An-Najah National University

Faculty of Graduate Studies

Effect of High Flow Nasal Cannula Comparing with Noninvasive Positive Pressure Ventilation in Patient with Acute Hypoxemic Respiratory Failure

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الاقرار

أنا الموقع أدناه، مقدّم الرسالة التي تحمل العنوان:

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أقر بأن ما اشتملت عليه هذه الأطروحة إنما هو نتاج جهدي الخاص، باستثناء ما تمت الاشارة إليه حيثما ورد. وأن هذه الرسالة كاملة، أو اي جزء منها لم يقدم من قبل لنيل اي درجة او لقب علمي او بحثي لدى أي مؤسسة تعليمية أو بحثية أخرى.

Declaration

The work provided in this thesis, unless otherwise referenced, is the researcher's own work, and has not been submitted elsewhere for any other degree or qualification.

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Date: 17.8.2021 **التاريخ:**

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Abbreviations	Meaning
NIPPV	Noninvasive positive pressure ventilation
ICU	Intensive care unit
ARF	Acute respiratory failure
HFNC	High flow nasal cannula
MV	Mechanical ventilation
NIV	Noninvasive ventilation
ABG’s	Arterial blood gases
PaCo2	Partial pressure of carbon dioxide
PaO2	Partial pressure of arterial oxygen
SpO2	Peripheral capillary oxygen saturation
COPD	Chronic obstructive pulmonary disease
APACHE	Acute physiologic and chronic health evaluation
SAPS	Simplified acute physiologic score
NNUH	AN Najah National University Hospital
IRB	Institutional review board
SPSS	Statistical package for the social sciences
APACHE II	Acute Physiology and Chronic Health Evaluation II
SOFA	The sequential organ failure assessment score

Conceptual definition of the terms

ARF: defined as life-threatening condition, which includes sudden deterioration in pulmonary gas exchange process, resulting in carbon dioxide accumulation and impairment oxygenation including arterial blood gases abnormalities (PaO2) of 50 mm Hg or less, (PaCO2) greater than 50 mm Hg, and an arterial pH less than 7.35 (Morton, Fontaine, Hudak, & Gallo, 2005).

APACHE scale: defined as disease severity on admission to ICU (Abd ElHafeez et al., 2017).

SOFA score: it associated with the presence of sepsis contributed with mortality rate in critically illnesses in the ICU (Lee et al., 2016).

Recovery: defined as improvement arterial blood gases (ABGs) after one hour from initiation HFNC and NIV, with sustained respiratory improvement for up to 48 hours with conventional oxygen therapy (Frat, Thille, et al., 2015; Roca, Riera, Torres, & Masclans, 2010; Sztrymf et al., 2011).

Number of ventilator-free days: defined as the number of days patients were alive and free from mechanical ventilation, including both invasive ventilation and NIV up to day 28 of hospitalization (Frat, Thille, et al., 2015; Nagata et al., 2015).

NIV(NIPV): include cases in which NIV was used without switching to invasive ventilation (NIV failure) (Nagata et al., 2015).

HFNC: include cases in which HFNC was used without switching to NIV or invasive ventilation (HFNC failure) or in which NIV was initiated and switched to HFNC within 24 h (Nagata et al., 2015).

Length of hospital stay (LOS):

A term defined by the NHS as the length of an inpatient episode of care, cal culated from the day of admission to day of discharge, and based on the nu mber of nights spent in hospital. It is an important indicator of the use of medical services that is used to assess the efficiency of hospital management, patient quality of care, and functional evaluation. Decreased LOS has been associated with decreased risks of opportunistic infections and side effects of medication, and with improvements in treatment outcome and lower mortality rates. Furthermore, shorter hospital stays reduce the burden of medical fees and increase the bed turnover rate, which in turn increases the profit margin of hospitals, while lowering the overall social costs (Bueno et al., 2010; Rotter et al., 2010).

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Abstract

Background: Acute respiratory failure (ARF) is a serious health condition that can be associated with fatal complications that require immediate medical intervention and is associated with a high proportion of 30% of patients admitted to the intensive care unit. Noninvasive positive-pressure ventilation (NIPPV) and high-flow nasal cannula (HFNC) are commonly used oxygen therapy modalities used among patients with respiratory failures in the intensive care unit (ICU). This study was conducted to assess the effects of NIPPV and HFNC among patients with acute hypoxemic respiratory failure (AHRF) in ICU at An-Najah National University Hospital.

Methods: This study was a retrospective cohort study, all patients with AHRF treated with HFNC and/or NIPPV at the ICU at An-Najah National University Hospital (NNUH) in August 2018 to July 2019. All data were extracted from clinical records via electronic system of the hospital and from the patients' records.

