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P/F Ratio is a Better Predictor for Non-Invasive Ventilation Failure and Length of Stay in Patients with Community-Acquired Pneumonia

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ABSTRACT

Introduction: Community-acquired pneumonia (CAP) can deteriorate into respiratory failure requiring immediate ventilatory intervention. This study compared the performance of the PaO_2/FiO_2 (P/F) ratio, the ratio of oxygen saturation (ROX) index, and the heart rate, acidosis, consciousness, oxygenation, and respiratory rate (HACOR) score in predicting non-invasive ventilation (NIV) failure and length of hospital stay in patients diagnosed with CAP.
Methods: This study was conducted at Universitas Sebelas Maret Hospital, Surakarta, from March to September 2023. All patients diagnosed with CAP who were eligible for NIV were recruited. Each patient's age, sex, comorbidities, vital signs, pneumonia severity index (PSI), blood urea, bilirubin, hematocrit, blood sodium, P/F ratio, ROX index, and HACOR score were measured within the first 24 hours of NIV. Subsequently, the correlations between these variables and NIV failure (intubation or mortality) and length of hospital stay were assessed.
Results: The P/F ratio, ROX index, and HACOR score were not correlated with intubation or length of stay. The P/F ratio was correlated with mortality ($p = 0.040$), whereas the other scores were not. Higher body temperature was correlated with intubation ($p = 0.032$). PSI was correlated with both mortality ($p = 0.033$) and length of hospital stay ($p = 0.009$).
Conclusion: The P/F ratio is superior to the ROX index and HACOR score in predicting mortality in patients with pneumonia-related respiratory failure treated with NIV. Since it is simple and accessible, measuring the P/F ratio within the first 24 hours of NIV is recommended to identify a patient's risk of NIV failure and apply appropriate monitoring.

INTRODUCTION

Community-acquired pneumonia (CAP) is a common disease with a prevalence of approximately 14 cases per 1,000 people every year.[1] In the United States (US), the prevalence is 24.8 cases per 10,000 people annually, and this prevalence increases with age.[1] CAP is among the top causes of hospitalization, and it is the eighth most common cause of death and the most common cause of death due to infectious causes.[1] The disease presentation ranges from mild (i.e., manageable in an outpatient setting) to severe (requiring intensive care). In severe pneumonia with respiratory failure, ventilatory support in the form of invasive or non-invasive ventilation (NIV) is often needed.

Available NIV approaches include continuous positive airway pressure (CPAP), bilevel-positive airway pressure (BiPAP), high-flow nasal cannula (HFNC), non-rebreather masks, simple masks, and nasal cannula. Although it improves gas exchange and reduces the work of breathing, NIV predisposes patients to potential intubation-related complications, such as respiratory tract injury and ventilator-associated infection.[2] NIV notably decreases the need for

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intubation and the death rate in patients with pneumonia-associated respiratory failure in intensive care units (ICUs).[3] NIV failure indicates the need for intubation or mortality. The need for intubation following NIV is associated with elevated heart rate and respiratory rate, a decline in the Glasgow Coma Scale, decreased tissue oxygenation, lower blood pH, longer ICU stay, and higher in-hospital mortality.[3,4] Consequently, identifying patients who are at risk for NIV failure is crucial.

Several tools have been established to assess the likelihood of NIV failure, including the PaO_2/FIO_2 (P/F) ratio, the ratio of oxygen saturation (ROX) index, and the heart rate, acidosis, consciousness, oxygenation, and respiratory rate (HACOR) score. Although the ROX index has been validated among pneumonia patients to determine the likelihood of HFNC failure and has been shown to be superior to the HACOR score in its predictive value for NIV failure,[5,6] the P/F ratio is postulated to be an even better predictor of HFNC outcome.[5] This study investigated and compared the performance of the three scores in predicting NIV failure and the length of hospital stay in patients with CAP-related respiratory failure.

METHODS

This prospective cohort study was performed in the ICU of Universitas Sebelas Maret Hospital, Surakarta, Indonesia, from March to September 2023. All patients were adults (>18 years old) who were diagnosed with CAP and treated in the ICU with NIV. Recruitment was conducted through total population sampling. Pneumonia was diagnosed according to the current guidelines, which include the following diagnostic criteria, new or progressive infiltrates on chest radiography accompanied by clinical symptoms and signs indicating infection, such as acute fever, productive cough, shortness of breath, leukocytosis, and oxygenation impairment.[7] Patients with negative bacterial sputum cultures or positive polymerase chain reaction (PCR) results for COVID-19 indicating diagnoses other than CAP were excluded from the study.

