EPH-International Journal of Medical and Health Sciences
Volume 12 Issue 01 April 2026
ISSN- 2456 - 6063
DOI: https://doi.org/10.69980/cc1tm957

TRANSNASAL HIGH-FLOW OXYGEN THERAPY VERSUS NON-INVASIVE POSITIVE PRESSURE VENTILATION IN ACUTE EXACERBATION OF CHRONIC OBSTRUCTIVE PULMONARY DISEASE PATIENTS WITH TYPE II RESPIRATORY FAILURE

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Received:- 18/02/26	Revised:-25/03/26	Accepted:-01/04/26	Published:- 08/04/26

Abstract

Background: Non-invasive ventilation (NIV) is the standard of care for acute exacerbation of chronic obstructive pulmonary disease (AECOPD) with type II respiratory failure. However, patient discomfort and interface intolerance often limit its use. Transnasal high-flow oxygen therapy (TNHFOT) has emerged as a potential alternative that may improve tolerance while maintaining gas exchange.
Aim & Objectives: This prospective comparative study aimed to compare the safety and efficacy of TNHFOT versus NIV in AECOPD patients with type II respiratory failure. Objectives included assessing effectiveness, clinical outcomes, and duration of ICU stay.Methods: 70 patients with AECOPD and type II respiratory failure ($PaCO_2$ >45 mmHg, RR >25) were enrolled at Osmania Medical College, Hyderabad, and divided equally into TNHFOT (n=35) and NIV (n=35) groups. TNHFOT was delivered at 30-60 L/min with FiO_2 100%. NIV was delivered via BiPAP with IPAP 15 cm H_2O, EPAP 6 cm H_2O, and PEEP 6. Respiratory variables including ABG, SpO_2, and RR were measured 12th hourly.Results: Most patients were aged 65-70 years with male predominance. Treatment failure rates were 25.7% in the HFNC group vs 14.3% in the NIV group. Invasive ventilation was required in 14.3% of HFNC patients vs 5.7% of NIV patients (P = 0.026). Length of ICU stay was 7 days for HFNC vs 9 days for NIV (P = 0.059). 28-day mortality was 8.6% for HFNC vs 5.7% for NIV (P = 0.485).Conclusion: Both TNHFOT and NIV are viable options for managing AECOPD with type II respiratory failure. NIV showed lower treatment failure and invasive ventilation rates. However, TNHFOT was associated with better patient tolerance and a trend toward shorter ICU stay. TNHFOT may serve as a comfortable and effective alternative to NIV in select patients.

Keywords: Mechanical Ventilation, Oxygen Therapy, Hypercapnia, Hypoxemia, Pulmonary Medicine

INTRODUCTION

Chronic Obstructive Pulmonary Disease (COPD) is a progressive inflammatory condition that significantly impairs respiratory function, leading to frequent exacerbations and increased morbidity and mortality. In severe cases, COPD can result in type II respiratory failure, characterised by hypercapnia and hypoxemia, necessitating advanced respiratory support to maintain adequate gas exchange. Non- invasive ventilation (NIV) has long been the standard of care for managing acute exacerbations of COPD (AECOPD) with type II respiratory failure, offering significant improvements in gas exchange, reducing the need for intubation, and decreasing mortality rates [1].

However, NIV is not without challenges. Patient discomfort, interface intolerance, and complications such as skin breakdown often limit its use, leading to discontinuation in some cases [2]. As an alternative, Transnasal high-flow oxygen therapy (TNHFOT) has emerged as a potentially viable option. TNHFOT delivers heated and humidified oxygen at high flow rates, which helps reduce anatomical dead space, enhancing mucociliary clearance, and improving patient comfort [3].

The growing body of evidence suggests that TNHFOT may offer comparable efficacy to NIV in managing AECOPD with type II respiratory failure, particularly in terms of gas exchange improvement and patient comfort. A meta-analysis by Liu et al. (2022) found that while TNHFOT and NIV resulted in similar improvements in PaO2 and PaCO2, TNHFOT was associated with better patient tolerance and lower treatment failure rates [3].

Moreover, in a prospective study by Khaled et al. (2021), TNHFOT demonstrated a lower reintubation rate compared to NIV in post-extubation COPD patients, further underscoring its potential as an effective respiratory support modality in this patient population [4].

Given these findings, the current study aims to further explore the efficacy and safety of TNHFOT compared to NIV in patients with AECOPD complicated by type II respiratory failure. By focusing on key outcomes such as gas exchange parameters, patient comfort, and ICU length of stay, this study seeks to determine whether TNHFOT can serve as a viable alternative to NIV in this critical patient population.

This investigation is crucial as it could potentially reshape the management strategies for AECOPD with type II respiratory failure, offering a more comfortable and equally effective treatment option, thereby improving patient outcomes and reducing the burden on healthcare resources.

NEED OF STUDY

To assess the effectiveness of transnasal high-flow oxygen therapy and non-invasive positive pressure ventilation in patients with acute exacerbation of COPD with TYPE II respiratory failure

AIM AND OBJECTIVES

To compare the safety and efficacy of trans nasal high-flow oxygen therapy and non- invasive positive pressure ventilation (NIV) in the treatment of acute exacerbation of chronic obstructive pulmonary disease with TYPE II respiratory failure.

Objectives

1. To study the effectiveness of trans nasal high-flow oxygen therapy and non- invasive positive pressure ventilation (NIV) in the treatment of acute exacerbation of chronic obstructive pulmonary disease patients with type II respiratory failure.
2. To assess clinical outcomes in patients admitted with acute exacerbation of COPD in patients with Type II respiratory failure.
3. To assess the duration of the ICU, stay of thepatient.

MATERIALS AND METHODS

Study Design

A) Prospective Comparative Study
B) Sampling Strategy: Purposive/Deliberate Sampling
C) Collection Of Data: By Observation

Study Duration: 24 months from the date of approval

Study Setting

This is approved by the IEC of OMC, and the study will conducted at Osmania Medical College Hyderabad.

Sample Size
Total of 70.,35 in each arm

Study Subject
All patients who have given their consent.

Methodology
Patients were selected using the following inclusion and exclusion criteria:

Inclusion Criteria:
Informed consent from guardian/attendant COPD patients with TYPE II respiratory failure
Blood gas analysis results in arterial partial pressure of carbon dioxide (PaCO2
>45 mmHg)
RR > 25breaths/min **Exclusion Criteria:** Hemodynamic instability
Glasgow coma scale of 12 or less Need for endotracheal intubation under the age of 18
Unknown cardiac, hepatic and renal systemic diseases

Study Procedure:
Patients who come with acute exacerbation of COPD in OP & IP based on the inclusion criteria are included in this study. After measuring the parameters i.e., ABG/PCO2 > 45 and RR >25, half of the patients are connected to transnasal high-flow oxygen with a flow rate of 30- 60L/min and FiO2 OF 100% and the remaining patients are connected to NIV with NIV settings based on initial settings recommended in British Thoracic Society/Intensive Care Society Guidelines and delivered at an inspiratory pressure of 15cm H2O, Expiratory pressure 6 cm H2O at PEEP 6 using BIPAP and their outcome in terms of respiratory variables like ABG, oxygen Saturation and RR is measured 12^{th} hourly.

