

# Arterial Blood Gas as a Predictor of Mortality in COVID Pneumonia Patients Initiated on Noninvasive Mechanical Ventilation: A Retrospective Analysis

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## ABSTRACT

**Background:** The alveolar–arterial oxygen (A–a) gradient measures the difference between the oxygen concentration in alveoli and the arterial system, which has considerable clinical utility.

**Materials and methods:** It was a retrospective, observational cohort study involving the analysis of patients diagnosed with acute COVID pneumonia and required noninvasive mechanical ventilation (NIV) over a period of 3 months. The primary objective was to investigate the utility of the A–a gradient (pre-NIV) as a predictor of 28-day mortality in COVID pneumonia. The secondary objective included the utility of other arterial blood gas (ABG) parameters (pre-NIV) as a predictor of 28-day mortality. The outcome was also compared between survivors and nonsurvivors. The outcome variables were analyzed by receiver-operating characteristic (ROC) curve, Youden index, and regression analysis.

**Results:** The optimal criterion for A–a gradient to predict 28-day mortality was calculated as  $\leq 430.43$  at a Youden index of 0.5029, with the highest area under the curve (AUC) of 0.755 ( $p < 0.0001$ ). On regression analysis, the odds ratio for the A–a gradient was 0.99. A significant difference was observed in ABG predictors, including PaO<sub>2</sub>, PaCO<sub>2</sub>, A–a gradient, AO<sub>2</sub>, and arterial–alveolar (a–A) (%) among nonsurvivors vs survivors ( $p$ -value  $< 0.001$ ). The vasopressor requirement, need for renal replacement therapy, total parenteral requirement, and blood transfusion were higher among nonsurvivors; however, a significant difference was achieved with the vasopressor need ( $p < 0.001$ ).

**Conclusion:** This study demonstrated that the A–a gradient is a significant predictor of mortality in patients initiated on NIV for worsening respiratory distress in COVID pneumonia. All other ABG parameters also showed a significant AUC for predicting 28-day mortality, although with variable sensitivity and specificity.

**Key messages:** COVID-19 pneumonia shows an initial presentation with type 1 respiratory failure with increased A–a gradient, while a subsequent impending type 2 respiratory failure requires invasive ventilation.

A significant difference was observed in ABG predictors, including PaO<sub>2</sub>, PaCO<sub>2</sub>, A–a gradient, AO<sub>2</sub>, and a–A (%) among nonsurvivors vs survivors. ( $p$ -value  $< 0.001$ ).

The vasopressor requirement, need for renal replacement therapy, total parenteral requirement, and blood transfusion need were higher among nonsurvivors than survivors; however, a significant difference was achieved with the vasopressor need ( $p < 0.001$ ).

**Keywords:** COVID-19 Acute Respiratory Distress Syndrome, Critically ill adults, Mortality predictors.

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## INTRODUCTION

Severe acute respiratory syndrome–related coronavirus-2 (SARS-CoV-2) is a virus-targeted respiratory disorder with a broad range of symptoms ranging from asymptomatic cases to severe pneumonia or acute respiratory distress syndrome (ARDS)<sup>1</sup>; the reported mortality rate is as high as 78% in critically ill patients.<sup>2</sup> For efficient use of limited healthcare resources, early detection of risk factors and timely management are critical to minimize the adverse outcome.<sup>3</sup>

The alveolar–arterial oxygen gradient (A–a gradient), which measures the difference between the oxygen concentration in alveoli and the arterial system, has considerable clinical utility in narrowing the differential diagnosis for the cause of hypoxemia.<sup>4</sup> Although a perfect system should have a zero A–a gradient, the underlying heterogeneity in capillary perfusion and alveolar ventilation from the apical to basal lung units leads to a physiological A–a gradient throughout the lung. It is further affected by demographic characteristics and various pathological

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processes. The pulmonary disorders that alter the ventilation–perfusion ratio or disturb the oxygen transfer from the alveoli to pulmonary circulation compromise the arterial oxygenation and increase this gradient.

