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Original Article

Predictors of Non-Invasive Ventilation failure in Acute Hypoxemic Respiratory Failure

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ABSTRACT

Background: The implementation of NIV has proven to be effective in treating acute hypercapnic respiratory failure caused by COPD and cardiogenic pulmonary edema. However, its effectiveness in treating de novo acute hypoxemic respiratory failure (AHRF) has yielded mixed results, alongside higher risks of intubation (failure of therapy) and greater risks of mortality.

Objectives: This study had been designed to determine the predictors of NIV failure among individuals with *de novo* acute hypoxemic respiratory failure.

Patients and Methods: The current work involved participants with *de novo* acute type I respiratory failure hospitalized at Respiratory Intensive Care Unit (RICU), Department of Chest Diseases, Sohag University Hospitals throughout the period from November 2020 to May 2023.

Results: 126 patients (50.79% males) were included with a mean age of 57.76 years, all participants had been diagnosed with ARDS due to pneumonia (61.11% viral and 38.89% bacterial) with 39.60% had mild, 45.24% moderate and 15.08% severe ARDS. NIV success rate was 62.7%. Severe ARDS was correlated with increased risk of NIV failure (84.21%). Many demographics, clinical and ventilatory parameters can predict the possibility of NIV failure.

Conclusion: This study confirmed that many parameters can predicted NIV failure in AHRF patients as older age, increasing ARDS severity, higher APACHE II score, higher SOFA score along with other clinical and ventilatory parameters.

Key Words: NIV, ARDS, AHRF.

Abbreviations**:** NIV: Non-Invasive ventilation, PEEP: Positive end expiratory pressure, AHRF: Acute hypoxemic respiratory failure, RICU: Respiratory intensive care unit, BMI: Body mass index, DM: Diabetes mellitus, HTN: Hypertension, CXR: Chest X-ray, APACHE: Acute physiology and chronic health evaluation, ARDS: Acute respiratory distress syndrome, SOFA: Sequential organ failure assessment.

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Introduction

In contrast to hypercapnic respiratory failure, NPPV is widely accepted as an effective treatment for managing acute on chronic hypercapnic respiratory failure caused by acute exacerbation of chronic obstructive pulmonary disease (AECOPD), restrictive thoracic diseases, and obesity hypoventilation syndrome.[1]The effectiveness of non-invasive ventilation (NIV) in treating acute hypoxemic respiratory failure (AHRF) is not well proven. The European Respiratory Society/American Thoracic Society guideline on acute respiratory failure did not provide a recommendation about the utilization of NIV in newly occurring AHRF due to the lack of reliable evidence . [2] Spontaneous breathing throughout NIV or CPAP might be detrimental among individuals with ARDS owing to patient self-induced lung injury (P-SILI), despite the minimal clinical evidence available. [3] Individuals suffering from AHRF have an abnormal regulation of their respiratory drive, leading to the production of large tidal volumes and contributing to the occurrence of P-SILI. The combination of forceful inhalation and irregularities in lung tissue may result in harmful patterns of lung inflation, known as the "pendelluft" phenomenon. This can exacerbate existing inflammation in the tissues of the lungs, resulting in worse clinical results. [4]

Patients and methods

Observational prospective non-randomized clinical trial conducted at the Respiratory Intensive Care Unit (RICU), Department of Chest Diseases, Sohag University Hospitals from November 2020 to May 2023. This study was conducted on 126 patients (62 females and 64 males) with acute type I RF as characterized by the sudden appearance (within 7 days) of clinical symptoms such as rapid breathing and increased effort to breathe, as well as radiographic findings of chest opacities on one or both sides, absence of any chronic chest or cardiac problems, post-operative, post-cardiac arrest, post trauma or post extubation respiratory failure and hypoxemia characterized as PaO_2 constantly (greater than 6 to 8 hours) fewer than 60 mmHg or pulse oximetry (SpO_2) consistently below 90% when inhaling regular oxygen at a maximum concentration of 60% and having low or normal $PaCO_2$ levels.

Ethical consideration

Written consent was taken from each patient or the first of kin of each patient to participate in the study and the study was approved by the Ethical Committee of Medical Research of Faculty of Medicine, Sohag University.

Criteria of inclusion

Participants hospitalized to the respiratory ICU with de novo acute hypoxemic RF requiring ventilatory support due to:

1. Tachypnea with respiratory rate >30 breath/min.
2. Other signs of respiratory distress as use of accessory muscles of respiration and/or paradoxical breathing with thoraco-abdominal asynchrony.
3. PaO_2/FiO_2 ratio <300.

Criteria for exclusion

1. Age less than 18 years old.
2. Participants with hypercapnic respiratory failure ($PaCO_2$ more than 50 mmHg) on admission.
3. Participants with underlying chronic pulmonary disorders (e.g., COPD, bronchial asthma, ILD).
4. Requirement for emergency endotracheal intubation and invasive mechanical ventilation.
5. Participants who admitted to RICU after cardiopulmonary arrest outside RICU.
6. Contraindications to the use of NIV as:

a) Recent esophageal, cranial, facial trauma or surgery.
b) Active upper gastrointestinal bleeding. Upper airway diseases or tracheotomy.
c) Vomiting.
d) Inability to clear respiratory secretions.
e) Hemoptysis.
f) Persistent hemodynamic instability with SBP <90 mmHg or MAP below 65 mmHg after giving a bolus of crystalloid fluid (30 ml/kg) and use of vasoactive agents or life-threatening arrhythmias.

7. Patients with chronic cardiac, hepatic or renal diseases.
8. Participants already experiencing cancer of the lung.

9. Participants under chemotherapy because of extra-pulmonary malignancy.
10. Patients with post-operative, post-extubation or post trauma respiratory failure.

Methods

Each participant had been exposed to:

1 .comprehensive taking of history.

2 .comprehensive clinical assessment: General examination, cardiac, abdominal and local chest examination.

Utilization of accessory respiratory muscles by **Patrick scale .** [5]

The following scale was used:

0. No phasic or tonic neck muscular activity is seen.
1. Tense neck muscles without any respiratory control, or tonic activities.
2. Slightly altered breathing with contraction of the neck muscles.
3. Moderate phasic activity (absence of indrawing of intercostal or supraclavicular).
4. Intense phasic activity accompanied by indrawing.
5. Intense phasing activity accompanied with abdominal paradox.

3 .Chest imaging:

- Chest X-Rays P.A. & Lateral views.
- Chest C.T. scan.
- CT pulmonary angiography if required.
- Chest ultrasound.

4 . Echocardiography and ECG if required.

5. Laboratory tests:

- full blood picture that includes differential count.
- • Full metabolic profile, including blood glucose, serum electrolytes (NA^+, Ca^{++}, K^+), serum total proteins, serum albumin, serum bilirubin, serum urea, serum creatinine, liver enzymes and coagulation profile (PT, PC, INR and aPTT).
- Arterial blood gases using ABL800 FLEX Blood Gas Analyzer (Denmark), we recorded the following variables: pH, $PaCO_2$, PaO_2, SaO_2, $HCO3^-$ and PaO_2/FiO_2 ratio.

