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# Noninvasive Ventilation versus High-Flow Nasal Cannula in Prevention of Reintubation of Patients with High Risk for Extubation Failure

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## ABSTRACT

**Background:** Extubation failure is known as the failure to sustain sufficient spontaneous breathing following the removal of an artificial airway, particularly in high-risk patients. This condition poses a significant risk of complications during and after reintubation. Non-invasive Positive pressure ventilation (NIV) and high-flow nasal cannula (HFNC) are used as successful strategies for reducing these risks. However, further research is needed to evaluate their effectiveness and conduct direct outcome comparisons.

**Objective:** This trial aimed to examine how non-invasive ventilation (NIV) and high-flow nasal cannula (HFNC) influence the necessity of reintubation for patients who are very likely to fail extubation.

**Patients and methods:** This prospective randomized controlled trial (RCT) enrolled 120 critically ill adult patients in the ICU who were at elevated risk of extubation failure. All participants had undergone invasive mechanical ventilation for a minimum of 24 hours and were deemed prepared for extubation post passing a spontaneous breathing trial (SBT). Following extubation, subjects were assigned randomly into 2 equal groups: One receiving non-invasive ventilation (NIV) and the other high-flow nasal cannula (HFNC) therapy.

**Results:** Of all the patients, 70 males were involved, the median age of the participants was 60 years (IQR: 55–63). No significant differences were detected among groups concerning baseline characteristics such as age, sex, BMI, APACHE II scores, or the presence of comorbid conditions. Clinical outcomes showed comparable effectiveness between respiratory support modalities. Reintubation was avoided in 75% of patients receiving non-invasive ventilation versus 78.3% of those using high-flow nasal cannula (p=0.672). Infectious complications occurred at similar frequencies, with ventilator-associated pneumonia rates of 15% and 16.7% (p=0.80), and sepsis incidence of 21.7% versus 26.7% (p=0.52) for non-invasive ventilation and high-flow nasal cannula respectively. However, treatment tolerance differed substantially, with non-invasive ventilation showing a significantly higher rate of device intolerance (15% vs 3.3%, p=0.02).

**Conclusions:** HFNC may be at least as effective as NIV in reducing the risk of reintubation in patients with likelihood of extubation failure. Additionally, HFNC oxygen therapy was linked to fewer adverse effects and was better tolerated.

**Keywords:** Extubation failure, High-flow nasal cannula, Mechanical ventilation, Non-invasive ventilation, Reintubation.

## INTRODUCTION

Invasive ventilation is critical for the management of patients with compromised airways, inadequate ventilation, or hypoxemic respiratory failure. However, the process of discontinuing ventilatory support can be complex, often leading to respiratory muscle fatigue and complicated by weaning or extubation failure [1, 2]. In intensive care, extended weaning from mechanical ventilation is a major issue due to its consistent association with a marked rise in the occurrence of various complications. This encompasses an increased risk of ventilator-associated pneumonia, greater susceptibility to nosocomial infections, and potential for airway injury due to prolonged intubation and manipulation. Furthermore, patients requiring extended weaning often experience prolonged hospitalizations, leading to increased healthcare costs and resource utilization. Critically, a substantial body of evidence also links prolonged weaning duration to significantly higher rates of mortality within the intensive care unit setting, highlighting the urgency of implementing effective and timely weaning strategies to improve patient outcomes and reduce the burden of critical illness [3].

The daily assessment of patients for readiness to be liberated from mechanical ventilation is a critical aspect of intensive care management, invariably including an evaluation of their suitability for a spontaneous breathing trial (SBT). While, the expertise and nuanced clinical judgment of the treating physician remain indispensable in this process, relying solely on subjective evaluation can lead to either premature or delayed weaning attempts, potentially impacting patient outcomes. Consequently, the integration of objective, readily accessible, and broadly applicable physiological measures is essential to augment clinical decision-making and provide a more data-driven approach to determining a patient's readiness for ventilator discontinuation [3, 4].

**Readiness criteria consist of four key components:** (1) Near-complete reversal of the root cause of respiratory failure, (2) Hemodynamic stability (Defined as the absence of shock, no high vasopressor



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requirements, no significant arrhythmias, and no active myocardial infarction), (3) Adequate mental status and respiratory drive to sustain spontaneous breathing, and (4) Sufficient oxygenation and ventilation within acceptable ventilator parameters [4].

If the patient fulfilled the criteria, he should undergo spontaneous breathing trials (SBTs), and if the patient passes the SBT, they should be given the opportunity for extubation. Prolonged weaning is clinically defined as a weaning process that extends beyond 7 days or requires more than three spontaneous breathing trials (SBTs) following the initial failed attempt. Difficult weaning refers to cases where patients fail their first SBT but achieve successful extubation after ≤ 3 SBTs within 7 days. Both conditions are linked to higher ICU stays, complications, and mortality rates, emphasizing the need for structured weaning protocols [5]. If the patient passes the SBT, they should be given the opportunity for extubation. Extubation failure is characterized by the inability to sustain adequate spontaneous breathing after the removal of an artificial airway, necessitating reintubation within 48 to 72 hours [6, 7].

NIV has demonstrated effectiveness in helping chronic obstructive pulmonary disease (COPD) patients transition from mechanical ventilation to independent breathing, leading to better outcomes and prognosis. However, around 15% to 25% of patients do not tolerate NIV well, often requiring reintubation [7, 8]. This underscores the importance of alternative respiratory support strategies for patients unable to tolerate NIV or are contraindicated for its use. Additionally, NIV has adverse effects such as skin damage, eye irritation, claustrophobia, mucosal dryness, and a heightened risk of aspiration, which can restrict its clinical application [9].