The recent literature on COVID-19 pneumonia shows an initial presentation with type 1 respiratory failure with increased A–a gradient, while a subsequent impending type 2 respiratory failure requires invasive ventilation.<sup>5</sup> A higher A–a gradient at the initiation of noninvasive mechanical ventilation (NIV) signifies a higher degree of ventilation–perfusion mismatch or interstitial pathology. So, we hypothesized that it should reflect subsequent mortality in such patients. Thus, we aimed to assess the utility of ABG parameters as a predictor of 28-day mortality in COVID pneumonia patients initiated on NIV.

## MATERIALS AND METHODS

After institutional ethical clearance (via letter no AIIMS/IEC/21/17, dated January 9, 2021), under a retrospective, observational cohort design, this study involved the collection, classification, and analysis of patients aged >18 years of either sex, admitted to this tertiary care institute in between July and September 2020 (3-month data), diagnosed with acute COVID pneumonia, and required NIV. We excluded those with any previous history of cardiopulmonary disease, renal disorder, psychiatric illness, pregnancy, lactation, recent hospitalization (past 3 months), immunocompromised status, or malignancy. We also followed the patient’s data till discharge or death or 28 days since admission, whichever occurred first, through hospital records.

We categorized a patient as COVID-positive case on getting a positive reverse-transcriptase–polymerase chain reaction report from a nasal or pharyngeal swab specimen. According to the institution guidelines, patients were classified as moderate- or severe based on the presence of hypoxia ( $SpO_2 < 93\%$ ) or radiological evidence of pneumonia or ARDS and organ impairment and shock. A high-resolution computed tomographic scan was done for COVID-19 patients with inconclusive chest X-ray and persistent symptoms. The indication for initiation of NIV included standard protocol as followed in our tertiary care institute. The indications included symptoms of ARDS, such as dyspnea at rest, respiratory rate >25 breath/minute, use of accessory respiratory muscles, or paradoxical breathing, and signs of disturbed alveolar gas exchange in ABG parameters, including partial pressure of carbon dioxide ( $PaCO_2 > 45$  mm Hg), arterial power of hydrogen (pH) <7.25, the partial pressure of oxygen ( $PaO_2 < 60$  mm Hg) or ratio of the partial pressure of oxygen or fraction of inspired oxygen ( $PaO_2/FiO_2 < 200$ ). The indication for initiation of invasive mechanical ventilation included the following: poor patient compliance/leaking interface with no improvement in respiratory condition despite all efforts, Glasgow coma scale <9 or deterioration >3, hemodynamic instability, cardiac arrhythmia, the inability of the NIV to improve respiratory distress or gas exchange disturbance within 2 hours of initiation, apnea or respiratory rate (RR)>35 breaths/minute, or inability to maintain a patent airway.

The data collected comprised stay and 28-day mortality. The ABG parameters included  $PaO_2$ ,  $PaCO_2$ , bicarbonate ( $HCO_3$ ), a fraction of inspired oxygen concentration ( $FiO_2$ ),  $PaO_2/FiO_2$ , A–a gradient, respiratory index, and arterial–alveolar (a–A) oxygen ratio, by following equations:

- A–a ratio was calculated by the following equations:  
 $PaO_2 = FiO_2 (P_B - 47) - PaCO_2/R$   
 $PaO_2 = 0.21 \times (760 - 47) - PaCO_2/0.8$

$$PaO_2 = 150 - PaCO_2/0.8$$

Here  $PaO_2$  = partial pressure of alveolar oxygen,  $PaCO_2$  = partial pressure of arterial carbon dioxide,  $FiO_2$  = fraction of inspired oxygen,  $P_{atm}$  = atmospheric pressure (at sea level = 760 mm Hg),  $P_{H_2O}$  = water partial pressure in alveolus, 100% saturated (at sea level = 47 mm Hg) and R = respiratory quotient (normally 0.8).

- Respiratory index was calculated by dividing  $pO_2$  from A–a gradient:  
Respiratory index (RI) ( $RI = pO_2(A - a)/pO_2(a)$ )
- $PaO_2/FiO_2$  ratio was calculated by dividing alveolar oxygen to inspired oxygen
- a–A ratio was calculated as a ratio of arterial and alveolar  $PaO_2$ .

