Section: Respiratory Medicine

Original Research Article

OBSERVATIONAL STUDY OF FACTORS PREDICTING CONVERSION FROM NON-INVASIVE VENTILATION TO INVASIVE VENTILATION IN PATIENTS WITH ACUTE RESPIRATORY DISTRESS SYNDROME ADMITTED TO THE ICU

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Received *: 17/11/2024*
Received in revised form *: 06/01/2025*
Accepted *: 22/01/2025*

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DOI: 10.70034/ijmedph.2025.1.65

Source of Support: Nil,
Conflict of Interest: None declared

Int J Med Pub Health
2025; 15 (1); 341-347

ABSTRACT

Background: ARDS is a critical condition with acute hypoxemia. Its diagnosis involves clinical, imaging, and laboratory findings. Its effective management includes addressing underlying causes, supportive care, prone positioning and lung-protective ventilation to improve outcomes and mitigate lung injury. Non-invasive ventilation (NIV) is an essential tool in managing mild to moderate ARDS, improving oxygenation and reducing the need for intubation. NIV failure often occurs due to worsening hypoxemia, respiratory acidosis or increased work of breathing. Delayed intubation after NIV failure is associated with higher mortality rates. Identifying factors associated with NIV failure in ARDS patients is crucial for timely intubation, preventing delayed interventions, and improving overall clinical outcomes.

Material and Methods: This was an observational study of patients with ARDS admitted to the ICU of a tertiary care hospital over one year. A total of 60 patients were included, and various demographic, clinical, biochemical and radiological parameters were analyzed. Outcomes such as ICU length of stay, hospital mortality, and other complications were compared between NIV success and failure groups using severity scores and diagnostic tools to identify key predictors of NIV failure. SSPS 23.0 software was used for statistical analysis and a P value less than 0.05 was taken as statistically significant.

Results: This study analyzed predictors of NIV failure in 60 ARDS patients. NIV failure was significantly associated with older age (mean 54.02 vs. 42.34 years, P = 0.0003) and comorbidities such as diabetes (66.67% vs. 25.64%, P = 0.002), chronic kidney disease (33.33% vs. 5.13%, P = 0.006), and liver cirrhosis (19.05% vs. 2.56%, P = 0.04). Physiological parameters like elevated heart rate (116.24 vs. 101.32 beats/min, P = 0.0002) and respiratory rate (30.12 vs. 22.88 breaths/min, P < 0.0001) also predicted failure. Severity scores, including higher APACHE II, SOFA, HACOR, and LUS scores were significantly worse in the NIV failure group. Patients with NIV failure had prolonged ICU stays (16.8 vs. 8.5 days, P < 0.0001) and higher hospital mortality (42.86% vs. 5.13%, P = 0.0007).

Conclusion: Identifying risk factors for NIV failure in ARDS is vital for timely intervention and improved outcomes. Factors such as Older age, comorbidities, and higher severity scores were associated with increased risk of NIV failure. Prompt identification of these predictors can reduce delays in intubation and mortality.

Key Words: Acute Respiratory Distress Syndrome (ARDS), Non-Invasive Ventilation (NIV), Mechanical Ventilation, Risk Factors.

INTRODUCTION

Acute Respiratory Distress Syndrome (ARDS) is a life-threatening condition that is characterized by acute onset of hypoxemia and bilateral pulmonary infiltrates that are not secondary to cardiac failure or fluid overload. The diagnosis of ARDS is usually made as per criteria laid down by Berlin Definition which provides a diagnostic framework for ARDS. ARDS severity is usually categorized (based on PaO2/FiO2 ratio) into mild (200-300 mmHg), moderate (100-200 mmHg) and severe (<100 mmHg). This definition underscores the critical role of mechanical ventilation in diagnosis and management and highlights the need for prompt recognition and intervention.[1] The pathophysiology of ARDS comprises of inflammatory and immune responses triggered by direct or indirect lung injuries. Direct lung injuries (pneumonia or aspiration) and indirect injuries (sepsis and trauma) lead to alveolar-capillary barrier disruption which results in increased permeability, interstitial and alveolar edema. These changes then culminate into impaired gas exchange. The ensuing hypoxemia is refractory to oxygen therapy and is a hallmark of ARDS. Histologically, ARDS progresses through three phases: the exudative phase (characterized by alveolar edema and inflammation) the proliferative phase (fibroblast activity) and the fibrotic phase (leading to long-term lung remodeling in severe cases).[2] Diagnosis of ARDS is clinical and relies on imaging and laboratory findings. Chest radiography or computed tomography reveals bilateral opacities consistent with pulmonary edema.