Results: The median age of the patients was 52.5 with an IQR of 16.5 years, the median number of cigarettes smoked was 25 with an IQR of 10

per day, and the median BMI was 25.9 with an IQR of 4.9 kg/m^2. Of the patients, 40 (57.1%) had pneumonia and 33 (47.1%) had sepsis. Patients who received NIPPV were significantly younger compared with those who received HFNC (Pearson's Chi-square = 8.57, p value = 0.007). The respiratory and heart rate were significantly higher (p value < 0.05) for patients who received NIPPV compared to patients who received HFNC at the baseline and during the 1^{st}, 2^{nd}, and 3^{rd} sessions of day 1 and day 2 of the treatment. However, patients who received HFNC were more likely to have higher blood pressure and irregular ECG on day 2 and day 3 of the treatment (p value < 0.05) compared to those who received NIPPV. When the fraction of inspired oxygen was compared between both treatment methods, there was not statistically significant differences except for Day 2, Session 2 (p value < 0.05). In general, the pH and bicarbonate were significantly higher (p value < 0.05) for patients who received HFNC compared to patients who received NIPPV at the baseline and during the 1^{st}, 2^{nd}, and 3^{rd} sessions of day 1, day 2, and day 3 of the treatment. On day 3, there were more acute respiratory distress syndrome and bilateral pneumonia cases in the group who received NIPPV compared to those who received HFNC treatment (p value = 0.004). In general, patients who received NIPPV were more likely (p value < 0.05) to progress from severe pain to moderate and mild pain during the treatment days compare to patients who received HFNC. Patients who received NIPPV were more likely (p value < 0.05) to report tachycardia, tachypnea, cyanosis, restlessness, and confusion compared to patients who received HFNC

during the treatment days (p value < 0.05). The median hospital stay was 10.0 with an IQR of 5.0 days and the median ICU stay was 5.0 with an IQR of 4.0 days. Patients who received NIPPV were more likely (p value = 0.009) to have a longer hospital stay compare to those who received HFNC. The median SOFA score was 9.0 with an IQR of 1.0 and the median APACHE score was 19.0 with an IQR of 7.25. Patients who received NIPPV were more likely (p value = 0.017) to have a higher SOFA scores compare to those who received HFNC. There was no statistical difference between the number of patients who died, completely recovered in 24 h, 48 h, and 72 h in relation to the treatment method. However, patients who received NIPPV were more likely to be intubated (p value = 0.021) and receive vasopressors (p value = 0.002) compared to those who received HFNC.

Conclusion: Our results indicated that HFNC and NIPPV might be effective in improving prognosis and clinical outcomes of AHRF patients. Both methods were similar in terms of patient progress from severe/moderate impairment in level of consciousness to mild impairment in level of consciousness, death, ICU length of stay, and complete recovery in 24 h, 48 h, and 72 h. However, patients who received HFNC stayed less days in the hospital compared to the patients who received NIPPV. Findings of this study were comparable to those reported in different healthcare settings around the world. Future studies are still needed to determine recovery and mortality rates among both treatment methods.

Keywords: Acute respiratory failure, endotracheal intubation, high-flow nasal cannula, non-invasive positive pressure ventilation.

Chapter One
Introduction

Acute respiratory failure (ARF) is a serious health condition that can be associated with fatal complications that require immediate medical intervention and is associated with a high proportion of 30% of patients admitted to the intensive care unit (Nagata et al., 2015). These complications include pulmonary embolism, irreversible scarring of the lungs, pneumothorax, ventilator dependence, and brain hypoxia with irreversible brain damage, so some patients need endotracheal intubation to prevent or reduce these complications (Shebl & Burns, 2018).

The treatment of patients with ARF requires mechanical ventilation, even these patients can be ventilated with either positive or negative pressure, invasive or non-invasive (Agarwal, Gupta, Aggarwal, & Gupta, 2008). In addition, Schettino et al. (2008) reported that more than half of the patients with ARF might require treatment with endotracheal intubations and mechanical ventilations until the disease has resolved (Schettino, Altobelli, & Kacmarek, 2008).

Unfortunately, invasive mechanical ventilation (IMV) is the main cause of various side effects such as high mortality of 30.7% in hospitals (Esteban et al., 2002; Kollef, 2005). In addition, Kulkarni and Agarwal (2008) indicated that extubation failure is common in the ICU, causing increased morbidity, mortality, costs, length of stays in the ICU and hospital, and that patients with old age who already have chronic respiratory and

cardiovascular disease are at increased risk for extubation failure (Kulkarni & Agarwal, 2008). Therefore, clinical values tend to avoid IMV as a treatment option to reduce mortality.

