

# Dynamic blood oxygen indices in mechanically ventilated COVID-19 patients with acute hypoxic respiratory failure: a cohort study



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## Introduction

Acute hypoxic respiratory failure is a hallmark of severe COVID-19 pneumonia and often requires supplementary oxygen therapy.<sup>1</sup> Critically ill COVID-19 patients may require invasive mechanical ventilation, which carries significant morbidity and mortality.<sup>2</sup> Understanding of the relationship between dynamic changes in blood oxygen indices and clinical variables is lacking. We evaluated the changes in blood oxygen indices – partial pressure of oxygen in arterial blood (PaO<sub>2</sub>), PaO<sub>2</sub>/fraction of inspired oxygen (FiO<sub>2</sub>) ratio, oxygen content (CaO<sub>2</sub>) and oxygen extraction ratio (O<sub>2</sub>ER) - in COVID-19 patients through the first 30-days of intensive care unit (ICU) admission and explored relationships with clinical outcomes.

## Methods

We performed a retrospective observational cohort study of all adult COVID-19 patients in a single institution (ethics through REACT COVID-19<sup>3</sup>) requiring invasive mechanical ventilation between March 2020 and March 2021. We collected baseline characteristics, clinical outcomes and blood oxygen indices. 50,505 blood gas data points were obtained from 184 patients over 30-days.

## Results

184 patients met inclusion criteria, providing 34,592 arterial blood gas data points over 30-days. Patient characteristics and outcomes are presented in Table 2. The median age was 59.5 (IQR 51, 67), and median BMI 30 (IQR 25.8, 35.5). The majority were men (62.5%) of white ethnicity (70.1%). Median mechanical ventilation duration was 15-days (IQR 8, 25) and 133 patients (72.3%) survived 30-days. Oxygen indices are presented in Table 1. Non-survivors exhibited lower oxygen extraction; there was an averaged mean difference in O<sub>2</sub>ER of -0.06 (95% CI -0.09, -0.03) across days one to seven and -0.09 (95% CI -0.10, -0.07) across days one to 30. While both survivors and non-survivors had sub-physiological CaO<sub>2</sub> (which trended down throughout their ICU admission), non-survivors tended to exhibit higher values; there is an averaged mean difference of 0.23 (95% CI 0.13, 0.34) across day one to day seven and 0.28 (95% CI 0.21, 0.35) across days one to 30.