High flow nasal cannula has emerged as a significant alternative to NIV for offering respiratory support post-extubation. Heated and humidified air is delivered by HFNC at high flow rates, which contributes to the generation of positive airway pressure, increases functional residual capacity, enhances oxygenation, and helps maintain stable oxygen levels. Humidified air improves airway hydration, aids in secretion clearance, protects epithelial cells, and enhances patient tolerance [2].

High-flow nasal cannula (HFNC) significantly improves patient tolerance compared to conventional oxygen therapy or non-invasive ventilation (NIV). Its heated and humidified airflow minimizes nasal and airway dryness, reducing discomfort and enhancing adherence, particularly in prolonged use. The open interface allows patients to speak, eat, and expectorate more easily than with tight-fitting NIV masks, which often cause claustrophobia or skin breakdown [10].

However, existing literature, including studies focusing on the broader population of critically ill patients (References 2 and 10) has indicated that high-flow nasal cannula (HFNC) is non-inferior to non-invasive ventilation (NIV) in terms of preventing reintubation. These prior findings suggest that HFNC can be an equally effective respiratory support strategy compared to NIV in a general critical care setting [2,10].

A notable gap exists in the current body of literature regarding studies specifically evaluating the comparative efficacy of non-invasive ventilation (NIV) and high-flow nasal cannula (HFNC) in participants within the Egyptian population who are identified as being at high risk for extubation failure. To address this deficiency, the present study was designed with the main objective of assessing the effect of NIV, as compared to HFNC, on the reduction of reintubation rates within this specific high-risk patient demographic in our local setting.

## PATIENTS AND METHODS

This prospective, randomized controlled trial (RCT) was carried out on a cohort of 120 critically ill adult patients admitted to the Intensive Care Unit (ICU) at Menoufia University Hospital. The study population comprised patients deemed at high risk for extubation failure who previously received invasive mechanical ventilation for a duration of one day or more and subsequently underwent extubation following positive achievement of a spontaneous breathing trial.

**Inclusion criteria:** Patients were defined as high-risk for extubation failure upon fulfilling ≥ 4 criteria: age > 65 years, mechanical ventilation primarily indicated for heart failure, prior diagnosis of moderate-to-severe COPD, APACHE II score >12 at time of extubation, or BMI > 30 kg/m², airway patency issues, difficult or prolonged weaning (Defined as the inability to successfully disconnect from mechanical ventilation after at least one attempt), presence of two or more comorbidities, a mechanical ventilation duration of seven days or more, and hypercapnia ($PaCO_2$ > 45 mmHg) at the end of the SBT.

**Exclusion criteria:** Patients who had a tracheostomy, experienced accidental or self-extubation, or were unable to manage respiratory secretions, defined as requiring suctioning more than twice within eight hours before extubation. Additionally, those with contraindications to non-invasive ventilation (NIV), including recent maxillofacial surgeries, active upper gastrointestinal bleeding, or excessive respiratory secretions.

The spontaneous breathing trial (SBT) was done using pressure support mode with the following initial settings: Positive end-expiratory pressure (PEEP) of 5 to 8 $cmH_2O$, driving pressure of 5 to 8 $cmH_2O$, and a fraction of inspired oxygen ($FIO_2$) ≤ 40%. An appropriate backup control mode and ventilator alarms were adjusted as

needed. Following the successful completion of the SBT, all patients were assigned randomly to one of 2 equal groups: Group A (HFNC, n = 60) and group B (NIV, n = 60) (Figure 1).

**Group A (HFNC):** A size-adjusted nasal cannula was applied using the high-flow nasal mode of the *Bellavista™ 1000* ventilator immediately after extubation. HFNC was administered continuously for 48 hours. The initial flow rate was set at 10 L/min and incrementally increased to 60 L/min or adjusted based on patient comfort. The temperature was maintained at 37 °C.

**Group B (NIV):** Non-invasive ventilation was initiated immediately after extubation and delivered continuously for 48 hours using the NIV mode of the *GE™ Healthcare CARESCAPE R860* ventilator. A properly fitted *ClassicStar® Plus NIV* oronasal mask was used. PEEP and pressure support parameters were set to ensure a respiratory rate below 26 breaths per minute, a tidal volume of 6–8 mL/kg of PBW, and adequate gas exchange ($SpO_2 \geq 92\%$, with a pH range of 7.35–7.45). No patients received any sedatives.

In both groups, $FIO_2$ was titrated to maintain a $SpO_2$ of ≥ 92%. Post 48 hours, HFNC and NIV were discontinued, and patients were transitioned to conventional oxygen therapy as needed based on their clinical condition. Both groups received standardized medical, nursing and respiratory therapy management and were monitored for 7 days post-extubation to assess primary and secondary outcomes. Intolerance to NIV/HFNC is defined as the inability or unwillingness to adhere to CPAP therapy due to discomfort, side effects, or patient-related factors, resulting in suboptimal or discontinued use. This includes persistent issues such as mask discomfort, claustrophobia, dry mouth, nasal congestion, air leaks, difficulty exhaling, or poor adherence.

**Sample size estimation:** Based on the review of past literature, a comparable incidence of reintubation in patients receiving NIV (66.7%,) vs HFNC (79.4%) ($p$ = 0.22) vs is noted (11). With an alpha error of 0.05 (two-tailed), 80% power, and 95% confidence intervals, the calculated minimum sample size was 60 participants per arm (total N=120).