These opacities are not explained by effusions , atelectasis or nodules. The absence of left atrial hypertension or other indicators of cardiac failure differentiates ARDS from cardiogenic pulmonary edema. In addition , imaging such as lung ultrasound and biomarkers such as surfactant proteins and interleukins are increasingly explored for early diagnosis.

Management of ARDS mainly depends upon managing the underlying cause of ARDS, optimizing oxygenation and preventing further lung injury. Supportive care in cases of ARDS mostly comprise hemodynamic monitoring, fluid management and oxygenation. Various studies have found that conservative fluid strategies improve lung function and reduce ICU stay duration. Pharmacological interventions such as corticosteroids may dampen inflammatory responses but their role remains controversial. Prone positioning is increasingly recognized as a beneficial adjunct in moderate to severe ARDS. In refractory cases interventions such as neuromuscular blockade and extracorporeal membrane oxygenation (ECMO) may be required.[4]

Mechanical ventilation is a cornerstone of ARDS management. Optimal use of various ventilation strategies needs to be carefully employed to minimize ventilator-induced lung injury (VILI). Low tidal volumes and higher Positive end expiratory pressures reduces alveolar overdistension as well as cyclic atelectasis. Recruitment manoeuvres and individualized PEEP settings further enhance lung recruitment while minimizing the risk of barotrauma. Non-invasive ventilation (NIV) (delivered via face masks or helmets) is increasingly employed in early ARDS to avoid intubation and its associated complications. However NIV is most effective in mild cases and requires close monitoring to prevent delayed intubation in patients particularly with worsening respiratory failure. High-flow nasal cannula (HFNC) oxygen therapy is another non-invasive modality offering better patient comfort and oxygenation. However When non-invasive strategies fail timely initiation of invasive mechanical ventilation is crucial to improve outcomes.[5]

The factors that needs to be considered for conversion from non-invasive to invasive ventilation in ARDS include the severity of hypoxemia (evidenced by PaO2/FiO2 ratios) and the degree of respiratory acidosis. Tachypnoea and increased work of breathing are early clinical signs of NIV failure. Presence of comorbid conditions such as chronic obstructive pulmonary disease (COPD), obesity and cardiac dysfunction may predispose patients to failure of non-invasive strategies. Delayed intubation due to prolonged use of NIV is associated with increased mortality. The timing and decision to transition to invasive ventilation depends upon a combination of clinical judgment and objective parameters, such as worsening oxygenation and hypercapnia. Predictive tools, such as the ROX index (ratio of SpO2/FiO2 to respiratory rate), are increasingly used to identify patients at risk of NIV failure.[6]

Despite significant advancements in ARDS management, gaps remain in understanding the predictors and timing of conversion from NIV to invasive ventilation. Current guidelines provide limited clarity on the optimal thresholds for intubation, leading to practice variability.[7] This observational study aims to address these gaps by systematically analyzing the factors predicting NIV failure in patients with ARDS

MATERIALS AND METHODS

This was a prospective observational study conducted in the department of pulmonary medicine of a tertiary care medical college. The duration of the study was 1 year. The patients admitted to the ICU with acute respiratory distress syndrome (ARDS) and initiated on non-invasive ventilation (NIV) were included in this study based on predefined inclusion and exclusion criteria. The sample size was calculated using the formula $n = Z^2 P (1-P)/d^2$ with OPENEPI software version 3 on the basis of pilot studies done on the topic of conversion from NIV to invasive mechanical ventilation (IMV) in ARDS. Assuming 90% power and a 95% confidence interval

the required sample size was 55 patients, therefore 60 patients were included in the study.

