Pneumonia

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Oxygenation indices and early prediction of outcome in hypoxemic patients with COVID-19 pneumonia requiring noninvasive respiratory support in pulmonary intermediate care unit

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Abstract

Background Early prediction of non-invasive respiratory therapy (NIRT) failure is crucial to avoid needless prolongation of respiratory support and delayed endotracheal intubation. Data comparing the predictive value of oxygenation indices (OI) in COVID-19 receiving NIRT are scant.

The aim of this monocentric retrospective study of prospectively collected data was to assess the effectiveness of different OI in predicting NIRT outcome at baseline (t0), 12 h (t12) and 24 h (t24) of treatment in hypoxemic patients with COVID-19-related pneumonia, managed in a Pulmonary Intermediate Care Unit (October 2020-June 2021).

Methods We assessed the predictive value of SpO2/FiO2, PaO2/FiO2, standardised PaO2/FiO2 ratio (s-PaO2/FiO2), respiratory index (RI), arterial–alveolar oxygen gradient (a-ADO2), age adjusted arterial–alveolar oxygen ratio (adj-a-ADO2D). Receiver operating characteristics (ROC), AUC and best sensitivity–specificity cut-off values were calculated at t0, t12, t24. NIRT failure risk was adjusted for non-oxygenation predictors.

Results Among 590 patients with COVID-19 infection, 368 met the eligibility criteria for inclusion in the study [mean (CI95%): PaO2/FiO2 214(206,8–221,9); PaCO2 mean 32,9 mmHg,(32,4–33,4)]. NIRT failure and hospital mortality rate were 23,4% and 19,6%, respectively. Older age, male gender, agitation/confusion, need for sedation, inability to tolerate prone positioning were independent predictors of NIRT failure. SpO2/FiO2, a-ADO2 and adj-aADO2 at t12 and t24, PaO2/FiO2 and RI at t24 were associated with NIRT failure. Prognostic predictivity of OI increased from t0 to t24. Greater ROC-AUC values were obtained with SpO2/FiO2 0,662 (0,60–0,72) (t0), PaO2/FiO2 0,697 (0,63–0,76) (t12) and s-PaO2/FiO2 0,769 (0,71–0,83) (t24). NIRT failure was independently predicted by PaO2/FiO2, s-PaO2/FiO2 and RI at any observation time and by SpO2/FiO2 and O2 gradients respectively at t0 and t24. SaO2/FiO2 ≤ 300 (t0), PaO2/FiO2 ≤ 151,7 (t12) and s-PaO2/FiO2 ≤ 160,4 (t24) turned out to be the best predictors of NIRT outcome.

Conclusions OI showed different effectiveness in predicting NIRT failure within 24 h of treatment in COVID-19 related pneumonia. This may be due to the multi-factorial pathophysiology of hypoxemia. Our study empathises

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furthermore the role of non-oxygenation-related parameters in contributing to the outcome. These findings may be useful to build a predictive model also in no COVID-19 related hypoxemic pneumonia.

Keywords Non invasive respiratory therapies, High flow nasal cannula, Non invasive ventilation, COVID-19, Pulmonary intermediate care unit, Oxygenation indexes

Introduction

At the beginning of the COVID-19 pandemic, immediate intensive care unit (ICU) admission with endotracheal intubation (ETI) and Invasive Mechanical Ventilation (IMV) was recommended in patients with Acute hypoxemic Respiratory Failure (ARF) [1–6]. Development of serious ETI-correlated complications, together with the unprecedented lack of ICU beds led clinicians to consider early application of Non-Invasive Respiratory Therapies (NIRT) outside ICU in patients with COVID-19 ARF [7–11]. NIRT, delivered by High Flow Nasal Cannula (HFNC), and/or Continuous Positive Airway Pressure (CPAP) and/or Non-Invasive Ventilation (NIV) may prevent the need for IMV and death in two third of COVID-19 hypoxemic pneumonia patients [11–14]. Early prediction of NIRT failure is crucial to either avoid an increase in mortality due to a delayed ETI or palliation in Do-Not-Intubate"(DNI)-patients [15–18].

Severity of hypoxemia at baseline and over the course of NIRT may accurately predict outcome; therefore, oxygenation Indices (OI), which combine different measurements to assess gas exchange, are frequently used [18]. Likely the most commonly used is PaO2/FiO2 ratio [19] despite its several physiologic drawbacks: dependence on the applied FiO2; lack of consideration of ventilatory effort; incapability to give information on mechanisms of hypoxemia [20]. Thus, other OI have been proposed. SpO2/FiO2 ratio has the advantage of being continuously non-invasively monitored. "Standardized" PaO2/FiO2 (s-PaO2/FiO2) is more reliable in concurrent hypocapnia; alveolar arterial O2 gradient and respiratory index (RI) are more accurate in detecting types of lung dysfunction [16, 21, 22]. As several pathophysiologic mechanisms underline evolution of hypoxemia in COVID-19 pneumonia, it could be speculated that the integrated application of OI exploring different physiologic lung abnormalities may enhance their predicting capability of NIRT failure [23, 24].

The aim of this study was to assess the effectiveness of multiple OI in predicting the outcome of NIRT within 24 h of treatment in hypoxemic patients with COVID-19 related pneumonia.

Material and methods

Study design and population

This monocentric observational retrospective study included prospectively collected data on COVID-19 hypoxemic patients admitted to the COVID section of Pulmonary Intermediate Care Unit (PIMCU) of S. Donato Hospital in Arezzo (Italy) between 20th October 2020 and 10th June 2021. Ethical Committee's approval (n°2733, 28th December 2020) and a written informed patient consent were achieved.

We included all patients fulfilling all the following criteria: 1) positive reverse-transcription polymerase chain reaction of nasopharyngeal swab samples for SARS-Cov-2, 2) radiologically confirmed pneumonia, 3) NIRT for $\geq$ 24 h to treat hypoxemic non-hypercapnic ARF (PaO2 < 70 mmHg and/or PaCO2 $\leq$ 45 mmHg while breathing on oxygen-therapy at PIMCU admission). Exclusion criteria were: 1) conventional oxygen-therapy without need of NIRT; 2) NIRT before admission to the Pneumo-COVID Unit; 3) NIRT after extubation.

Hospital setting and NIRT algorithm

The study was performed in the 28-beds COVID-19 section of PIMCU [25], a specialized monitored area with an active full-day shift run by Pulmonologists with a nurse–patient ratio to 1:6, two physiotherapists working over 12 h daytime. Non-invasive parameters were monitored (SpO2, heart rate, blood pressure, RR) and transmitted to a central monitor in the nurse-working station. PIMCU COVID-19 Section managed the majority of SARS-Cov2 patients requiring NIRT in the Hospital. Non-DNI patients failing NIRT were endotracheally intubated and transferred to the ICU COVID-19 section of the Hospital.