**Ethical Approval: Following the acquisition of comprehensive informed consent from each participant or his legally authorized representative. Prior to the commencement of any study-related procedures, ethical approval for the research protocol was formally granted by the institutional review board (IRB) of Menoufia University, ensuring adherence to stringent ethical guidelines and the protection of patient rights and welfare throughout the duration of the study. This ethical oversight underscores the commitment to responsible research practices and the well-being of all participants involved. (Approval No. 11/2023 ANES38). The Helsinki Declaration was followed throughout the course of the study.**

***Statistical analysis***

All statistical analyses for this study were conducted using the Jamovi software (version 2.6.19, 64-bit). For continuous variables, normality of distribution was assessed, and those adhering to a normal distribution are presented using the mean ± standard deviation. Conversely, continuous variables exhibiting a skewed distribution were represented by the median, which is less sensitive to outliers, along with the interquartile range (IQR) to indicate the spread of the central 50% of the data. When comparing continuous data between different groups, Student's independent samples t-test was employed if the data in both groups were normally distributed and had approximately equal variances. As an alternative, if the assumptions of normality or equal variances were violated, non-parametric tests such as the Mann-Whitney U test (for independent groups) or the Wilcoxon signed-rank test (for paired or related samples) were utilized. Categorical variables were analyzed using either the Chi-square ($\chi^2$) test of independence or Fisher's exact test, with the choice between these tests determined by the expected frequencies within the cells of the contingency tables. To evaluate survival outcomes over time, Kaplan-Meier survival curves were made for all groups, moreover, the log-rank test was utilized to statistically assess any significant differences in survival distributions between these groups. Throughout the entire statistical analysis process, a two-sided probability value (p-value) of ≤ 0.05 was consistently used as the predetermined threshold to establish statistical significance.

## RESULTS

**Demographic data:** Figure (1) outlines the study's participant flow. This prospective investigation enrolled 120 patients, equally distributed into two intervention arms: 60 patients receiving high-flow nasal cannula (HFNC) and 60 patients managed with non-invasive ventilation (NIV).

Invasive mechanical ventilation lasted significantly longer before extubation in the HFNC group in comparison with the NIV group (Mean of 11.5 days versus 8 days, p = 0.011). No statistically significant difference was detected in the distribution of primary causes for intensive care unit (ICU) admission among both groups. However, sepsis was noted to be the furthermost common reason for admission among patients treated with NIV.