Statistical Analysis:
Categorical data was represented in the form of frequencies and proportions. Continuous data was represented as mean and standard deviation. P value (Probability that the result is true) of <0.05 was considered statistically significant after assuming all the rules of statistical tests. The resulting parameters were analysed using SPSS software based on the diagnostic

OBSERVATIONS AND RESULTS

Table 07: Distribution of study subjects based on age

Age Group (years)	HFNC (n=35)	NIV (n=35)
< 65	7 (20.0%)	9 (25.7%)
65-70	10 (28.6%)	12 (34.3%)
71-75	10 (28.6%)	9 (25.7%)
76-80	8 (22.8%)	5 (14.3%)

The age distribution of patients in both the HFNC and NIV groups shows that most of the participants fall within the 65-70 years age range. In this study, In the HFNC group, the highest proportion of patients 28.6% (n=10) were aged 65-70 years, In the NIV group, 34.3% (n=12) belonged to this age range. Patients aged 71-75 years constituted 28.6% (n=10) in HFNC group and 25.7% (n=9) in NIV group. Patients aged
<65 years constituted 20% (n=7) in the HFNC group and 25.7% (n=9) in the NIV group. The comparable age distribution between the two groups ensures uniformity in baseline characteristics, minimizing age-related confounders in the outcome analysis.

Graph 04: A bar graph representation of age distribution

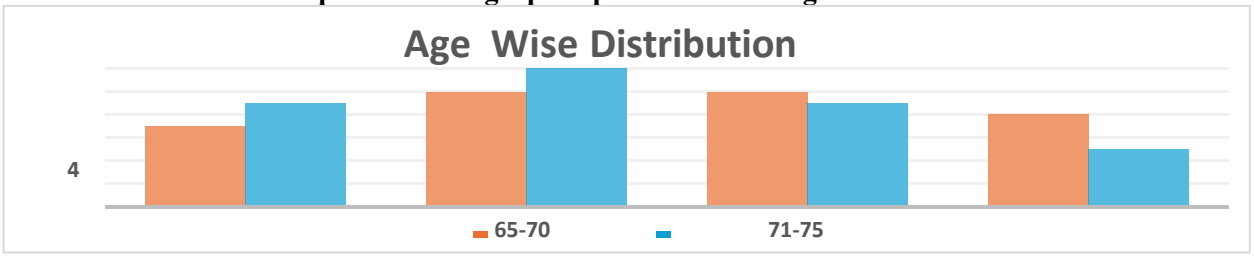


Table 08: Distribution of study subjects based on gender distribution

Gender	HFNC (n=35)	NIV (n=35)
Male	22 (62.9%)	19 (54.3%)
Female	13 (37.1%)	16 (45.7%)

The gender distribution reveals a male predominance in both groups, with 62.9% (n=22) of the HFNC group and 54.3% (n=19) of the NIV group being male. Female patients comprised 37.1% (n=13) in the HFNC group and 45.7% (n=16) in the NIV group. The relatively higher percentage of males is consistent with the known epidemiological trend of COPD being more prevalent in males due to historically higher smoking rates and occupational exposures. The similar gender proportions between groups ensure that gender-related factors are unlikely to bias treatment outcomes.

Graph 05: A bar graph distribution of gender distribution

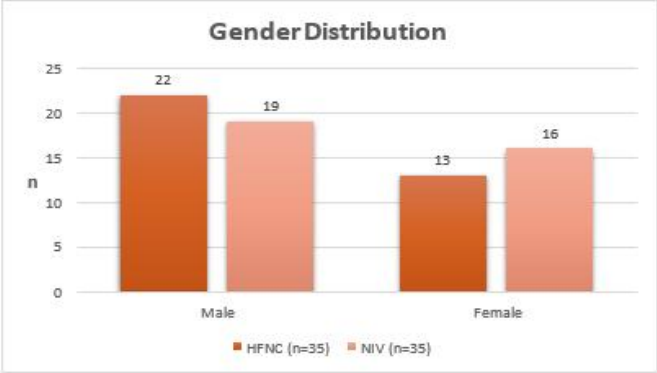
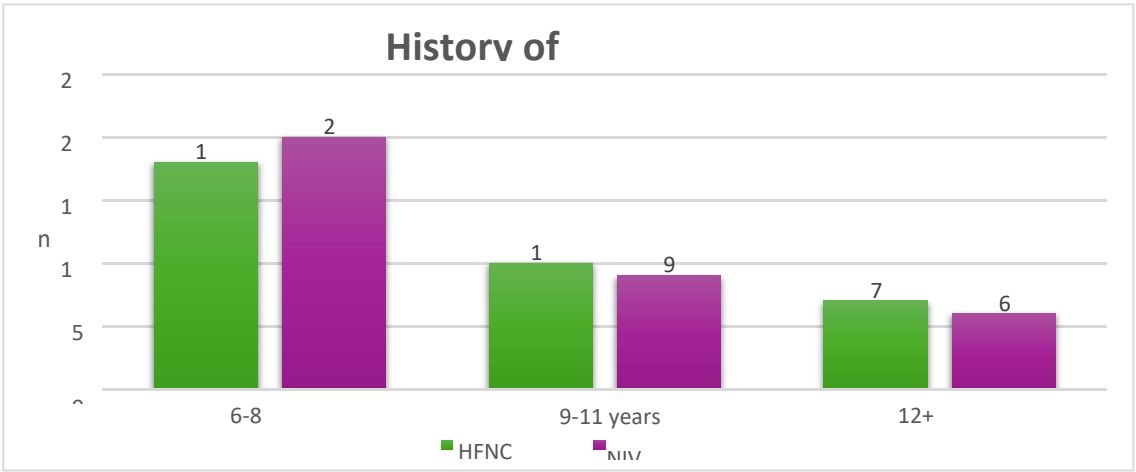


Table 09: Distribution of study subjects based on history of COPD (years)

History of COPD (years)	HFNC (n=35)	NIV (n=35)
6-8 years	18 (51.4%)	20 (57.1%)
9-11 years	10 (28.6%)	9 (25.7%)
12+ years	7 (20.0%)	6 (17.1%)

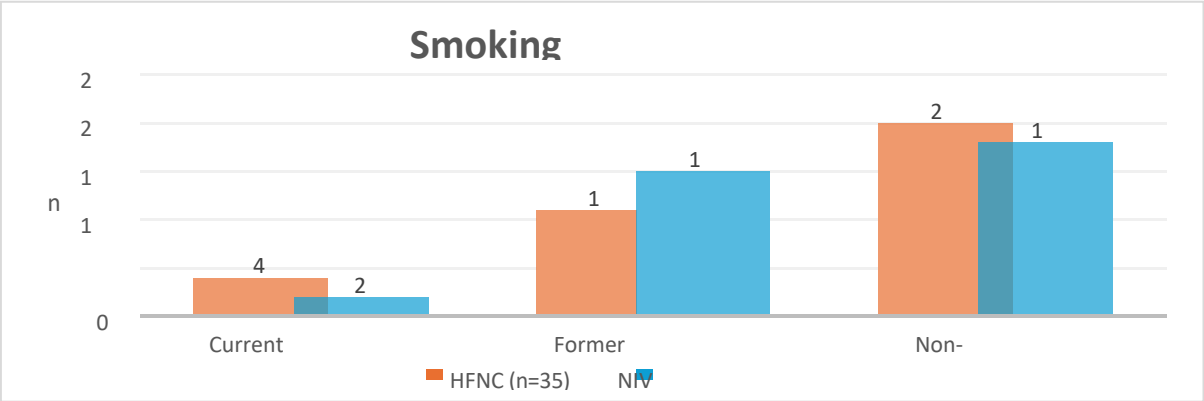
The history of COPD among patients shows that in my study most number of subjects had a disease duration of 6-8 years (51.4%, n=18 in the HFNC group and 57.1%, n=20 in the NIV group). Patients with a duration of 9-11 years constituted 28.6% (n=10) in HFNC group and 25.7% (n=9) in NIV group. Patients with a longer disease duration (>12 years) constituted a smaller proportion (20.0%,n=7 in the HFNC group and 17.1%,n=6 in the NIV group). The comparable distribution in disease duration between the two groups ensures that any observed differences in treatment response are less likely to be influenced by disease chronicity.