NIRT was administered by means of a single or multiple devices based on algorithm adopted in the unit during the COVID-19 pandemic [14] (Fig. 1 supplementary). An initial 2–4 h's trial of HFNC was applied in patients showing mild hypoxemia (PaO2/FiO2 = 200–300) without signs of respiratory distress: flow was started from 40 and increased till 60 l/min according to PaCO2 level and patient comfort; FiO2 was titrated to achieve SpO2 between 94–96%. If HFNC trial did not improve oxygenation, concurrent pronation was attempted (2–3 h sessions three times/day). In case of failure/intolerance

of HFNC, next step was application of CPAP titrating flow-rate from 60 to 120 l/min according to PaCO2 level and patient's comfort, Positive End-Expiratory Pressure (PEEP) level from 5 to 15 cmH2O and FiO2 targeted to achieve SpO2 of 94–96%. Pronation was combined with CPAP if there was no improvement. In case of failure/intolerance of both HFNC and CPAP, next step was a NIV trial, delivered in Pressure Support (PS) mode. If applied with oronasal/full-face mask, PS was titrated to achieve an expiratory Tidal Volume (TV) of 6 ml/kg and PEEP values and FiO2 targeted to SpO2 of 94–96%. For patients treated with helmet, setting of PS and PEEP were augmented by 50% compared to mask setting [26]. CPAP or NIV were the first-choice NIRT option to manage more demanding severely hypoxemic and tachi-dyspnoic patients [PaO2/FiO2 < 200, respiratory rate(RR) > 25/bpm].

For safety reasons related to the reduced risk of SARS-CoV2 spreading among healthcarers, the following precautions were taken: surgical mask was over the mouth during HFNC; helmet was the preferred interface in patients receiving CPAP/NIV devices; for patients undergoing NIV with oronasal/full face, double limb circuits and non-vented interfaces were the preferred equipment [27].

If patients undergoing NIRT with/without pronation became agitated (Richmond Agitation Sedation Score, RASS ≥ 2), analgosedation was provided using drugs alone or in combination (Morphine, Dexdemetomidine, Promazina, Propofol). Pharmacologic treatment with either demonstrated or suggested efficacy against COVID-19 syndrome (steroids, heparin, Remdesivir) were administered, together with either enteral or parenteral nutritional support and therapy for non-pulmonary organ dysfunctions [28–30].

NIRT outcomes

The primary outcome of the study was the effectiveness of OI in predicting NIRT failure at baseline (t0), 12 (t12) and 24 (t24) hours of treatment. The secondary outcome was the predictive prognostic value of non-OI variables for NIRT failure.

Failure of NIRT was defined as requirement of ETI/IMV (no-DNI patients) or in-hospital death (DNI patients). ETI was indicated if one or more of the following criteria were achieved: 1) cardiac arrest; 2) haemodynamic instability/shock despite infusion of vasoactive amines; 3) worsening of hypoxemia (PaO2/FiO2 lower than 20% versus baseline) and or hypercapnic acidosis (pH < 7,25) associated with persistent signs of respiratory distress, worsening of neurological conditions (Kelly score < 3); 4) psychomotor agitation (RASS ≥ + 2) despite analgosedation; 5) inability to maintain a patent airway with impaired cough reflex and accumulated secretions..

Oxygenation indices (OI)

The following OI were collected: SpO2/FiO2, PaO2/FiO2, s-PaO2/FiO2 ratio, Respiratory Index (RI) and O2- gradients (a-ADO2, adj-a-ADO2D).

The following equations were used to calculate:

(1) s-PaO2/FiO2 as the ratio to FiO2 of standardised PaO2 [(s-PaO2) = 1,66xPaCO2 value + PaO2 value-66,4];
(2) a-ADO2 = [(FiO2)x(atmospheric pressure−H2O pressure)−(PaCO2/0,8)]−PaO2;
(3) adjA-aDO2 = expected-measured A-aDO2; the expected gradient was derived using the following formula (Age/4) + 4.
(4) RI = A-aDO2/PaO2.

Statistical analysis

Continuous variables were expressed as mean ± standard deviation (SD) and categorical variables as number (percentage). Comparisons between NIRT success and failure groups were performed using independent samples t tests and the Chi-square test, respectively.

OI and non-OI related (demographic and clinical) variables were evaluated through logistic regression analysis to identify predictors of NIRT failure.

Demographic and clinical variables were individually evaluated as independent predictors of NIRT outcome adjusted for age, introduced as a covariate in the logistic regression model. The odds ratio (OR) for each predictor was calculated. P values < 0.05 were considered statistically significant. Variables that were found to be correlated with NIRT outcome with $p < 0.05$ were entered into a multivariable regression model.

Changes in mean OI values at t12 and t24 compared to t0 were assessed with the paired t test.

To define the accuracy of OI in predicting NIRT failure, Receiver Operating Characteristics (ROC) curves with area under the curve (AUC) analysis were used. The sensitivity and specificity of the scores were determined; the cut-off points corresponded to the maximum of the Youden index. Finally, cut-off values were entered into the multivariable analysis to calculate the OR for NIRT failure at t0, t12, t24 after adjusting for age, as well as for demographic and clinical predictors.

Statistical analysis was performed using Stata Release 13/MP2 (Stata Corp,TX, USA).

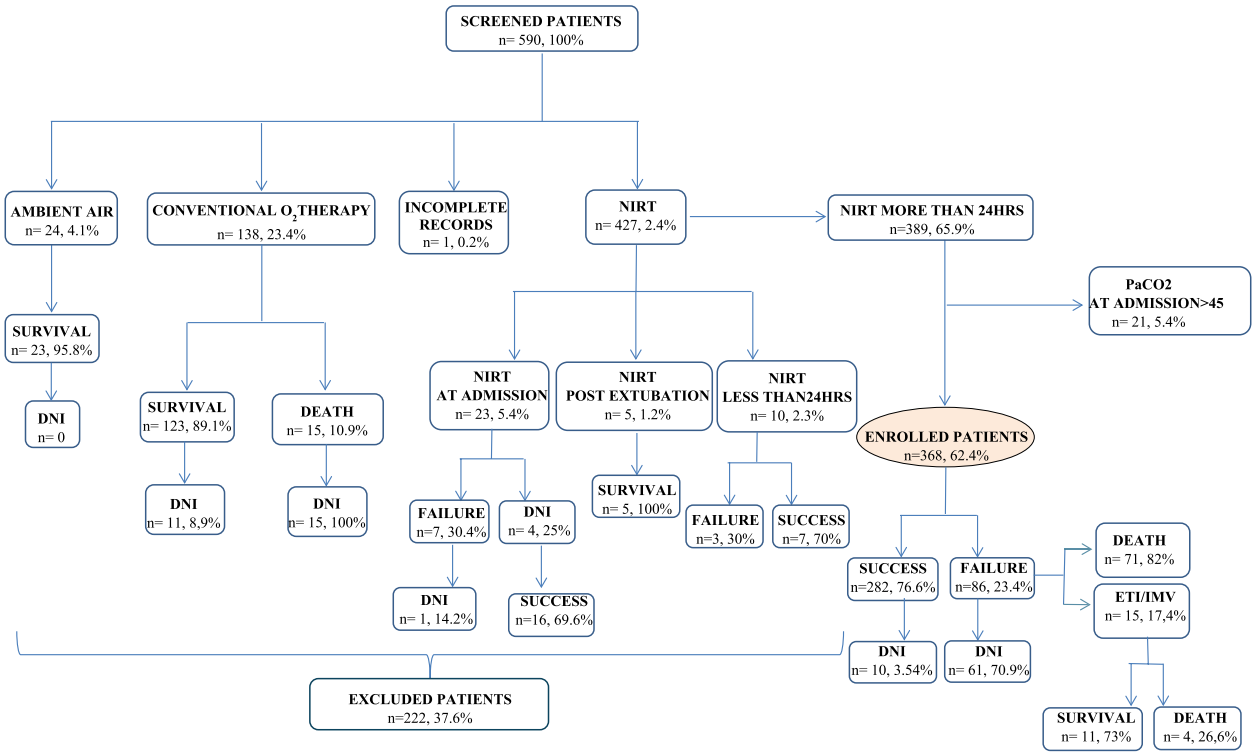

Fig. 1 Flow chart of enrolled and excluded patients. NIRT= non invasive respiratory therapies; DNI= do not intubate; ETI= endotracheal intubation; IMV= invasive mechanical ventilation

Results

Among the 590 patients screened, 368 (62,4%) were enrolled in the study. Reasons for the exclusion were reported in the Fig. 1.