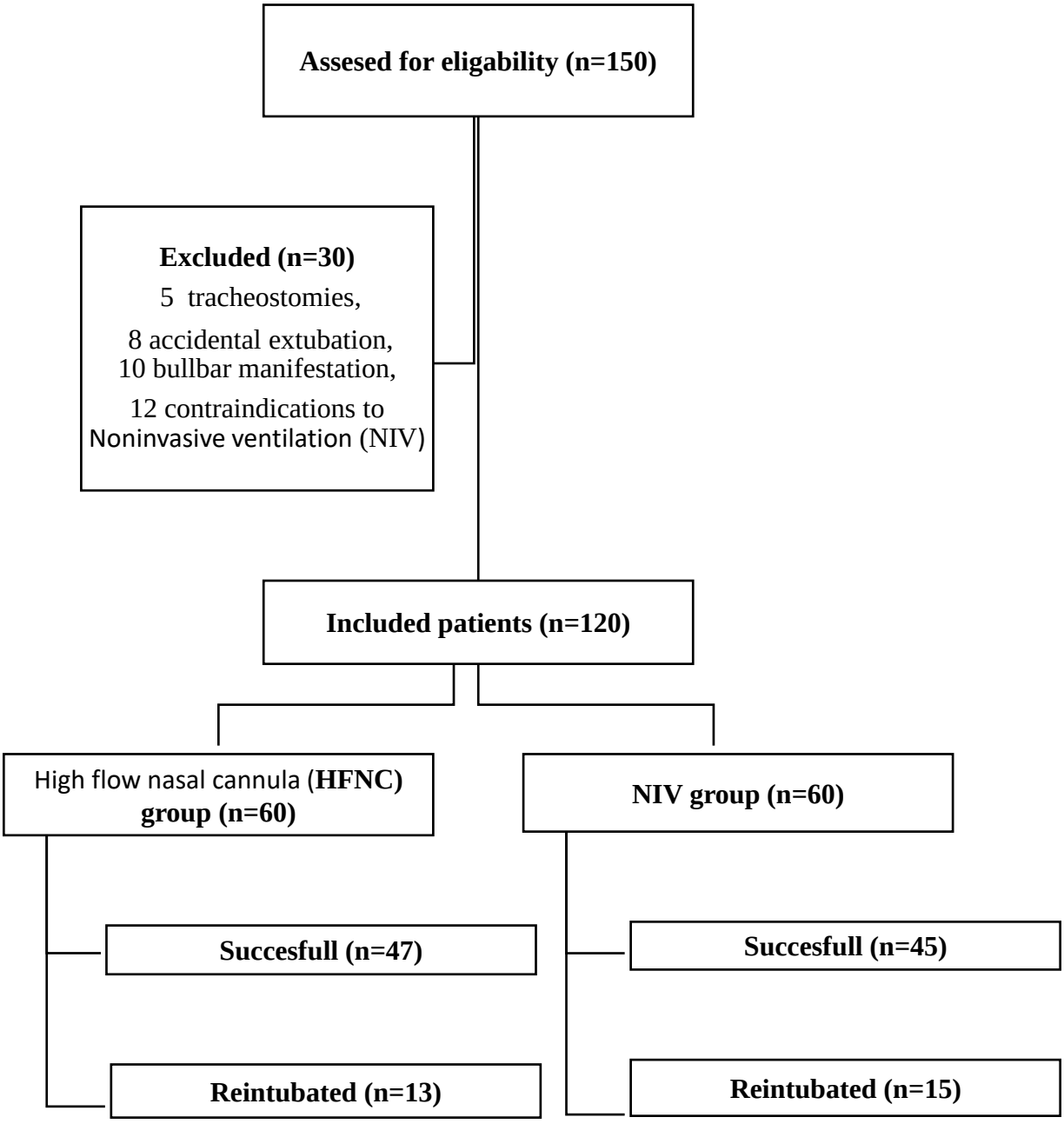


**Figure (1):** The flowchart of the study.

Table (1) detailed the baseline characteristics of the recruited cohort demonstrating no statistically significant differences between the HFNC and NIV groups regarding age, gender, body mass index (BMI), or Acute Physiology and Chronic Health Evaluation II (APACHE II) scores. Furthermore, statistical analysis revealed no significant disparities in the occurrence of comorbid conditions among both groups. Both of them included hypertension, diabetes mellitus, chronic heart failure (CHF), chronic kidney disease (CKD), chronic liver disease (CLD), or chronic obstructive pulmonary disease (COPD).

**Table (1):** Baseline characteristics of the studied groups

| | NIV (n=60) | HFNC (n=60) | Test of significance | P value |
|---|---|---|---|---|
| **Age, mean (SD), y** | 60 (5.7) | 59 (6.1) | T= -0.845 | 0.40 |
| **Sex (male)** | 33 (55%) | 37 (61%) | $X^2$=0.5 | 0.46 |
| **BMI, mean (SD)[a]** | 29.8 (5.1) | 30.5 (4.72) | T = 0.701 | 0.485 |
| **APACHE II mean (SD)[b]** | 19.767 (4.018) | 19.583 (4.236) | T = 0.130 | 0.897 |
| **Comorbidities** | | | | |
| **HTN** | 41 (68.3%) | 37 (61.6%) | $X^2$= 0.59 | 0.44 |
| **DM** | 38 (63.3%) | 40 (66.7%) | $X^2$= 0.15 | 0.70 |
| **Chronic heart disease** | 39 (65%) | 35 (58.3%) | $X^2$= 0.56 | 0.45 |
| **Chronic renal disease** | 26 (43.3%) | 21 (35%) | $X^2$= 0.87 | 0.35 |
| **COPD** | 31 (51.7%) | 27 (45%) | $X^2$= 0.53 | 0.46 |
| **Chronic Liver disease** | 17 (28.3%) | 20 (33.3%) | $X^2$= 0.35 | 0.55 |
| **Day of MV** | 8 (6-11) | 11.5 (7.75-12) | U=1320 | **0.011*** |
| **Diagnosis on admission** | | | | |
| **Acute heart failure** | 12 (20%) | 15 (25%) | $X^2$=0.43 | 0.51 |
| **Sepsis** | 18 (30%) | 15 (25%) | $X^2$=0.38 | 0.54 |
| **Pneumonia** | 16 (26.7%) | 15 (25%) | $X^2$=0.04 | 0.83 |
| **AECOPD** | 12 (20%) | 15 (25%) | $X^2$=0.43 | 0.51 |
| **AE of IPF** | 1 (1.7%) | 0 (0%) | FE | 0.315 |
| **ARDS** | 1 (1.7%) | 0 (0%) | FE | 0.315 |

APACHE II, Acute Physiology and Chronic Health Evaluation II; ARDS, acute respiratory distress syndrome; COPD, chronic obstructive pulmonary disease; IPF, Interstitial pulmonary fibrosis; IQR, interquartile range; MV, mechanical ventilation; SD, standard deviation; HTN: Hypertension, DM: Diabetes Mellitus; U: Mann–Whitney U test, $X^2$: Chi-squared test, FE: Fisher's exact test; AECOPD, acute exacerbation of chronic obstructive pulmonary disease. a Calculated as weight in kilograms divided by height in meters squared, b APACHE II score was calculated from 17 variables. Data are presented as either, mean (SD), median (IQR), or frequency (%).

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**Physiological parameters:**

Table (2) presented a comparative summary of key respiratory parameters, including arterial blood gas (ABG) values (Encompassing pH, partial pressure of carbon dioxide [$PaCO_2$], partial pressure of oxygen [$PaO_2$], and bicarbonate levels), respiratory rate (RR), and the fraction of inspired oxygen ($FiO_2$), recorded at two critical time points: immediately following extubation and subsequently at 48 hours post-extubation. The analysis of these baseline measurements at the precise moment of extubation revealed a statistically significant disparity in respiratory rate between both study groups. Specifically, patients managed with non-invasive ventilation (NIV) exhibited a significantly lower respiratory rate compared to those in the high-flow nasal cannula (HFNC) group (p = 0.03).

This initial difference suggests a potential immediate impact of the ventilatory support strategy on the patient's breathing pattern upon removal of the endotracheal tube. However, a subsequent comprehensive assessment of respiratory rates conducted at the 48-hour mark post-extubation demonstrated a convergence between the two groups, with no statistically significant difference observed in respiratory rates between the NIV and HFNC cohorts at this later time point. This temporal evolution suggests that while NIV may exert an initial influence on respiratory rate immediately post-extubation, this effect appears to diminish or equalize within the first 48 hours.
While, the initial ABG parameters, including pH, $PaO_2$, $PaCO_2$, and $FiO_2$, were comparable between both groups at the time of extubation, a notable difference emerged after 48 hours. Patients receiving HFNC demonstrated significantly higher $PaO_2$ levels compared to those on NIV (p=0.016). However, other parameters, such as pH, $PaCO_2$, and respiratory rate, remained similar among both groups, with no substantial variances at the 48-hour mark.