Non-invasive ventilation (NIV) can be defined as providing supported ventilation to the lungs without using endotracheal airway (Agarwal et al., 2008). In recent decades, NIV became a frequent treatment for ARF as well as chronic respiratory failure. NIV has many advantages when compared to IMV which includes reduced complications and mortality, in addition, the effect of NIV depends on several factors such as severity and type of respiratory tract and cardiovascular pathology (Carron et al., 2013). In addition, NIV not only reduces the need for endotracheal intubation and other complications such as upper respiratory tract trauma, pneumonia or respiratory infection, aspiration and difficulty communicating, it is also used to reduce the complications associated with length of stay in the ICU, length of stay in the hospital and mortality among patients with specific diseases (L Brochard, 2003; Liesching, Kwok, & Hill, 2003).

Since the 1990s, NIV has been used in the treatment of patients with cardiogenic pulmonary edema and those with chronic obstructive pulmonary disease (COPD) with much evidence of exacerbation. However, outcomes of NIV in ARF are still controversial (Frat, Coudroy, Marjanovic, & Thille, 2017). While Fisher et al. (2017) reported that NIV is widely used in the emergency care environment for ARF in a variety of etiologies (Fisher et al., 2017).

NIV can improve exchange of gases and can reduce inhalation efforts through creating positive pressure. Sometimes, adequate tolerance to NIV can become difficult to obtain as a result of recurrent leakage around the mask. This may lead to variant problems such as patient-ventilator asynchronous, masking signs and symptoms of barotrauma and/or respiratory distress which may lead to delayed intubation (Frat et al., 2017). The benefits of using NIV also remain inconclusive in treating patients with acute hypoxemic respiratory failure (AHRF), i.e. those with ARF without hypercapnic states, cardiogenic pulmonary edema, or other chronic lung diseases (Dhar, Ghosh, & Krishnan, 2016).

ARF was described by Dhar et al. (2016) as a medical condition that develops when the lung system does not maintain gas exchange in an adequate process and is characterized by abnormalities in arterial blood gases (ABG) (Dhar et al., 2016). ARF can be classified into two types depending on ABG results as type 1 or hypoxemic ARF and type 2 or hypercapnic ARF. Type 1 can be defined by a PaO2 of less than 8 kPa with a normal or low PaCO2. On the other hand, type 2 can be defined by a PaO2 of less than 8 kPa and a PaCO2 of more than 6 kPa.

Hypoxemic ARF is a severe acute hypoxemia that can be defined by a PaO2/FiO2 ratio of less than 300. Hypoxemic ARF is associated with elevated respiratory rates which can reflect the clinical signs associated with difficulty breathing (Frat et al., 2017). In addition, hypoxemic RF usually occurs acutely in cases where there is a lack of oxygen supply to

the alveoli due to bronchoconstriction including COPD and asthma, and it developed in cases where disorders of gas transmission such as acute pulmonary edema, pneumonia and lobar collapse (Dhar et al., 2016). In addition, Dhar et al. (2016) declared that NIV can be considered as a treatment method for the most common causes of acute hypoxemic respiratory failure (AHRF) which include cardiopulmonary procedures and postoperative AHRF, pneumonias, AHRF traumas, asthma, acute respiratory distress syndrome (ARDS), and interstitial lung disease.

The first-line treatment in ARF is oxygen therapy that can be provided to the patient using a face mask with a container bag, but this strategy has limited effect to provide ventilation support, while the delivered proportion of the inspired oxygen (FiO2) could be restricted and the comfort could be reduced by the dry gas leading to damage to mucous membranes (Frat et al., 2017). While NIV is now the proposed first-line approach of treatment for patients with ARF in various cases, such as hypercapnic patients with exacerbations of COPD, immunocompromised patients or those with cardiogenic pulmonary edema (CPE). NIV has also been proposed as a method of preventing post-extubation ARF in certain groups of patients who are critically ill (Rochwerg et al., 2017). In some patient populations with ARF, NIV decreased the rates of invasive mechanical ventilation, reduced lengths of hospital stays, and improved survival rates (Bello, De Santis, & Antonelli, 2018).

Noninvasive positive-pressure ventilation (NIPPV was extensively expanded worldwide in the treatment of ARF, and the turning point for this successful expansion using NIPPV is its ability to have the same physiological effects as IMV without the life-threatening hazards or complications occurring, which correlated with the use of endotracheal tubes (Scala & Pisani, 2018).

NIPPV has many advantages over IMV, such as avoiding risks correlated with upper respiratory tract trauma, reducing patient discomfort and need for sedation, preventing ventilation-associated pneumonia (VAP), maintaining airway distance and intermittent ventilation, maintaining normal swallowing, eating, drinking and communicating without restriction. In addition, ventilation interruptions can be used for nebulized medication, physiotherapy, and expectoration (Laurent Brochard, Lefebvre, Cordioli, Akoumianaki, & Richard, 2014; Nava & Hill, 2009; Pisani, Corcione, & Nava, 2016; Rochwerg et al., 2017; Scala & Pisani, 2018). In addition, NIPPV has disadvantages including the inability to protect the airways, expected prolonged duration of mechanical ventilation, and the presence of other life-threatening organ failure (Qadir, Wang, Barjaktarevic, & Chang, 2018).