6. Sputum sample for bacterial culture and sensitivity was taken.
7. Nasopharyngeal swab for serological detection of Influenza A, H1N1 and H5N1 virus in suspected cases.
8. Nasopharyngeal swab for PCR testing for SARS-CoV-2 in suspected cases.
9. Evaluation of severity of disease:

a) **Acute Physiology and Chronic Health Evaluation II (APACHE II)** scoring was adopted as a severity scoring on admission.[6]

b) **Sequential Organ Failure Assessment (SOFA)** was used for assessment of Severity of organ failure at baseline and daily to assess for the appearance of sepsis and septic shock [7].

c) **The ratio of partial pressure of arterial oxygen (PaO_2) to the fraction of the inspired oxygen (FiO_2) [PaO_2/FiO_2] ratio** for assessment of severity of hypoxemia and ARDS based on **the Berlin Definition of ARDS, 2016.** [8]

PaO2/FiO2 ratio (mmHg)	ARDS category
>200 and ≤300	Mild
>100 and ≤200	Moderate
≤100	Severe

10.The Third International Consensus Definitions for Sepsis and Septic Shock were accepted as the criteria for identifying sepsis and septic shock. [9]

a) The term "sepsis" refers to potentially fatal organ failure brought on by an abnormal host reaction to an infection.

b) An abrupt shift in the overall SOFA score of equal to or over two points as a result of the infection indicates the presence of organ failure.

c) In individuals without a history of organ failure, the baseline SOFA score may be taken as 0.

d) Sepsis subtype known as "septic shock" occurs when underlying problems related to the circulatory system and cells/metabolism are severe enough to significantly raise death rates.

e) Individuals with a clinical construct of sepsis that includes persistent hypotension needing vasopressors to preserve a MAP equal to or higher than 65 mmHg and a serum lactate level exceeding two mmol/L (18 mg/dL) in spite of sufficient volume resuscitation may be recognized as having septic shock.

11. Initiation of NIV*:*

a) After fulfillment of inclusion criteria, the studied patients were connected to Carescape R860 ventilator (GE, USA), via double limb circuit with the interface of a clear non-vented oronasal face mask with a soft cushion seal. The mask was secured with head straps avoiding a tight fit.

b) The ventilator is switched to NIV mode with the following initial settings:

i) PEEP 10 cmH_2O and increased in 2 cmH_2O increments every 1 hour if needed to maintain SpO_2 above 92% provided that PaO_2 not exceeding 110 mmHg.

ii) Pressure Support at 6 cmH_2O and increased in 2 cmH_2O increments to maintain expiratory tidal volume between 4 and 6 ml/kg ideal body weight, a respiratory rate of fewer than 30 breaths/minute.

iii) FiO_2 60% and adjusted by 5% every 2 hours to keep PaO_2 of more than 65 mmHg or PaO_2/FiO_2 ratio of more than 120.

iv) Expiratory Trigger 25%.

v) Inspiratory Trigger 5 L/min.

vi) NIV was interrupted only during meals and was replaced by high flow nasal cannula (HFNC) when available.

c) In the event of a leak, an algorithm was implemented that included the following steps: adjusting the mask; lowering the PEEP level to 2 cmH2O; lowering the pressure-support level by 2 cmH2O increments until the minimum expiratory tidal volume was attained; and modifying the mask interface.

d) The head of the bed was raised to a 30-degree angle for all of the patients. Continuous oximetry and serial ABG readings were used to modify the ventilator settings. There was no sedation administered to the participants.

12. Monitoring during NIV:

a. HR, MAP, respiratory rate (RR), and oxygen saturation (SpO_2) were all continuously monitored. Follow up of **clinical data** including utilization of accessory respiratory muscles by Patrick scale every 6 hours.

b. **ABGs** at baseline before application of NIV and after 1 h, 6 h to assure **initial stability** and after 24 h to assure **sustained stability** and every 6 hours thereafter, before weaning and if needed in case of deterioration.

➢ The capacity to **raise the PaO_2/FiO_2 ratio over 200 or by more than 100 from the baseline** was considered an **enhancement in gas exchange.** Within an hour after starting NIV **(initial improvement)** and throughout time **(sustained improvement),** improvements in gas exchange were assessed. Serial arterial blood gas measurements verified the capacity to sustain the stated improvements in the PaO_2/FiO_2 ratio until the discontinuation of NIV, which was the definition of **sustained improvement** in gas exchange.

c. **Parameters of Ventilation**:

i. Minute Ventilation $\dot{V}_E$.

ii. Tidal Volume V_T.

iii. Peak Inspiratory Pressure PIP.

iv. Inspiratory Time to Total Cycle Time ratio (Inspiratory Duty Time) T_i/T_{tot}.

v. Leak L/min.

13. Weaning from NIV was achieved on a gradual concept:

i. Decrease FiO_2 to 40%, then

ii. Decrease pressure support every 2 hours by 2 cmH_2O down to 8 cmH_2O, then

iii. Decrease PEEP by 2 cmH_2O every 2 hours down to 5 cmH_2O.

14. Outcome measures:

➢ **The main results** were **the necessity for invasive mechanical ventilation and endotracheal intubation** at any point throughout the trial, as well as the risk variables for NIV failure.

1. **Successful outcome** is defined as discontinuation of NIV for 72 hours after weaning to conventional oxygen therapy with:

a. RR <24 BPM.

b. HR <110 BPM.

c. SpO_2 >90% on FiO_2 <35%.

The recipient was switched back to NIV if they had respiratory distress or desaturation following weaning off of NIV.

2. **Failure of non-invasive ventilation** is defined by criteria that necessitate **endotracheal intubation** using cuffed endotracheal tubes (internal diameters 7.5-8.5 mm) and shifting the patient to invasive mechanical ventilation.

The research participants were promptly intubated without any hesitancy in order to prevent the negative consequences of delayed intubation.

Intubation

was conducted for patients receiving NIV if any of the following conditions were met;

1. **Disturbed conscious level** in the form of agitation hindering nursing care and requiring sedation or GCS < less than 8 or seizures disorders.
2. **Severe hemodynamic instability** defined as **Persistent hypotension is characterized by a SBP less than 90 mmHg or a MAP less than 65 mmHg, even after receiving fluid resuscitation. It can also be indicated by the requirement of vasopressors at a dosage of over 300 ng/kg/min of norepinephrine for maintaining a SBP above 90 mmHg.** Additionally, it can be identified by ECG instability accompanied by **life-threatening arrhythmias.**
3. **The patient is experiencing significant respiratory distress with a respiratory rate exceeding 40 breaths per minute.**
4. **Severe hypoxemia characterized by a PaO_2/FiO_2 ratio of below 100.** or SpO_2 **remaining below 90%** despite FiO_2 **100%**.