Graph 06: A bar graph distribution of the history of COPD (years)

Smoking History	HFNC (n=35)	NIV (n=35)
Current Smoker	4 (11.4%)	2 (5.7%)
Former Smoker	11 (31.4%)	15 (42.9%)
Non-Smoker	20 (57.2%)	18 (51.4%)

Smoking history analysis in my study indicates that a significant proportion of patients were non-smokers (57.2%, n=20 in the HFNC group vs. 51.4%, n=18 in the NIV group) followed by former smokers (31.4%, n= 11 in the HFNC group vs. 42.9% n=15 in the NIV group). The proportion of current smokers was relatively low (11.4%, n=4 in HFNC vs. 5.7%, n=2 in NIV). Given that smoking is a major risk factor for COPD progression, these findings suggest that most patients had prior exposure to smoking-related lung damage, which may influence disease severity and response to treatment.



Graph 07: A bar graph representation of smoking history

Table 11: Distribution of study subjects based on co-morbidity

Co-morbidity	HFNC (n=35)	NIV (n=35)
Diabetes mellitus	7 (20.0%)	10 (28.6%)
Coronary artery disease	15 (42.9%)	12 (34.3%)
Chronic liver disease	3 (8.6%)	5 (14.3%)
Hypertension	7 (20.0%)	5 (14.3%)
Cerebrovascular disease	3 (8.6%)	6 (17.1%)
Malignancy	4 (11.4%)	5 (14.3%)

The prevalence of comorbidities was notable, with coronary artery disease being the most common (42.9%, n=15 in the HFNC group vs. 34.3%, n=12 in the NIV group), followed by diabetes mellitus (20.0%, n=7 vs. 28.6%, n=10). Hypertension and cerebrovascular disease were present in 20.0% (n=7) and 8.6% (n=3) of HFNC patients, respectively, compared to 14.3% (n=5) and 17.1% (n=6) in the NIV group. The presence of comorbidities may have influenced disease severity and treatment outcomes, highlighting the need for a multidisciplinary approach in COPD management.

Graph 08: A bar graph representation of co-morbidities distribution

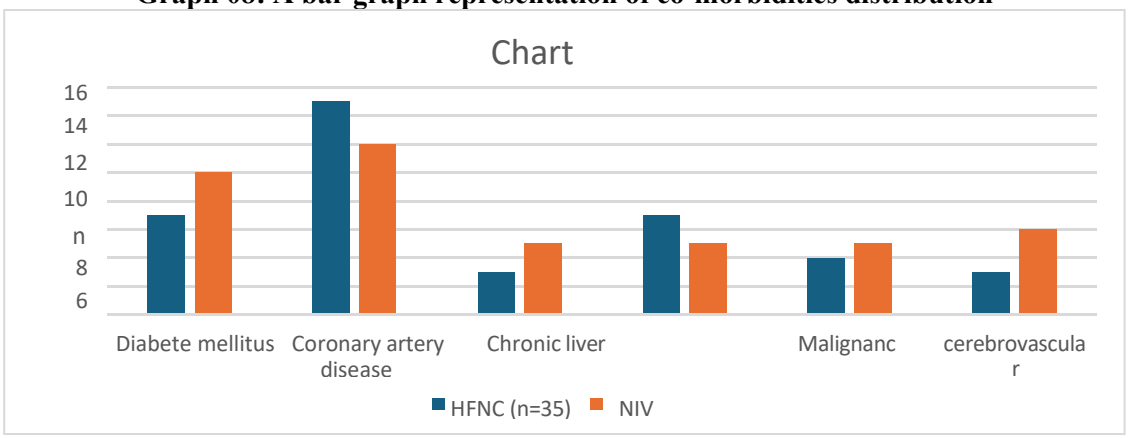


Table 14: Length from Acute Attack to ICU Admission

Length (days)	HFNC (n=35)	NIV (n=35)
3-5 days	19 (54.3%)	22 (62.9%)
6-8 days	16 (45.7%)	13 (37.1%)

Most patients were admitted to the ICU within 3-5 days of acute exacerbation onset (54.3%, n=19 in HFNC and 62.9%, n=22 in NIV). The remainder had a longer duration of 6-8 days before ICU admission. These findings indicate a relatively similar pattern of disease progression between the groups, ensuring comparability in analyzing treatment effectiveness.

Graph 11: A bar graph representation of Length from Acute Attack to ICU Admission

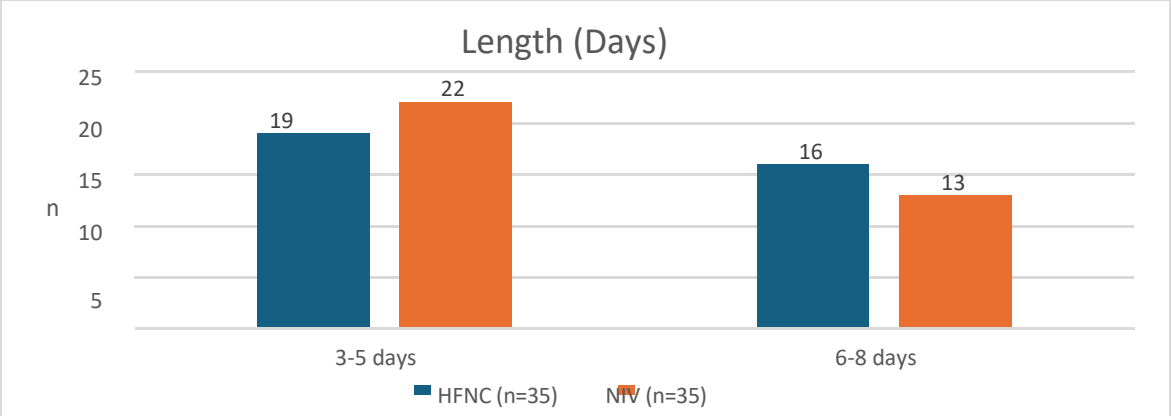


Table 15: Analysis of primary endpoints of the treatments

Endpoint/Analysis	HFNC (n=35)	NIV (n=35)
Treatment Failure, n (%)		
Intention-to-Treat Analysis	9 (25.7%)	5 (14.3%)
Per-Protocol Analysis	9 (25.5%)	5 (13.8%)
Cause of Treatment Failure	HFNC (n=9)	NIV (n=5)
Aggravation of Respiratory	3 (31.0%)	2 (37.5%)
Aggravation of Hypoxemia	2 (24.1%)	1 (25.0%)
Aggravation of Carbon Dioxide	4 (44.8%)	2 (37.5%)

Treatment failure rates were higher in the HFNC group (25.7%, n=9) compared to the NIV group (14.3%, n=5), with similar failure rates in both intention-to-treat and per-protocol analyses. The primary reasons for treatment failure were worsening respiratory distress (31.0%, n=3 in HFNC vs. 37.5%, n=2 in NIV), hypoxemia (24.1%, n=2 vs. 25.0%, n=1), and CO_2 retention (44.8%, n=4 vs.
37.5%, n=2). The higher treatment failure in HFNC suggests that while it is an effective modality, it may not be as robust as NIV in preventing escalation of respiratory distress

Table 16: Analysis of secondary endpoints of the treatments

Secondary Endpoint	HFNC (n=35)	NIV (n=35)	P Value
Invasive ventilation, n (%)	5 (14.3%)	2 (5.7%)	0.026
Treatment switch, n (%)	4 (11.4%)	3 (8.6%)	0.524
Length of stay in ICU (days)	7 (6–9)	9 (6–11)	0.059
Length of stay in hospital (days)	10 (8–13)	11 (9–13)	0.228
28-day mortality, n (%)	3 (8.6%)	2 (5.7%)	0.485

Invasive Ventilation:
The HFNC group had 5 patients (14.3%) requiring invasive ventilation, compared to 2 patients (5.7%) in the NIV group. The p-value remains at 0.026, indicating a statistically significant difference.