NIRT outcome

NIRT failure occurred in 86/368 patients (23.4%) with an overall hospital mortality of 19,6% (72/368): 15/86 (17,4%) received ETI/IMV, with 4 patients died after intubation (Fig. 1).

DNI status was recorded in 71/368 (19.3%) patients.

The majority of the patients received multiple NIRT devices. The rate of success was lower with CPAP/NIV support (38,0%) versus CPAP/NIV/HFNC (82,7%) and HFNC alone (82,6%); this finding is correlated with the fact that the CPAP/NIV was applied as first-choice ventilatory option to more severe patients as compared to the latter supports (Fig. 2 supplementary).

Non-oxygenation indices

Elderly, DNI status, multiple pre-existing comorbidities were significantly associated with NIRT failure in the logistic regression analysis (Table 1). In Table 1 we note the variables significantly associated with NIRT failure in the multivariate analysis after the adjustement for age; as the matter of the fact, need of sedation showed the highest risk of NIRT failure.

Oxygenation indices

The study population showed at t0 mild hypoxemia and hypocapnia (Table 1 supplementary). In patients failing NIRT, a significant worsening was observed over time for SpO2/FiO2, a-ADO2, adj-aADO2 at t12 and t24, and for PaO2/FiO2 and RI at t24 (Table 2). In patients in which NIRT failed, PaCO2 level was significantly lower at t0, but it was significantly higher at t12 and t24 as respect to those in whom NIRT had success (Table 2 supplementary). ROC curves for each OI at to,t12,t24 were reported in the supplementary Figs. 3, 4 and 5. In Table 3, the cut-off values of OI were reported according to the best sensitivity and specificity of ROC curves at t0, t12, t24. In the final multivariate analysis, PaO2/FiO2, s-PaO2/FiO2 and RI were significantly associated with NIRT failure at any time (at t0: PaO2/FiO2 ≤ 200, s-PaO2/FiO2 ≤ 159, RI > 1,74; at t12: PaO2/FiO2 ≤ 181, s-PaO2/FiO2 ≤ 151,7, RI > 2,60; at t24: PaO2/FiO2 ≤ 180, s-PaO2/FiO2 ≤ 160,4, RI > 2,37) while SpO2/FiO2 ≤ 300 and O2 gradients (a-ADO2 > 220,7, adj-a-ADO2D > 128,86, RI > 2,37) predicted NIRT failure, respectively at t0 and t24.

Table 1 Demographic data, clinical pathological and behavior aspects and specific interventions during hospitalizationaccordingto the NITR success and failure

Parameters	All patients	Patients Group			Logistic regression model adjusted for age			Multivariate analysis		
		NIRT success	NIRT failure	*p*	OR	*p*	95% CI	OR	*p*	95% CI
General										
Age (years) (mean±SD)	69,2±14,5	65,7±13,9	80,7±9,5	<0,0001	-	-	-	1,07	0,004	1,02-1,11
Male	227 (61,7%)	171 (75,3%)	56 (24,7%)	0,455	1,74	0,049	1,00-3,04	2,73	0,005	1,35-5,53
DNI (do not intubate order)	71 (19,3%)	10 (14,1%)	61 (85,9%)	<0,0001	31	<0,0001	14,34-66,96			
Time in NIRT (h)	9,9±7,6	9,5±6,6	11,1±10,3	0,10	1	0,738	0,97-1,04			
Clinical pathological and behaviour aspects										
Charlson index >3	177 (48,1%)	102 (57,6%)	75 (42,4%)	<0,0001	2,82	0,025	1,14-6,95	1,84	0,261	0,64-5,33
Neurological comorbidities	62 (16,8%)	33 (53,2%)	29 (46,8%)	<0,0001	2,08	0,028	1,08-3,98	1,26	0,576	0,57-2,78
Psychiatric comorbidities	70 (19,0%)	58 (82,7%)	12 (17,1%)	0,171	0,67	0,284	0,32-1,40			
Delirium	27 (7,3%)	14 (51,9%)	13 (48,1%)	0,002	2,17	0,085	0,90-5,25			
Agitation/confusion	140 (38,0%)	73 (52,1%)	67 (47,9%)	<0,0001	5,51	<0,0001	2,96-10,25	2,42	0,021	1,14-5,14
Diabetes	77 (20,9%)	64 (83,1%)	13 (16,9%)	0,13	0,6	0,166	0,29-1,24			
Cardiovascular comorbidities	84 (22,8%)	53 (63,1%)	31 (36,9%)	0,001	1,02	0,957	0,55-1,88			
Specific interventions during hospitalization										
No Pronation	102 (27,7%)	55 (53,9%)	47 (46,1%)	<0,0001	2,84	0,001	1,57-5,14	3,65	0,001	1,74-7,62
Sedation	190 (51,6%)	113 (59,5%)	77 (40,5%)	<0,0001	9,07	<0,0001	4,21-19,58	8,53	<0,0001	3,47-21,00

Logistic regression model performed for NIRT failure: individual parameters with age and model with parameters independently associated with NIRT failure

The predictive capability of NIRT failure expressed by OR increased from t0 (between 2,01 and 2,55) to t12 (between 3,19 and 3,67) and t24 (between 2,24 to 5,89). The highest OR at t0, t12 and t24 were expressed respectively by SpO2/FiO2, PaO2/FiO2, s-PaO2/FiO2 (Table 4).

Discussion

To our knowledge, this is the first study that analysed the independent prognostic value of multiple OI in predicting early failure within 24 h of NIRT applied outside ICU to a large series of patients with ARF due to SARS-CoV-2 Pneumonia; furthermore, it empathises the role of non-oxygenation-related parameters in contributing to their outcome.

The main findings of the study are:

1)effectiveness in predicting NIRT failure varies across the OI and increased over time, being highest after 24 h of respiratory support; conventional and standardized PaO2/FiO2, as well as RI showed significant prognostic value at any time of observation, while O2 gradients predicted NIRT outcome only after 24 h of treatment;

2)SpO2/FiO2 ≤ 300, PaO2/FiO2 ≤ 151,7 and s-PaO2/FiO2 ≤ 160,4 resulted the best predictors of NIRT outcome, respectively at baseline, 12 and 24 h of NIRT;

3) among non-oxygenation parameters, elderly age, male gender, Charlson Index > 3, neurological comorbidities, agitation/confusion, need of sedation, inability to tolerate pronation were independently correlated with NIRT failure, with sedation status being the best prognostic factor.

These findings are coherent with the fact that pathophysiology of hypoxemia in COVID-19 pneumonia is complex and multi-factorial [1, 31–34]. In the early phase, impairment in alveolar diffusing capacity is the main "driver" of "silent hypoxemia" which is likely to respond to increased FiO2. In the later phases, alveolar consolidations develop, resulting in V/Q mismatch and shunt-related hypoxemia which is more likely to respond to NIRT by means of improving alveolar recruitment [14, 31, 35, 36]. Microvascular thrombosis may worsen hypoxemia shifting V/Q towards higher values [32, 33]. As lung damage progresses, persistent poor oxygenation induces hyperventilation with hypocapnia and tachidyspnea [37].