➢ **The secondary outcomes** involved:

a. Length of time on mechanical ventilation.
b. Duration of stay in the ICU,

Statistical methods used for data analysis

The data was analyzed utilizing STATA version 17.0, a statistical software developed by StataCorp LP and released in College Station, TX. The graphs were generated utilizing the Excel, STATA, or Medcalc for Windows (version 11.0) software programs. A P value was deemed significant if it was < 0.05 and very significant if it was < 0.001.

Results

Our study was conducted on 126 patients selected after application of criteria for inclusion and exclusion. The outcome of NIV showed 79 individuals (62.7%) had successful NIV while 47 individuals failed the NIV trial (37.3%).

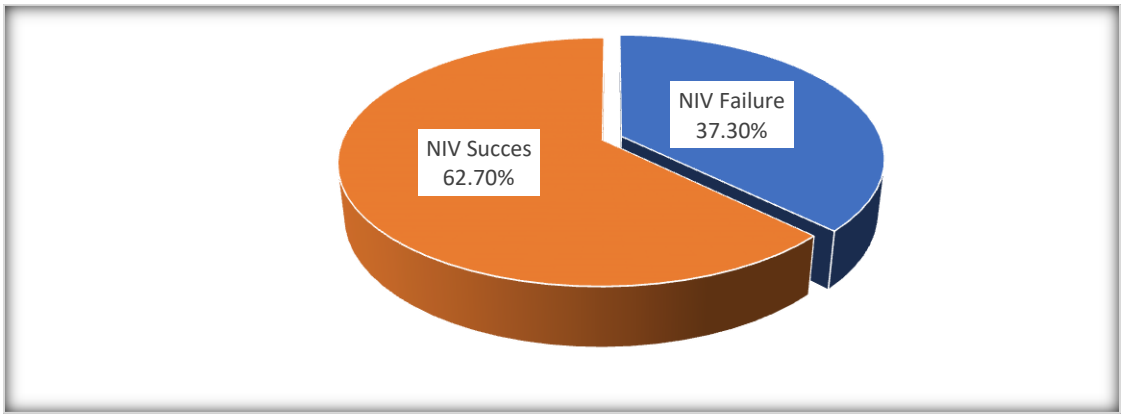

Figure 1: Outcome of NIV in studied patients

There was a significant improvement in **GCS**, a significant drop in the **heart rate**, a significant increase in the **systemic blood pressure (both systolic and diastolic)**, a significant drop in the **respiratory rate** and a significant drop in **Patrick scale** of accessory respiratory muscle use among NIV successful group after 1 hour of NIV and this significance was maintained on follow up on NIV (6, 24 hours of NIV and before weaning).

There were significant differences in clinical parameters between NIV success and failure groups with NIV success groups had higher **GCS**, lower **heart rate**, higher **systolic and diastolic blood pressures**, lower **respiratory rate** and lower **Patrick scale** of accessory respiratory muscle use after 1 and 6 hours of NIV (**P value <0.0001 each**) and after 24 hours (**P value 1.00, <0.0001. <0.0001, 0.002, <0.0001 and <0.0001 respectively**) as shown in **figure 2**.

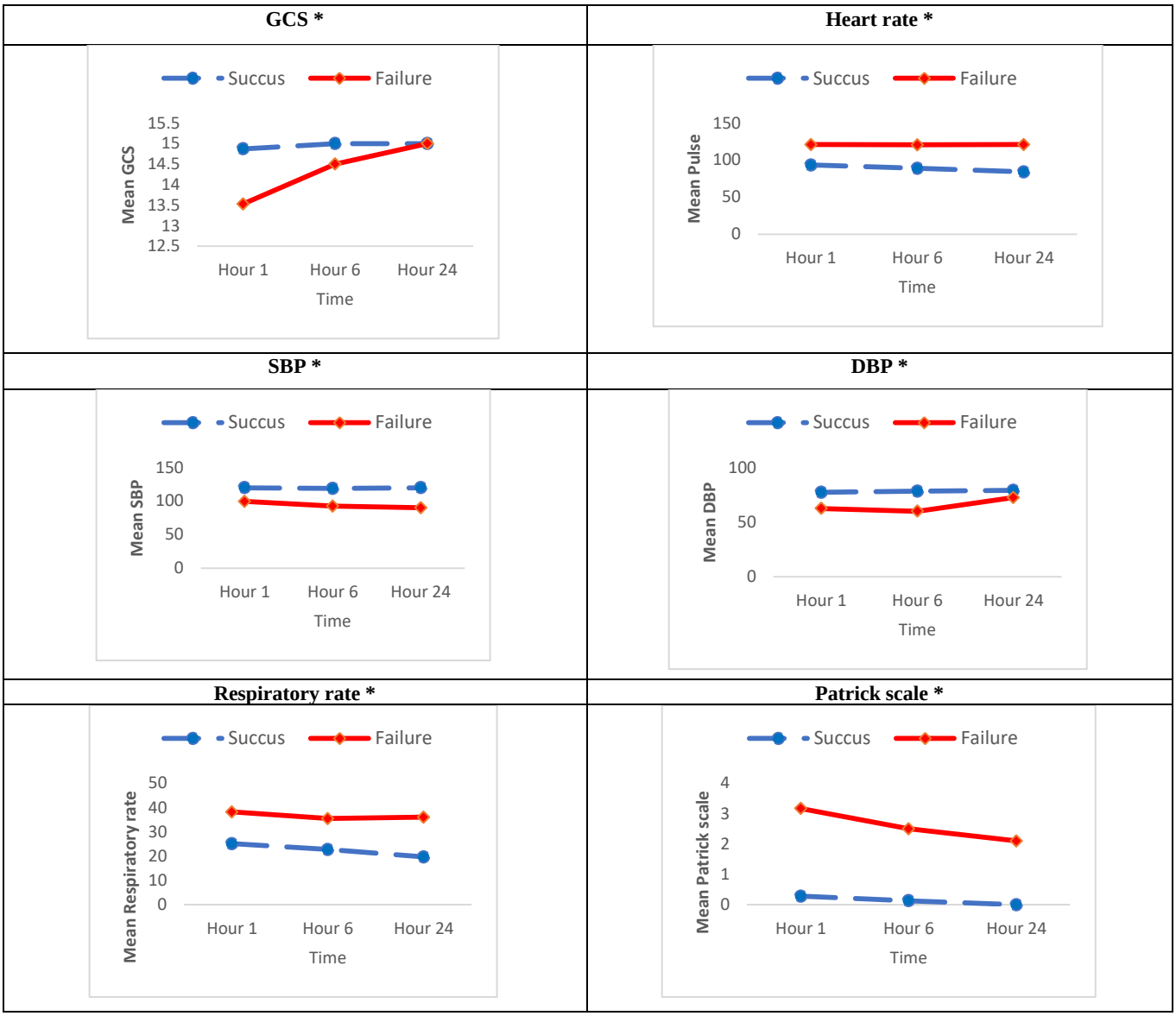

Figure 2: Clinical parameters among both NIV success and failure groups during NIV

There was a significant increase in the **SaO_2**, **PaO_2** and **P/F ratio** among NIV successful group after 1 hour of NIV and this significant increase was maintained on follow up on NIV (6, 24 hours of NIV and before weaning).