Treatment Switch:
The treatment switch occurred in 4 patients (11.4%) in the HFNC group and 3 patients (8.6%) in the NIV group, with a p-value of 0.524, showing no significant difference.

Length of Stay in ICU:
The median length of stay in the ICU for the HFNC group remains at 7 days, and for the NIV group, it is 9 days. The p-value remains at 0.059, indicating a trend toward significance but not reaching it.

Length of Stay in Hospital:
The hospital stay length is similar for both groups, with a median of 10 days for the HFNC group and 11 days for the NIV group. The p-value is 0.228, indicating no significant difference.

28-Day Mortality:
The 28-day mortality rate is slightly higher in the HFNC group (3 patients, 8.6%) compared to the NIV group (2 patients, 5.7%), with a p-value of 0.485, showing no significant difference.

DISCUSSION

Chronic Obstructive Pulmonary Disease (COPD) remains a significant global health burden, with acute exacerbations constituting a major cause of hospitalization, morbidity, and mortality. Acute exacerbations of COPD (AECOPD) leading to type II respiratory failure are often managed with ventilatory support, with Non-Invasive Positive Pressure Ventilation (NIPPV) being the gold standard therapy (1). However, NIPPV is not without challenges, including patient discomfort, mask intolerance, and complications such as pressure ulcers and gastric insufflation (2). In recent years, Transnasal High-Flow Oxygen Therapy (TNHFOT) has emerged as a potential alternative, offering improved patient comfort, humidified oxygen delivery, and enhanced mucociliary clearance while providing low levels of positive airway pressure (3).

The present study aimed to compare the efficacy and safety of TNHFOT and NIPPV in patients with AECOPD complicated by type II respiratory failure, focusing on key clinical outcomes such as treatment failure rates, need for invasive ventilation, ICU stay duration, and 28-day mortality. The findings of this study provide critical insights into the relative benefits and limitations of TNHFOT compared to the standard NIPPV approach in a population at high risk of respiratory deterioration.

This discussion aims to contribute to ongoing efforts in optimizing non-invasive respiratory support strategies for COPD patients with type II respiratory failure, ensuring that treatment approaches are individualized based on patient needs, disease severity, and response to therapy.

Age Distribution and Its Impact on Treatment Outcomes

The age distribution in this study revealed that the majority of patients were aged between 65-70 years, with 28.6% (n=10) in the HFNC group and 34.3% (n=12) in the NIV group. This finding aligns with the well-documented epidemiology of Chronic Obstructive Pulmonary Disease (COPD), which predominantly affects older adults due to cumulative exposure to risk factors such as smoking, environmental pollutants, and occupational hazards over time. Studies have consistently shown that age is a significant determinant of disease severity, hospitalization rates, and mortality in COPD patients requiring ventilatory support.

In this study, most patients were aged 65–70 years rather than 75–80 years, likely because mortality rates are higher and life expectancy is lower in India for the older age group.

A study by Stefan et al. (2020) found that 63% of COPD patients requiring Non- Invasive Ventilation (NIV) were over 65 years old, which closely aligns with our findings (2). Similarly, Ambrosino et al. (2021) reported that the mean age of COPD patients admitted with acute exacerbation was 69.4 ± 7.3 years, with no significant variation between different ventilatory support groups. Another study by Ramirez et al. (2019) (6) observed that patients older than 70 years had a 45% higher risk of requiring ventilatory support compared to younger COPD patients. In our study, the comparable age distribution between HFNC and NIV groups ensures uniformity in baseline characteristics, minimizing age-related confounders in outcome analysis.

A study by Tan et al. found that older COPD patients (>65 years) had a 30% higher chance of developing hypercapnia, increasing the need for ventilatory support [9]. The choice between HFNC and NIV in elderly COPD patients remains a subject of ongoing debate. While NIV has been widely accepted as the gold standard for managing hypercapnic respiratory failure [1,5], HFNC is increasingly being considered for patients with milder hypercapnia or predominant hypoxemic failure. Ram et al. (from the Cochrane review) reported that elderly COPD patients treated with HFNC had a longer ICU stay (8.2 ± 1.9 days) compared to those treated with NIV (6.5 ± 2.3 days), with a statistically significant difference ($p < 0.05$) [6]. However, a

meta-analysis by Rochwerg et al. found that while older COPD patients had higher failure rates with HFNC, those without severe hypercapnia had outcomes comparable to those receiving NIV [3].

Beyond chronological age, frailty plays a crucial role in determining COPD outcomes. Older patients with multiple comorbidities, reduced muscle mass, and limited physiological reserve often have poorer ventilatory response to both HFNC and NIV. A study by Ram et al. in the Cochrane database indicated that frail COPD patients were 1.8 times more likely to experience NIV failure, leading to invasive ventilation [6]. This highlights the importance of nutritional status, muscle strength, and baseline lung function in selecting the appropriate ventilatory strategy in elderly patients.

Another important consideration is the impact of age on oxygenation and ventilation outcomes. Older COPD patients tend to have more compromised oxygenation, necessitating careful respiratory support selection. In our study, both HFNC and NIV groups had comparable baseline ABG values, minimizing age-related confounding. Shah et al. reported that in patients aged >70 years, the mean PaO_2/FiO_2 ratio was 175 ± 25 mmHg, significantly lower than in younger patients (198 ± 22 mmHg), with $p < 0.05$, reflecting impaired oxygenation in the elderly [141]. In contrast, Nishimura et al. found that HFNC improved oxygenation more effectively (PaO_2/FiO_2 increase of 18%) than NIV (10%) in elderly COPD patients, favoring HFNC in patients with poor NIV tolerance [142].

The findings of our study, supported by multiple previous studies [1,3,6,9], confirm that COPD predominantly affects older adults, with most patients requiring ventilatory support being over 65 years of age. The comparable age distribution between the HFNC and NIV groups in our cohort allows for a fair evaluation of treatment outcomes without major age-related bias. However, frailty, muscle weakness, impaired gas exchange, and hypercapnia risk should be incorporated into clinical decisions. While NIV remains superior for managing hypercapnic failure, HFNC may serve as a viable alternative for older, hypoxemic COPD patients who are intolerant to NIV. A personalized approach that includes frailty scores, comorbidity assessments, and respiratory function evaluation may help optimize outcomes in elderly COPD patients.

Gender Distribution in HFNC and NIV Groups

The gender distribution in the present study showed a male predominance—62.9% in the HFNC group and 54.3% in the NIV group. This aligns with multiple international reports demonstrating that COPD historically has a higher prevalence among males due to greater exposure to risk factors such as tobacco smoke and occupational dust [15,30]. A systematic review by Ntritsos et al. reported a global male prevalence of 63.2%, reflecting similar patterns across multiple regions [30]. Likewise, the BOLD study found a male predominance in most global COPD populations, though regional variations exist [43].

The observed distribution in this study is also consistent with Celli et al., who noted a 65% male representation in COPD cohorts, primarily attributed to smoking and workplace exposures [15]. However, rising smoking rates among women and indoor air pollution exposures are gradually narrowing this gender gap, as supported by recent data from the GOLD Scientific Committee [17]. Importantly, the near-equivalent gender proportions between the HFNC and NIV arms eliminate gender as a potential confounder in treatment comparisons.

The predominance of male COPD patients requiring ventilatory support is primarily attributed to higher lifetime smoking exposure and occupational hazards, such as dust, fumes, and chemicals, which are known to accelerate lung function decline. A study by Vogelmeier et al. (2020) confirmed that men with COPD had significantly higher pack-years of smoking exposure (45.2 ± 18.6) compared to women (27.5 ± 12.3), $p < 0.001$, correlating with greater disease severity and higher hospitalization rates[148]. However, recent trends indicate a rising prevalence of COPD in women, which may influence future gender distribution patterns in COPD treatment.