PaO2/FiO2 ratio is the most widely applied OI which correlates with mortality in ARDS [19] and COVID-19 related hypoxemia [38, 39]. However, it has important physiologic drawbacks. Firstly, PaO2/FiO2 is strongly FiO2-dependent; if the administered oxygen flow is inappropriately increased, PaO2/FiO2 ratio drops and severity of ARF may be overweighted. Secondly, PaO2/FiO2 may underweight the severity of ARF in

Table 2 Comparison of oxygenation indices at t12 vs t0 and at t24 vs t0

Arterial blood gases parameters	t0		t12		t12 vs t0		t24		t24 vs t0	
	mean	95%CI	mean	95%CI	*P*	var%	mean	95%CI	*P*	var%
Total Patients (*N*=368)										
PaCO2, mmHg	32,9	32,4-33,4	34,0	33,5-34,6	0,0000	3%	34,9	34,2-35,6	0,0000	6%
PaO2/FiO2	214,4	206,8-221,9	205,8	197,2-214,4	0,0942	-4%	211,6	202,6-220-6	0,5980	-1%
sPaO2/FiO2	174,3	167,5-181,0	185,0	176,5-193,5	0,0322	6%	192,1	183,4-200,7	0,0007	10%
SpO2/FiO2	302,1	290,6-313,6	196,8	191,7-201,8	0,0000	-35%	206,7	201,1-2012,2	0,0000	-32%
a-ADO2	150,1	138,4-161,7	221,3	212,9-229,6	0,0000	47%	208,1	199,1-217,1	0,0000	39%
adj-a-ADO2D	128,7	117,1-140,4	199,9	191,7-208,2	0,0000	55%	186,8	177,8-195,7	0,0000	45%
RI	2,24	2,06-2,42	2,57	2,42-2,72	0,0010	15%	2,50	2,34-2,67	0,0117	12%
NIRT success (*n*= 282)										
PaCO2, mmHg	32,6	32,1-33,1	33,7	33,1-34,3	0,0003	3%	34,5	33,9-35,1	0.0000	6%
PaO2/FiO2	223,1	214,9-231,3	217,6	207,9-227,3	0,3544	-2%	228,8	218,7-138,9	0,3623	3%
sPaO2/FiO2	180,0	172,7-187,3	195,2	185,5-204,8	0,0110	8%	208,2	198,4-217,9	0,0000	16%
SpO2/FiO2	316,6	303,4-329,8	200,7	194,9-206,6	0,0000	-37%	213,3	206,9-219,7	0,0000	-33%
a-ADO2	138,0	125,5-150,5	211,1	202,2-220,1	0,0000	53%	191,7	182,8-200,6	0,0000	39%
adj-a-ADO2D	117,5	105,0-130,0	190,6	181,7-199,5	0,0000	62%	171,2	162,4-180,0	0,0000	46%
RI	2,00	1,82-2,18	2,33	2,17-2,48	0,0033	17%	2,14	1,98-2,29	0,2212	7%
NIRT failure (*n*= 86)										
PaCO2, mmHg	33,9	32,8-33,4	35,3	33,9-36,6	0,0184	4%	36,30	34,3-38,4	0,0171	7%
PaO2/FiO2	185,7	168,9-202,6	167,3	151,1-183,5	0,0567	-10%	155,1	140,5-169,7	0,0023	-16%
sPaO2/FiO2	155,4	139,8-171,0	151,8	135,8-167,7	0,6827	-2%	139,2	125,8-152,6	0,0824	-10%
SpO2/FiO2	254,3	233,2-275,5	183,6	173,7-193,5	0,0000	-28%	185,1	174,8-195,3	0,0000	-27%
a-ADO2	189,8	162,7-216,8	254,5	235,6-273,4	0,0000	34%	262,9	239,9-284,0	0,0000	39%
adj-a-ADO2D	165,6	138,5-192,7	230,3	211,5-249,2	0,0000	39%	237,8	215,7-259,8	0,0000	44%
RI	3,03	2,53-3,52	3,39	3,02-3,76	0,1307	12%	3,7	3,31-4,09	0,0075	22%

sPaO2/FiO2 standardized PaO2/FiO2 ratio, *a-ADO2* alveolar-arterial oxygen gradient, *adj-a-ADO2D* alveolar-arterial oxygen gradient adjusted for age, *RI* Respiratory Index, *NIRT* non invasive respiratory therapies, *t0* baseline, *t12* after 12 hours of NIRT, *t24* after 24 hours of NIRT

tachypneic-hypocapnic patients. Thirdly, PaO2/FiO2 cannot provide information on the mechanisms underlying hypoxemia [20]. Despite these patho-physiologic limitations, in our study, PaO2/FiO2 ratio kept a significant prognostic value in COVID-19 related Pneumonia in agreement with other experiences. In our study, PaO2/FiO2 ratio equal or lower than 200 (AUC = 0,654), 181 (AUC = 0,697) and 180 (AUC = 0,776) were independently associated with NIRT failure showing a OR of 2,14, 3,67 and 4,94 respectively at t0, t12 and t24. In the study of Prediletto et al. [40] conducted in 349 COVID-19-related hypoxemic patients (mean PaO2/FiO2 189,4; NIRT used in < 40% of patients), PaO2/FiO2 < 180 significantly predicted failure (AUC 0,742) defined as deaths or need of IMV.

SpO2/FiO2 closely mirrors hypoxemia strata defined by PaO2/FiO2 ratio [35, 36]. Due to the leftward shift of oxy-haemoglobin dissociation curve in hypoxemic and hypocapnic patients, SpO2/FiO2 is less dependent on changes of FiO2, keeping fairly stable values even for larger changes of PaO2 and FiO2. Conversely, SpO2/FiO2 measurement is poorly reliable in shock. Furthermore, it shares the same limitations reported for PaO2/FiO2 being not able to provide information on ventilatory status and mechanisms of hypoxemia. In the earlier phases of COVID-19 with "silent hypoxemia" [35, 36], SpO2/FiO2 may perform as well as ROX index (ratio between SpO2/FiO2 and RR) [41]; this may be explained by the fact that hyperventilation-induced hypocapnic compensation of hypoxemia in COVID-19 is mainly obtained by increase of tidal volume rather than by an increase in RR [40]. Furthermore, SpO2/FiO2 and ROX index at baseline significantly correlated to PaO2/FiO2 in a series of 100 COVID-19 patients with moderate-severe hypoxemia [42].