## AIMS AND OBJECTIVES

The primary objective was to investigate the utility of A–a gradient (pre-NIV) as a predictor of 28-day mortality in COVID pneumonia patients initiated on NIV.

The secondary objective included the utility of other ABG parameters (pre-NIV) as a predictor of 28-day mortality in the above patients. The outcome studied in terms of ABG parameters and other variables like the vasopressor requirement, the need for renal replacement therapy, total parenteral requirement, and blood transfusion was compared between survivors and nonsurvivors.

The sample size was calculated using Medcalc statistical software version 14.8.1. Taking into account a receiver-operating characteristic (ROC) curve value of 0.70 as significant for pre-NIV A–a gradient as a predictor of 28-day mortality, a null hypothesis ROC curve value of 0.50, an alpha error of 0.05, an 80% power, and a survival: mortality ratio of 3:1, we required sample size of 88 (66:22). To increase the significance of results, we aim to recruit all eligible cases for the assessment period. The statistical analysis was performed with Statistical Package for the Social Sciences version 23.0 software (SPSS, IBM Corp. Armonk, New York, United States). The data were expressed as means and standard deviation (SD) or as number and percentage. The outcome variables were analyzed by a ROC curve, Youden index, and regression analysis. Continuous data were analyzed by Student’s *t*-test. The Chi-square test analyzed the categorical parameters. A *p*-value <0.05 denotes statistical significance.

## RESULTS

We included 165 patients in the final analysis. Thirty-four patients expired (nonsurvivors), while the remaining (survivors) had a successful outcome. The mean age of included patients was 53.3 years; males were 61% and females 39%, most had no comorbidities, while others had hypertension or diabetes. The mean pre-NIV A–a gradient was 403.83 (range: 379.66–427.99). The mean  $FiO_2$  patients were receiving at this time point was 69.7% (range: 21–100%) through nasal prongs, face masks, venturi masks, or rebreathing masks. The mean pre-NIV  $PaO_2$  was 56.03 mm Hg (range: 28–96 mm Hg), and the mean  $PaCO_2$  was 29.7 mm Hg (range: 18–53 mm Hg), suggesting type I respiratory failure in the majority of the patients. The mean pH was 7.432 (range 7.28–7.54), while the mean  $HCO_3$  was 21.48 mEq/L (range 12.5–34), and the mean  $pO_2/FiO_2$  ratio was 89.87 (22.3–217.85) (Table 1). Mean ICU stay was 14.2 days.

For validity analysis, we plotted a ROC curve for each ABG parameter. The optimal criterion for A–a gradient to predict 28-day mortality was calculated as  $\leq 430.43$  (sensitivity: 67.94%, specificity: 82.35%) at a Youden index of 0.5029, with the highest area under the curve (AUC) of 0.755 ( $p < 0.0001$ ). On regression analysis (Table 2), the odds ratio (OR) for the A–a gradient was 0.99, indicating no further increase in the log-odds of mortality with an increase in A–a gradient above the threshold value.

The optimal criterion for PaO<sub>2</sub>/FiO<sub>2</sub> to predict 28-day mortality was measured as  $>110$  (sensitivity 31.3%, specificity 100%) at a Youden index of 0.31 and AUC of 58% ( $p$ -value: 0.0793). The optimal criterion for the respiratory index to predict 28-day mortality was found to be  $\leq 4.96$  (sensitivity 35.11%, specificity 100%) at a Youden index of 0.35 and AUC of 60% ( $p$ -value: 0.0194). The optimal criterion for a–A percentage to predict 28-day mortality was observed to be  $>24.9$  (sensitivity 35%, specificity 100%) at a Youden index of 0.35 and AUC of 60% ( $p$ -value: 0.0194). The optimal criterion for PaCO<sub>2</sub> to predict 28-day mortality was observed to be  $>24.9$  (sensitivity 88.5%, specificity 55.9%) at a