**Table (2):** ABG tests, RR, $FiO_2$ of the studied groups at the time of extubation and over 48 hr. of intervention

| | NIV (n=60) | HFNC (n=60) | U-test | P value |
|---|---|---|---|---|
| **At the time of extubation** | | | | |
| **PH** | 7.39 (7.37-7.41) | 7.37 (7.36-7.41) | 1474 | 0.085 |
| **PaO2 (mmHg)** | 84 (79 - 88) | 85 (82 - 88) | 1441 | 0.059 |
| **PaCO2 (mmHg)** | 42 (39.7 – 45.2) | 43 (39 – 52.7) | 1693 | 0.573 |
| **FiO2(%)** | 45% (40% - 50%) | 50% (40% - 55%) | 1560 | 0.198 |
| **RR** | 20 (19-21) | 21 (20-23) | 1391 | **0.030*** |
| **48hr of intervention** | | | | |
| **PH** | 7.39 (7.36-7.41) | 7.39 (7.38-7.41) | 1775 | 0.897 |
| **PaO2 (mmHg)** | 84 (74-90) | 90 (80.8-93) | 1341 | **0.016*** |
| **PaCO2 (mmHg)** | 40 (38-42.3) | 42 (40-53) | 1453 | 0.068 |
| **FiO2(%)** | 35% (30%-55%) | 30% (30%-46%) | 1641 | **0.029*** |
| **RR** | 18 (16-20) | 17 (15-19) | 1393 | 0.401 |

ABG, Arterial blood gases, NIV, Noninvasive ventilation. HFNC, high flow nasal cannula, PaO2, Partial pressure of arterial oxygen, PaCO2, Partial pressure of arterial carbon dioxide, FiO2, Fraction of inspired oxygen, RR, Respiratory rate, Data are presented as median (IQR), *: Statistically significant as P value<0.05, U: Mann–Whitney U test.

**Outcome:** Table (3) presented the primary outcomes of patients in the NIV and HFNC groups. Overall, 92 patients (76.7%) avoided reintubation during their ICU stay. There was no statistically significant difference in the reintubation rate between both groups. Similarly, no significant differences were observed in the incidence of ventilator-associated pneumonia in patients receiving NIV vs HFNC (15% vs. 16.7% respectively, p = 0.80) or the development of sepsis (21.7% vs. 26.7% respectively, p = 0.52). However, device intolerance was significantly higher in the NIV group, affecting nine patients (15%), compared to only two patients (3.3%) in the HFNC group (p = 0.02). Additionally, there were no significant disparities in critical care outcomes between the groups. The median ICU length of stay was comparable (NIV: 18 days [IQR 13–21] vs. HFNC: 16 days [IQR 13–19]; p=0.151), and ICU mortality rate was also comparable between groups (NIV: 13.3% vs. HFNC: 11.7%; p=0.608).

**Table (3):** Patient outcomes in non-invasive ventilation versus high-flow oxygen therapy

| | NIV (n=60) | HFNC (n=60) | Test of significance | P value |
|---|---|---|---|---|
| **Avoidance of reintubation** | 45 (75%) | 47 (78.3%) | X2=0.19 | 0.672 |
| **Total reintubation rates** | 15 (25%) | 13 (21.7%) | X2=0.19 | 0.672 |
| **Days to reintubation** | 4 (3-6) | 4 (4-5) | U = 96.5 | 0.981 |
| **Rate of VAP development** | 9 (15%) | 10 (16.7%) | X2=0.06 | 0.802 |
| **Rate of Sepsis development** | 13 (21.7%) | 16 (26.7%) | X2=0.41 | 0.522 |
| **Rate of intolerance** | 9 (15%) | 2 (3.3%) | X2=0.5.04 | 0.022* |
| **ICU stay** | 18 (13-21) | 16 (13-19) | U = 1526.5 | 0.151 |
| **Overall mortality** | 8 (13.3%) | 7 (11.7%) | X2=0.08 | 0.782 |

NIV, Noninvasive ventilation. HFNC, high flow nasal cannula. (n), Number. VAP, Ventilator-associated Pneumonia. ICU, Intensive Care Unit. Data are presented as median (IQR), *: Statistically significant as P value<0.05, U: Mann–Whitney U test, X2: Chi-squared test.

**Subgroup analysis of Intubated Vs Non intubated group:** Comparative analysis between patients who required reintubation and those who were successfully extubated revealed no statistically significant differences in baseline characteristics. These included age, sex, body mass index (BMI), and the prevalence of comorbidities such as hypertension, cardiac disease, renal disease, respiratory disease, and chronic liver disease. Furthermore, the duration of mechanical ventilation prior to extubation was similar between the two groups, as detailed in table (4). Regarding arterial blood gas parameters, respiratory rate and $FiO_2$ at the time of extubation, a statistically significant difference was observed only in respiratory rate, with reintubated patients exhibiting a higher respiratory rate at the time of extubation (P=0.01). However, after 48 hours of intervention, there were significant differences in pH, $PaO_2$, respiratory rate, and $FiO_2$ (P<0.001), whereas $PaCO_2$ remained similar amid both groups (P=0.864).