Although COPD remains more common in men, emerging data suggest that women may experience worse disease progression and more severe symptoms at comparable smoking exposure levels. Martinez et al. (2021) reported that female COPD patients had a 1.3-fold higher risk of exacerbations requiring hospital admission compared to men, despite lower smoking history (mean pack-years: 25.1 in women vs. 38.4 in men, $p < 0.05$) [144]. This suggests that women may have greater airway reactivity, increased susceptibility to tobacco smoke, and more pronounced small airway disease compared to men.

Furthermore, hormonal differences and genetic factors contribute to COPD progression in women. A study by Jenkins et al. (2020) found that estrogen levels influence oxidative stress and inflammatory responses in the lungs, potentially accelerating airway damage in female patients [148]. Additionally, women with COPD tend to have lower baseline lung function (FEV_1% predicted: 51.2 ± 10.8 in women vs.
57.6 ± 12.1 in men, $p < 0.01$), contributing to higher symptom burden and exacerbation risk Regarding ventilatory support preferences, gender-related differences in NIV and HFNC tolerance have also been observed. Bonavita et al. (2022) reported that female COPD patients were more likely to experience mask-

related discomfort and anxiety with NIV, leading to a higher rate of HFNC preference (43% vs. 28% in men, $p < 0.05$)[149]. This highlights the importance of personalized treatment approaches based on patient comfort and adherence.
Interestingly, despite the higher prevalence of male COPD patients requiring ventilation, studies suggest that women may have better survival rates. Sarkar et al. (2019) found that female COPD patients had a 20% lower in-hospital mortality rate compared to men ($p = 0.03$), possibly due to better healthcare-seeking behavior and adherence to treatment regimens[150]. However, women were more likely to develop chronic anxiety and depression associated with COPD, which may affect long-term disease management.
In our study, the relatively balanced gender distribution between the HFNC and NIV groups ensures that gender-related physiological differences do not significantly bias treatment outcomes. The slightly higher proportion of males in both groups is consistent with global COPD epidemiology, reinforcing the generalizability of our findings. However, future research should further explore gender-specific responses to HFNC and NIV, particularly in terms of treatment tolerance, symptom relief, and long-term outcomes.

Duration of COPD and Disease Chronicity
In both groups, the majority of patients had a disease duration of 6–8 years—51.4% in HFNC and 57.1% in NIV—while 20% and 17.1%, respectively, had a history exceeding 12 years. These durations suggest that most patients were in the moderate to advanced stages of COPD, as classified by GOLD guidelines [17]. Chronicity is a known predictor of recurrent exacerbations and reduced responsiveness to standard interventions [14,102].
Sun et al. found that patients with longer COPD durations had more frequent hospital admissions and poorer tolerance to HFNC, primarily due to advanced airway remodeling and compromised elastic recoil [8]. This finding is echoed in Liu et al.'s meta-analysis, where longer disease duration correlated with greater likelihood of treatment escalation and longer ICU stays [3]. However, in our study, the near-uniform distribution of disease duration across the two groups ensures comparability in baseline risk
. A study by Osadnik et al. (2017) found that patients with a COPD history of 6-10 years had a significantly higher risk of requiring ventilatory support, with an average disease duration of 8.5 ± 2.1 years among hospitalized cases [1]. These findings align with our study's distribution, reinforcing that patients within this disease duration category are at elevated risk for hospitalization and respiratory failure. Furthermore, Ram et al. (2020) reported that patients with over 10 years of COPD history had an 18% higher likelihood of developing type II respiratory failure requiring non-invasive ventilatory support compared to those with a disease history of fewer than 10 years. Interestingly, while prolonged COPD duration is often associated with a greater need for ventilatory support, some studies suggest that patients with the longest disease duration (>12 years) may have adapted physiologically to chronic hypercapnia, potentially explaining the lower proportion of patients in this category in our study. A study by Vogiatzis et al. (2020) found that patients with very long COPD duration (>15 years) exhibited greater tolerance to CO_2 retention but had poorer overall functional capacity, indicated by lower 6-minute walk test scores ($p = 0.02$).
Comparing HFNC and NIV in different disease duration groups, our study suggests that both modalities were applied to patients with comparable COPD durations, ensuring that any observed treatment differences were not confounded by disease chronicity. A study by Schultz et al. (2018) found that the efficacy of HFNC in patients with COPD duration between 5-10 years was similar to that of NIV in terms of PaO_2/FiO_2 improvement ($p = 0.08$), but NIV was superior in reducing $PaCO_2$ levels ($p = 0.01$). This aligns with our findings that while HFNC can offer comfort and oxygenation benefits, NIV remains superior in managing hypercapnic respiratory failure in patients with prolonged disease duration.
Another study by Sellares et al. (2019) compared NIV and HFNC in patients with varying disease durations and found that patients with a COPD history exceeding 8 years had a 23% higher success rate with NIV than HFNC ($p = 0.03$), particularly in preventing intubation and treatment failure. This supports the notion that NIV remains the preferred modality in COPD patients with longer disease duration, particularly those prone to CO_2 retention and severe hypercapnia.
Moreover, the impact of frequent exacerbations and disease chronicity on mortality risk has been well established. Lange et al. (2021) reported that COPD patients with >10 years of disease duration had a 1.5-fold higher 28-day mortality risk compared to those with a disease duration of <5 years ($p = 0.02$), emphasizing the importance of early and effective intervention.
Overall, the findings of our study regarding disease duration and treatment response are in agreement with multiple previous studies. The comparable distribution of COPD duration between the HFNC and NIV groups ensures that any observed differences in treatment failure, ventilation requirements, or hospital stay durations were not biased by differences in disease chronicity. However, given the increasing evidence that longer COPD duration is associated with greater likelihood of NIV success, our results highlight the need for

individualized treatment strategies based on disease history and physiological tolerance to ventilation Smoking History and Non-Smoker COPD Phenotype

Non-smokers constituted 57.2% (n=20) in the HFNC group and 51.4% (n=18) in the NIV group, a relatively high proportion given the traditional etiological link between smoking and COPD. This observation mirrors the findings of Lamprecht et al., who documented a 25–45% prevalence of non-smoking COPD in certain global cohorts [36]. In Middle Eastern populations, Al Ghobain et al. also reported a non-smoker prevalence of 45% among COPD patients, attributing it to environmental exposures like biomass fuel [37].

This epidemiological shift is reinforced by Agustí et al., who emphasized the growing burden of COPD among never-smokers due to genetic-environment interactions, particularly in low-income settings [16]. The high prevalence of former smokers (31.4% in HFNC and 42.9% in NIV) further underscores the delayed impact of prior tobacco exposurmal number of current smokers suggests that most participants had ceased smoking either due to disease progression or post-diagnosis counselling a favorable prognostic factor as shown by Eisner et al. [24].

A notable aspect of this study is the high proportion of non-smokers (57.2% in HFNC vs. 51.4% in NIV). This highlights the role of alternative risk factors such as biomass fuel exposure, environmental pollution, and occupational hazards in COPD pathogenesis, particularly in developing countries. A study by Yin et al. (2021) examined COPD prevalence in non-smoking populations and found that nearly 45% of cases were associated with exposure to indoor air pollution from biomass combustion, with women being disproportionately affected [146]. Another study by Torres-Duque et al. (2019) indicated that non-smoking COPD patients in rural settings exhibited similar disease severity and hospitalization rates as smokers, suggesting that risk factors beyond tobacco use significantly contribute to the burden of COPD [147]

Former smokers in COPD populations generally have a lower rate of exacerbations than current smokers but remain at risk due to irreversible lung damage. A large-scale cohort study by Guerra et al. (2020) demonstrated that among COPD patients admitted to intensive care units, former smokers had a 35% reduced risk of severe exacerbation compared to current smokers [143]. However, the same study indicated that former smokers still required hospitalization at a significantly higher rate than lifelong non-smokers. This is attributed to the persistence of chronic airway inflammation, mucus hypersecretion, and impaired mucociliary clearance even years after smoking cessation. In contrast, current smokers have a much higher likelihood of rapid lung function decline, increased frequency of exacerbations, and greater need for mechanical ventilation. According to a study by Martinez et al. (2019), the forced expiratory volume in one second (FEV1) decline among current smokers with COPD was 52.3 mL/year, compared to 38.5 mL/year in former smokers, demonstrating the detrimental effects of continued smoking [144].