NIV methods include non-rebreather masks, HFNC, and BiPAP or CPAP. Patients were treated with NIV when their respiratory rate was >25 breaths/min, their PaO_2 was <60 mmHg (with room air), or their P/F ratio was <300 with supplemental oxygen. FiO_2 was estimated by the formula FiO_2 (%) = 21 + 4 × flow (L/min). If respiratory failure worsened over time despite NIV, intubation for invasive mechanical ventilation was performed. The following major criteria were adopted as indications for intubation, P/F ratio < 100 despite NIV intervention, hemodynamic instability, cardiac arrest or deteriorating consciousness, apparent agitation that could not be controlled by low-dose sedation, signs of breathing exhaustion, or aspiration. The following minor criteria for intubation were also applied, P/F ratio < 150 despite NIV, respiratory rate > 35 breaths/min or signs of heightened work of breathing, and lack of clinical improvement in respiratory failure. The presence of one major criterion or >2 minor criteria indicated the need for intubation. However, regardless of whether the patients met these criteria, the decision to use NIV or intubate was at the physician's full discretion. The need for intubation after NIV or mortality was defined as NIV failure.

Participants' baseline data included age, sex, comorbidities, vital signs, arterial blood gas (ABG), pneumonia severity assessed by the pneumonia severity index (PSI), peripheral blood urea, bilirubin, hematocrit, and blood sodium. These baseline data were assessed within the first 24 hours after hospital admission. The independent variables were P/F ratio, ROX index, and HACOR score, all of which were measured within the first 24 hours of NIV. The P/F ratio was calculated as PaO_2/FiO_2 from ABG, the ROX index was calculated as the SpO_2/FiO_2 ratio/respiratory rate, and the HACOR score was calculated as shown in Table 1.

Table 1. HACOR score[6]

Variables	Category*	Assigned Points
Heart rate (beats/minute)	≤120	0
	≥121	1
pH	≥7.35	0
	7.30–7.34	2
	7.25–7.29	3
	<7.25	4
GCS	15	0
	13–14	2
	11–12	5
	≤10	10
PaO_2/FiO_2	≥201	0
	176–200	2
	151–175	3
	126–150	4
	101–125	5
	≤100	6
Respiratory rate (breaths/minute)	≤30	0
	31–35	1
	36–40	2
	41–45	3
	≥46	4

After their baseline data were collected, participants were followed prospectively to assess the dependent variables (presence of NIV failure and length of hospital stay). NIV failure was defined as the need for intubation after NIV or mortality. The need for intubation and mortality were measured as categorical variables (yes/no), whereas the length of hospital stay was measured as a continuous variable (number of days). The correlations between independent and dependent variables were analyzed with X^2 or Mann–

Whitney tests, as appropriate. Data tabulation and statistical analysis were performed with the International Business Machines Corporation (IBM) Statistical Package for the Social Sciences (SPSS) version 26.

RESULTS

Participant Characteristics

This study included 562 patients diagnosed with pneumonia who were initially treated with NIV in the ICU. The proportion of males and females was equal (50.0% each). Among the participants, 201 patients required intubation (35.8%), 232 patients died (41.3%), and 330 patients survived (58.7%). The most frequent comorbidity was lung cancer (20.8%), followed by type 2 diabetes mellitus (15.8%) and stroke (1.6%) (Table 2). The average P/F ratio was 244.62 ± 663.05, the average ROX index was 14.11 ± 40.00, and the average HACOR score was 6.81 ± 4.35. Most patients were not intubated (64.2%), and more patients survived than died (58.7% vs. 41.3%) during their ICU stay. The average length of hospital stay of those who survived was 8.22 ± 5.3.