**Table (4):** Relation between intubation and baseline characteristics

| | Not-reintubated (n=92) | Reintubated (n=28) | Test of significance | P value |
|---|---|---|---|---|
| **Age, median (IQR), y** | 59 (55-63) | 62 (55.8-66.3) | U= 1088 | 0.215 |
| **Sex (male)** | 51 (55.4%) | 19 (67.8%) | $X^2$=1.36 | 0.24 |
| **BMI, median (IQR), d** | 30 (27-33) | 30.5 (27-34.3) | U = 1196 | 0.569 |
| **Comorbidities** | | | | |
| **HTN** | 60 (65.2%) | 18 (64.2%) | $X^2$= 0.01 | 0.93 |
| **DM** | 61 (66.3%) | 17 (60.7%) | $X^2$= 0.29 | 0.59 |
| **Chronic heart disease** | 58 (63%) | 16 (57.1%) | $X^2$= 0.32 | 0.57 |
| **Chronic renal disease** | 33 (35.8%) | 14 (50%) | $X^2$= 1.80 | 0.18 |
| **COPD** | 44 (47.8%) | 14 (50%) | $X^2$= 0.04 | 0.84 |
| **Chronic Liver disease** | 26 (28.2%) | 11 (39.2%) | $X^2$= 1.22 | 0.27 |
| **Days of Mechanical ventilation before extubation, median (IQR), d** | 10 (6-12) | 8 (6.75-11.25) | U=1160 | 0.426 |

NIV, Noninvasive ventilation. HFNC, high flow nasal cannula, BMI, Body mass index, COPD, Chronic obstructive pulmonary disease. (n), Number. ICU, Intensive Care Unit. Data are presented as median (IQR), *: Statistically significant as P value<0.05, U: Mann–Whitney U test, X2: Chi-squared test.

**Survival Analysis of HFNC vs NIV:** Survival analysis was performed to compare the hazard ratios between the HFNC and NIV groups. The hazard ratio for the HFNC group was 1.31 (95% CI: 0.46–2.16), while for the NIV group, it was 0.83 (95% CI: 0.19–1.47) (P=0.342), as shown in table (5).

**Table (5):** Survival analysis of HFNC vs NIV regarding ICU mortality at 28 days.

| | Hazard Risk | 95%CI | HR | CI of HR | P value |
|---|---|---|---|---|---|
| **HFNC (n=60)** | 1.31 | 0.46 to 2.16 | **1.58** | **0.57 to 4.35** | **0.342** |
| **NIV (n=60)** | 0.83 | 0.19 to 1.47 | | | |

NIV, Noninvasive ventilation. HFNC, high flow nasal cannula.HR: Hazard ratio, CI: Confidence interval

There was no statistically significant difference in survival probabilities or 28-day mortality rates between the two groups (HR=1.58, 95% CI: 0.57–4.35, P=0.342), as illustrated in figure (2).

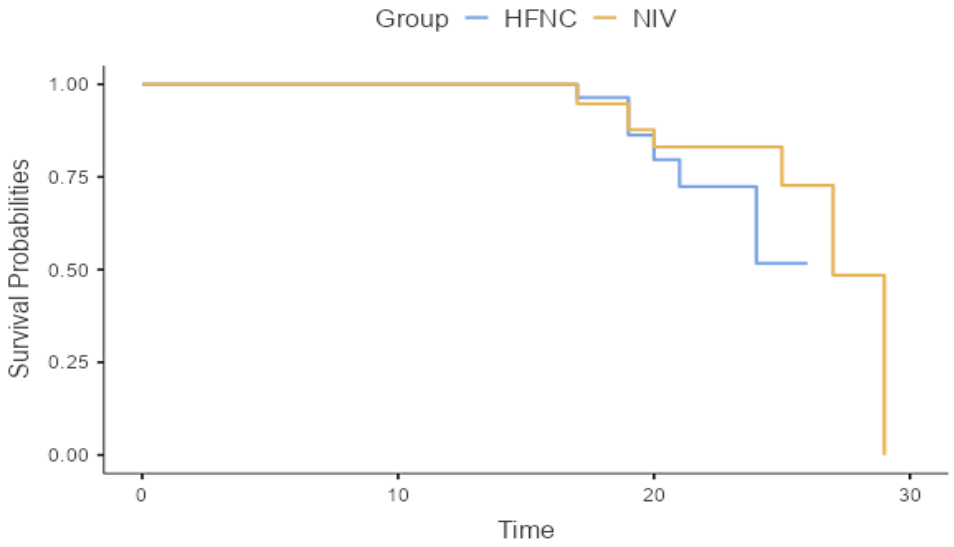


**Figure (2):** Kaplan Meier curve for survival analysis regarding ICU mortality

## DISCUSSION

This prospective investigation evaluated the clinical effectiveness of two non-invasive respiratory support strategies—non-invasive ventilation (NIV) and high-flow nasal cannula (HFNC)—in critically ill patients deemed at elevated risk for extubation failure within intensive care settings. The primary objective centered on assessing the capacity of these modalities to prevent reintubation, a critical outcome influencing patient morbidity and ICU resource utilization. Analysis of the study revealed no statistically meaningful disparity in the primary endpoint of reintubation rates between the two intervention arms, suggesting comparable efficacy in this high-risk population, and highlighting the usefulness of HFNC as an emerging strategy.

However, secondary outcomes highlighted clinically relevant distinctions. Patients receiving HFNC exhibited superior oxygenation parameters, as evidenced by significantly higher arterial partial pressure of oxygen ($PaO_2$) measurements at the 48-hour post-extubation interval compared to those managed with NIV. Furthermore, the HFNC cohort demonstrated enhanced tolerability, with substantially fewer instances of therapy discontinuation due to patient discomfort or interface-related complications. The proportion of patients successfully avoiding reintubation stood at 66.7% in the NIV group versus 79.4% among HFNC recipients, ($p$ = 0.223). These findings contribute valuable insights to the ongoing discourse regarding optimal respiratory support strategies, particularly when balancing physiological benefits against practical implementation challenges. The absence of significant differences in the primary outcome, juxtaposed with HFNC's advantages in secondary measures, suggest that while both modalities demonstrated similar capacity to prevent reintubation, HFNC may offer distinct advantages in specific clinical scenarios. The improved oxygenation profile and enhanced patient tolerance associated with HFNC could position it as a preferable first-line option for certain high-risk subgroups, particularly those with heightened susceptibility to interface discomfort or those requiring prolonged respiratory support. However, the comparable reintubation avoidance rates reinforce the need for individualized patient assessment, considering factors such as underlying pathophysiology, clinician expertise, and institutional protocols.