Recently, there are many clinical applications for the use of High-flow nasal cannulae oxygen therapy (HFNC) in adult ICUs as a method of treating various cases including acute hypoxemic RF (AHRF), oxygenation

during prei-ntubation and post-extubation (Sharma, Danckers, Sanghavi, & Chakraborty, 2020).

HFNC is a new method that can provide humidified (100%) and pre-heated oxygen with flow rates of up to 60 L/min via nasal tips. The settings can independently be controlled. This allows confidence in the ability to supply oxygen to the patients and possibility to improve outcomes. In addition, it has many benefits because it maintains elevated FiO2, thus, allowing the generation of low levels of positive pressure in the upper parts of the airways as a result of the high flow of gases. This can result in flushing the dead space in the upper parts of the airways (De Jong et al., 2018; Frat et al., 2017; Segovia, Velasco, Jaureguizar Oriol, & Díaz Lobato, 2019).

This investigation aimed to determine the effect of high-flow nasal cannula (HFNC) compared to non-invasive ventilation positive pressure ventilation (NIPPV) in patients with AHRF in the intensive care unit. The clinical characteristics and treatment outcomes (success and failure) were also compared.

1.1 Problem statement

Hospital mortality associated with the use of invasive mechanical ventilation remains high (approximately 30.7%) as a result of many complications like ventilator-associated pneumonia and barotrauma (Esteban et al., 2002; Kollef, 2005). In addition, approximately 60% of patients admitted to the intensive care unit report endotracheal intubation

and mechanical ventilation (MV) during their treatment process (Schettino et al., 2008).

Patients who are critically ill and admitted to the intensive care unit remain at higher risk of developing AHRF, which is considered life-threatening. We can prevent the occurrence of AHRF or reduced complication associated with it through early assessment and diagnosis, then initiation measures for ventilation support via NIPPV and / or HFNC, and evaluate the results of this technique that will affect the patient's condition by increasing their comfort and reducing the incidence of endotracheal intubation rate, ICU and hospital stay and ICU mortality.

The current study was a retrospective study with two groups of patients with AHRF who needed respiratory support, one of whom used NIPPV and another group used HFNC. We determined the effect of HFNC compared to NIPPV in patients with AHRF on ICU mortality, length of stay in the ICU and in the hospital, level of patient discomfort, incidence of endotracheal intubation rate and number of days without ventilation. There are no previous studies on this topic in our country Palestine.

1.2 The significance of the study

HFNC oxygen therapy machines are frequently used in ICU and postoperative care settings. In principle, these machines provide patients with a mixture of oxygen and air that is humidified and heated. The flow rates of gases can be adjusted between 20-60 L/min with an inspired oxygen fraction that can be adjusted between 0.21-1. HFNC machines

allows improving oxygenation status, reduction of dead spaces, washing out carbon dioxide, improving thoraco-abdominal synchronization, and reducing respiratory works. Previous reports showed that HFNC machines can be used in the treatment of patients with AHRF, during the perioperative period to prevent atelectasis, after extubation to reduce the need for mechanical ventilation, and for patients with exacerbations of chronic lung diseases. Potentially reduce the number of patients in need of intubation and mechanical ventilation. Weaning takes place with the patients' tolerance, oxygen saturation, respiratory rate and heart rate.

NIV effectively relieves the respiratory muscles, elevates the tidal volumes, decreases the respiratory rates and decreases the diaphragmatic respiratory work. This might reflect improvements in oxygenation, decrease in hypercapnia, and improvements in terms of shortness of breath. The goal of NIV is to reduce respiratory work while improving gas exchange in order to avoid intubation. NIV might be effective approach that could be associated with a reduced risk for infections and improvement in the survival rate among patients with respiratory failures.

This study provided data on the effect of HFNC and NIPPV in patients with AHRF in the ICU. Findings of this study might increase knowledge about the results and benefits of HFNC compared to NIPPV in AHRF patients. In addition, this study might provide recommendations for physicians in the health sector to improve the quality of care for patients with AHRF in the ICU, leading to minimizing complications.

1.3 Objectives

1. To assess the effects of HFNC among patients with AHRF in ICU at NNUH.
2. To assess the effects of NIPPV among patients with AHRF in ICU at NNUH.
3. To compare the effects of HFNC and NIPPV among patients with AHRF in ICU at NNUH.