Variables	All patients n=184	Survivors n=133	Non-survivors n=51	p-value
Age	59.5 (51.0, 67.0)	57.0 (49.0, 64.0)	65.0 (59.5, 72.0)	<0.01
Sex, n (%)				
Male	115 (62.5%)	79 (59.4%)	36 (70.6%)	0.18
Female	69 (37.5%)	54 (40.6%)	15 (29.4%)	
BMI (kg/m <sup>2</sup> )	30.0 (25.8, 35.5)	30.1 (25.2, 35.8)	29.4 (26.6, 33.8)	0.75
Ethnicity, n (%)				
White	129 (70.1%)	95 (71.4%)	34 (66.7%)	0.59
Asian	31 (16.8%)	21 (15.8%)	10 (19.6%)	0.52
Black	14 (7.6%)	10 (7.5%)	4 (7.8%)	1.0
Mixed	6 (3.3%)	5 (3.8%)	1 (2.0%)	1.0
Unknown	4 (2.2%)	2 (1.5%)	2 (3.9%)	0.31
Clinical Frailty Score	2.0 (2.0, 3.0)	2.0 (2.0, 3.0)	3.0 (2.0, 4.0)	0.06
Charlson Comorbidity Index	2.0 (1.0, 3.0)	2.0 (1.0, 3.0)	3.0 (3.0, 4.5)	<0.01
Comorbidities, n (%)				
Asthma	19 (10.3%)	12 (9.0%)	7 (13.7%)	0.42
Chronic obstructive pulmonary disease	11 (6.0%)	6 (4.5%)	5 (9.8%)	0.18
Diabetes mellitus	56 (30.4%)	40 (30.1%)	16 (31.4%)	0.86
Hypertension	78 (42.4%)	57 (42.9%)	21 (41.1%)	0.87
Ischaemic heart disease	16 (8.7%)	7 (5.3%)	9 (17.6%)	0.02
Chronic kidney disease	11 (3.3%)	5 (3.8%)	6 (11.8%)	0.07
Immunosuppression	22 (12.0%)	16 (12.0%)	8 (15.7%)	0.63
Admission arterial blood gas				
pH	7.44 (7.38, 7.48)	7.44 (7.40, 7.48)	7.43 (7.35, 7.48)	0.22
PaO <sub>2</sub> (kPa)	9.4 (8.5, 11.1)	9.3 (8.4, 11.5)	9.6 (8.7, 10.5)	0.98
PaCO <sub>2</sub> (kPa)	5.0 (4.5, 5.9)	5.0 (4.5, 5.7)	5.0 (4.5, 6.5)	0.58
PaO <sub>2</sub> /FiO <sub>2</sub>	15.0 (12.1, 19.1)	15.0 (12.3, 18.9)	15.4 (12.1, 19.7)	0.51
HCO <sub>3</sub> <sup>-</sup> (mmol/L)	25.7 (23.2, 28.1)	25.9 (23.9, 28.2)	24.9 (20.7, 27.2)	0.01
Base excess (mmol/L)	1.4 (-1.0, 3.6)	1.6 (-0.1, 3.8)	1.2 (-3.2, 2.9)	0.03
Lactate (mmol/L)	1.2 (0.9, 1.6)	1.1 (0.8, 1.5)	1.4 (1.0, 1.8)	0.01
Admission lab variables				
Bilirubin (µmol/L)	11 (8, 14)	11 (7, 15)	10 (8, 13)	0.93
Creatinine (µmol/L)	73 (55, 98)	68 (51, 96)	84 (66, 106)	0.01
Creatinine kinase (IU/L)	128 (57, 386)	132 (64, 393)	99 (54, 329)	0.75
CRP (mg/L)	125 (67, 192)	133 (77, 192)	97 (51, 184)	0.29
D-Dimer (µg/L)	619 (340, 1283)	614 (324, 1148)	667 (358, 2017)	0.31
Ferritin (µg/L)	687 (381, 1168)	656 (373, 1093)	871 (543, 1339)	0.14
INR	1.1 (1.0, 1.2)	1.1 (1.0, 1.2)	1.1 (1.0, 1.2)	0.25
LDH (IU/L)	968 (760, 1276)	910 (755, 1231)	1098 (829, 1431)	0.05
Lymphocytes (x10 <sup>9</sup> /L)	0.7 (0.5, 1.0)	0.7 (0.5, 1.0)	0.7 (0.5, 0.9)	0.70
Neutrophil/lymphocyte ratio	10.5 (6.7, 18)	10.3 (6.1, 17.5)	10.6 (6.8, 19.6)	0.58
Procalcitonin (ng/L)	0.3 (0.1, 1.0)	0.3 (0.1, 0.9)	0.3 (0.1, 1.0)	0.67
Troponin (ng/L)	15 (9, 53)	15 (8, 37)	20 (10, 71)	0.11
ICU severity scores on admission				
APACHE II	18.0 (12.0, 23.0)	16.0 (11.0, 23.0)	19.0 (14.3, 24.8)	0.01
SOFA	4.0 (3.0, 7.0)	4.0 (3.0, 6.0)	5.5 (4.0, 8.0)	0.09
ICU interventions				
Pre-intubation NIV/CPAP, n (%)	113 (61.4%)	93 (69.9%)	32 (62.7%)	0.38
Prone positioning, n (%)	147 (79.9%)	109 (82.0%)	38 (74.5%)	0.30
Renal replacement therapy, n (%)	50 (27.2%)	30 (22.6%)	20 (39.2%)	0.03
Duration mechanical ventilation (days)	15 (8, 25)	16 (11, 29)	8 (5, 15)	<0.01
ICU length of stay (days)	20 (11, 36)	24 (17, 42)	11 (6, 17)	<0.01
Hospital length of stay (days)	28 (19, 53)	41 (27, 64)	16 (10, 20)	<0.01