This is consistent with prior studies that have shown comparable efficacy between these two modalities in preventing reintubation in general ICU populations. Our findings align with **Wang *et al.*** [12] in their recent meta-analysis. They studied the clinical usefulness of HFNC versus NIV in patients at high risk of extubation failure. The review included 1457 patients from 30 RCTs. The HFNC and NIV groups showed no differences in reintubation (RR 1.10, 95% CI 0.87-1.40, I2 = 0%, P = 0.42) and mortality (RR 1.09, 95% CI 0.82-1.46, I2 = 0%, P = 0.54). However, HFNC had fewer rates of intolerance (95% CI 0.08-0.57, I2 = 0%, P < 0.01), among other adverse effects. This is consistent with our results regarding the incidence of adverse events, reintubation, and mortality.

**Ge *et al*.** [13] did a retrospective analysis of the MIMIC-IV database. They concluded that HFNC therapy demonstrated comparable efficacy to non-invasive ventilation (NIV) regarding reduction in reintubation rates in patients with high BMI. They also concluded that HFNC appears to be advantageous in morbidly obese patients. However, NIV is associated with significantly shorter hospital, and ICU stays. In our study, BMI in patients in the NIV group was not statistically different from HFNC group 29.8 (5.1) vs 30.5 (4.72). However, no patient in our study was morbidly obese (BMI>40). Also, there were no statistically significant differences regarding hospital stays between NIV, and HFNC groups in our study.

Another meta-analysis by **Guo *et al.*** [14] reviewed the data of 1746 patients and concluded that HFNC had comparable results to NIV in the avoidance of reintubation (20.40% with HFNC and 20.92% with NIV). However, HFNC decreased the rate of skin complications (10.28% versus 23.82%, 95% CI: 0.26-0.53, P < 0.00001), and post-extubation respiratory failure (23.76% versus 25.56%, 95% CI: 0.46-0.88, P = 0.006).

In a prior investigation by **Yoo *et al.*** [11], the clinical outcomes of HFNC and NIV were systematically compared in patients experiencing post-extubation respiratory failure. Their analysis revealed no statistically significant difference in treatment success rates between the two modalities, with HFNC achieving success in 79.4% of cases compared to 66.7% in the NIV cohort (p = 0.22). Notably, HFNC demonstrated superior tolerability, as evidenced by the absence of intolerance events in the HFNC group, whereas five patients in the NIV arm discontinued therapy due to interface-related discomfort (p = 0.057). **Yoo *et al.*** [11] further reported a clinically meaningful reduction in hospital duration for HFNC recipients (13.4 days vs. 20.6 days; p = 0.015), though no significant intergroup differences were observed in ICU mortality outcomes. Our findings align with these observations in several key areas. Similar to **Yoo *et al.*** [11], our study identified equivalent rates of treatment success and reintubation avoidance between HFNC and NIV. However, while **Yoo *et al.*** [11] documented a shorter hospitalization period for HFNC patients, our analysis found no statistically significant disparity in duration of stay between the two groups. The consistency in tolerability outcomes across both studies underscores a critical advantage of HFNC in clinical practice.

However, some studies suggested that NIV may be superior in specific subgroups, such as those with COPD or hypercapnia, which were not separately analyzed in our trial. A systematic review by **Feng *et al.*** [15] comparing HFNC and NIV in COPD patients following extubation found HFNC was associated with fewer treatment-related adverse events, though both modalities demonstrated equivalent reintubation rates. Notably, NIV showed greater effectiveness in preventing reintubation among non-hypercapnic patients, while no significant differences emerged in ICU stay duration or mortality outcomes.

Emerging evidence underscores the clinical utility of HFNC as a respiratory support modality in extubated patients, with multiple investigations positioning it as a viable alternative—if not superior option—to conventional oxygen delivery systems. Comparative analyses have demonstrated that HFNC achieves equivalent or enhanced physiological outcomes relative to traditional simple face masks, particularly in domains of patient tolerance and oxygenation efficacy [16, 17]. Also, HFNC was better tolerated than NIV, with fewer complications and better treatment adherence.[14, 15, 17].

Of all the patients, 70 (58.3%) were males, with a median age of 60 years (IQR: 55–63). Baseline characteristics were balanced between groups, with comparable age and sex distribution, BMI, APACHE II scores, and prevalence of major comorbidities (all P>0.05). No significant differences were observed between groups regarding ventilator-associated pneumonia (VAP) or sepsis rates. The incidence of VAP was 9% in patients receiving NIV vs 10% in patients receiving HFNC, while sepsis occurred in 13% and 16% of patients respectively. These findings indicate that post-extubation respiratory support mode did not significantly influence infection rates, which were more likely determined by other factors such as patient comorbidities, sedation levels, and ICU management practices.

In our study, subgroup analysis of patients who were reintubated regarding pH, $PaO_2$, $PaCO_2$, respiratory rate, and $FiO_2$ at the time of extubation revealed that a significant difference was observed in respiratory rate at the time of extubation, with lower values in the NIV group compared to HFNC (P = 0.03). However, this difference was no longer present at 48 hours post-extubation. This suggests that NIV may provide initial respiratory muscle unloading and may indicate that a higher respiratory rate was associated with a higher risk of treatment failure.