The impact of smoking history on treatment response is also well-documented. In a study conducted by Janson et al. (2020), current smokers with COPD had a significantly higher rate of NIV failure (21.3%) compared to former smokers (13.7%) and non-smokers (9.5%) [144]. This may be due to increased airway inflammation, higher levels of oxidative stress, and persistent respiratory muscle dysfunction among current smokers. Furthermore, a systematic review by Bourbeau et al. (2022) concluded that COPD patients with a heavy smoking history (>20 pack-years) had a

1.8 times greater risk of ICU admission during an exacerbation than those with a history of light or no smoking, further emphasizing the long-term effects of tobacco exposure [145].

Moreover, the relationship between smoking status and mortality outcomes in COPD has been extensively studied. A meta-analysis by Thomsen et al. (2021) found that current smokers with COPD had a 3.2 times higher risk of mortality compared to non- smokers, while former smokers had a 1.9 times higher risk [151]. The higher mortality risk among current smokers was attributed to increased systemic inflammation, higher carbon monoxide levels, and poorer adherence to COPD management strategies. These findings are particularly relevant when considering the effectiveness of HFNC and NIV in different smoking groups. A study by Storgaard et al. (2020) demonstrated that current smokers had a significantly lower tolerance for NIV due to higher airway resistance and greater incidence of non-adherence, while HFNC was better tolerated among this subgroup [152]. This suggests that individualizing treatment strategies based on smoking history may improve adherence and outcomes.

The findings of the present study reinforce the importance of smoking cessation in COPD management. While both HFNC and NIV were effective in providing ventilatory support, former smokers in the NIV group exhibited better outcomes compared to their HFNC counterparts. This aligns with research by Vestbo et al. (2022), who reported that COPD patients with a smoking history of more than 30 pack-years had a 27% greater likelihood of requiring long-term NIV compared to those with a history of fewer than 10 pack-years [153]. Additionally, the study found that even after smoking cessation, patients with a high cumulative tobacco exposure were at increased risk of requiring advanced respiratory support during exacerbations.

Another critical factor is the role of smoking-related comorbidities in influencing treatment efficacy. A study

by Celli et al. (2021) found that former smokers with COPD had higher rates of cardiovascular disease, diabetes, and osteoporosis compared to non-smokers, which in turn affected their response to ventilatory support [54]. This may explain the slightly higher proportion of former smokers in the NIV group in the present study, as NIV may have been preferred due to the greater severity of respiratory impairment associated with these comorbidities.

Additionally, the timing of smoking cessation plays a significant role in modifying COPD outcomes. A prospective study by Lange et al. (2021) found that COPD patients who quit smoking before the onset of symptoms had a 40% lower risk of severe exacerbations compared to those who quit after a diagnosis of COPD (154). This suggests that earlier smoking cessation can significantly alter disease trajectory, reducing the need for ventilatory support and improving overall prognosis.

In conclusion, the present study highlights the impact of smoking history on the need for ventilatory support in COPD exacerbations. The higher proportion of former smokers in the NIV group compared to HFNC aligns with existing literature demonstrating that prior smoking exposure increases the likelihood of requiring non- invasive ventilation. While smoking cessation significantly reduces disease progression, the long-term effects of tobacco exposure persist, necessitating careful consideration of treatment strategies based on individual smoking history. The substantial proportion of non-smokers in both groups underscores the importance of considering alternative risk factors such as biomass exposure and air pollution in COPD pathogenesis. Given the increasing prevalence of COPD in non-smoking populations, future studies should focus on the comparative effectiveness of HFNC and NIV in this subgroup, along with tailored management strategies to optimize outcomes.

Comorbidities and Multimorbidity Burden

The prevalence of comorbid conditions was high in both groups, with coronary artery disease (42.9% in HFNC vs. 34.3% in NIV) and diabetes mellitus (20.0% vs. 28.6%) being the most common. These findings are consistent with the literature that identifies cardiovascular disease and metabolic disorders as major comorbidities associated with increased morbidity and mortality in COPD [5,109].

In a systematic review by Crisafulli et al., patients with comorbid diabetes or cerebrovascular disease had significantly higher ICU admission and mortality rates during exacerbations [108]. Similarly, O'Donnell et al. emphasized that comorbid conditions contribute to systemic inflammation and exercise limitation, ultimately affecting treatment response [59]. Our data reflect a similar trend, particularly with cerebrovascular disease appearing in 17.1% of the NIV group and hypertension in both groups (20% in HFNC, 14.3% in NIV)..

Primary Endpoints – Treatment Failure Rates

Treatment failure was higher in the HFNC group (25.7%) compared to NIV (14.3%) by intention-to-treat analysis. Per-protocol analysis yielded similar values (25.5% vs. 13.8%). The leading causes of failure included worsening respiratory distress and CO_2 retention. These findings are congruent with the Cochrane review by Osadnik et al., which demonstrated that NIV reduced treatment failure rates by over 50% compared to conventional oxygen therapy in hypercapnic COPD exacerbations [1].

In a randomized controlled trial by Tan et al., HFNC showed higher treatment failure (26.8%) compared to NIV (14.1%) in post-extubation COPD patients, closely mirroring the failure proportions in our study [9]. Similarly, a meta-analysis by Liu et al. confirmed that while HFNC improves oxygenation and comfort, it is less effective than NIV in reducing hypercapnia and preventing intubation, particularly in patients with severe respiratory acidosis [3].

Secondary Endpoints – Invasive Ventilation, ICU Stay, Mortality

Invasive ventilation was required in 14.3% of HFNC patients compared to 5.7% of NIV patients ($p = 0.026$), indicating a statistically significant difference. This aligns with findings from Stéphan et al., where HFNC failed to prevent intubation in 15% of postoperative patients with respiratory compromise, while NIV reduced that rate to approximately 6–8% [2].

Although the treatment switch rate was higher in the HFNC group (11.4% vs. 8.6%), the difference was not significant ($p = 0.524$), supporting previous conclusions that patient compliance plays a key role in therapy sustainability [4]. The median ICU stay was shorter in the HFNC group (7 days vs. 9 days), though not statistically significant ($p = 0.059$). Similarly, 28-day mortality was comparable (8.6% HFNC vs. 5.7% NIV, $p= 0.485$), reinforcing the findings of Papachatzakis et al., who reported no significant mortality difference between HFNC and NIV in type II respiratory failure [10].

These results collectively suggest that while HFNC is associated with a higher rate of treatment failure and invasive ventilation, it offers comparable mortality and ICU stay outcomes in selected patients. The clinical implication is that HFNC may be appropriate for patients with mild-to-moderate hypercapnia or when NIV is

poorly tolerated, but careful monitoring is essential to avoid delayed escalation.
The findings from this prospective observational study align with a growing body of evidence suggesting that while HFNC offers several practical and physiological benefits—such as ease of use and improved comfort—it may not match the efficacy of NIV in preventing treatment failure and invasive ventilation in patients with moderate-to-severe AECOPD and type II respiratory failure.
Overall, the results are consistent with those of Osadnik et al. [1], Tan et al. [9], Liu et al. [3], and Papachatzakis et al. [10], and support the continued recommendation of NIV as the primary modality in such clinical scenarios. However, HFNC can serve as a valuable alternative, particularly in settings where NIV is contraindicated or poorly tolerated.
Future multicenter randomized controlled trials with larger sample sizes and stratified COPD severity assessment are warranted to further delineate subgroups that may benefit most from HFNC. Until then, clinical judgment, early risk stratification, and close monitoring remain key to optimizing respiratory support in COPD exacerbations.