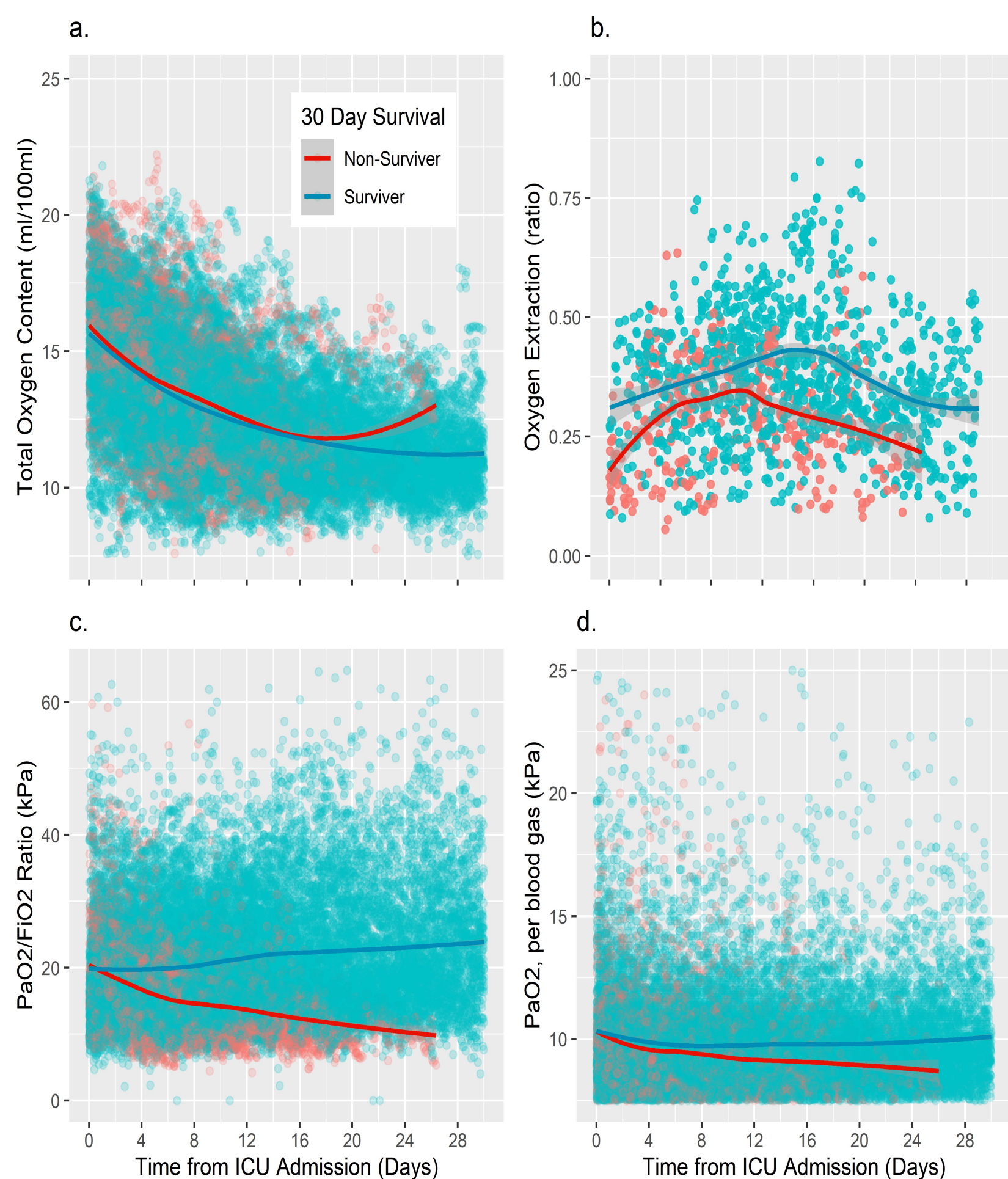
**Table 1. Patient characteristics and outcomes of all patients meeting inclusion criteria (n=184).** All scores and laboratory variables were performed at the time of ICU admission. APACHE II: Acute physiology and chronic health evaluation; BMI: Body mass index; CRP: C-Reactive protein; ICU: Intensive care unit; INR: International normalised ratio; LDH: Lactate dehydrogenase; SOFA: Sequential organ failure assessment