Regarding the parameters measured 48 h after initiation of intervention, there was a statistically significant difference in $PaO_2$ and $FiO_2$ (P= 0**.029**), and no difference in terms of $PaCO_2$ (P=0.864) values 48 h after initiation of intervention. The $PaO_2$ was significantly higher in the HFNC group at 48 hours post-extubation (P = 0.016). This supports previous findings that HFNC improves oxygenation by providing heated, humidified oxygen at high flow rates, reducing anatomical dead space, and enhancing mucociliary clearance. Despite this, no differences were observed in other parameters such as pH, $PaCO_2$, and respiratory rate at 48 hours, suggesting that the overall impact on gas exchange was comparable between both groups. Also, the fact that there was no statistical difference in $PaCO_2$ between the intubated group, and the non-intubated group, may reflect the fact that patients' cause of admission, and the cause of reintubation may be covariables. Patients with COPD and reintubated for type 2 respiratory failure are expected to have higher $PaCO_2$ and patients with sepsis and reintubated for hemodynamic instability are expected to have lower $PaCO_2$.

One key finding of this study was that patients undergoing NIV therapy demonstrated substantially poorer device tolerance, with intolerance rates of 15% versus just 3.3% in patients receiving HFNC treatment. (P = 0.02). Previous research has highlighted that NIV is often less tolerated due to discomfort from the tight-fitting mask, air leaks, and pressure-related issues [11, 12]. This may impact adherence to therapy and, in some cases, necessitate discontinuation. HFNC, on the other hand, offers better patient comfort, which could be a critical consideration in clinical decision-making.

Furthermore, statistical analysis revealed no significant inter-group differences concerning the incidence of ventilator-associated pneumonia (VAP), the development of sepsis, or the duration of critical clinical outcomes, including the number of days requiring respiratory support, the length of intensive care unit (ICU) stay, and survival duration until the point of reintubation. These findings collectively reinforce the notion that the two ventilatory strategies under investigation exhibited comparable long-term clinical effectiveness in high-risk patients following extubation. Notably, the occurrence of mortality did not show significant differences between the high-flow nasal cannula (HFNC) group and the non-invasive ventilation (NIV) group (13.3% vs 11.7%, $\chi^2$=0.08, P=0.782). This lack of statistically significant difference in mortality aligns with evidence from previously published studies, which have similarly suggested that HFNC is non-inferior to NIV in this clinical context and may offer the additional benefit of improved patient tolerance. The consistency of our results with existing literature strengthens the clinical equipoise between these two strategies for post-extubation respiratory support in high-risk individuals [11, 14–17].

## CONCLUSION

This study demonstrated the comparable effectiveness of high-flow nasal cannula (HFNC) and non-invasive ventilation (NIV) in preventing reintubation

in high-risk extubated patients. We found no significant differences between the two modalities in treatment success, reintubation rates, ventilator-associated pneumonia, sepsis development, or overall mortality.

However, HFNC reduced rate of device intolerance compared to NIV. These findings suggest that both HFNC and NIV are viable options for averting reintubation in patients who are likely to experience extubation failure, with HFNC potentially offering benefits in oxygenation and notably tolerance. Considering the higher device intolerance with NIV, clinicians might prioritize HFNC, especially in patients likely to have issues with mask interfaces. Ultimately, the choice of modality should be individualized, considering patient tolerance and specific clinical factors.

## STRENGTHS

This is a prospective, randomized design, which promotes a balanced comparison between the intervention groups. Furthermore, the focus on high-risk patients provides valuable, targeted insights into post-extubation management within this complex clinical population. This robust design strengthens our ability to attribute observed effects directly to the studied interventions. Moreover, the specific focus on a cohort of high-risk patients, characterized by their increased susceptibility to post-extubation complications, provides particularly valuable and clinically relevant insights into the nuances of respiratory management in this complex and often challenging clinical population. By concentrating on this vulnerable group, our findings offer targeted guidance for optimizing post-extubation care where it is most critically needed.

## LIMITATIONS

Several limitations should be considered. Firstly, the single-center design could restrict the broader scalability of these results to different healthcare settings and patient populations. Secondly, the lack of predefined stratification for specific high-risk subgroups, such as individuals with COPD or hypercapnia, potentially limits our ability to identify differential treatment responses that might be more pronounced in these conditions. Lastly, the relatively brief follow-up duration of 7 days post-extubation may not adequately capture the incidence of longer-term respiratory complications or late reintubation events.

## RECOMMENDATIONS

To further elucidate the comparative effectiveness and long-term impact of different post-extubation respiratory support strategies, upcoming research efforts need to focus on carrying out randomized controlled trials that are multicenter and large-scale. These studies should incorporate extended follow-up periods to comprehensively assess the sustained clinical outcomes and potential long-term sequelae associated with each strategy.

Furthermore, to facilitate a more personalized approach to post-extubation care, subsequent investigations should incorporate robust subgroup analyses. These analyses should specifically focus on patient populations characterized by distinct underlying conditions, such as hypercapnia, neuromuscular disorders, or cardiac failure, to identify potential differential treatment effects and ultimately tailor respiratory support interventions to individual patient-specific needs and clinical profiles. Such focused investigations hold substantial promise for significantly informing the development of robust, evidence-based guidelines aimed at optimizing the clinical management of high-risk patients in the critical period following extubation. This targeted approach to research will yield specific data crucial for formulating best-practice recommendations.

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