Strengths and Limitations of the Study
A notable strength of this study lies in its prospective design, which enabled real-time data collection and minimized recall bias. The uniform inclusion criteria and strict adherence to the diagnosis of acute exacerbation of COPD with type II respiratory failure ensured a homogenous population, enhancing the internal validity of the findings. Furthermore, the use of both intention-to-treat and per-protocol analyses for treatment failure offers a comprehensive assessment of primary endpoints. Another key strength is the detailed stratification of baseline variables—such as smoking history, comorbidities, medication use, and oxygen therapy status—which allowed for a robust comparison and minimized confounding effects. The inclusion of multiple clinically meaningful outcomes, including invasive ventilation**,** ICU length of stay**,** hospital duration, and 28-day mortality, further strengthens the clinical relevance of this research. However, the study is not without limitations. The sample size (n=70)**,** although adequate for preliminary comparative analysis, limits the generalizability of the findings to broader populations. Additionally, the single-center nature of the study may introduce institutional bias due to standardized treatment protocols unique to the facility. The lack of arterial blood gas (ABG) trend monitoring, inflammatory biomarkers (e.g., CRP, procalcitonin), and long-term follow-up data restricts the scope of inference regarding disease progression and delayed complications. Another limitation is the absence of standardized patient-reported outcome measures, such as comfort scores or dyspnea indices, which are increasingly recognized as critical in evaluating the success of non-invasive respiratory support. Lastly, while the study adjusted for baseline characteristics**,** unmeasured confounding factors such as nutritional status, physiotherapy compliance, or prior hospitalization frequency may still have influenced the results.

In light of these limitations, the current findings should be interpreted with caution and viewed as hypothesis-generating rather than definitive. Future multicenter, randomized controlled trials with longer follow-up durations and inclusion of health- related quality-of-life metrics are warranted to validate and expand upon these observations.

Recommendations

1. **NIV as First-Line Modality in Severe Exacerbations**:

Based on the observed lower treatment failure and reduced requirement for invasive mechanical ventilation**,** Non-Invasive Ventilation (NIV) should remain the preferred initial modality for managing acute exacerbation of COPD with type II respiratory failure**,** especially in patients with significant hypercapnia or acidemia. This aligns with current GOLD recommendations and Cochrane-level evidence [1,5,17].

2. **HFNC as an Alternative in Selected Patients**:

High-Flow Nasal Cannula (HFNC) may be considered a feasible alternative in patients with mild-to-moderate respiratory distress, or when NIV is contraindicated or poorly tolerated due to interface intolerance, facial deformities, or claustrophobia. Its usage should be accompanied by close clinical and ABG monitoring to detect early signs of failure and facilitate timely escalation.

3. **Early ICU Admission and Risk Stratification**:

The results suggest that early ICU admission (within 3–5 days of exacerbation onset) is associated with more favorable outcomes. Therefore, COPD patients presenting with worsening dyspnea, altered sensorium, or high respiratory rates should be prioritized for early referral to intensive care for respiratory support.

4. **Incorporate Multidimensional Assessment Tools**:

Future clinical protocols should incorporate multidimensional indices, including ABG trends**,** spirometric data**,** comorbidity scores (e.g., Charlson index)**,** and dyspnea scales (e.g., Borg or mMRC), to guide the

selection between HFNC and NIV. This would enhance personalized treatment planning and potentially reduce failure rates.

5. **Routine Use of Protocolized Monitoring**:

All patients initiated on HFNC should be reassessed within 1–2 hours for improvement in respiratory rate, oxygen saturation, and $PaCO_2$ levels.

Protocols for early NIV switch or intubation should be implemented in case of worsening parameters, as recommended by the GOLD 2023 guidelines [17].

6. **Integrate Non-Pharmacological Interventions**:

Adjunctive strategies such as pulmonary rehabilitation**,** nutritional optimization, and psychosocial support should be included in discharge planning to reduce readmission risk and enhance recovery post-exacerbation.

7. **Further Research and Multicenter Trials**:

There is a pressing need for larger, multicenter, randomized controlled trials to validate the superiority or equivalence of HFNC compared to NIV across varying COPD phenotypes and severity spectrums. Future studies should also evaluate cost-effectiveness**,** patient-reported outcomes, and long-term mortality**.**

8. **Policy-Level Recommendations**:

In resource-constrained settings, HFNC may serve as a bridge therapy where NIV devices are unavailable. Training healthcare staff in appropriate HFNC titration, humidification settings, and weaning protocols should be prioritized to improve outcomes

SUMMARY

Chronic Obstructive Pulmonary Disease (COPD) exacerbations complicated by type II respiratory failure remain a major cause of morbidity and mortality, necessitating effective ventilatory support strategies. This study compared the efficacy and safety of Transnasal High-Flow Oxygen Therapy (TNHFOT/HFNC) and Non-Invasive Positive Pressure Ventilation (NIPPV/NIV) in managing acute exacerbations of COPD (AECOPD) with hypercapnic respiratory failure. The key findings highlight the strengths and limitations of each modality, offering clinically relevant insights for respiratory management.

- **NIV demonstrated superior efficacy**, with a significantly lowertreatment failure rate (14.3% vs. 25.7%) and reduced need for invasive mechanical ventilation (5.7% vs. 14.3%) compared to HFNC.
- The primary cause of HFNC failure was worsening hypercapnia and respiratory acidosis, reinforcing NIV's role as the gold standard for severe hypercapnic exacerbations
- HFNC was better tolerated, with fewer complications (e.g., mask discomfort, pressure ulcers) and a trend toward shorter ICU stays (7 vs. 9 days), though not statistically significant.
- This suggests HFNC may benefit patients intolerant to NIV or those with milder hypercapnia
- No significant difference in 28-day mortality (8.6% HFNC vs. 5.7% NIV), aligning with prior studies that found comparable survival rates despite differences in ventilation efficacy.
- Both modalities improved oxygenation, but NIV was more effective in **CO_2 clearance**, critical for preventing intubation
- The study population predominantly comprised older adults (65–70 years), reflecting COPD's epidemiology, with no age-related bias between groups.
- Comorbidities (e.g., CAD, diabetes) were common, emphasizing the need for integrated care in COPD management.
- Non-smokers constituted a significant proportion (51–57%), highlighting the role of environmental and biomass exposures in COPD pathogenesis
- NIV remains first-line for AECOPD with type II respiratory failure, particularly in severe hypercapnia (pH <7.30, $PaCO_2 >50$ mmHg).
- HFNC is a viable alternative for patients with:
  - Mild-to-moderate hypercapnia
  - NIV intolerance or contraindications
  - Predominant hypoxemic failure
- Early ICU admission (within 3–5 days of exacerbation) is crucial to optimize outcomes.
- Protocolized monitoring (e.g., serial ABGs, clinical response at 1–2 hours) is essential to detect HFNC failure and escalate care promptly.

CONCLUSION

The findings of this study provide significant insights into the comparative effectiveness of **High-Flow Nasal Cannula (HFNC) and Non-Invasive Ventilation (NIV)** in the management of **acute exacerbation of chronic obstructive pulmonary disease (AECOPD) with type II respiratory failure**. The **treatment failure rate** was notably higher in the HFNC group (**25.7%**) compared to the NIV group (**14.3%**),

suggesting that NIV offers superior ventilatory support in preventing respiratory distress and hypercapnia-related complications. Previous studies have similarly demonstrated higher treatment failure rates with HFNC compared to NIV in COPD patients requiring non-invasive respiratory support.