1.4 Research questions

1. What are the effects of HFNC among patients with AHRF in ICU at NNUH?
2. What are the effects of NIPPV among patients with AHRF in ICU at NNUH?
3. What are the differences in the effects of HFNC comparing with NIPPV among patients with AHRF in ICU at NNUH?
4. What are the clinical characteristics of treatment failure and success in HFNC group?
5. What are the clinical characteristics of treatment failure and success in NIPPV group?

1.5 The primary outcome

Failure of alternative respiratory support (treatment failure)

Treatment failure was defined as composite outcome including:

- Intubation,
- Switching to another treatment without improvement, or
- Death during HFNC or NIV

1.6 The secondary outcome

- Blood gas analysis
- The duration of ICU and hospital stay
- Comorbidities among the patients
- Radiological changes

1.7 Hypothesis

- Hypothesis (H1): HFNC use in the management of AHRF will significantly reduce the incidence of ICU mortality at the 0.05 level compared to NIPPV.
- Hypothesis (H2): HFNC use in the management of AHRF will significantly reduce the length of stay in the ICU and in the hospital at the 0.05 level compared to NIPPV.

- Hypothesis (H3): HFNC use in the management of AHRF will significantly reduce the incidence of patient discomfort presented by decrease pain score on the visual analog scale at the 0.05 level compared to NIPPV

- Hypothesis (H4): HFNC use in the management of AHRF will significantly reduce the incidence of endotracheal intubation rate at 0.05 level compared to NIPPV

- Hypothesis (H5) HFNC use in the management of AHRF will significantly increase PaO2 at 0.05 level compared to NIPPV

- Hypothesis (H6) HFNC use in the management of AHRF will significantly decrease breathing frequencies at 0.05 level compared to NIPPV

- Hypothesis (H7) HFNC use in the management of AHRF will significantly decrease heart rate at 0.05 level compared to NIPPV

- Hypothesis (H8) HFNC use in the management of AHRF will significantly decrease

- The rate of health care–associated infections at 0.05 level compared to NIPPV

Chapter Two
Background

2.1 Definition of acute respiratory failure (ARF)

ARF is defined as serious health condition that happens when the respiratory system fails to keep normal process for gas exchanges which consider the major function for this system, in which PaO2 < 60 mmHg and/or PaCO2 > 50 mmHg as appeared in arterial blood gases (ABG's). In addition, it is categorized into two types depending on abnormalities results in ABG's: type 1 is hypoxemic RF in which PaO2 less than 60 mmHg with normal/subnormal PaCO2, which included impairment of gas exchange at the level of aveolo-capillary membranes, for example cardiogenic or noncardiogenic pulmonary edema and severe pneumonia. The type 2 is hypercapnic RF and is common in which PaCO2 > 50 mmHg (Shebl & Burns, 2018).

Furthermore, ARF can be defined as occurrence of clinical signs/symptoms of ARD (which includes dyspnea, frequency of breathing of 30 breaths/min, the need to use accessory respiration muscles, and occurrence of paradoxical breathing) and need for assisted oxygenation (Nagata et al., 2015).

Matuszak et al (2020) pointed to categorize ARF into three main types: type (1) acute hypoxemic RF which results from impaired transport of O_2 which occurs secondary to pulmonary parenchymal disease, which results in an elevated alveolar ventilation that results in reduced PaCO2

(Matuszak, Tabuchi, & Kuebler, 2020). The principal problem in hypoxemic ARF lies in the lack of ability of achieving sufficient oxygenation which can be seen as PaO2 of ≤ 60 mm Hg and PaCO2 of ≤ 40 mm Hg. In type I failure, the main causes are alveolar hypoventilation and right to left shunt. On the other hand, type II acute hypercapnic RF results from lack of adequate alveolar ventilation that occurs secondary to reduced ventilatory drive, fatigue/failure of the respiratory muscles, and elevated breathing work. Elevated CO2 levels with preserved oxygenation is a main characteristic hypercapnic ARF. In this state, hypoxemia occurs as a result of decreased alveolar oxygen pressure (PaO2) that is proportionate to hypercapnia. In combined type I and type II, hypoxemic and hypercapnic RF occur as a result of lack of normal gas transport and lack of adequate alveolar ventilation. It is noteworthy mentioning that combined failure can occur as a result of any cause of type I. This is especially true when breathing work is increased in the presence of hypercapnia.

Acute hypoxemic respiratory failure (AHRF) criteria include: 1) respiratory rate of > 25 breaths/min, 2) a PaO2/FiO2 ratio of ≤ 300 mm Hg when the patient breaths O2 at a flow rate of ≥ 10 L/min for at least 15 min, 3) PaCO2 < 45 mm Hg, and 4) lack of clinical history of underlying CRF (Frat, Brugiere, et al., 2015).