In our study, SpO2/FiO2 ratio equal or less than 300 (AUC = 0,662) was associated with NIRT failure showing a OR of 3,05 of at t0; this finding turned out to be the strongest predictive OI at that time. These reports are similar to what found in other studies [43, 44]. In a series of 133 severely hypoxemic COVID-19 patients treated with HFNC, Kim et al. demonstrated that SpO2/FiO2

Table 3 ROC-AUC values and best sensitivity and specificity cut off for all oxygenation indices at t0, t12, t24

Oxygenation indices	AUC	95%CI	Sensitivity %	Specificity %	Cut off
At t0					
PaO2/FiO2	0,654	0,59-0,72	66	59,3	200
s-PaO2/FiO2	0,615	0,56-0,67	65,2	58,1	159
SpO2/FiO2	0,662	0,60-0,72	55,7	70,9	300
a-ADO2	0,644	0,58-0,71	68,6	57,1	114,4
adj-a-ADO2D	0,628	0,56-0,69	65,1	58,9	100,31
RI	0,654	0,59-0,72	65,1	59,9	1,74
At t12					
PaO2/FiO2	0,697	0,63-0,76	62,4	70,9	181
s-PaO2/FiO2	0,672	0,62-0,72	64,5	64	151,7
SpO2/FiO2	0,625	0,55-0,70	54,6	60,5	181,5
a-ADO2	0,644	0,57-0,71	60,5	58,9	239,5
adj-a-ADO2D	0,632	0,56-0,70	60,5	57,1	214,08
RI	0,69	0,63-0,75	66,3	63,8	2,6
At t24					
PaO2/FiO2	0,776	0,73-0,82	68,4	80,2	180
s-PaO2/FiO2	0,769	0,71-0,83	70,2	79,1	160,4
SpO2/FiO2	0,666	0,60-0,73	57,1	64	192,1
a-ADO2	0,703	0,64-0,77	66,3	62,4	220,7
adj-a-ADO2D	0,693	0,63-0,76	70,9	57,8	186,26
RI	0,768	0,71-0,83	80,2	66,7	2,37

sPaO2/FiO2 standardized PaO2/FiO2 ratio, *a-ADO2* alveolar-arterial oxygen gradient, *adj-a-ADO2D_* alveolar-arterial oxygen gradient adjusted for age, *RI* Respiratory Index, *NIRT* non invasive respiratoy therapies, *t0* baseline, *t12* after 12 hours of NIRT, *t24* after 24 hours of NIRT

ratio was more accurate than ROX index as predictor of failure, providing the greatest predictivity at 1 h of treatment [43]. In a population of 456 hypoxemic COVID-19 patients managed outside ICU, Cattazzo et al. found that PaO2/FiO2, ROX index and SpO2/FiO2 predicted ETI or death with similar accuracy [44].

s-PaO2/FiO2 well estimates V/Q mismatch in hypocapnic patients [45–47] because it adjusts the conventional ratio to the PaCO2 value; thus avoid to underestimate the worsening of lung gas-exchange in hyperventilating patients. In our study, s-PaO2/FiO2 ratio equal or lower than 159 (AUC = 0,615), 151,7 (AUC = 0,672) and 160.4 (AUC = 0,769) were associated with NIRT failure showing a OR of 2,23, 2,56 and 6,88 respectively at t0, t12 and t24; this resulted the strongest predictive OI after 24 h of NIRT. Prediletto et al. [40] demonstrated that s-PaO2/FiO2 predicted death better than conventional PaO2/FiO2; s-PaO2/FiO2 values lower than 170 and 125 best prognosticated failure and mortality, respectively [40].

Oxygen gradients and RI gives information on the patho-physiology of hypoxemia and are influenced by capnia and respiratory effort [48–50]. A-aO2 values pathologically increases in case of worsening of V/Q matching and shunt due COVID-19 interstitial and vascular abnormalities [51].

In our study, RI cut-offs were able to predict NIRT outcome failure at any time of observation; its prognostic value increased at 24 h of NIRT. RI cut-off greater than 2,37 at 24 h of treatment was associated with NIRT failure showing a OR of 4,5. Conversely, increased oxygen gradients predicted NIRT failure only after 24 h. In non-COVID-19 pneumonia A-a gradient was a useful indicator of severity and outcome [52–54]. In COVID-19 mildly hypoxemic patients, AaDO2 predicted occurrence of severe pneumonia, ICU admission and hospital readmission, but not mortality [55–57]. In a series of severely hypoxemic 165 patients started on NIV for COVID-19 pneumonia, the capability of A–a gradient > 430,83 to predict mortality was higher than what found for other arterial blood gas values, including PaO2/FiO2 [17]. Conversely, in a recent study, Singh et al. [18] found that aADO2, adjaADO2 and RI were not sensitive nor specific, with a poor accuracy in predicting mortality in severe COVID-19 pneumonia.

The comparison of our findings with the available scanty published data investigating the prognostic value of OI in NIRT-treated COVID 19 patients is biased by differences in terms of severity of ARF, degree of hypocapnia, types of NIRT, and setting of treatment.

Table 4 Multivariate analysis for assessing capability of different OI in predicting NIRT failure a t0,t12 and t24 according to ROC-related cut off

Oxygenation indices at t0	ROC cut-off	NIRT failure %		Ref. Categhory	Logistic regression model adjusted for age			Multivariate Analysis*		
		≤ cut-off	> cut-off	OR=1	OR	*p*	95%CI	OR	*p*	95% CI
PaO2/FiO2 ≤ 200	200	34,2	15,7	>200	2,58	0,001	1,47-4,55	2,14	0,026	1,09-4,17
sPaO2/FiO2 ≤ 159	159	33,1	16,6	>159	2,23	0,005	1,27-3,91	2,01	0,04	1,03-3,93
SpO2/FiO2 ≤ 300	300	34,6	13,8	>300	3,05	<0,0001	1,69-5,52	2,55	0,008	1,28-5,11
a-ADO2>114,4	114,4	14,8	32,4	≤ 114,4	2,63	0,001	1,48-4,69	1,92	0,056	0,98-3,75
adj-a-ADO2D >100,31	100,3	15,7	32,2	≤100,31	2,22	0,006	1,26-3,92	1,78	0,088	0,92-3,46
RI>1,74	1,74	15,5	32,7	≤1,74	2,35	0,003	1,33-4,15	2,17	0,023	1,11-4,23
Oxygenation indices at t12	ROC cut-off	NIRT failure %		Ref. Categhory	Logistic regression model adjusted for age			Multivariate Analysis*		
		≤ cut-off	> cut-off	OR=1	OR	*p*	95%CI	OR	*p*	95% CI
PaO2FiO2 ≤ 181	181	35,7	12,7	>181	3,01	<0,0001	1,67-5,40	3,67	<0,0001	1,82-7,43
sPaO2/FiO2 ≤ 151,7	151,7	35,3	14,6	>151,7	2,56	0,001	1,45-4,51	3,19	0,001	1,59-6,40
SpO2/FiO2 ≤ 181,5	181,5	28,7	18,2	>181,5	*1,55*	*0,125*	0,89-2,71	1,62	0,154	0,83-3,15
a-ADO2>239,5	239,5	17,4	30,5	≤239,5	*1,55*	*0,122*	0,80-2,72	1,63	0,146	0,84-3,15
adj-a-ADO2D >214,08	214,1	17,9	29,7	≤214,08	*1,56*	*0,118*	0,89-2,73	1,55	0,192	0,80-3,01
RI>2,60	2,6	14,3	35,4	≤2,60	2,68	0,001	1,52-4,75	3,26	0,001	1,62-6,57
Oxygenation indices at t24	ROC cut-off	% of failure		Ref. Categhory	Logistic regression model adjusted for age			Multivariate Analysis*		
		≤ cut-off	> cut-off	OR=1	OR	*p*	95%CI	OR	*p*	95% CI
PaO2/FiO2 ≤180	180	43,4	8,3	>180	7,2	<0,0001	3,76-13,76	4,94	<0,0001	2,40-10,17
sPaO2/FiO2 ≤ 160,4	160,4	44,4	8,4	>160,4	6,88	<0,0001	3,64-12,99	5,89	<0,0001	2,82-12,30
SpO2/FiO2 ≤ 192,1	192,1	31,1	16,2	>192,1	2,39	0,005	1,29-4,04	1,69	0,124	0,87-3,29
a-ADO2>220,7	220,7	14,6	34,6	≤220,7	2,79	<0,0001	1,57-4,95	2,24	0,011	1,22-4,65
adj-a-ADO2D >186,26	186,3	13,8	33,5	≤186,26	3,09	<0,0001	1,71-5,57	2,35	0,016	1,17-4,71
RI>2,37	2,37	8,7	42,0	≤2,37	6,25	<0,0001	3,30-11,85	4,5	<0,0001	2,18-9,30