There were significant differences in ABG parameters between NIV success and failure groups after 1,6 and 24 hours of NIV with NIV success group had higher **SaO_2**, **PaO_2** and **P/F ratio** than the NIV failure groups (**P value <0.0001 each**) as shown in **figure 3**.

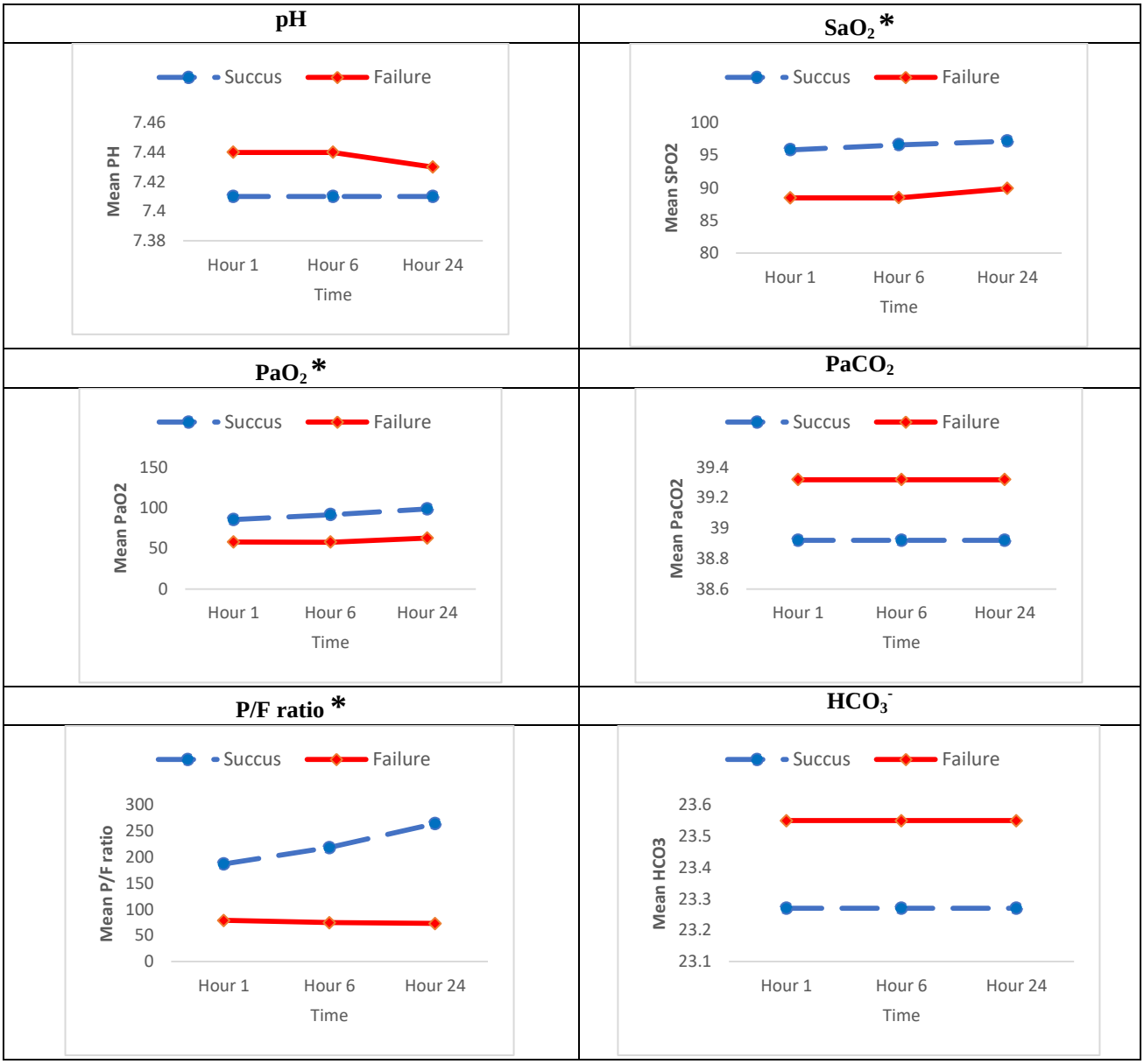

Figure 3: ABG parameters among both NIV success and failure groups during NIV

There was a significant drop in the **FiO_2**, **PEEP** level, **PS** level, **PIP** level, **$\dot{V}_E$** and **T_i/T_{tot}** and a significant increase in **V_T** among NIV successful group after 1 hour of NIV and this significant increase was maintained on follow up on NIV (6, 24 hours of NIV and before weaning).

There were significant differences in NIV mechanical parameters between NIV success and failure groups after 1,6 and 24 hours of NIV with NIV success group had lower **FIO_2**, **PEEP** level, **PS** level, **PIP** level, **$\dot{V}_E$** and **T_i/T_{tot}** and higher **V_T** (**P value <0.0001 each**) as shown in **figure 4**.