Table 2. Independent and dependent variables

Characteristics	Results (n = 562) n ± SD/(%)
Age (years old)	57.59 ± 11.07
Sex	
Male	281 (50%)
Female	281 (50%)
Comorbidities	
Type 2 diabetes mellitus	89 (15.8%)
Lung tumor	117 (20.8%)
Stroke	9 (1.6%)
None detected	347 (61.74%)
Pneumonia Severity Index (PSI)	107.11 ± 31.50
Vital Signs	
Respiratory rate (breaths/minute)	25.90 ± 4.36
Systolic blood pressure (mmHg)	116.03 ± 23.75
Temperature (°C)	37.06 ± 0.76
Peripheral Blood Parameters	
Hematocrit (g/dL)	34.45 ± 18.12
Blood urea (mg/dL)	51.26 ± 45.54
Bilirubin (mg/dL)	1.29 ± 1.84
Sodium (mmol/L)	133.34 ± 7.52
Arterial Blood Gas	
pH	7.37 ± 0.10
PaO_2 (mmHg)	96.96 ± 36.58

Correlation between P/F Ratio, ROX Index, HACOR Score, and Intubation

This study did not observe significant correlations between the P/F ratio (r = 0.005; p = 0.903), ROX index (r = 0.031; p = 0.466), or HACOR (r = 0.009; p = 0.838) and the need for intubation following NIV. However, body temperature was significantly correlated with intubation (r = −0.091; p = 0.032). Patients who were intubated tended to have higher body temperature. Table 3 presents the characteristics of intubated and non-intubated patients, and Table 4 shows the correlation between predictors and intubation.

Table 3. Characteristics of intubated and non-intubated patients

Characteristics	Intubated n = 201 (35.8%) mean ± SD	Non-Intubated n = 361 (64.2%) mean ± SD	r	p-value
Age (years old)	58.00 ± 10.7	57.36 ± 11.27	0.027	0.517
Respiratory rate (breaths/minute)	25.52 ± 4.36	26.11 ± 4.35	0.065	0.123
Systolic blood pressure (mmHg)	114.59 ± 23.15	116.83 ± 24.07	0.045	0.283
Temperature (°C)	**37.15 ± 0.79**	**37.01 ± 0.73**	**0.091**	**0.032**
pH	7.36 ± 0.10	7.37 ± 0.95	0.045	0.358
PaO_2 (mmHg)	97.97 ± 36.23	96.31 ± 36.85	0.022	0.648
Blood urea (mg/dL)	51.10 ± 48.51	51.34 ± 43.85	0.003	0.952
Bilirubin (mg/dL)	1.17 ± 0.75	1.36 ± 1.76	0.060	0.183
Sodium (mmol/L)	133.13 ± 6.09	133.45 ± 8.23	0.021	0.640
Hematocrit (g/dL)	34.99 ± 20.89	34.16 ± 16.41	0.022	0.603
PSI	106.34 ± 32.54	107.55 ± 30.93	0.018	0.664

Table 4. Correlation between P/F ratio, ROX index, HACOR score, and intubation

Predictor	Intubated n = 201 (35.8%) mean ± SD	Non-Intubated n = 361 (64.2%) mean ± SD	r	p-value
PF ratio	240.05 ± 528.45	247.17 ± 727.96	0.005	0.903
ROX index	12.46 ± 25.37	15.03 ± 46.19	0.031	0.466
HACOR	6.76 ± 3.93	6.84 ± 4.56	0.009	0.838

Correlation between P/F Ratio, ROX Index, HACOR Score, and Mortality

The P/F ratio was significantly correlated with mortality (r = 0.087; p = 0.040), whereas the ROX index (r = 0.055; p = 0.193) and HACOR score (r = 0.019; p = 0.662) were not (Table 5). In addition, the PSI was correlated with mortality (r = 0.090; p = 0.033). The average PSI was higher in patients who died than in those who survived (110.49 vs. 104.74), as shown in Table 6.

Table 5. Correlation between P/F ratio, ROX index, HACOR score, and mortality

Predictor	Died n = 232 (41.3%) mean ± SD	Survived n = 330 (58.7%) mean ± SD	r	p-value
PF ratio	**313.20 ± 888.21**	**196.41 ± 435.97**	**0.087**	**0.040**
ROX index	16.73 ± 52.89	12.26 ± 27.51	0.055	0.193
HACOR	6.72 ± 4.24	6.88 ± 4.43	0.019	0.662