Youden index of 0.388 and AUC of 72.9% ( $p$ -value  $< 0.0001$ ). The optimal criterion of PaO<sub>2</sub> to predict 28-day mortality was observed to be  $\leq 54$  (sensitivity 56.5%, specificity: 82.5%, % LR+ 3.2) at a Youden index of 0.44 and AUC of 66.7% ( $p$ -value: 0.0014). The optimal pH criterion to predict 28-day mortality was observed to be  $\leq 7.468$  (sensitivity 79.4%, specificity: 64.7%, %LR+ 2.25, LR-0.32) at a Youden index of 0.44 and AUC of 66% ( $p$ -value: 0.0076). The optimal criterion of HCO<sub>3</sub> to predict 28-day mortality was observed to be  $>19.7$  (sensitivity: 61.1%, specificity: 82.4%) at a Youden index of 0.4342 and an AUC of 66.3% ( $p$ -value: 0.0016) (Table 3 and Fig. 1).

A significant difference was observed in ABG predictors, including PaO<sub>2</sub>, PaCO<sub>2</sub>, A–a gradient, AO<sub>2</sub>, and a–A (%) among nonsurvivors vs survivors ( $p$ -value  $< 0.001$ ). The vasopressor requirement, need for renal replacement therapy, total parenteral requirement, and blood transfusion need were higher among nonsurvivors than survivors; however, a significant difference was achieved with the vasopressor need ( $p < 0.001$ ) (Table 4).

### DISCUSSION

This study demonstrated that the A–a gradient is a significant predictor of mortality in patients initiated on NIV for worsening respiratory distress in COVID pneumonia. The optimal criterion for the A–a gradient to predict above was observed to be  $\leq 430.43$ . All other ABG parameters also showed a significant AUC for predicting 28-day mortality, although with variable sensitivity and specificity.

It is known that increased cardiopulmonary vascular shunt or altered alveolar diffusion barrier can substantially affect the A–a gradient.<sup>6</sup> Given the impact of COVID-19 interstitial pulmonary involvement on gas exchange, ventilation–perfusion mismatch,<sup>7</sup> and shunting, we decided to test ABG parameters' validity, particularly A–a gradient, in predicting mortality. The available data indicate that around 40% of COVID-19 patients develop ARDS (20% severe cases), with 5–10% requiring ICU admission and invasive ventilation. Although most patients survive an acute illness, a subset develops fibro-proliferative response marked

**Table 1:** Pre-noninvasive ventilation, arterial blood gas, and other parameters

Parameters	Mean and SD	95% CI
Age (years)	53.30 ± 12.99	51.305–55.301
ICU length of stay (days)	14.20 ± 6.80	4–40
A–a gradient	403.83 ± 157.21	379.663–427.998
PaO <sub>2</sub> /FiO <sub>2</sub>	89.88 ± 3.42	22.3–217.86
Respiratory index	8.35 ± 0.40	1.39–28.99
A–A (%)	26.08 ± 2.75	3.58–250
FiO <sub>2</sub>	69.70 ± 22.02	66.318–73.088
HCO <sub>3</sub>	21.48 ± 12.98	19.489–23.482
K <sup>+</sup>	3.74 ± 0.48	3.672–3.823
Na <sup>+</sup>	135.07 ± 6.46	134.085–136.073
PaCO <sub>2</sub>	29.692 ± 6.08	28.756–30.627
PaO <sub>2</sub>	56.03 ± 19.54	53.033–59.042
PaO <sub>2</sub> /FiO <sub>2</sub>	89.87 ± 43.94	83.119–96.632
pH	7.432 ± 0.06	7.423–7.442

PaCO<sub>2</sub>, partial pressure of carbon dioxide (mm Hg); pH, arterial power of hydrogen; PaO<sub>2</sub>, the partial pressure of oxygen (mm Hg); PaO<sub>2</sub>/FiO<sub>2</sub>, ratio of the partial pressure of oxygen or fraction of inspired oxygen; A–a gradient, alveolar–arterial gradient (mm Hg); HCO<sub>3</sub>, bicarbonate (mEq/L); a–A (%), arterial–alveolar (percentage); K<sup>+</sup>, Potassium (mEq/L); Na<sup>+</sup>, Sodium (mEq/L); SD, standard deviation; CI, confidence interval