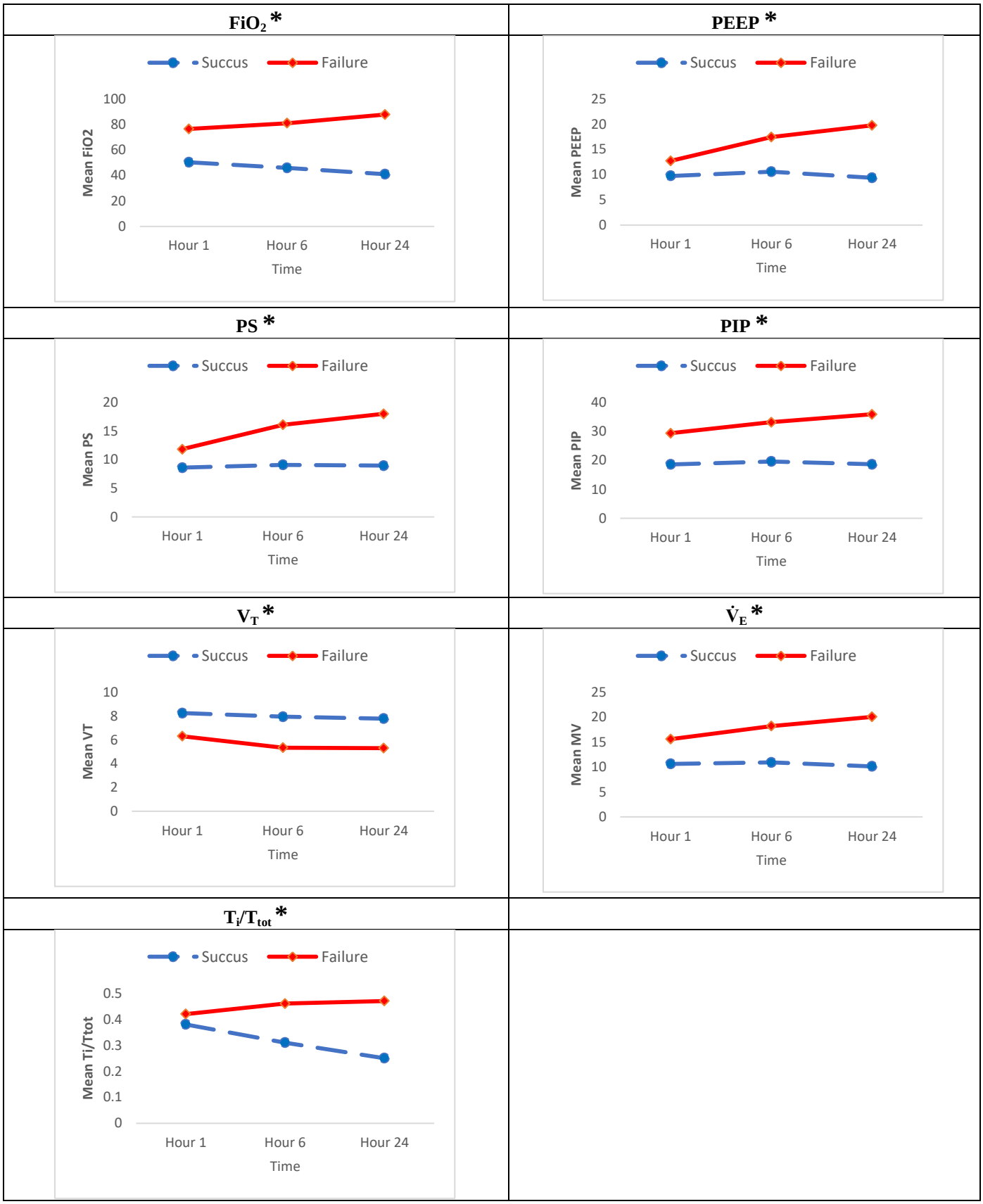

Figure 4: NIV mechanical parameters among both NIV success and failure groups during NIV

Table 1: ROC curve analysis of baseline parameters to predict failure of NIV

Variable	Cut off point	AUC (95% CI)	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	Accuracy (%)	P value
Age (years)	>62	1.0 (0.971-1.0)	100	100	100	100	100	**<0.0001**
Respiratory rate (cpm)	>35	0.985 (0.945-0.998)	93.6	92.4	88.0	96.1	93	**<0.0001**
Patrick scale	>1	0.974 (0.928-0.994)	93.6	96.2	93.6	96.2	94.9	**<0.0001**
APACHE II score	>23	0.978 (0.934-0.996)	93.6	88.6	83.0	95.9	91.1	**<0.0001**
SaO_2 (%)	≤77	0.659 (0.569-0.741)	31.9	92.4	71.4	69.5	62.2	**0.002**
P/F ratio	≤88	0.659 (0.569-0.741)	31.9	92.4	71.4	69.5	62.2	**0.002**
Creatinine (mg/dl)	>1.1	0.663 (0.573-0.744)	48.9	77.22	56.1	71.8	63.1	**0.001**
CRP (mg/dl)	>82	0.761 (0.677-0.833)	68.1	74.7	61.5	79.7	71.4	**<0.0001**

SaO_2: Oxygen saturation of arterial blood ***cpm: Cycle per minute***
APACHE II: Acute physiology and chronic health evaluation type II score ***CI: Confidence interval***
AUC: Area under ROC curve ***ROC: Receiver operating characteristic curve***
P/F ratio: Ratio of pressure of O_2 in arterial blood PaO_2 to fraction of inspiratory oxygen concentration FiO_2
PPV: Positive predictive value ***NPV: Negative predictive value***

For the patients` demographic data, regarding the patient's **age**, we calculated a cut-off point of **>62 years** as a baseline predictor of NIV failure **(AUC 1, P value <0.0001)**.
Regarding the baseline vital signs, we calculated a cut-off value for baseline **respiratory rate >35** to be a baseline predictor of NIV failure **(AUC 0.99, P value <0.0001)**, also a cut-off value for **Patrick scale >1** to be predictor of NIV failure **(AUC 0.97, P value <0.0001)**.
Regarding the severity of illness, we calculated a cut-off value for **APACHE II score >23** on admission to be a predictor of NIV failure **(AUC 0.98, P value <0.0001)**.
Regarding the baseline gasometric parameters, we calculated cut-off values for **SaO_2 ≤77** and **P/F ratio ≤ 88** to be predictors of NIV failure **(AUC 0.66 each, P value 0.002 each)**.
For baseline laboratory investigations, we calculated cut-off values for serum **creatinine >1.1 mg/dl** and serum **CRP >82 mg/dl** to be predictors of NIV failure **(AUC 0.66 and 0.76 and P values 0.001 and <0.0001 respectively)**.

Table 2: Predictors (Odds ratios) of NIV failure by different significant baseline parameters

Variable	Odds ratio (95% CI)	P value
Respiratory rate >35 cpm	178.44 (42.47-749.78)	**<0.0001**
Patrick scale >1	371.56 (71.87-1920.82)	**<0.0001**
APACHE II score >23	114.07 (29.28-444.44)	**<0.0001**
SaO_2 ≤77 %	5.70 (2.03-16.04)	**0.001**
P/F ratio ≤88	5.70 (2.03-16.04)	**0.001**
Creatinine >1.1 mg/dl	3.25 (1.49-7.06)	**0.001**
CRP >82 mg/dl	6.29 (2.83-13.95)	**<0.0001**

SaO_2: Oxygen saturation of arterial blood ***APACHE II: Acute physiology and chronic health evaluation type II score***
AUC: Area under ROC curve ***CI: Confidence interval***
P/F ratio: Ratio of pressure of O_2 in arterial blood PaO_2 to fraction of inspiratory oxygen concentration (FiO_2)

Calculation of the Odds ratio for significant baseline variables that are associated with increased risk for NIV failure revealed that **Patrick scale >1** use was associated with an increased risk of NIV failure **(Odds ratio 372)** followed by **respiratory rate >35 cpm (Odds ratio 178)**, then **APACHE II score >23 (Odds ratio 114)**, then **SaO_2 ≤77 %** and **P/F ratio ≤88 (Odds ratio 5.7 each)**, serum **CRP >82 mg/dl (Odds ratio 6.29)** and serum **creatinine >1.1 mg/dl (Odds ratio 3.25)**.