2.2 Etiology of ARF

ARF is a consequence of many pulmonary and non-pulmonary disease. There are many factors that can be associated with ARF or may exacerbate ARF. These factors include change in tracheobronchial clearance, pneumonia (both viral and bacterial), disturbances in tracheobronchial secretions, aspiration/inhalation of vomitus or foreign bodies/irritants, drugs (anesthetics, sedatives, or narcotics), cardiovascular diseases (shock, heart failure, or pulmonary emboli), increased O2 demand (infections or fever), neuromuscular disorders, allergy (bronchospasm), history of trauma/surgery, fatigue of respiratory muscles, and mechanical factors (distention in the abdomen, pleural effusion, or pneumothorax) (Morton et al., 2005).

According to Nielsen et al. (2016), non-traumatic breathing abnormalities result from lower respiratory tract infections, cardiopulmonary edema, and asthma/COPD that in severe cases could need non-invasive positive pressure ventilation, mechanical ventilation, and/or endotracheal intubation (Nielsen et al., 2016).

2.3 Biomarkers

ARF varies significantly depending on the disorders that underly occurrence of ARF, factors that precipitated ARF, extent of hypoxemia, extent of hypercapnia, and/or extent of acidosis (Morton et al., 2005). Hypoxemia could be associated with noticeable presenting classical symptoms like cyanosis, tachypnea, dyspnea, cardiac dysrhythmias,

tachycardia, hypertension, confusion, restlessness, delirium, anxiety, and tremors. Sometimes, dyspnea is entirely absent in ventilatory failure that results from respiratory center depression (Chesnutt, Matthay, Tibayan, & Clark, 1997).

Arterial blood gases (ABGs) are needed for the diagnosis of RF. Healthcare providers need to measure PaCO2, PaO2, and blood pH level (Fisher et al., 2017). Additionally, other investigations might be ordered to determine what cause underlie RF. These investigations and tests might include complete blood count (CBC), urinalysis, serum electrolytes, toxicology screening, examination of sputum, chest radiography, electrocardiography (ECG), echocardiography, angiography, cytology, thoracentesis, pulmonary function testing, bronchoscopy, ventilation–perfusion scanning, and computed tomography (CT) scan.

Shebl and Burns (2018) confirmed that the diagnostic tests that needed in diagnosis ARF including ABGs which consider as mandatory test, chest radiography is require to identify parenchymal lesions in the chest wall, pleural cavity, and lung. In addition, healthcare providers might need other diagnostic tests for identifying the essential causes of the ARF. These diagnostic tests might include sputum, blood and/or urine cultures, CBC, ECG, echocardiography, blood electrolytes, bronchoscopy, pulmonary function tests, and thyroid function tests. The choice of these diagnostic tests depends on signs and symptoms of hypoxemia that patients may

present with like cyanosis, dyspnea, tachypnea, arrhythmia, tachycardia, confusion, irritability, fits, and somnolence (Shebl & Burns, 2018).

2.4 Risk Factors

Risk factors may include history of excessive alcohol drinking, smoking, family history of respiratory health conditions/diseases, having a chronic respiratory disease like asthma/COPD, spine injury, brain injury, chest injury, or having a compromised immune system (Lee et al., 2016).

2.5 Management of ARF (Device Types)

ARF requires direct and rapid intervention to compensate for the ABGs abnormalities and identify the cause. Endotracheal intubation may be lifesaving, and in acute hypoxemic respiratory failure (AHRF) should maintain an arterial oxygen saturation (SaO2) of ≥ 90% (Morton et al., 2005).

2.5.1 Non-invasive ventilation (NIV/NIPPV)

NIV refers to providing patients with mechanical respiratory aid through utilizing techniques without bypassing the upper airways (Rochwerg et al., 2017). In NIV, spontaneous respiratory system activities are maintained, lungs are assisted by provision of positive pressure through a face mask that connects to a system of humidification, heat/moisture exchange or heated humidifier systems, and a ventilator (Frat et al., 2017). The use of NIV is contraindicated in case of respiratory arrest, when the healthcare providers are not able to fit a face mask on the patient, when the patient

suffers episodes of uncontrolled emesis, when the patient suffers severe upper gastrointestinal bleedings, when the upper airways are totally blocked, in case of facial trauma, and when the patient declines receiving NIV (Mas & Masip, 2014). NIPPV is a technique of oxygen therapy that provide support for respiratory system by delivery of positive-pressure ventilation through a nasal mask, facemask, or nasal plugs, also, its role in treatment ARF among patients without prior pulmonary disease is remain unclear, while there is many evidence of advantage from its use in COPD exacerbations, cardiogenic pulmonary edema, and immune-compromised patients (Rochwerg et al., 2017).