The diagnosis of ARDS in this study was made based on the Berlin Definition ie an acute onset of respiratory symptoms within one week of a known clinical insult or new or worsening symptoms. Radiographic evidence of bilateral opacities, consistent with pulmonary edema which was not fully explained by cardiac failure or fluid overload. Oxygenation impairment was categorized as mild (PaO2/FiO2 200–300 mmHg with PEEP or CPAP ≥ 5 cm H2O) , moderate (PaO2/FiO2 100–200 mmHg with PEEP ≥ 5 cm H2O) or severe (PaO2/FiO2 ≤100 mmHg), under a positive end-expiratory pressure (PEEP) of at least 5 cm H2O.

Demographic details such as age and gender were documented. A detailed clinical history and examination were performed. Hemodynamic and clinical parameters, such as heart rate, respiratory rate and left ventricular ejection fraction (LVEF) were recorded. Blood gas parameters, including pH, were analyzed at admission. Severity scores like the APACHE II score,[8] SOFA score,[9] at admission and after 48 hours, and HACOR scores,[10] (at 0, 12, and 24 hours) were calculated. Lung ultrasound scores (LUS)11 at baseline (T0) and 24 hours (T24) were also measured to evaluate the extent of lung involvement.

Lactate levels at admission (T0) and 24 hours (T24) were also recorded. The data were stratified into two groups NIV success and NIV failure (patients requiring IMV). Comparisons were made between these groups for demographic characteristics such as age and gender, comorbidities including diabetes, hypertension, chronic kidney disease, and liver cirrhosis, as well as baseline physiological parameters like heart rate and respiratory rate. Severity scores, including APACHE II, SOFA (at admission and 48 hours), HACOR (T0, T12, T24), and LUS (T0, T24), were evaluated alongside complications and outcomes such as ICU stay duration and hospital mortality.

Statistical analysis was performed using SPSS version 23.0 software. Quantitative data were presented as mean ± standard deviation and qualitative data were presented as percentages. For group comparisons, an unpaired t-test was applied to quantitative data, while a Chi-square test was used for qualitative data. A p-value less than 0.05 was considered statistically significant.

Inclusion Criteria

1. Patients admitted to the ICU with the diagnosis of ARDS as per the Berlin Definition.
2. Patients initiated on NIV as the primary respiratory support modality.
3. Patients aged 18 years and older.
4. Informed written consent obtained from the patient or their relatives.

Exclusion Criteria

1. Patients under 18 years of age.
2. Patients with do-not-intubate (DNI) orders.
3. Patients with pre-existing neuromuscular disorders, advanced malignancies, or other terminal conditions precluding ICU interventions.
4. Patients already on invasive ventilation at admission.

RESULTS

In this study of 60 patients admitted to ICU for acute respiratory distress syndrome as determined by berlin criteria there were 44 (73.33%) males and 16 (26.67%) females with a M:F ratio of 1: 0.36. [Figure 1]

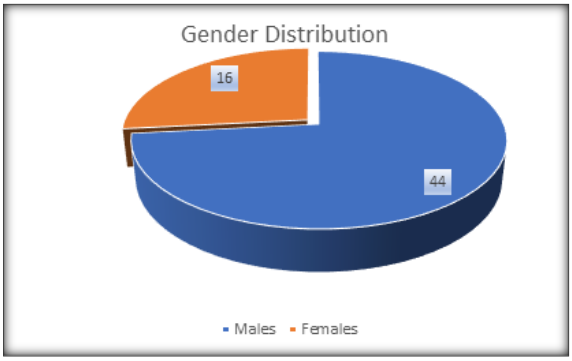

Figure 1: Gender Distribution of studied cases.

Analysis of patients on the basis of age group showed that amongst males the most common age group was 41-50 years (33.33%) followed by above 50 years (21.67%). Among females the most common affected age group was above 50 years (11.67%) followed by 41-50 years (10.00%). The mean age was slightly higher in males (49.36 ± 12.12 years) than in females (46.84 ± 11.26 years). However, the difference in mean age of males and females was comparable with no statistically significant difference. [Table 1]

The analysis of precipitating factors for ARDS among the studied cases showed that pneumonia was the most common risk factor (33.33%), followed by sepsis in 15 patients (25.00%) and elderly age in 12 patients (20.00%). Preexisting lung disease and shock were each noted in 10 patients (16.67%). Among the least common risk factors, thoracic and vascular surgery and drowning (near-drowning) were each identified in 2 patients (3.33%). Severe burns and pancreatitis were precipitating factors in 3 patients (5.00%). [Figure 2]