Table 3: ROC curve analysis of follow up parameters (1 hr after NIV) to predict failure of NIV

Variable	Cut off point	AUC (95% CI)	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	Accuracy (%)	P value
Respiratory rate (cpm)	>32	0.987 (0.948-0.999)	93.6	100	100	96.3	96.8	**<0.0001**
Patrick scale	>1	1.0 (0.971-1.0)	100	100	100	100	100.0	**<0.0001**
SaO_2 (%)	≤93	0.963 (0.913-0.988)	83.0	96.2	92.9	90.5	89.6	**<0.0001**
P/F ratio	≤107	0.939 (0.881-0.974)	78.7	96.2	92.5	88.4	87.5	**<0.0001**
PEEP (cmH_2O)	>11	0.839 (0.763-0.898)	72.3	78.5	66.7	82.7	75.4	**<0.0001**
PS (cmH_2O)	>9	0.942 (0.885-0.976)	93.6	93.7	89.8	96.1	93.7	**<0.0001**
PIP (cmH_2O)	>22	0.985 (0.946-0.998)	95.7	96.2	93.8	97.4	96.0	**<0.0001**
V_T (ml/kg PBW)	≤6.8	0.918 (0.855-0.959)	74.5	93.7	87.5	86.0	84.1	**<0.0001**
$\dot{V}_E$ (L/min)	>12	1.0 (0.971-1.0)	100	100	100	100	100.0	**<0.0001**
T_i/T_{tot}	>0.37	1.0 (0.971-1.0)	100	100	100	100	100.0	**<0.0001**

SaO2: Oxygen saturation of arterial blood
APACHE II: Acute physiology and chronic health evaluation type II score
AUC: Area under ROC curve ***ROC: Receiver operating characteristic curve***
CI: Confidence interval
P/F ratio: Ratio of pressure of O2 in arterial blood PaO2 to fraction of inspiratory oxygen concentration FiO2
PPV: Positive predictive value ***NPV: Negative predictive value***
PEEP: Positive end expiratory pressure ***PS: Pressure support***
VT: Tidal volume ***$\dot{V}E$: Minute ventilation***
PIP: Peak inspiratory pressure ***Ti/Ttot: Inspiratory time to total cycle time***
PBW: Predicted body weight

For follow up of vital signs 1 hour after NIV, we calculated cut-off values for respiratory rate >32 cpm and Patrick scale >1 to be predictors of NIV failure (AUC 0.99 and 1 respectively, P value <0.0001 each).
For follow up of gasometric parameters 1 hour after NIV initiation, we calculated cut-off values for SaO_2 ≤93% and P/F ratio ≤150 to be predictors of NIV failure (AUC 0.96 and 0.94 respectively and P value <0.0001 each).
For follow up of ventilatory parameters 1 hour after NIV, we calculated cut-off points for PEEP >11 cmH_2O, PS >9 cmH_2O, PIP >22 cmH_2O, V_T ≤6.8 ml/kg PBW, $\dot{V}E$ >12 L/min, and T_i/T_{tot} >0.37 to be predictors of NIV failure (AUC 0.84, 0.94, 0.99, 0.92, 1 and 1 respectively, P values <0.0001 each).

Table 4: Predictors (Odds ratios) of NIV failure by different parameters (1 hr after NIV)

Variable	Odds ratio (95% CI)	P value
SaO_2 ≤93%	123.5 (31.01-491.85)	**<0.0001**
P/F ratio ≤150	93.73 (24.33-361.10)	**<0.0001**
PEEP >11 cmH_2O	9.54 (4.14-21.97)	**<0.0001**
PS > cmH_2O	217.07 (49.45-952.79)	**<0.0001**
PIP >22 cmH_2O	570 (91.73-3541.89)	**<0.0001**
V_T ≤6.8 ml/kg PBW	43.17 (14.11-132.04)	**<0.0001**

SaO_2: Oxygen saturation of arterial blood
P/F ratio: Ratio of pressure of O_2 in arterial blood PaO_2 to fraction of inspiratory oxygen concentration FiO_2
PS: Pressure s **V_T: Tidal volume** **PIP: Peak inspiratory pressure**
PEEP: Positive end expiratory pressure **PBW: Predicted body weight**

Calculation of the Odds ratio for significant variables 1 hour after NIV that are associated with increased risk for NIV failure revealed that **PIP >22 cmH_2O** was associated with an increased risk of NIV failure **(Odds ratio 570)** followed by **PS >9 cmH_2O (Odds ratio 217)**, then **SaO_2 ≤93% (Odds ratio 123.5)**, **P/F ratio <150 (Odds ratio 94)** and **V_T ≤6.8 ml/kg PBW (Odds ratio 43)**.

Table 5: ROC curve analysis GCS, vital signs, blood gases and NIV settings parameters (24 hrs after NIV) to predict failure of NIV

Variable	Cut off point	AUC (95% CI)	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	Accuracy (%)	P value
Respiratory rate (cpm)	>24	1.0 (0.959-1.0)	100	100	100	100	100	**<0.0001**
Patrick scale	>0	1.0 (0.959-1.0)	100	100	100	100	100	**<0.0001**
SaO_2 (%)	≤94	0.975 (0.917-0.996)	90	100	100	98.7	95.0	**<0.0001**
P/F ratio	≤170	1.0 (0.959-1.0)	100	100	100	100	100	**<0.0001**
PEEP (cmH_2O)	>14	1.0 (0.959-1.0)	100	100	100	100	100	**<0.0001**
PS (cmH_2O)	>12	1.0 (0.959-1.0)	100	100	100	100	100	**<0.0001**
PIP (cmH_2O)	>24	1.0 (0.959-1.0)	100	100	100	100	100.0	**<0.0001**
V_T (ml/kg PBW)	≤6.8	0.997 (0.953-1.0)	100	96.2	76.9	100	98.1	**<0.0001**
$\dot{V}_E$ (L/min)	>12	1.0 (0.959-1.0)	100	100	100	100	100.0	**<0.0001**
T_i/T_{tot}	>0.31	1.0 (0.959-1.0)	100	100	100	100	100.0	**<0.0001**

SaO2: Oxygen saturation of arterial blood I: Confidence interval
APACHE II: Acute physiology and chronic health evaluation type II score
AUC: Area under ROC curve ROC: Receiver operating characteristic curve
P/F ratio: Ratio of pressure of O2 in arterial blood PaO2 to fraction of inspiratory oxygen concentration FiO2
PPV: Positive predictive value NPV: Negative predictive value
PEEP: Positive end expiratory pressure PS: Pressure support
VT: Tidal volume V̇E: Minute ventilation
PIP: Peak inspiratory pressure Ti/Ttot: Inspiratory time to total cycle time
PBW: Predicted body weight

For follow up of vital signs 24 hours after NIV, we calculated cut-off values for **respiratory rate >24 cpm** and **Patrick scale >0** to be predictors of NIV failure **(AUC 1 each, P value <0.0001 each)**.
For follow up of gasometric parameters 24 hours after NIV initiation, we calculated cut-off values for **SaO_2 ≤94%** and **P/F ratio ≤170** to be predictors of NIV failure **(AUC 0.98 and 1 respectively and P value <0.0001 each)**.
For follow up of ventilatory parameters 24 hours after NIV, we calculated cut-off points for **PEEP >14 cmH_2O**, **PS >12 cmH_2O**, **PIP >24 cmH_2O**, **V_T ≤6.8 ml/kg PBW**, **$\dot{V}E$ >12 L/min**, and **T_i/T_{tot} >0.31** to be predictors of NIV failure **(AUC 1, 1, 1, 0.99, 1 and 1 respectively, P values <0.0001 each)**.