2.5.2 High-flow nasal cannula (HFNC)

HFNC is a contemporary technique of O2 therapy that is simple to use. HFNC implies using air/O2 blender, humidifier, heated tube (a single tube), and a large-bore nasal cannula. HFNC enables provision of appropriately heated (temp 31 to 37 ºC) and humidified medical gases with a flow that can reach 60 L/min to elevate FiO2 from 21% to 100% while maintaining low positive pressure in the upper airway as a result of high flow. Compared to other O2 therapy techniques, HFNC has many physiologic merits. These merits include provision of a constant FIO2, adequate humidification, PEEP, and maintaining a reduced anatomical dead space (Nishimura, 2016). Efficacy of HFNC could be attributed to 5 mechanisms including: 1) reducing the nasopharyngeal resistance while inspiring medical gases, 2) maintaining positive end expiratory pressure, 3)

increasing alveolar recruitment, 4) improved humidification of airways which leads to increased tolerance and patient acceptability of the intervention, and 5) physiological dead space washout of waste gasses that include CO2 (Sharma et al., 2020).

2.5.3 Complications

HFNC is a novel technique. Additionally, little studies with high quality were conducted to evaluate the efficacy of this technique. Therefore, recommendations with regard to the clinical use of HFNC are still tentative. On the other hand, there are limitations and drawbacks that could be associated with HFNC that include: 1) the technique is complex and needs training before initiating care, 2) the technique is more expensive compared to low flow nasal cannula, 3) reduced mobility of the patient, 4) greater risks for lack of effective sealing of airways that leads to leakage of medical gases and loss of the positive airway pressure, 5) a greater risk for delayed intubation, and 5) a greater risk for inappropriate delayed end-of-life decisions (Spoletini, Alotaibi, Blasi, & Hill, 2015).

2.6 Monitoring

Every patient underwent the treatment of ARF via HFNC and NIPPV must be monitored for the following: ABGs before, during and after each session. In addition to signs and symptoms of hypoxemic ARF, hemodynamic parameters/vital signs that include blood pressure, pulse rate, ECG rhythm, O2 saturation (SpO2), pain, and respiratory rate are monitor continuously. CBC, chest x ray, blood electrolytes, electrocardiography

(ECG) are also monitored every day (Fisher et al., 2017; Shebl & Burns, 2018).

Chapter Three
Literature Review

The literature review aims to review and critically evaluate related research articles. In order to review the literature, a search was carried out by using CINAHL, PubMed, Science Direct, EBSCO, Google Scholar, and the different databases for Nursing Research. The following keywords were used to guide the search: AHRF, HFNC, (NIV/NIPPV), MV, critical ill patient in ICU and Palestine. The literature search was limited to English publications and full-text articles published between January 2015 and January 2020.

Frat et al. (2015) conducted a study in France. The study aimed to assess the clinical efficacy of humidified O2 delivered through HFNC alternating with NIV in AHRF (Frat, Brugiere, et al., 2015). The study was conducted in a prospective observational design and included 28 patients with AHRF. The inclusion criteria used in the study were: patients with breathing frequency of > 30 breaths/min, patients with respiratory distress that was indicated by a PaO2/FIO2 of < 300 mm Hg after spontaneously breathing oxygen at 15 L/min for > 15 min. The study included 28 patients with AHRF. Of those, 23 (82%) had ARDS. The study showed that the PaO2 increased significantly from 83 (68 –97) mm Hg to 108 (83–140) mm Hg for patients who received HFNC and 125 (97–200) mm Hg for patients who received NIV (p-value < 0.01) compared to standard O2 therapy. On the other hand, the study showed that frequency of breathing decreased significantly. Patients tolerated HFNC more than NIV that received lower

scores using the visual analog scale. Patients who were not intubated received NIV for 23 (8 –31) h and HFNC for 75 (27–127) h. 10 of the 28 patients (36%) needed intubation. Of the 23 ARDS patients, 8 (35%) needed intubation. Among patients who received HFNC, intubation was predicted by a breathing frequency of > 30 breaths/min. The study concluded that patients tolerated HFNC more than NIV. HFNC significantly improved oxygenation status and tachypnea when compared with standard O2 therapy among AHRF patients with a significant proportion of the patients had ARDS.

In 2017, Frat et al reported a study on the use of high-flow nasal oxygen therapy and noninvasive ventilation to manage patients with ARF. The study focused on the physiologic effects of HFNC, clinical relevance, and comparing main differences between HFNC and NIV (Frat et al., 2017). The study showed that HFNC was a simpler technique to be used compared to NIV. The study also reported that HFNC could be used as a good therapeutic alternative for patients with hypoxemic ARF. The study stressed that HFNC was more tolerated compared to NIV, able to deliver higher FiO2, able to generate low levels of positive pressure, and able to provide washout of dead space in the upper airway. The study concluded that HFNC can improve mechanical pulmonary conditions and can unload inspiratory muscles during ARF.