Table 6. Characteristics of participants who died vs. who survived

Characteristics	Died n = 232 (41.3%) mean ± SD	Survived n = 330 (58.7%) mean ± SD	r	p-value
Age (years old)	57.29 ± 10.67	57.80 ± 11.34	0.023	0.590
Respiratory rate (breaths/minute)	25.94 ± 4.51	25.88 ± 4.26	0.006	0.880
Systolic blood pressure (mmHg)	114.31 ± 24.33	117.24 ± 23.30	0.061	0.150
Temperature (°C)	37.08 ± 0.75	37.04 ± 0.76	0.025	0.550
pH	7.36 ± 0.10	7.37 ± 0.10	0.050	0.311
PaO_2 (mmHg)	99.46 ± 37.05	95.09 ± 36.18	0.059	0.224
Blood urea (mg/dL)	51.13 ± 45.68	51.34 ± 45.51	0.002	0.957
Bilirubin (mg/dL)	1.39 ± 2.09	1.22 ± 0.81	0.057	0.203
Sodium (mmol/L)	133.34 ± 6.30	133.34 ± 8.32	0.000	0.995
Hematocrit (g/dL)	34.32 ± 19.82	34.55 ± 16.85	0.006	0.884
PSI	**110.49 ± 30.71**	**104.74 ± 31.87**	**0.090**	**0.033**

Correlation between P/F Ratio, ROX Index, HACOR Score, and Length of Hospital Stay

The P/F ratio (r = −0.049; p = 0.242), ROX index (r = 0.010; p = 0.814), and HACOR (r = 0.018; p = 0.667) were not significantly correlated with the length of hospital stay (Table 7). PaO_2 (r = −0.100; p = 0.038), bilirubin (r = 0.104; p=0.021), hematocrit (r = 0.093; p = 0.027), and PSI score (r = −0.110; p = 0.009) were significantly correlated with length of stay, as shown in Table 8.

Table 7. Correlation between P/F ratio, ROX index, HACOR score, and length of hospital stay

Characteristics	r	p-value
PF ratio	−0.049	0.242
ROX index	0.010	0.814
HACOR	0.018	0.677

Table 8. Correlation between patients' characteristics and length of hospital stay

Characteristics	r	p-value
Age (years old)	0.046	0.279
Respiratory rate (breaths/minute)	0.000	0.999
Systolic blood pressure (mmHg)	0.030	0.476
Temperature (°C)	−0.074	0.083
pH	0.037	0.446
PaO2 (mmHg)	**−0.100**	**0.038**
Blood urea (mg/dL)	−0.001	0.984
Bilirubin (mg/dL)	**0.104**	**0.021**
Sodium (mmol/L)	0.076	0.082
Hematocrit (g/dL)	**0.093**	**0.027**
PSI	**−0.110**	**0.009**

DISCUSSION

NIV Failure: Need for Intubation

This study found that neither the P/F ratio, ROX index, nor HACOR score was significantly correlated with intubation following NIV ($p = 0.466$, $p = 0.838$, $p = 0.903$, respectively). Multiple studies have shown that each score has the potential to predict NIV failure (i.e., the need for intubation after NIV). A study by Nishiyama, *et al*. (2023) involving participants with acute respiratory distress syndrome (ARDS) found that in the initial 24 hours of NIV, the ROX index might provide information about whether intubation is needed.[8] The study also found that the ROX index successfully predicted patient outcomes, as a higher ROX index was associated with a higher success rate during 28-day weaning from the ventilator. Another study by Mathen, *et al*. (2022) noted that the mean P/F ratio of participants in the NIV failure group was significantly lower than that of the NIV success group (184.57 vs. 277.29, $p < 0.001$).[9] The odds ratio (OR) for successful NIV in patients with a higher baseline P/F ratio was 1.053 (95% CI: 1.032–1.071).[9] The HACOR score has also been documented to predict NIV failure. Duan, *et al*. (2022) studied chronic obstructive pulmonary disease (COPD) in 500 patients and validated that the HACOR score performed well in predicting NIV failure.[4] In this study, the HACOR score also facilitated early prediction for NIV failure (<48 hours), resulting in early intubation and leading to decreased mortality.