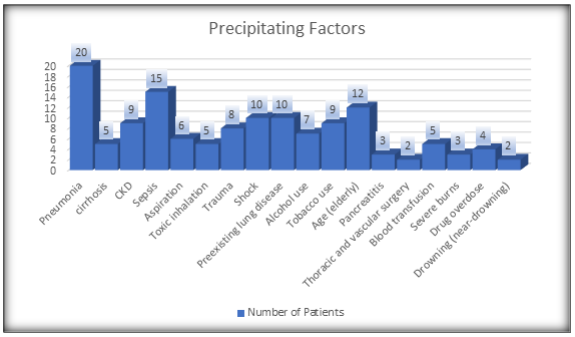

Figure 2: Precipitating Factors for ARDS in studied cases

*Some patients had multiple risk factors.

The analysis revealed that patients with higher mean age were predisposed to NIV failure, as the mean age in the NIV failure group (54.02 ± 13.19 years) was significantly higher than in the NIV success group (42.34 ± 10.20 years) (P = 0.0003). Diabetes was strongly associated with NIV failure (P = 0.002). Similarly, chronic kidney disease (33.33% vs. 5.13%, P = 0.006) and liver cirrhosis (19.05% vs. 2.56%, P = 0.04) were significant risk factors for NIV failure. Additionally, patients in the NIV failure group exhibited higher heart rates (116.24 ± 16.24 beats/min) compared to those in the success group (101.32 ± 12.08 beats/min) (P = 0.0002) and elevated respiratory rates (30.12 ± 3.64 breaths/min vs. 22.88 ± 2.11 breaths/min, P < 0.0001). While males were predominant in both groups, the difference in gender distribution was not statistically significant (P = 0.064). Hypertension did not show a significant association with NIV failure (P = 0.785). [Table 2]

The APACHE II score was significantly higher in the NIV failure group (22.40 ± 5.10) compared to the NIV success group (15.50 ± 3.90) (P < 0.0001). Similarly, SOFA scores at admission (12.10 ± 2.50 vs. 7.80 ± 1.80, P < 0.0001) and at 48 hours (13.50 ± 2.70 vs. 8.10 ± 1.90, P < 0.0001) were markedly elevated in the failure group. HACOR scores were also significantly higher in the NIV failure group, including HACOR T0 (9.00 ± 1.40 vs. 6.80 ± 1.10, P < 0.0001), HACOR T12 (9.80 ± 1.35 vs. 7.10 ± 1.15, P < 0.0001) and HACOR T24 (10.20 ± 1.60 vs. 6.90 ± 1.20, P < 0.0001). Additionally, lung ultrasound scores (LUS) were significantly elevated in the NIV failure group, both at T0 (22.10 ± 3.50 vs. 17.20 ± 2.60, P < 0.0001) and T24 (23.80 ± 3.60 vs. 16.80 ± 2.50, P < 0.0001). [Table 3]

The average ICU stay was significantly longer in the NIV failure group (16.8 ± 5.10 days) compared to the NIV success group (8.5 ± 1.90 days) (P < 0.0001). Hospital mortality was also higher among patients with NIV failure, with 42.86% (9/21) succumbing, compared to only 5.13% (2/39) in the NIV success group, showing a statistically significant difference (P = 0.0007). [Table 4]

Table 1: Gender Wise Distribution of age groups

	Male		Female	
	No of patients	**Percentage**	**No of patients**	**Percentage**
< 30 years	4	6.67%	1	1.67%
31-40 years	7	11.67%	2	3.33%
41-50 years	20	33.33%	6	10.00%
Above 50 years	13	21.67%	7	11.67%
Total	44	73.33%	16	26.67%
Mean Age	49.36 +/- 12.12 years		46.84 +/- 11.26 years	
P = 0.4713 (Not Significant)				