**Table 3:** Regression analysis for A–a gradient

Variable	Odds ratio	95% CI	p-value
A–a gradient	0.9934	0.9904–0.9964	$< 0.0001$
Sample size	165	Nonsurvivors: 34 (20.61%) Survivors: 131 (79.39%)	

A–a gradient, alveolar–arterial gradient (mm Hg); CI, confidence interval

**Table 2:** Validity parameters for arterial blood gas and derived parameters

Parameter	AUC	YI	Criterion	Sensitivity	Specificity	+LR	–LR	p-value
A–a gradient	0.76	0.5	$\leq 430.43$	67.94 (59.2–75.8)	82.35 (65.5–93.2)	3.85	0.39	$< 0.0001$
PaO <sub>2</sub> /FiO <sub>2</sub>	0.58	0.31	$> 110$	31.30 (23.5–40.0)	100.00 (89.7–100.0)		0.69	0.0793
Respiratory index	0.60	0.35	$\leq 4.96$	35.11 (27.0–43.9)	100 (89.7–100.0)		0.65	0.0194
A–A (%)	0.60	0.35	$> 24.99$	35.11 (27.0–43.9)	100.00 (89.7–100.0)		0.65	0.0194
PaO <sub>2</sub>	0.67	0.39	$\leq 54$	56.49 (47.6–65.1)	82.35 (65.5–93.2)	3.2	0.53	0.0014
PaCO <sub>2</sub>	0.73	0.44	$> 24.9$	88.55 (81.8–93.4)	55.88 (37.9–72.8)	2.01	0.2	$< 0.0001$
pH	0.66	0.44	$\leq 7.47$	79.39 (71.4–86.0)	64.71 (46.5–80.3)	2.25	0.32	0.0076
HCO <sub>3</sub>	0.66	0.43	$> 19.7$	61.07 (52.2–69.5)	82.35 (65.5–93.2)	3.46	0.47	0.0016

PaCO<sub>2</sub>, carbon dioxide; pH, arterial power of hydrogen; PaO<sub>2</sub>, the partial pressure of oxygen; PaO<sub>2</sub>/FiO<sub>2</sub>, ratio of the partial pressure of oxygen or fraction of inspired oxygen; A–a gradient, alveolar–arterial gradient; HCO<sub>3</sub>, bicarbonate; a–A (%), arterial–alveolar (percentage)



**Table 4:** Comparison of demographic, arterial blood gas, and other outcome parameters among survivors vs nonsurvivors

Parameters	Survivors (n = 131)	Nonsurvivors (n = 34)	p-value
Age	51.34 ± 13.09	60.97 ± 9.34	0.154
pH	7.43 ± 0.0595	7.46 ± 0.061	0.012
pCO <sub>2</sub> (mm Hg)	30.67 ± 6.08	25.93 ± 4.49	0.000
pO <sub>2</sub> (mm Hg)	53.77 ± 19.29	64.79 ± 18.24	0.003
HCO <sub>3</sub> (mm Hg)	22.21 ± 14.37	18.70 ± 3.7	0.162
A–a gradient based on pO <sub>2</sub>	375.49 ± 157.15	513.04 ± 100.31	0.000
ICU length of stay	13.927 ± 6.86	15.206 ± 6.61	0.334
respiratory index	8.27 ± 5.6	8.69 ± 3.22	0.676
AO <sub>2</sub>	321.71 ± 161.2	448.25 ± 99.92	0.000
a–A (%)	28.90 ± 39.21	15.19 ± 5.75	0.000
Mechanical ventilation days	12.00 ± 1.2	11.40 ± 5.56	0.917
Vasopressor requirement	0.130 ± 0.33	0.515 ± 0.50	0.000
CRRT requirement	0.137 ± 0.345	0.176 ± 0.387	0.568
TPN requirement	0.092 ± 0.28	0.176 ± 0.38	0.159
Blood transfusion requirement	0.099 ± 0.30	0.206 ± 0.410	0.09