sPaO2/FiO2 standardized PaO2/FiO2 ratio, *a-ADO2* alveolar-arterial oxygen gradient, *adj-a-ADO2D_* alveolar-arterial oxygen gradient adjusted for age, *RI* Respiratory Index, *NIRT* non invasive respiratory therapies, *t0* baseline, *t12* after 12 hours of NIRT, *t24* after 24 hours of NIRT

*Multivariate logistic regression analysis for each OI adjusted for sex, age, confusion state, Charlson index , neurologic comorbidities, pronation, sedation

For what non-OI variables concerns, our findings are in agreement with literature data [11, 43, 58, 59]. Accordingly, in our study, age, comorbidities, agitation and delirium were independently associated with NIRT failure, while success in performing pronation had a favourable prognostic value [60]. The rate of NIRT failure observed in our study (< 25%) is consistent with literature data on COVID-19 patients managed with NIRT outside ICU [61, 62]. It should be considered that a substantial proportion of our patients (19.3%) were not candidate to escalation to IMV; in DNI patients NIRT failure was by far greater than in the rest of population (85,9 vs 8,4%) in agreement with the literature [61, 62].

The study has several limitations. Firstly, the retrospective, single center and uncontrolled design of the study may reduce the strength of the results due to potential missed data, such as the smoke habits, and BMI; respiratory comorbities were not entered in the statistical analysis because of very low incidence (COPD, asthma and ILD in < 5% of the study population) in agreement with literature data. However, in the context of the global pandemic, challenges were reported in conducting RCTs. Secondly, the application of NIRT according to a specific internal algorithm may limit the generalizability of our findings compared to centres using other protocols. Thirdly, the analysis did not include RR, has been shown to be a strong predictor of NIRT outcome, especially if applied as a component of the ROX index; the lack of this parameter should have been mitigated by the peculiarity of "silent" COVID-19 ARF where tachypnea and dyspnoea arise usually late in the course of the pneumonia. Fourthly, the incidence of pulmonary embolism and vascular abnormalities as well as CT features and extension of lung infiltrated were not available; however, the aim of the study was to investigate the role of OI in hypoxemia independently on the underlying mechanisms. Finally, we have not been able to include in the prognostic analysis some severity scores (ie. Apache, Saps, Sofa) which are strong predictors of outcome in critically ill patients.

The strengths of this study include the large population analysed and the ability to assess for the first time a wide range of OI at multiple time of NIRT use, to identify the prognostic value of each one in the earlier phases of COVID-19 pneumonia managed outside ICU. This research on OI has potential important implication in non- COVID-19 related hypoxemic patients managed by NIRT in PMICU to select those who are more likely to require ETI and ICU admission.

Conclusions

In this study, the predictivity capability of OI varied according to the index and the time of NIRT. Early identification of patients for whom NIRT is likely to fail reduces the risk of a delayed ETI or a uselessly prolongation of respiratory support in COVID-19 related pneumonia managed outside ICU. The integrated prognostic values of different OI are likely to better match the complex pathophysiologic mechanisms underlying hypoxemia in COVID-19 pneumonia. Understanding the prognostic values of OI may help to develop algorithms aiming at improving mortality, need for intubation, and length of stay. These findings may be useful to build a predictive model also in no COVID-19 related hypoxemic pneumonia.

Abbreviations

a-ADO2	Arterial–alveolar oxygen gradient
adj-a-ADO2D	Age adjusted arterial–alveolar oxygen ratio
ARF	Acute hypoxemic respiratory failure
AUC	Area under the curve
CPAP	Continuous positive airway pressure
DNI	Do not intubate
ETI	Endotracheal intubation
HFNC	High flow nasal cannula
IMV	Invasive mechanical ventilation
NIRT	Non invasive respiratory therapies
NIV	Non invasive ventilation
PEEP	Positive end-expiratory pressure
PS	Pressure support
OI	Oxygenation indices
OR	Odds ratio
PIMCU	Pulmonary intermediate care unit
RASS	Richmond agitation sedation score
RI	Respiratory index
ROC	Receiver operating characteristics
RR	Respiratory rate
s-PaO2/FiO2	Standardised PaO2/FiO2
t0	Baseline
t12	At 12 h of NIRT
t24	At 24 h of NIRT
TV	Tidal volume

Supplementary Information

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Supplementary Material 1.

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Authors' contributions
All authors made substantial contributions as follows: (1) the conception and design of the study (RS), or acquisition of data (LC, LG), or analysis and interpretation of data (SA, SB, RS), (2) drafting the article or revising it critically for important intellectual content (RS, TR, SO), (3) final approval of the version to be submitted (RS, TR, SO).

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Declarations

Ethics approval and consent to participate

-Ethical Committee's approval and a written informed patient consent were achieved.
-The name of Ethical Committee is referred to Usl Toscana Sudest, Arezzo, Italy.
-Ethical issues for any animal data or tissue: NA.

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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References