## Acknowledgments

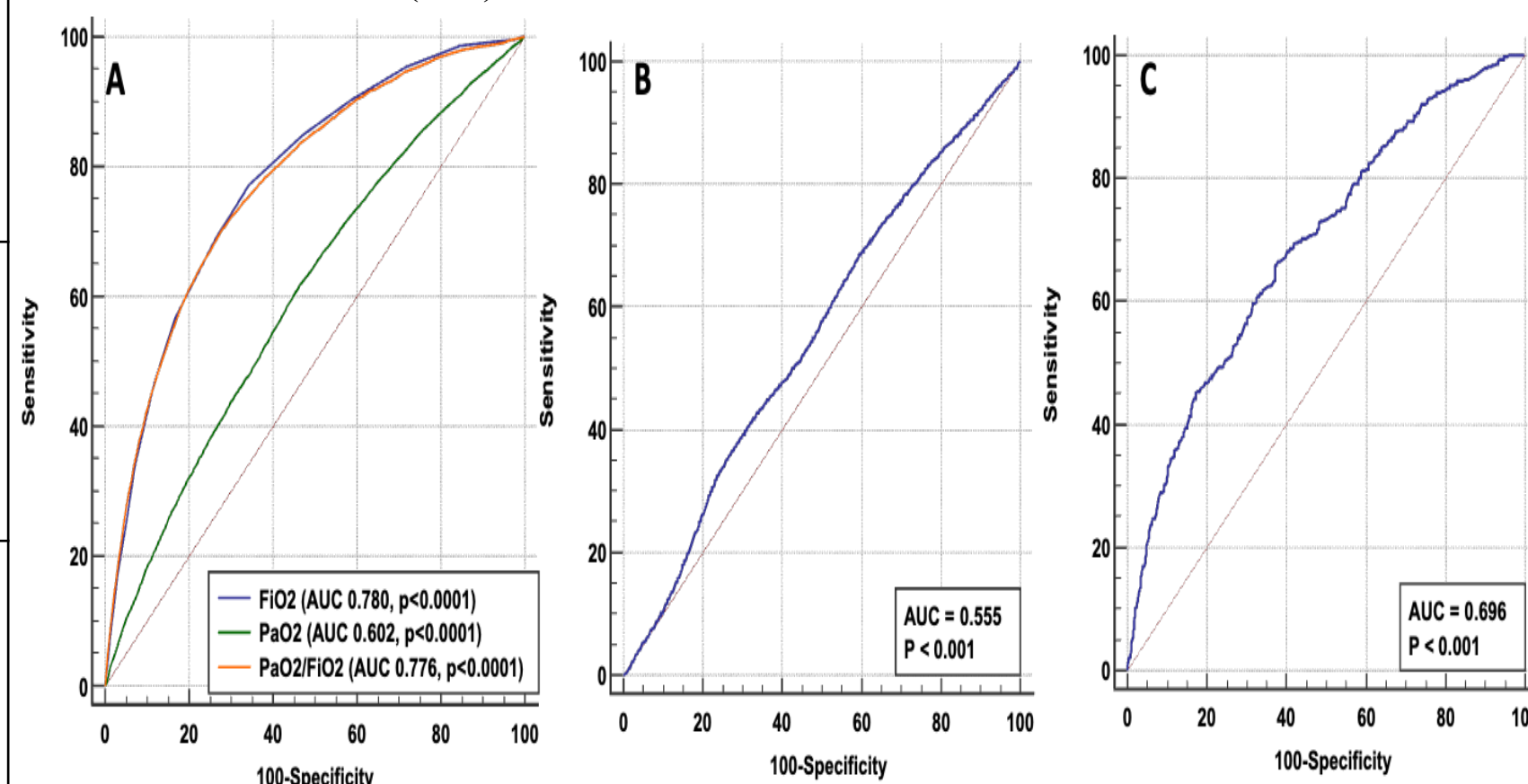
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	Survivors	Non-survivors	Mean Difference	95% CI	p-value*
PaO <sub>2</sub> (kPa)					
Day 1-7	9.80	9.49	-0.31	-0.41, -0.20	<0.01
Day 1-30	9.73	9.21	-0.52	-0.59, -0.46	<0.01
PaO <sub>2</sub> (kPa) / FiO <sub>2</sub> ratio					
Day 1-7	19.74	17.51	-2.23	-2.55, -1.91	<0.01
Day 1-30	21.19	15.56	-5.64	-5.85, -5.43	<0.01
CaO <sub>2</sub> (ml/dL)					
Day 1-7	14.33	14.63	0.31	0.19, 0.42	<0.01
Day 1-30	12.78	13.62	0.83	0.75, 0.91	<0.01
O <sub>2</sub> ER					
Day 1-7	0.34	0.27	-0.07	-0.09, -0.04	<0.01
Day 1-30	0.38	0.29	-0.08	-0.09, -0.07	<0.01

**Table 2. Comparison of mean averaged blood oxygen indices.** Day one-seven, and day one-30; survivors (n=133) vs. non-survivors (n=51). \* adjusted using the Benjamini-Hochberg Procedure



**Fig 1. Blood oxygen indices over time between survivors and non-survivors. A.** Arterial oxygen content (ml/dL), B. Oxygen extraction ratio (O<sub>2</sub>ER), C. PaO<sub>2</sub> (kPa), D. PaO<sub>2</sub> / FiO<sub>2</sub> ratio (kPa)



**Fig 2. Blood oxygen indices operating characteristics analysis. A.** AUC for FiO<sub>2</sub>, PaO<sub>2</sub> and PaO<sub>2</sub>/FiO<sub>2</sub>, B. Total oxygen content (CaO<sub>2</sub>), C. Oxygen extraction ratio (O<sub>2</sub>ER)

## Conclusion

The COVID-19 pandemic offers a unique opportunity to study a homogenous cohort of hypoxic critically unwell patients, with similar underlying pathology. In a cohort of mechanically ventilated adult ICU patients with hypoxic respiratory failure due to COVID-19, oxygen extraction is significantly lower in non-survivors compared to survivors during the first 30 days of ICU admission, despite having higher CaO<sub>2</sub> values. This suggests COVID-19 may cause impaired oxygen utilisation. Urgent further evaluation of the relationship between mitochondrial function and survival in COVID-19 is justified.

## References

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