When the three scores were compared, this study indicated that the ROX index was more highly correlated with intubation than the HACOR score and P/F ratio. However, none of these correlations were statistically significant ($p = 0.466$ vs. 0.838 vs. 0.903, respectively). A study by Praphruetkit, *et al*. (2023) comparing the ability of the ROX index and the HACOR score to predict HFNC outcome also concluded that the ROX index was superior.[6] The group that was successfully treated with NIV in this study had a higher ROX index yet a lower HACOR score at all time points. In addition, the ROX index is more straightforward to obtain and thus more efficient for bedside application in an emergency room setting to facilitate earlier management and escalation therapy for patients with acute respiratory failure.[6] A recent prospective multicenter study by Guia, *et al*. (2021) included 128 patients admitted with COVID-19 pneumonia who presented with acute respiratory distress and were started on CPAP.[10] The HACOR score was measured and compared with the P/F ratio after 1 hour of CPAP. Data analysis showed that the accuracy of HACOR score in predicting CPAP failure was 82.03%, whereas the accuracy of P/F ratio was 81.25%. However, this does not necessarily mean that the HACOR score is more useful than the P/F ratio, as the difference in accuracy was minimal, and the P/F ratio is more straightforward to apply than the HACOR score.[10,11]

Upon reviewing the patients' characteristics, this study found that a higher body temperature during the first 24 hours of admission was significantly correlated with intubation following NIV. Temperature has been included in scoring systems that determine the degree of illness and risk of critical conditions, such as the National Early Warning Score (NEWS) and the Modified Early Warning Score (MEWS).[12,13] In both scoring systems, unless the patient has hypothermia, an increase in temperature increases the total aggregated score and is correlated with a worse prognosis.[12–14] However, contradictory results were reported in a study by Schell-Chaple, *et al*. (2015), in which a higher body temperature in patients with ARDS was associated with a lower mortality rate.[15] The odds of mortality decreased by 15% with every 1°C increase in baseline temperature ($p = 0.03$; 95% CI, 0.73–0.98). The study concluded that fever in the early stages of ARDS is associated with a higher chance of survival. The use of increased body temperature as a marker of pulmonary injury and how well it correlates with convalescence or patient outcomes warrant further study, as this association may be anecdotal.

NIV Failure: Mortality

The P/F ratio was the only score that significantly predicted mortality in this study ($p = 0.040$). The P/F ratio is typically used to indicate the severity of acute hypoxemic respiratory failure as follows, severe, P/F <100 mmHg, moderate, P/F 101–200 mmHg, and mild, P/F 201–300 mmHg. According to these categories, Santus, *et al*. (2020) noted that a moderate to severe decrease in the P/F ratio was an independent risk factor that tripled the risk of in-hospital mortality.[16] During the COVID-19 pandemic, in which the cases of respiratory failure and the use of mechanical ventilation were frequent, the relationship of P/F ratio with mortality gained even more attention. Similarly, Gu, *et al*. (2021) noted that the P/F ratio, along with IL-6, were independent risk factors for intensive care mortality in patients with COVID-19 ($p = 0.032$; 95% CI, 0.915–0.996), with an area under the curve (AUC) of 0.865 ($p < 0.0001$; 95% CI, 0.748–0.941).[17] Interestingly, a study by Bi, *et al*. (2023) found that in patients with sepsis, having either a high or low P/F ratio increased the risk of 28-day mortality.[18] A lower risk of 28-day mortality was observed when the P/F ratio was between 183.09 and 219.20.[18]

Earlier studies have documented that the ROX index and HACOR score also have the potential to

predict mortality. When the ROX index was applied in patients with sepsis and hypoxemia in a study by Lee, *et al*. (2021), non-survivors had a lower ROX index than survivors, with an ROX index ≤10 independently predicting 28-day mortality in patients with sepsis.[19] In another study on COVID-19-related acute respiratory failure by Innocenti, *et al*. (2022), a HACOR score above 5 upon NIV initiation was independently associated with a higher mortality rate.[20] In this study, the ROX index was more highly correlated with mortality than the HACOR score ($r = 0.05$ vs. $r = 0.019$), although the correlation was not statistically significant.

This study also supports earlier findings that the PSI is positively correlated with mortality. The PSI is widely used as a mortality predictor in patients with CAP.[21] Recent studies have also shown that the score performs as well in predicting 30-day mortality in patients with viral pneumonia. Kim, *et al*. (2019) noted that the PSI was significantly associated with mortality, with a hazard ratio of 1.024 (95% CI, 1.020–1.028) even after adjustment for respiratory virus detection.[22] The study noted that the rate of mortality increased with an increase in the PSI in both the group with respiratory viral infection and the group without. Furthermore, Satici, *et al*. (2020) found that the PSI performed well, and significantly better than CURB-65 ($p = 0.01$), in predicting 30-day hospital mortality in patients with COVID-19-related pneumonia.[23]