1. Alhazzani W, Møller MH, Arabi YM, et al. Surviving Sepsis Campaign: guidelines on the management of critically ill adults with coronavirus disease 2019 (COVID-19). Intensive Care Med. 2020;46(5):854–87. https://doi.org/10.1007/S00134-020-06022-5.
2. Aziz S, Arabi YM, Alhazzani W, et al. Managing ICU surge during the COVID-19 crisis: rapid guidelines. Intensive Care Med. 2020;46(7):1303–25. https://doi.org/10.1007/S00134-020-06092-5.
3. Grasselli G, Greco M, Zanella A, et al. Risk factors associated with mortality among patients with COVID-19 in intensive care units in Lombardy, Italy. JAMA Intern Med. 2020;180(10):1345–55. https://doi.org/10.1001/JAMAINTERNMED.2020.3539.
4. Guan WJ, Ni ZY, Hu Y, et al. Clinical characteristics of coronavirus disease 2019 in China. N Engl J Med. 2020;382(18):1708–20. https://doi.org/10.1056/NEJMOA2002032.
5. Wu Z, McGoogan JM. Characteristics of and important lessons from the coronavirus disease 2019 (COVID-19) outbreak in China: summary of a report of 72 314 cases from the Chinese Center for Disease Control and Prevention. JAMA. 2020;323(13):1239–42. https://doi.org/10.1001/JAMA.2020.2648.
6. Zuo M, Huang Y, Ma W, et al. Expert recommendations for tracheal intubation in critically ill patients with noval coronavirus disease 2019. Chin Med Sci J. 2020;35(2):105–109. https://doi.org/10.24920/003724.
7. Estenssoro E, Loudet CI, Ríos FG, et al. Clinical characteristics and outcomes of invasively ventilated patients with COVID-19 in Argentina (SATICOVID): a prospective, multicentre cohort study. Lancet Respir Med. 2021;9(9):989–98. https://doi.org/10.1016/S2213-2600(21)00229-0.
8. Maslove DM, Sibley S, Boyd JG, et al. Complications of critical COVID-19. Chest. 2022;161(4):989–98.
9. Lu X, Xu S. Intensive care for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) in a makeshift ICU in Wuhan. Crit Care. 2020;24(1): 199. https://doi.org/10.1186/S13054-020-02914-6.
10. Scala R, Renda T, Corrado A, Vaghi A. Italian pulmonologist units and COVID-19 outbreak: "mind the gap"! Crit Care. 2020;24(1): 381. https://doi.org/10.1186/S13054-020-03087-Y.
11. Franco C, Facciolongo N, Tonelli R, et al. Feasibility and clinical impact of out-of-ICU noninvasive respiratory support in patients with COVID-19-related pneumonia. Eur Respir J. 2020;56(5):2002130. https://doi.org/10.1183/13993003.02130-2020.
12. Vaschetto R, Barone-Adesi F, Racca F, et al. Outcomes of COVID-19 patients treated with continuous positive airway pressure outside the intensive care unit. ERJ Open Res. 2021;7(1):1–8. https://doi.org/10.1183/23120541.00541-2020.
13. Coppadoro A, Benini A, Fruscio R, et al. Helmet CPAP to treat hypoxic pneumonia outside the ICU: an observational study during the COVID-19 outbreak. Crit Care. 2021;25(1): 80. https://doi.org/10.1186/S13054-021-03502-Y.
14. Winck JC, Scala R. Non-invasive respiratory support paths in hospitalized patients with COVID-19: proposal of an algorithm. Pulmonology. 2021;27(4):305–12. https://doi.org/10.1016/j.pulmoe.2020.12.005.
15. Ramirez GA, Bozzolo EP, Gobbi A et al. Outcomes of noninvasive ventilation as ceiling of treatment in patients with COVID19. Panminerva Med. 2022;64 (4):506–516. https://doi.org/10.23736/S0031-0808.21.04280-4.
16. Gabrielli M. Relationship between arterial-alveolar oxygen gradient, mortality and admission to intensive care unit in severe covid-19 related pneumonia: a pilot study. Biomed J Sci Tech Res. 2020;31(1). https://doi.org/10.26717/BJSTR.2020.31.005039.
17. Gupta B, Jain G, Chandrakar S, Gupta N, Agarwal A. Arterial blood gas as a predictor of mortality in COVID pneumonia patients initiated on noninvasive mechanical ventilation: a retrospective analysis. Indian J Crit Care Med. 2021;25(8):866. https://doi.org/10.5005/JP-JOURNALS-10071-23917.
18. Singh A, Soni KD, Singh Y, et al. Alveolar arterial gradient and respiratory index in predicting the outcome of COVID-19 patients; a retrospective cross-sectional study. Arch Acad Emerg Med. 2022;10(1):e28-e28. https://doi.org/10.22037/AAEM.V10I1.1543.
19. Definition Task Force ARDS, Ranieri VM, Rubenfeld GD, Thompson BT, Ferguson ND, Caldwell E, Fan E, Camporota L, Slutsky AS. Acute respiratory distress syndrome: the Berlin definition. JAMA. 2012;307(23):2526–33. https://doi.org/10.1001/jama.2012.5669.
20. Tobin MJ, Jubran A, Laghi F. PaO2/FIO2 ratio: the mismeasure of oxygenation in COVID-19. European Respiratory Journal. 2021;57(3):2100274. https://doi.org/10.1183/13993003.00274-2021.
21. Secco G, Salinaro F, Bellazzi C, et al. Can alveolar-arterial difference and lung ultrasound help the clinical decision making in patients with COVID-19? Diagnostics (Basel). 2021;11(5). https://doi.org/10.3390/DIAGNOSTICS11050761.
22. de Roos MP, Kilsdonk ID, Hekking PPW, et al. Chest computed tomography and alveolar–arterial oxygen gradient as rapid tools to diagnose and triage mildly symptomatic COVID-19 pneumonia patients. ERJ Open Res. 2021;7(1): 00737-2020. https://doi.org/10.1183/23120541.00737-2020.
23. Osuchowski MF, Winkler MS, Skirecki T, et al. The COVID-19 puzzle: deciphering pathophysiology and phenotypes of a new disease entity. Lancet Respir Med. 2021;9(6):622–42. https://doi.org/10.1016/S2213-2600(21)00218-6.
24. Swenson KE, Hardin CC. Pathophysiology of hypoxemia in COVID-19 lung disease. Clin Chest Med. 2023;44(2):239–48. https://doi.org/10.1016/j.ccm.2022.11.007.
25. Renda T, Scala R, Corrado A, Ambrosino N, Vaghi A, Scientific Group on Respiratory Intensive Care of the Italian Thoracic Society (ITS-AIPO). Adult pulmonary intensive and intermediate care units: the Italian Thoracic Society (ITS-AIPO) position paper. Respiration. 2021;100(10):1027–37. https://doi.org/10.1159/000516332. Epub 2021 Jun 8.
26. Vargas F, Thille A, Lyazidi A, et al. Helmet with specific settings versus facemask for noninvasive ventilation. Crit Care Med. 2009;37:1921–8. https://doi.org/10.1097/CCM.0b013e31819fff93.
27. Ferioli M, Cisternino C, Leo V, et al. Protecting healthcare workers from SARS-CoV-2 infection: practical indications. Eur Respir Rev. 2020;29(155):200068. https://doi.org/10.1183/16000617.0068-2020.
28. RECOVERY Collaborative Group, Horby P, Lim WS, et al. Dexamethasone in hospitalized patients with Covid-19. N Engl J Med. 2021;384(8):693–704. https://doi.org/10.1056/NEJMoa2021436.
29. Salton F, Confalonieri P, Centanni S, et al. Prolonged higher dose methylprednisolone versus conventional dexamethasone in COVID-19 pneumonia: a randomised controlled trial (MEDEAS). Eur Respir J. 2023;61(4):2201514. https://doi.org/10.1183/13993003.01514-2022.
30. Agarwal A, Hunt B, Stegemann M, et al. A living WHO guideline on drugs for covid-19. BMJ. 2020;4(370):m3379. https://doi.org/10.1136/bmj.m3379.
31. Bendjelid K, Raphaël G. Treating hypoxemic patients with SARS-COV-2 pneumonia: back to applied physiology. Anaesth Crit Care Pain Med. 2020;39(3):389–90. https://doi.org/10.1016/j.accpm.2020.04.003.