Table 2: Factors associated with NIV failure in studied cases

Variable	All patients (n=60)	NIV success (n=39)	NIV failure (n=21)	P-value
Mean Age (years)	48.1 +/- 11.69	42.34 ± 10.20	54.02 ± 13.19	P = 0.0003
Gender Distribution	Males (44/60) Females (16/60)	Males (32/39) Females (7/39)	Males (12/21) Females (9/21)	0.064
Diabetes (%)	Yes (24/60) No (36/60)	Yes (10/39) No (29/39)	Yes (14/21) No (7/21)	0.002
Hypertension (%)	Yes (26/60) No (34/60	Yes (16/39) No (23/39)	Yes (10/21) No (11/21)	0.785
Chronic kidney disease (%)	Yes (9/60) No (51/60)	Yes (2/39) No (37/39)	Yes (7/21) No (14/21)	0.006
Liver cirrhosis (%)	Yes (5/60) No (55/60)	Yes (1/39) No (38/39)	Yes (4/21) No (17/21)	0.04
Heart rate (beats/min)	108.78 ± 14.16	101.32 ± 12.08	116.24 ± 16.24	0.0002
Respiratory rate (breath/min)	26.50 ± 2.87	22.88 ± 2.11	30.12 ± 3.64	< 0.0001

Table 3: Comparison of APACHE II, SOFA, HACOR and LUS in patients with NIV success and Failure

Variable	NIV success (n=39)	NIV failure (n=21)	P-value
APACHE II	15.50 ± 3.90	22.40 ± 5.10	< 0.0001
SOFA at admission	7.80 ± 1.80	12.10 ± 2.50	< 0.0001
SOFA at 48h	8.10 ± 1.90	13.50 ± 2.70	< 0.0001
HACOR T0	6.80 ± 1.10	9.00 ± 1.40	< 0.0001
HACOR T12	7.10 ± 1.15	9.80 ± 1.35	< 0.0001

HACOR T24	6.90 ± 1.20	10.20 ± 1.60	< 0.0001
LUS T0	17.20 ± 2.60	22.10 ± 3.50	< 0.0001
LUS T24	16.80 ± 2.50	23.80 ± 3.60	< 0.0001

Table 4: Comparison of ICU stay and Hospital Mortality in studied cases

Variable	All patients (n=60)	NIV success (n=39)	NIV failure (n=21)	P-value
ICU days	12.65 ± 3.50	8.5 ± 1.90	16.8 ± 5.10	P < 0.0001
Hospital mortality (%)	11/60	2/39	9/21	0.0007

DISCUSSION

Non-invasive ventilation (NIV) is an important part of management of acute respiratory distress syndrome (ARDS). It offers a non-invasive means of supporting respiratory function while potentially avoiding the complications associated with invasive mechanical ventilation (IMV). Despite its numerous advantages, the use of NIV in ARDS is not without challenges. A significant proportion of patients fail NIV and ultimately require intubation which is associated with higher morbidity and mortality. The factors contributing to NIV failure in ARDS are multifaceted and often involve patient-specific factors such as severity of underlying disease and quality of supportive interventions. Understanding these factors is important as early identification of patients at risk of failure can guide timely escalation to IMV. Severity scores, imaging modalities, and dynamic clinical parameters are frequently employed to assess disease progression and the likelihood of NIV success. Importantly, the decision to transition from NIV to IMV should not be delayed in the presence of worsening clinical parameters as prolonged ineffective NIV is reported to be associated with adverse outcomes.[12]

In our study, there were 44 (73.33%) males and 16 (26.67%) females with a M:F ratio of 1: 0.36 . The mean age was slightly higher in males (49.36 ± 12.12 years) than in females (46.84 ± 11.26 years). However, the difference in mean age of males and females was comparable with no statistically significant difference. McNicholas BA et al conducted a prospective cohort study to assess the influence of sex on the management and outcomes of acute respiratory distress syndrome (ARDS) in the LUNG SAFE study.[13] For this purpose, the authors analyzed 2377 ARDS patients, including 905 females (38%) and 1472 males (62%), adjusting for clinical and geographic confounders. The study found no sex differences in clinician recognition of ARDS or severity of illness. However, females received higher tidal volumes (8.2±2.1 mL/kg vs. 7.2±1.6 mL/kg; p<0.0001) and higher plateau and driving pressures compared to males. Only 50% of females received lower tidal volume ventilation, compared to 74% of males (p<0.0001). Shorter females (≤1.69 m) were significantly less likely to receive lower tidal volumes. Surviving females had a shorter duration of invasive mechanical ventilation and reduced hospital stays compared to males. Overall mortality was the same for both sexes (40.2%), but females with severe ARDS had higher mortality (OR for male vs. female: 0.35, 95% CI 0.14–0.83). Male preponderance in this study was similar to our study. However authors such as Heffernan DS et al,[14] reported ARDS to be more common in females as compared to males.