PaCO<sub>2</sub>, carbon dioxide; pH, arterial power of hydrogen; PaO<sub>2</sub>, the partial pressure of oxygen; PaO<sub>2</sub>/FiO<sub>2</sub>, ratio of the partial pressure of oxygen to fraction of inspired oxygen; A–a gradient, alveolar–arterial gradient; HCO<sub>3</sub>, bicarbonate; a–A (%), arterial–alveolar (percentage); CRRT, continuous renal replacement therapy; TPN, total parenteral nutrition

by fibroblast aggregation and deposition of collagen and other extracellular matrix components in the lung. Historically, the occurrence of severe fibro-proliferative pulmonary<sup>8</sup> disease has been associated with a poor prognosis, causing high mortality and/or prolonged ventilation dependence. In the present study, we found that the A–a gradient effectively predicted mortality in moderate to severe COVID-19 patients. Previous studies<sup>9</sup> have shown that the A–a gradient was higher among nonsurvivors than survivors who had community-acquired pneumonia (AUC 0.78), with a mean A–a gradient of 148.64 and 90.16 among nonsurvivors and survivors, respectively. In another published literature, AaDO<sub>2</sub> (A–a gradient) and AaDO<sub>2</sub> augmentation displayed good accuracy (AUC: 0.952 and 0.810, respectively) to predict ICU admission in patients with COVID-19. However, their cutoff value was 56.6 ± 17.5 in the ICU group and 25.9 ± 9.7 in the non-ICU group; given small sample size, strong emphasis cannot be laid upon results. Farina et al.<sup>10</sup> also investigated the role of A–a gradient in predicting the need for hospitalization, the survival rate, and identifying pneumonia in patients with SARS-CoV-2 infection. They reported that out of 168 patients with AaDO<sub>2</sub> ≤27, only 3 (1.8%) required readmission within 7 days; it could be attributed to the inclusion of patients with less disease severity. In our study, all patients were in respiratory failure requiring NIV, which could account for higher cutoff values of observed mean A–a gradient.