32. Copin MC, Parmentier E, Duburcq T, et al. Time to consider histologic pattern of lung injury to treat critically ill patients with COVID-19 infection. Intensive Care Med. 2020;46(6):1124–6. https://doi.org/10.1007/s00134-020-06057-8.
33. Li LQ, Huang T, Wang YQ, et al. COVID-19 patients' clinical characteristics, discharge rate, and fatality rate of meta-analysis. J Med Virol. 2020;92(6):577–83. https://doi.org/10.1002/jmv.25757.
34. Gattinoni L, Chiumello D, Caironi P, et al. COVID-19 pneumonia: different respiratory treatments for different phenotypes? Intensive Care Med. 2020;46(6):1099–102. https://doi.org/10.1007/s00134-020-06033-2.
35. Tobin MJ, Laghi F, Jubran A. Why COVID-19 silent hypoxemia is baffling to physicians. Am J Respir Crit Care Med. 2020;202(3):356–60. https://doi.org/10.1164/rccm.
36. Simonson TS, Baker TL, Banzett RB, et al. Silent hypoxaemia in COVID-19 patients. J Physiol. 2021;599(4):1057–65. https://doi.org/10.1113/JP280769.
37. World Health Organization. COVID-19 clinical management: living guidance. World Health Organization; 2021. https://apps.who.int/iris/handle/10665/338882. License: CC BY-NC-SA 3.0 IGO.
38. Cortinovis M, Perico N, Remuzzi G. Long-term follow-up of recovered patients with COVID-19. Lancet. 2021;397(10270):173–5. https://doi.org/10.1016/S0140-6736(21)00039-8.
39. Goh KJ, Choong MC, Cheong EH, et al. Rapid progression to acute respiratory distress syndrome: review of current understanding of critical illness from coronavirus disease 2019 (COVID-19) infection. Ann Acad Med Singap. 2020;49(3):108–18.
40. Prediletto I, D'Antoni L, Carbonara P, et al. Standardizing PaO2 for PaCO2 in P/F ratio predicts in-hospital mortality in acute respiratory failure due to Covid-19: a pilot prospective study. Eur J Intern Med. 2021;92:48–54. https://doi.org/10.1016/j.ejim.2021.06.002.
41. Roca O, Caralt B, Messika J, Samper M, et al. An index combining respiratory rate and oxygenation to predict outcome of nasal high-flow therapy. Am J Respir Crit Care Med. 2019;199(11):1368–76. https://doi.org/10.1164/rccm.201803-0589OC.
42. Zaccagnini G, Berni A, Pieralli F. Correlation of non-invasive oxygenation parameters with paO2/FiO2 ratio in patients with COVID-19 associated ARDS. Eur J Intern Med. 2022;96:117–9. https://doi.org/10.1016/j.ejim.2021.12.015.
43. Kim JH, Baek AR, Lee SI, et al. ROX index and SpO2/FiO2 ratio for predicting high-flow nasal cannula failure in hypoxemic COVID-19 patients: a multicenter retrospective study. PLoS One. 2022;17(5):e0268431. https://doi.org/10.1371/journal.pone.0268431.
44. Cattazzo F, Inglese F, Dalbeni A, et al. Performance of non-invasive respiratory function indices in predicting clinical outcomes in patients hospitalized for COVID-19 pneumonia in medical and sub-intensive wards: a retrospective cohort study. Intern Emerg Med. 2022;17(4):1097–106. https://doi.org/10.1007/s11739-021-02922-6.
45. Rahn H, Fenn WOO. A graphical analysis of the respiratory gas exchange. The American Physiological Society; 1955. Mays EE. An arterial blood gas diagram for clinical use. Chest. 1973;63(5):793–800.
46. Grasselli G, Tonetti T, Protti A, et al. Pathophysiology of COVID-19-associated acute respiratory distress syndrome: a multicentre prospective observational study. Lancet Respir Med. 2020;8(12):1201–8. https://doi.org/10.1016/S2213-2600(20)30370-2.
47. Covelli HD, Nessan VJ, Tuttle WK. Oxygen derived variables in acute respiratory failure. Crit Care Med. 1983;11(8):646–9. https://doi.org/10.1097/00003246-198308000-00012.
48. Sarkar M, Niranjan N, Banyal PK. Mechanisms of hypoxemia. Lung India. 2017;34(1):47–60. https://doi.org/10.4103/0970-2113.197116.
49. Harris DE, Massie M. Role of alveolar-arterial gradient in partial pressure of oxygen and PaO2/fraction of inspired oxygen ratio measurements in assessment of pulmonary dysfunction. AANA J. 2019;87(3):214–21.
50. Tobin MJ. Basing respiratory management of COVID-19 on physiological principles. Am J Respir Crit Care Med. 2020;201(11):1319–20. https://doi.org/10.1164/rccm.202004-1076ED.
51. Dhont S, Derom E, Braeckel E, Depuydt P, Lambrecht BN. The pathophysiology of 'happy' hypoxemia in COVID-19. Respir Res. 2020;21(1):198. https://doi.org/10.1186/s12931-020-01462-5.
52. Moammar MQ, Azam HM, Blamoun AI, et al. Alveolar-arterial oxygen gradient, pneumonia severity index and outcomes in patients hospitalized with community acquired pneumonia. Clin Exp Pharmacol Physiol. 2008;35(9):1032–7. https://doi.org/10.1111/j.1440-1681.2008.04971.x.
53. Shin JB, Lee WJ, Park JH, Choi SP, Jung SK, Woo SH. The prognostic value of alveolar-arterial oxygen gradient for community-acquired pneumonia in the ED. J Korean Soc EmergMed. 2013;24(5):571–8.
54. Avci S, Perincek G. The alveolar-arterial gradient, pneumonia severity scores and inflammatory markers to predict 30-day mortality in pneumonia. Am J Emerg Med. 2020;38(9):1796–801. https://doi.org/10.1016/j.ajem.2020.05.048).
55. Pipitone G, Camici M, Granata G, et al. Alveolar-arterial gradient is an early marker to predict severe pneumonia in COVID-19 patients. Infect Dis Rep. 2022;14(3):470–8. https://doi.org/10.3390/idr14030050.
56. Carlino MV, Valenti N, Cesaro F, et al. Predictors of intensive care unit admission in patients with coronavirus disease 2019 (COVID-19). Monaldi Arch Chest Dis. 2020;90(3). https://doi.org/10.4081/monaldi.2020.1410.
57. Xie C, Deng J, Li F, Wu C, Xu M, Yu B, Wu G, Zhong Y, Tang D, Li J. The association between alveolar-arterial oxygen tension difference and the severity of COVID-19 in patients. Infect Dis Ther. 2023;12(2):577–87. https://doi.org/10.1007/s40121-022-00752-3.
58. Pun BT, Badenes R, Heras La Calle G, et al. COVID-19 Intensive Care International Study Group. Prevalence and risk factors for delirium in critically ill patients with COVID-19 (COVID-D): a multicentre cohort study. Lancet Respir Med. 2021;9(3):239–50. https://doi.org/10.1016/S2213-2600(20)30552-X.
59. Liu L, Xie J, Wu W, et al. A simple nomogram for predicting failure of non-invasive respiratory strategies in adults with COVID-19: a retrospective multicentre study. Lancet Digit Health. 2021;3(3):e166–74. https://doi.org/10.1016/S2589-7500(20)30316-2.
60. Myatra SN, Alhazzani W, Belley-Cote E, et al. Awake proning in patients with COVID-19-related hypoxemic acute respiratory failure: a rapid practice guideline. Acta Anaesthesiol Scand. 2023;67(5):569–75. https://doi.org/10.1111/aas.14205.
61. Bellani G, Grasselli G, Cecconi M, et al. Noninvasive ventilatory support of patients with COVID-19 outside the intensive care units (WARd-COVID). Ann Am Thorac Soc. 2021;18(6):1020–6. https://doi.org/10.1513/AnnalsATS.202008-1080OC.
62. Cammarota G, Esposito T, Azzolina D, et al. Noninvasive respiratory supporct outside the intensive care unit for acute respiratory failure related to coronavirus-19 disease: a systematic review and meta-analysis. Crit Care. 2021;25(1):268. https://doi.org/10.1186/s13054-021-03697-0.

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