Discussion

Our study was conducted on 126 patients (64 males and 62 females). The **outcome** of NIV showed 79 patients (62.7%) had successful NIV while 47 patients failed the NIV trial (37.3%). On follow up clinical parameters during NIV, we found that NIV successful group showed a significant improvement in **GCS**, a substantial decrease in the **heart rate** and a substantial raise in **blood pressure (systolic and diastolic)**, a substantial decrease in the **respiratory rate** and a substantial drop in **Patrick scale** of accessory respiratory muscle use after 1 hour of NIV which was maintained on follow up on NIV (at

6, 24 hours of NIV and before weaning) in line with the findings by **Duan et al., 2022 .**[10] who reported improvements in GCS, heart rate, respiratory rate and blood pressure in NIV success group on 1-2 hours after NIV initiation and the results by Yaroshetskiy et al., 2022.[11] who found improvement in Patrick scale and respiratory rate on NIV on daily follow up which is maintained till weaning. Also, we found that NIV success group had significantly higher **GCS**, lower **HR**, higher **SBP and DBP**, lower **respiratory rate** and lower **Patrick scale** of accessory respiratory muscle use after 1 and 6 hours of NIV (P value <0.0001 each) and after 24 hours (P value 1.00, <0.0001. <0.0001, 0.002, <0.0001 and <0.0001 respectively) in line with the findings by Duan et al., 2022. [10] (P value <0.01, <0.01, 0.03, 0.02 and <0.01 correspondingly) on follow up 1-2 hours after NIV initiation, Rana et al., 2006. [12] who found that lower baseline GCS was a predictor of NIV failure and the findings by Yaroshetskiy et al., 2022 .[11] who stated significant lower Patrick scale in success than in failure group at 24 hours after NIV initiation (P value <0.001) but no substantial variation in respiratory rate among NIV failure and success groups 24 hours after NIV initiation (mean 28 cpm Vs 27 cpm in failure and success groups respectively, P value >0.05) disagreeing with our results. Also, Thille et al., 2013 [13] stated that no substantial variation was existed in respiratory rate among NIV success and failure groups at NIV initiation (mean 32.7 cpm Vs 33.9 cpm respectively, P value 0.601) in contrast to our results. During follow up of ABG parameters during NIV we found a significant increase in the **SaO_2**, **PaO_2** and **P/F ratio** among NIV successful group after 1 hour of NIV and this significant increase was maintained on follow up on NIV (6, 24 hours of NIV and before weaning) as shown in the results by Duan et al., 2022.[10] who reported improvements in SaO_2 and P/F ratio 1-2 hours after NIV initiation (mean 90% and 167 before NIV initiation Vs 97% and 213 1-2 hours after NIV respectively) and the results by **Yaroshetskiy et al., 2022**. [11] who stated sustained improvement in SpO_2, PaO_2 and P/F ratio in NIV success group on daily follow up on NIV till weaning. We also found that after 1,6 and 24 hours, NIV success group had higher **SaO_2**, **PaO_2** and **P/F ratio** than the NIV failure groups (P value <0.0001 each) agreeing with the results by **Duan et al., 2022.** [10] (mean SpO_2 97% Vs 95%, mean P/F ratio 213 Vs 156 in success and failure groups 1-2 hours after NIV, P values <0.01 each), ***González et al., 2016*** [14] who found that P/F ratio was greater in NIV success group than in NIV failure group 2 hours after NIV (mean 194.5 Vs 145.1 respectively, P value <0.001) and ***Yaroshetskiy et al., 2022 .*** [11] who stated that after 24 hours of NIV, success group had significantly higher SpO_2, PaO_2 and P/F ratio than the failure group (mean 98%, 94 mmHg and 128 Vs 95%, 73 mmHg and 90, P values <0.001, <0.01 and <0.001 respectively). Agreeing with our results, **Thille et al., 2013.**[13] found that P/F ratio was substantially lower in NIV failure contrasted to in the success group (mean 163 Vs 211 respectively, P value 0.003). In the current work we found no substantial variation in **pH** nor **$PaCO_2$** among NIV success and failure groups during follow up at 1, 6 and 24 hours following initiation of NIV, while **Duan et al., 2022 .** [10] found that pH was substantially greater in NIV success contrasted to in failure group 12 hours following NIV initiation (mean 7.44 Vs 7.41 respectively, P value <0.01) as in their study NIV failure group had severe sepsis and septic shock with lactic acidosis that led to decrease in pH and that $PaCO_2$ didn`t vary among NIV success and failure groups (mean 33 mmHg VS 34 mmHg respectively, P value 0.17) agreeing with our results. contrasting to our results, ***Yaroshetskiy et* al., 2022.** [11] reported substantial increase in $PaCO_2$ level on daily follow up on NIV till weaning and that after 24 hours of NIV initiation, NIV success group had significantly higher $PaCO_2$ level than the failure group (mean $PaCO_2$ 37 mmHg Vs 35 mmHg respectively, P value <0.05). **Monitoring of NIV parameters** in our study revealed that there was a significant drop in the **FiO_2**, **PEEP** level, **PS** level, **PIP** level, **$\dot{V}_E$** and **inspiratory duty cycle T_i/T_{tot}** and a significant increase in **V_T** among NIV successful group after 1 hour of NIV and this significance was maintained on follow up on NIV and that NIV success groups had lower **FIO_2**, **PEEP** level, **PS** level, **PIP** level, **$\dot{V}_E$** and **T_i/T_{tot}** and higher **V_T** (P value <0.0001 each) after 1,6 and 24 hours of NIV contrasted to the NIV failure group. Agreeing with our results, Yaroshetskiy et al., 2022.