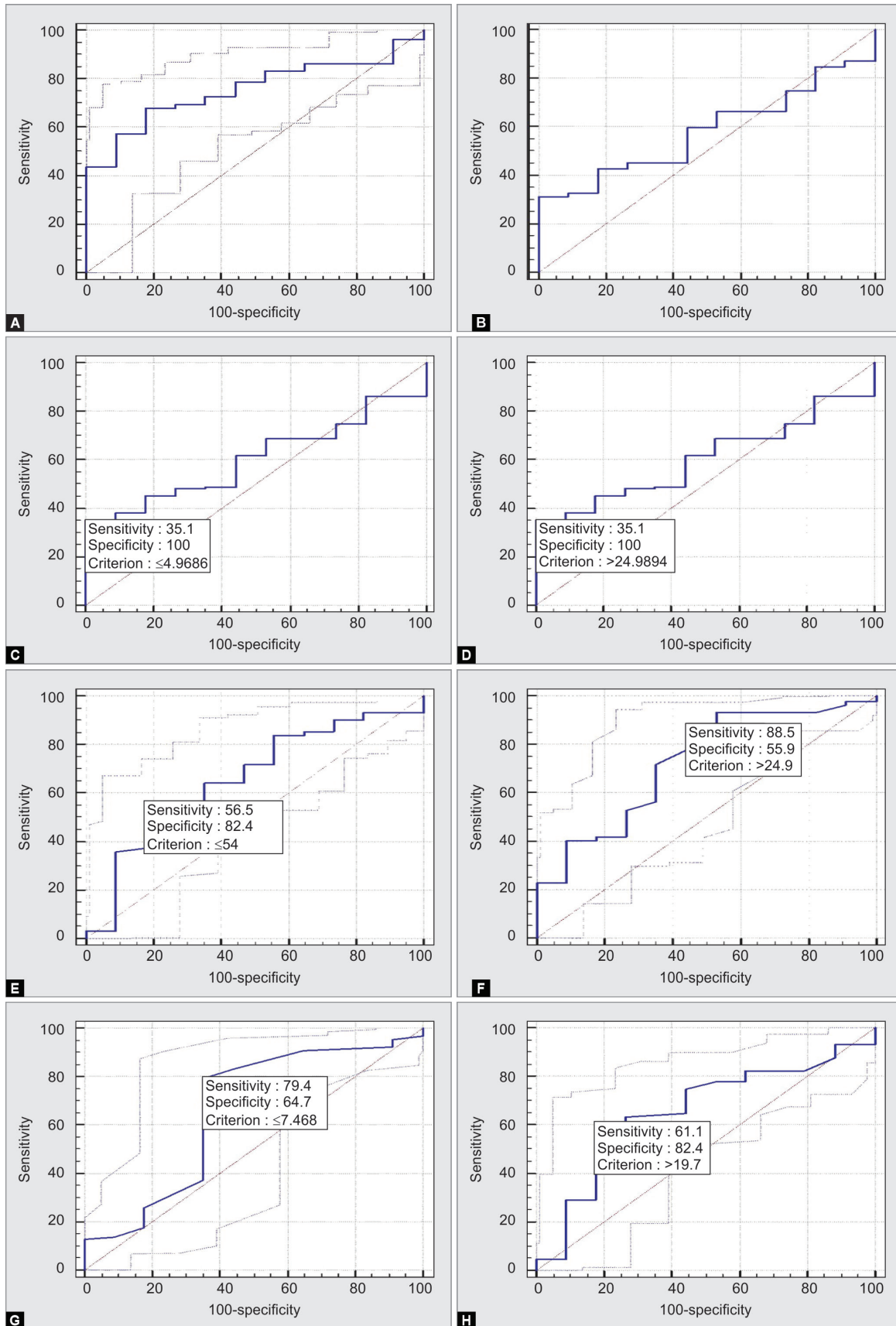
In recent years, the a–A tension ratio (PaO<sub>2</sub>/PaO<sub>2</sub>), sometimes denoted a–APO<sub>2</sub>, has been used as an index of pulmonary gas exchange. While the A–a tension difference (A–aPO<sub>2</sub>) is known to depend strongly on the FiO<sub>2</sub>, a–APO<sub>2</sub> is less dependent on the extrapulmonary factors.<sup>11</sup> The PaO<sub>2</sub>/FiO<sub>2</sub> ratio is also widely used as a clinical indicator of hypoxemia, though its diagnostic utility is controversial. The optimal criterion for PaO<sub>2</sub>/FiO<sub>2</sub>, respiratory index, and a–A percentage to predict 28-day mortality in our study were also found to have significant differences, as expected. We observed a considerable difference in ABG predictors, including PaO<sub>2</sub>, PaCO<sub>2</sub>, A–a gradient, AO<sub>2</sub>, and a–A (%) among

nonsurvivors vs survivors (*p*-value <0.001), which was expected in the disease. The hallmark of disease severity in COVID-19 patients is hypoxemia, although the associated symptoms, including respiratory distress, develop late in the disease (“silent hypoxemia”<sup>12</sup>). We calculated a criterion value of >24.9, ≤54, and ≤7.468 for PaCO<sub>2</sub>, pO<sub>2</sub>, and pH, respectively, to predict 28-day mortality in patients developing respiratory distress and requiring NIV. Tendon et al.<sup>13</sup> also demonstrated a significant difference in PaO<sub>2</sub> among survivors and nonsurvivors; a statistical difference was not observed for PaCO<sub>2</sub> and pH.

We also compared morbidity predictors, and patient course during the ICU stay, and higher need for vasopressor requirement, continuous renal replacement therapy requirement, total parenteral nutrition requirement, and blood transfusion need among nonsurvivors. The underlying cause is multifactorial, including hypovolemia (fever, restricted fluid administration to prevent overload), vasodilation (sepsis, deep sedation during mechanical ventilation), and right or/and left ventricular dysfunction (mechanical ventilation with high positive end-expiratory pressure, pulmonary embolism, and circulating cytokines decreasing contractility, myocarditis). Although the requirement for vasopressor support is quite common in COVID-19 ICU patients, the detailed hemodynamic profile or phenotype remains poorly documented. A similar duration of ICU stay was due to the development of the fibro-proliferative phase requiring oxygen supplementation, and it is further reflected by the similar need for parenteral nutrition, blood transfusion, and renal replacement therapy.