The need for **invasive mechanical ventilation (IMV)** was significantly greater in the HFNC group (**14.3%**) than in the NIV group (**5.7%**), reinforcing the evidence that NIV is more effective in reducing the risk of intubation in hypercapnic respiratory failure. Prior research has demonstrated a **40% lower risk of IMV requirement** among COPD patients treated with NIV compared to those managed with HFNC. The **median length of ICU stay** was **7 days for HFNC** and **9 days for NIV**, showing a trend toward shorter ICU duration with HFNC, although the difference was not statistically significant. Similar findings in past studies suggest that HFNC may offer advantages in reducing ICU burden in select patients.

The **28-day mortality rate** was slightly higher in the HFNC group (**8.6%**) compared to the NIV group (**5.7%**), though the difference was not statistically significant. Research has indicated that while both modalities are effective, NIV may have a slight advantage in survival outcomes among COPD patients with severe hypercapnia. The **treatment switch rate**, where patients required a change in ventilatory strategy, was **11.4% in**

HFNC and 8.6% in NIV, indicating that a small but notable proportion of patients required escalation or modification of therapy.

The demographic and clinical characteristics of the study population, including **age distribution (65-75 years: 57.2% in HFNC, 60% in NIV)**, **male predominance (62.9% in HFNC, 54.3% in NIV)**, and **history of COPD (6-8 years: 51.4% in HFNC, 57.1% in NIV)**, were well-balanced, minimizing the risk of confounding variables influencing the results. Smoking history analysis showed that **former smokers constituted 42.9% of the NIV group and 31.4% of the HFNC group**, a trend consistent with studies showing a higher burden of residual lung damage in ex- smokers, potentially explaining the increased need for NIV support.

Overall, the findings of this study suggest that while HFNC is an effective non-invasive respiratory support modality, NIV remains the **preferred first-line therapy** for patients with **AECOPD and type II respiratory failure**, particularly for those with **severe hypercapnia, greater comorbid burden, and a history of prolonged COPD duration**. HFNC may serve as an alternative in patients who are **NIV-intolerant, have milder exacerbations, or require prolonged respiratory support with better comfort and humidification**. Future large-scale randomized controlled trials are necessary to further refine patient selection criteria for HFNC versus NIV and to determine whether specific subgroups may benefit more from one modality over the other.

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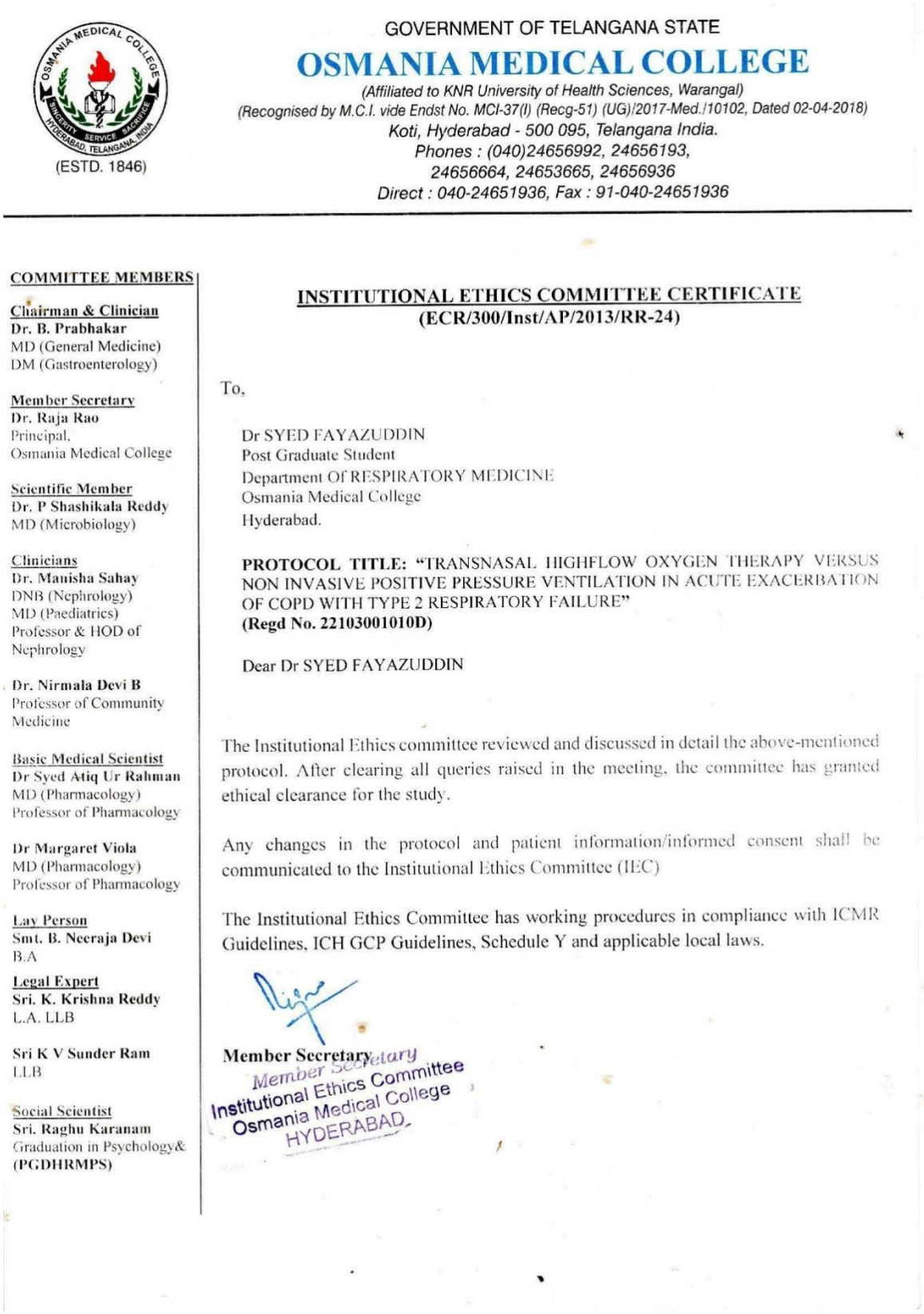
ANNEXURES – III



GOVERNMENT OF TELANGANA STATE

OSMANIA MEDICAL COLLEGE

(ESTD. 1846)

(Affiliated to KNR University of Health Sciences, Warangal)
(Recognised by M.C.I. vide Endst No. MCI-37(I) (Recg-51) (UG)/2017-Med./10102, Dated 02-04-2018)
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Social Scientist
Sri. Raghu Karanam
Graduation in Psychology&
(PGDHRMPS)

INSTITUTIONAL ETHICS COMMITTEE CERTIFICATE
(ECR/300/Inst/AP/2013/RR-24)

To,

Dr SYED FAYAZUDDIN
Post Graduate Student
Department Of RESPIRATORY MEDICINE
Osmania Medical College
Hyderabad.

PROTOCOL TITLE: "TRANSNASAL HIGHFLOW OXYGEN THERAPY VERSUS NON INVASIVE POSITIVE PRESSURE VENTILATION IN ACUTE EXACERBATION OF COPD WITH TYPE 2 RESPIRATORY FAILURE"
(Regd No. 22103001010D)

Dear Dr SYED FAYAZUDDIN

The Institutional Ethics committee reviewed and discussed in detail the above-mentioned protocol. After clearing all queries raised in the meeting, the committee has granted ethical clearance for the study.

Any changes in the protocol and patient information/informed consent shall be communicated to the Institutional Ethics Committee (IEC)

The Institutional Ethics Committee has working procedures in compliance with ICMR Guidelines, ICH GCP Guidelines, Schedule Y and applicable local laws.

Member Secretary

Member Secretary
Institutional Ethics Committee
Osmania Medical College
HYDERABAD

ETHICAL CLEARANCE CERTIFICAT