In our study pneumonia was the most common risk factor, observed in 20 patients (33.33%), followed by sepsis in 15 patients (25.00%) and elderly age in 12 patients (20.00%). Preexisting lung disease and shock were each noted in 10 patients (16.67%). Odeyemi Y et al conducted a comprehensive review to identify factors predisposing patients to acute respiratory distress syndrome (ARDS).[15] For this purpose, the authors analyzed predisposing conditions, genetic variants, risk modifiers, hospital-acquired factors, and prevention strategies to better understand ARDS development and outcomes. The study found that sepsis, pneumonia, and shock are the most common predisposing conditions for ARDS. Genetic variants, such as mutations in surfactant protein B and the SELPLG gene, were associated with ARDS susceptibility. Risk modifiers included alcohol and tobacco use, malnutrition, obesity, and hypoalbuminemia. Hospital-acquired factors, including high tidal volume ventilation, high oxygen concentration, and plasma transfusion, were implicated in ARDS development. Preventive strategies like the Lung Injury Prediction Score (LIPS) and the Checklist for Lung Injury Prevention (CLIP) were highlighted as tools to identify high-risk patients and minimize iatrogenic exposures. Despite numerous studies, no pharmacologic interventions have been proven effective for ARDS prevention. On the basis of these findings, the authors concluded that early identification of high-risk patients and adherence to best practices, including lung-protective ventilation, are critical strategies for reducing the burden of ARDS. Similar risk factors for development of ARDS has also been reported by the authors such as Dai Q et al,[16] and Jia X et al.[17]

Our study identified several factors associated with NIV failure, including older age, higher prevalence of diabetes, chronic kidney disease, and liver cirrhosis. Patients in the NIV failure group exhibited higher heart and respiratory rates and poorer clinical scores, such as APACHE II, SOFA, HACOR, and lung ultrasound scores, at admission and during follow-up. While gender distribution and hypertension did not show significant associations with NIV outcomes. Shu W et al conducted a multicenter prospective observational study to evaluate the factors associated with failure of noninvasive ventilation in patients with acute respiratory distress syndrome.[18] The study included

306 patients, of whom 146 had pulmonary acute respiratory distress syndrome, while 160 had extrapulmonary acute respiratory distress syndrome. The findings demonstrated that failure of noninvasive ventilation occurred in 55% of patients with pulmonary acute respiratory distress syndrome compared to 28% of those with extrapulmonary acute respiratory distress syndrome. The presence of pulmonary acute respiratory distress syndrome was strongly associated with a higher risk of failure, with an adjusted odds ratio of 5.47. Patients with septic shock also exhibited an elevated risk of noninvasive ventilation failure. Higher non-pulmonary sequential organ failure assessment scores further increased the likelihood of failure. Additionally, baseline disease severity and physiological responses were found to influence outcomes. Patients with pulmonary acute respiratory distress syndrome showed slower improvements in respiratory rate, heart rate, arterial oxygen pressure to fraction of inspired oxygen, and arterial carbon dioxide pressure during the initial 24 hours of noninvasive ventilation compared to those with extrapulmonary acute respiratory distress syndrome. The study highlighted the importance of considering etiology and other clinical variables when managing patients with acute respiratory distress syndrome undergoing noninvasive ventilation. Similar risk factors for failure of non-invasive ventilation in cases of ARDS and acute respiratory failure have also been reported by the authors such as Tucci MRet al,[19] and Jolliet P et al.[20]

CONCLUSION

Identifying risk factors for NIV failure in ARDS patients is crucial for timely intervention and improving outcomes. Factors such as older age, comorbidities, elevated physiological parameters, and higher severity scores can guide early recognition and decision-making. Prompt identification of these predictors can minimize delays in intubation, reduce mortality, and enhance overall patient outcome in cases of ARDS.

Conflict of Interest: None.

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