[11] found significant drop in the mean level of **PS**, $\dot{V}_E$ and **I/E ratio** and a substantial raise in the mean V_T in the NIV success group on daily follow up till weaning, meanwhile, in their work, no substantial variation was existed in the level of **PS**, $\dot{V}_E$, **I/E ratio** and V_T among NIV success and failure group after 24 hours of NIV initiation, disagreeing with our results. Also, Dargent et al., 2022.[15] found that at baseline, in comparison to the NIV failure group, the NIV success group had significantly lower FiO_2 (mean 55% VS 90%, P value <0.001), lower $\dot{V}_E$ (mean 11 L/min Vs 15 L/min, P Value 0.006) and lower **inspiratory duty cycle** T_i/T_{tot} (mean 0.36 Vs 0.42, P value 0.003) in line with our findings, while they stated no substantial variation in V_T among NIV success and failure groups (mean 6.2 ml/kg PBW Vs 8.2 ml/Kg PBW, P value 0.196) in contrast to our study. In the work by Bellani et al., 2017.[16], they stated that at baseline, NIV success group had significantly lower FiO_2 (mean 58% Vs 67%, P value 0.007) and lower **PIP** (mean 17.43 cmH_2O Vs 26.77 cmH_2O, P value <0.001) agreeing with our results. On the other hand, they found no statistically substantial variation among NIV success and failure groups regarding **PEEP** (mean 7 cmH_2O each, P value 0.478), $\dot{V}_E$ (mean 12.71 L/min Vs 14.03 L/min, P value 0.107) and V_T (mean 8.38 ml/kg Vs 8.65 ml/kg, P value 0.795) disagreeing with our results. Disagreeing with our results, Thille et al., 2013. [13] found that after NIV initiation, NIV success group had significantly higher level of **PEEP** than the NIV failure group (mean level 4.8 cmH_2O Vs 4.4 cmH_2O, P value 0.011) meanwhile, they reported no substantial variation among NIV success and failure groups regarding **PS** level (mean 8.1 cmH_2O Vs 8.0 cmH2O, P value 0.915) nor V_T (mean 5.76 ml/kg PBW Vs 6.19 ml/kg PBW, P value 0.157), González et al., 2016. [17] who found no substantial variation in **IPAP** nor **EPAP** among NIV success and failure groups at 2 hours after NIV initiation (mean IPAP 16.3 cmH_2O Vs 15.5 cmH_2O and mean EPAP 6.6 cmH_2O Vs 6.9 cmH_2O in success and failure groups respectively, P value 0.06 and 0.11 respectively) and ***Antonelli et al.,*** 2001.[18] who stated no substantial variation in baseline **PEEP** level among NIV success and failure groups (mean 7 cmH_2O each, P value 0.6). On **follow up of clinical parameters on NIV**, our study showed that NIV successful group showed improvement in **RR**, **HR**, **SBP and DBP** and **Patrick scale** which is maintained on follow up till weaning agreeing with the findings by Salwa et al., 2019.[19] who revealed that failure of improvement in HR (Odds ratio 1.193 (1.072–1.329) CI 95%, P value 0.001), RR (Odds ratio 1.135 (1.044–1.234) 95% CI, P value 0.003) from NIV start to 2 hours after NIV was correlated with increased risk of NIV failure while ***González et al.,*** 2016. [17] reported that failure of improvement in RR form NIV initiation to 2 hours after NIV was a risk for NIV failure (Odds ratio 1.94 (1.89-1.99) 95% CI, P value 0.025) while failure of improvement of HR from NIV initiation to 2 hours post NIV wasn`t correlated with elevated risk of NIV failure (Odds ratio 0.98 (0.96-1.01) 95% CI, P value 0.077). On **follow up of ABG parameters on NIV**, our study showed that NIV success group showed maintained improvement on SaO_2, PaO_2 and **P/F ratio** on follow up till weaning agreeing with the findings by Salwa et al., 2019. [19] who stated that failure of improvement in PaO_2 (Odds ratio 1.076 (1.003–1.049) CI 95%, P value 0.043) from NIV start to 2 hours after NIV was correlated with elevated risk of NIV failure and González et al., 2016 .[17]

who found that failure of improvement of P/F ratio from NIV start to 2 hours after NIV was a predictor of NV failure (Odds ratio 1.01 (1.001-1.02) 95% CI, P value 0.028). Regarding the **baseline predictors of NIV failure**, we stated that patient`s age >62 years was correlated with elevated risk of NIV failure (AUC 1.0, P value <0.0001) disagreeing with the findings by ***Antonelli et al., 2001*** [18] who revealed that patients age > 40 years was a predictor of NV failure. We also calculated a cut-off value for **baseline respiratory rate >35 cpm** as a predictor of NIV failure and agreeing with the results by Antonelli et al., 2001 .[18] who stated that baseline respiratory rate >38 cpm (Odds ratio 1.89 (1.06-3.37) 95% CI) was a risk factor for NIV failure, González et al., 2016.[17] who reported that baseline RR >35 cpm was a predictor of NIV failure and Bellani et al., 2017. [7] who found that higher respiratory rate was as correlated with elevated risk of NIV failure. We calculated a cut-off value for **APACHE II score >23** on admission to be a risk factor for NIV failure (AUC 0.98, P value <0.0001)

agreeing with the results by ***Salwa et al., 2019*** [19] who found that APACHE II score >23 (Se 94.745, Sp 92.68%, AUC 0.98, P value 0.002) and ***González et al., 2016*** [17] who found that high APACHE II score was a predictor of NIV failure (Odds ratio 1.09 (1.03–1.14) 95% CI, P value 0.001). **After 1 hour of NIV**, we calculated a **P/F ratio ≤107** to be a predictor of NIV failure which was lower that calculated by Antonelli et al., 2001 .[18] who found that P/F ratio ≤146 after 1 hour of NIV was correlated with elevated risk of NIV failure, ***Bellani et al., 2017*** [20] who stated that P/F ratio <150 at NIV initiation was a predictor of NIV failure and Thille et al., 2013. [13] who found that P/F ratio <150 at NIV initiation was correlated with elevated risk of NIV failure (Odds ratio 2.97 (1.77 to 4.99) 95% CI, P value < 0.001) and in contrast to the results by Ferrer et al., 2003.[21] who stated that presence of ARDS at NIV initiation (P/F ratio <300) was a predictor of NIV failure. **24 hours after NIV**, we found that **RR >24 cpm** and **Patrick score >0 points** was correlated with elevated risk of NIV failure, close to the results by Yaroshetskiy et al., 2022. [11] who found that respiratory rate >27 cpm (Odds ratio 4.4 (1.4–13.6) 95% CI, P value < 0.001) and Patrick score ≥2 points (Se 71%, Sp 90%, AUC 0.87 (0.78–0.96), P value 0.006) 48 hours after NIV was correlated with elevated risk of NIV failure. Also, we found that **P/F ratio <170** after 24 hours of NIV was a predictor of NIV failure, while Yaroshetskiy et al., 2022.[11] found that P/F <112 mmHg following 48 hours of NIV was a predictor of NIV failure (Se 85%, Sp 83%, AUC 0.90, P value < 0.001).

Conclusion

NIV plays a crucial role in the therapy of de novo AHRF and ARDS. The rate of NIV success in patients with de novo AHRF and ARDS is 62.70%. NIV is effective in managing individuals with mild to moderate ARDS but not in severe ARDS. Individuals with more severe disease at presentation as revealed by the significantly more severe ARDS degree, the presence of septic shock on admission, higher APACHE II and higher SOFA score on the 1st day and on subsequent days are more liable to fail NIV.

Recommendation:

NIV should be an integral part in the managing individuals with *de novo* AHRF and ARDS in the absence of immediate indications for endotracheal intubation and/or any contraindication for NIV, particularly in mild to moderate ARDS and less severe disease at presentation. Close monitoring of AHRF and ARDS patients put on NIV for the detection of any sign of deterioration and/or complication which necessitate invasive mechanical ventilation and endotracheal intubation. A low threshold for invasive mechanical ventilation and endotracheal intubation should be adopted upon any sign of deterioration and/or complication or failure to achieve enhancement in exchange of gas and/or improvement in signs of respiratory distress.

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