* Corresponding author at: Department of Forensic Medicine, Wroclaw Medical University, Mikulicz-Radeckiego 4, 50-345 Wroclaw, Poland.  
E-mail address: [rorat.marta@gmail.com](mailto:rorat.marta@gmail.com) (M. Rorat).

## 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
- PaO<sub>2</sub>/FIO<sub>2</sub> 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.

**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.

SaO<sub>2</sub>, oxygen saturation in central venous blood (ScvO<sub>2</sub>), PaO<sub>2</sub>, PaO<sub>2</sub>/FiO<sub>2</sub>, oxygen delivery (DO<sub>2</sub>), oxygen consumption (VO<sub>2</sub>) and oxygen extraction (O<sub>2</sub>ER) were compared in all participating individuals.

A BGA 101 gas analyser (Wondfo, Guangzhou, China) was used to measure PaO<sub>2</sub>, SaO<sub>2</sub> and ScvO<sub>2</sub>. The cardiac index was estimated using a portable non-invasive cardiometer (ICON; Cardiometric, Inc., La Jolla, CA, USA).

DO<sub>2</sub> (ml/min) was calculated as:

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

blood haemoglobin concentration (g/l), SaO<sub>2</sub> is arterial oxygen saturation (%), CO is cardiac output (l/min), and 100 is the unit conversion index.

VO<sub>2</sub> (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 Huffer's constant; SaO<sub>2</sub> and ScvO<sub>2</sub> are oxygen saturation in arterial blood and oxygen saturation in central venous blood, respectively (%); and 100 is the unit conversion index.

FiO<sub>2</sub> was calculated as:

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

here O<sub>2</sub> is the oxygen supply speed.

O<sub>2</sub>ER 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 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 <sub>2</sub> , mean (SD), %	97.07 (0.98)	44.90 (2.06)	40.02 (3.03)	<0.001	<0.001	<0.001
ScvO <sub>2</sub> , mean (SD), %	66.07 (3.05)	33.18 (1.93)	17.94 (1.64)	<0.001	<0.001	<0.001
PaO <sub>2</sub> , mean (SD), mm Hg	95.36 (3.15)	32.14 (1.70)	29.64 (1.99)	<0.001	<0.001	<0.001
PaO <sub>2</sub> /FiO <sub>2</sub> , mean (SD), mm Hg	475.71 (16.03)	152.12 (3.73)	140.53 (5.49)	<0.001	<0.001	<0.001
DO <sub>2</sub> , mean (SD), ml/min	905.90 (39.39)	421.99 (18.95)	375.55 (23.87)	<0.001	<0.001	<0.001
VO <sub>2</sub> , mean (SD), ml/min	281.75 (11.29)	112.18 (4.95)	206.02 (15.31)	<0.001	<0.001	<0.001
O <sub>2</sub> ER, 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<sub>2</sub>, oxygen saturation in arterial blood; SD, standard deviation; ScvO<sub>2</sub>, oxygen saturation in central venous blood; PaO<sub>2</sub>, arterial partial pressure of oxygen; FiO<sub>2</sub>, fraction of inspired oxygen; PaO<sub>2</sub>/FiO<sub>2</sub>, respiratory index; DO<sub>2</sub>, oxygen delivery; VO<sub>2</sub>, oxygen consumption; O<sub>2</sub>ER, 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<sub>2</sub>, PaO<sub>2</sub>, PaO<sub>2</sub>/FiO<sub>2</sub> and DO<sub>2</sub>. SaO<sub>2</sub> 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<sub>2</sub> 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<sub>2</sub> 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<sub>2</sub>/FiO<sub>2</sub> 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<sub>2</sub>, VO<sub>2</sub> and O<sub>2</sub>ER. ScvO<sub>2</sub> in survivors and deceased patients was 1.99 and 3.68 times lower, respectively, compared with healthy subjects. ScvO<sub>2</sub> in survivors was 1.85 times higher compared with deceased patients (15.24 mmHg higher). VO<sub>2</sub> in deceased patients was 1.84 times higher compared with survivors (93.84 ml/min higher). Similarly, O<sub>2</sub>ER in deceased patients was 1.76 times higher compared with healthy subjects, and 2.07 times higher compared with survivors. O<sub>2</sub>ER 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<sub>2</sub>, VO<sub>2</sub> and O<sub>2</sub>ER [area under curve (AUC) 1.0] being the strongest predictors of mortality, and PaO<sub>2</sub> 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
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AUC, area under curve; CI, confidence interval; SaO<sub>2</sub>, oxygen saturation in arterial blood; ScvO<sub>2</sub>, oxygen saturation in central venous blood; PaO<sub>2</sub>, arterial partial pressure of oxygen; FiO<sub>2</sub>, fraction of inspired oxygen; PaO<sub>2</sub>/FiO<sub>2</sub>, respiratory index; DO<sub>2</sub>, oxygen delivery; VO<sub>2</sub>, oxygen consumption; O<sub>2</sub>ER, oxygen extraction.

## Discussion

A limited number of studies on hypoxia have been undertaken in patients with COVID-19. SaO<sub>2</sub>, PaO<sub>2</sub> and PaO<sub>2</sub>/FiO<sub>2</sub> 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<sub>2</sub> measurements provide insight into the balance between oxygen supply and tissue oxygen demand. Physiologically, ScvO<sub>2</sub> 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<sub>2</sub> can be caused by tissue hypoperfusion, arterial desaturation or a decline in haemoglobin concentration. In critical conditions, dynamic changes in ScvO<sub>2</sub> are more significant than changes in SaO<sub>2</sub> (Jones et al., 2010; Smetkin and Kirov, 2018).

ScvO<sub>2</sub> values can differ considerably in various clinical situations. Patients with chronic heart failure may have ScvO<sub>2</sub> as low as 65% without signs of tissue hypoxia due to a compensatory increase in O<sub>2</sub>ER in response to reduced DO<sub>2</sub> (Nebout and Pirracchio, 2012). In patients with respiratory insufficiency, ScvO<sub>2</sub> 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<sub>2</sub> <60% was 1.7 times higher compared with patients with higher ScvO<sub>2</sub> values. Treatment attempts only resulted in a slight increase in ScvO<sub>2</sub>, 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<sub>2</sub> 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<sub>2</sub> <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<sub>2</sub> is another marker of life support mechanism, and DO<sub>2</sub> 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<sub>2</sub> 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 (Nevarés 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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This study is part of the clinical research of the Department of Anaesthesiology and Intensive Care of Kyiv National Medical University on the topic ‘Optimization of respiratory support methods for patients with severe forms of respiratory insufficiency, including acute respiratory distress syndrome’ registered in the Clinical Trials Register of the State Expert Centre of the Ministry of Healthcare of Ukraine (Registration No. 0112U001413). This work was undertaken according to the subject register in Simple System SUB.A120.19.036, and was supported by statutory subvention granted by the Ministry of Science and Higher Education in Poland.

## 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.rtf/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<sub>2</sub> 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.