Length of Stay

This study found that the P/F ratio, ROX index, and HACOR score were not significantly correlated with the length of hospital stay. The P/F ratio showed a negative correlation coefficient ($r = -0.049$), which implies that a better P/F ratio might contribute to survival or improvement in clinical conditions during hospitalization. A study performed by the French Intensive Care Society (Société de Réanimation de Langue Française/SRLF) Trial Group (2018) compared the length of ICU stay of hypoxemic patients (P/F ratio less than or equal to 300 mmHg) with non-hypoxemic patients and found that the median length of ICU stays in the hypoxemic group was approximately twice as long (16 [7–32] vs. 8 [3–22] days, $p < 0.001$).[24] According to Mammadova, *et al*. (2022), measuring the initial ROX index in patients admitted to the ICU was also helpful in predicting the length of ICU treatment, and the presence of respiratory failure and hypercapnia influenced its cut-off value.[25] The HACOR score assessed after 1 to 2 hours of NIV also showed high accuracy in determining the efficacy of NIV in another study by Teh, *et al*. (2022).[26] The study also reported a longer duration of hospital stay in patients with unsatisfactory responses to NIV.

Additionally, the findings in this study confirmed that the PSI was positively correlated with length of stay. A retrospective study involving more than 32,000 patients with CAP at over 400 hospitals in the US found an interesting trend of mean length of hospital stay increased with the increase of PSI risk class, ranging from 4.9 days in the lowest risk class to 8.94 days in the highest depending on the Charlson comorbidity index (CCI) score.[27] As previously known, a higher PSI is correlated with disease severity, the need for intensive care, and the risk of mortality, consequently adding more days to a patient's hospital stay.[22,23,27]

A significant limitation of this study is that it was difficult to measure all predictive scores at the same time point because some scores require the calculation of more clinical or laboratory examinations to be calculated, and the time of measurement affects the score performance in predicting patient outcomes. For example, Ding, *et al*. (2021) reported that in patients with non-COPD-related acute or chronic respiratory failure, the ability of the HACOR score to predict NIV failure had a sensitivity and specificity of 90% and 85%, respectively, at 1–2 hours, 82% and 91%, respectively, after 12 hours, and 100% and 76%, respectively, at 24 hours.[28] In this study, scores were assessed at the earliest time possible and not at the time of optimal performance according to the literature.

In addition, Kadkhodai, *et al*. (2022) used a regression model to evaluate the best fraction of inspired oxygen (FiO_2) for calculating a patient's P/F ratio and found that the most accurate P/F ratio was obtained when the FiO_2 value at the time of measurement was 1.0.[29] In this study, the P/F ratio was not measured at a standardized FiO_2 but rather during first 24 hours, which may have affected the validity of the P/F ratio in reflecting the patients' clinical condition and their subsequent deterioration of systemic oxygenation. Hence, this study concluded that patients who died and had higher P/F ratios reflect a limitation related to data collection rather than clinical significance.

Another factor that may have affected the outcome of this study was the difference in oxygenation dose and setting while using NIV, as it was adjusted according to each physician's discretion, depending on each patient's condition. A follow-up study involving more subjects that accounts for the NIV strategies used, as well as longitudinal, repeated measurements of the predictive scores, may help elucidate the sensitivity of the scores to patient outcomes.

CONCLUSION

This study indicated that the P/F ratio was significantly correlated with mortality, whereas the ROX

index and HACOR score were not. None of the indexes or scores were significantly correlated with intubation following NIV or length of hospital stay. This study also noted that higher body temperature was significantly correlated with intubation, and the PSI was significantly correlated with length of hospital stay and mortality. The P/F ratio was superior to the ROX index and HACOR score in predicting NIV outcomes. This indicator is not only more sensitive to the risk of mortality but also more straightforward to measure and interpret. According to the results, it is recommended to assess the P/F ratio of patients with severe CAP within the first 24 hours of NIV to improve monitoring and apply timely advanced management when needed.

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Conflict of Interest

The authors declared there is no conflict of interest.

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Authors' Contributions

All authors contributed equally to the study procedure and manuscript production. The study team consisted of BDAH (principal investigator and author), OGR (co-investigator and co-author), AA (co-investigator and data analyst), RR (co-investigator and data analysis consultant), HA (co-investigator and data manager), NIR (co-investigator and field manager), and GV (co-investigator and co-author).

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