There were several limitations in this study. Although we followed a standard protocol for initiating invasive and NIV, changing guidelines from time to time concerning steroid therapy, antiviral therapy initiation, and self-proning protocol may have affected the patient outcome. Another limitation included the delayed availability of high-flow nasal cannula, which can also affect the outcome. The fact that the research was performed at





**Figs 1A to H:** Receiver-operating characteristic curve for (A) a gradient; (B)  $pO_2/FiO_2$ ; (C) respiratory index; (D) a-A (%); (E)  $PaO_2$ ; (F)  $PaCO_2$ ; (G) pH; (H)  $HCO_3$



one center is also a limitation of the study, restricting the findings' generalizability.

## CONCLUSION

The A–a gradient is a significant predictor of mortality in patients initiated on NIV for worsening respiratory distress in COVID pneumonia. All other ABG parameters also showed a significant AUC for predicting 28-day mortality, although with variable sensitivity and specificity.

## HIGHLIGHTS

The routine analysis of these simple, quick, readily accessible, and cost-effective ABG parameters, especially the A–a gradient, reliably predicted the poor prognosis of patients at NIV initiation. It will aid in the early initiation of NIV and prognostication of adverse outcomes.

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## REFERENCES

- Li X, Ma X. Acute respiratory failure in COVID-19: is it "typical" ARDS? *Crit Care* 2020;24(1):198. DOI: 10.1186/s13054-020-02911-9.
- Armstrong RA, Kane AD, Cook TM. Outcomes from intensive care in patients with COVID-19: a systematic review and meta-analysis of observational studies *Anaesthesia* 2020;75(10):1340–1349. DOI: 10.1111/anae.15201.
- Grasselli G, Greco M, Zanella A, Albano G, Antonelli M, Bellani G, 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):1345–1355. DOI: 10.1001/jamainternmed.2020.3539.
- Sarkar M, Niranjana N, Banyal PK. Mechanisms of hypoxemia. *Lung India* 2017;34(1):47–60. DOI: 10.4103/0970-2113.197116.
- Dhont S, Derom E, Braeckel E, Depuydt P, Lambrecht BN. The pathophysiology of 'happy' hypoxemia in COVID-19. *Respir Res* 2020;21(1):198. DOI: 10.1186/s12931-020-01462-5.
- Sharma S, Hashmi M, Burns B. Alveolar gas equation. In: *Treasure Island (FL)*; 2020.
- Brosnahan S, Jonkman A, Kugler M, Munger J, Kaufman D. COVID-19 and respiratory system disorders. *Arterioscler Thromb Vasc Biol* 2020;40(11):2586–2597. DOI: 10.1161/ATVBAHA.120.314515.
- Burnham EL, Janssen WJ, Riches DH, Moss M, Downey GP. The fibroproliferative response in acute respiratory distress syndrome: mechanisms and clinical significance. *Eur Respir J* 2014;43(1):276–285. DOI: 10.1183/09031936.00196412.
- 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):1796–1801. DOI: 10.1016/j.ajem.2020.05.048.
- Farina G, Gianstefani A, Salvatore V, Anziati M, Baldassarri F, Beleffi M, et al. Alveolar-to-arterial oxygen gradient: role in the management of COVID-19 infection mild population. *Res Sq [Internet]* 2021. DOI: 10.21203/rs.3.rs-100668/v1.
- Gilbert R, Keighley JF. The arterial-alveolar oxygen tension ratio. An index of gas exchange applicable to varying inspired oxygen concentrations. *Am Rev Respir Dis* 1974;109(1):142–145. DOI: 10.1164/arrd.1974.109.1.142.
- Xie J, Tong Z, Guan X, Du B, Qiu H. Clinical characteristics of patients who died of coronavirus disease 2019 in China. *JAMA Netw Open* 2020;3(4):e205619. DOI: 10.1001/jamanetworkopen.2020.5619.
- García-Tardón N, Abbes AP, Gerrits A, Slingerland RJ, Den Besten G. Laboratory parameters as predictors of mortality in COVID-19 patients on hospital admission. *J Lab Med* 2020;44(6):357–359. DOI: 10.1515/labmed-2020-0087.