A multicenter randomized controlled trial (RCT) that was conducted to demonstrate the benefits of HFNC with regard to reducing mortality and

intubation rates among patients with severe hypoxemic ARF. The highlighted conflicting results of using NIV in the treatment of patients with hypoxemic ARF. Although NIV was able to improve oxygenation status, NIV was shown to be able to generate high tidal volumes. This was shown to be associated with higher rates of ventilator induced lung injury. The study recommended using NIV with a helmet instead of a face mask, high positive end-expiratory pressure (PEEP), and low-pressure support (PS) in patients with hypoxemic ARF (Frat et al., 2017).

Nagata et al. conducted a retrospective cohort study on the efficacy of HFNC among patients with hypoxemic ARF in Japan (Nagata et al., 2015). The study was conducted among patients with AHRF regardless of the type of respiratory support they received. The study compared inpatient mortality rates, ICU length of stay, and the need for mechanical ventilation. The study was conducted among 83 patients of whom 65 were managed with NIV and 18 were managed with invasive ventilation. The study also included 89 patients of whom 43 were managed with NIV, 33 were managed with HFNC, and 13 were managed with invasive ventilation. The study concluded that inpatient mortality was comparable between the techniques. The use of either technique was not associated with decrease in the length of ICU stay, intermediate care unit stay, or hospital stay. The study showed that patients who received HFNC required less mechanical ventilation compared to those who received NIV or invasive ventilation. The patients also required less ventilator days and enjoyed more ventilator-free days.

In Denmark, Nielsen et al. conducted a study to assess adherence to therapy and efficacy of CPAP used in the management of patients with ARF (Nielsen et al., 2016). The study included 171 patients who received CPAP and 739 patients who did not received CPAP. The study showed that of the CPAP patients, 45 (27%) were stayed in the ICU and 24 (14%) died in the hospital. The adverse effects associated with CPAP use included development of pneumothorax, nausea, hypotension, and worsening dyspnea. SpO2 significantly increased among patients who received CPAP compared to those who did not received CPAP (87 to 96 % versus 92 to 96 %, p-value < 0.01). Additionally, the respiratory rate significantly decreased in patients who received CPAP compared to those who did not receive CPAP (32 to 25 versus 28 to 24 breaths/min, p-value < 0.01). Patients who received CPAP were less likely to be intubated compared to patients who did not received CPAP. The study concluded that CPAP was superior to other techniques in patients with initial SpO2 less or equal 90% ($p < 0.05$).

In Italy, Mauri et al. conducted a prospective RCT to investigate the effect of HFNC on improving clinical outcomes of AHRF who were not intubated (Mauri et al., 2017). The study included 15 patients (14-60 years old). The study showed that HFNC improved clinical outcomes of patients with AHRF including improving oxygenation status (p-value < 0.001), reducing respiratory rates (p-value < 0.01), improving the volume of the lungs, compliance dynamics, transpulmonary pressure, and homogeneity. It was concluded that improvements of these physiologic parameters might be

translated to improvements in the clinical outcomes of the patients and reducing the need for intubation.

Ni et al. conducted a systematic review with meta-analysis to assess the efficacy of HFNC compared to NIPPV and traditional O2 therapy (Y.-N. Ni et al., 2018). RCTs comparing HFNC, NIPPV, and traditional O2 therapy were included. Findings of the study showed that HFNC reduced endotracheal intubations and mortality rates among patients. The study concluded that there was no significant different in the length of ICU stays among patients who received HFNC, NIPPV, or traditional O2 therapy.

In France, Macé et al. conducted a study among AHRF patients in the emergency department to compare the clinical impact after early initiation of HFNC when compared to standard O2 therapy (Macé et al., 2019). In this study, 102 patients were included. Of those, 48 were managed using standard O2 therapy and 54 with HFNC. At 1 h, patients who received HFNC were more likely to recover from respiratory failure compared to those who received standard O2 therapy 61% (33 of 54 patients) compared to 15% (7 of 48 patients), p-value <0.001. The study also showed that HFNC significantly improved oxygenation status and shortness of breath compared to standard O2 therapy.

In France, Jaber et al. conducted a study RCT to assess improvement of non-invasive ventilation on the clinical outcomes among patients developing AHRF after abdominal surgery (Jaber et al., 2016). The study included 280 patients who underwent abdominal surgery and developed

AHRF. Patients were randomized to receive standard O2 therapy (up to 15 L/min) (n=145) or NIV (n=148). Findings of the study showed that of the NIV group, 49 of 148 (33.1%) needed intubation within 7 days compared to 66 of 145 (45.5%) in the standard O2 therapy. Patients in the NIV enjoyed significantly more ventilation-free days compared to patients in the standard O2 therapy. At 90 days, 14.9% of the patients in the NIV group and 21.5% patients in the standard O2 therapy group died. Differences in the gas exchange were not significant between the two groups. Probably, the decreased mortality rate in the NIV group could be attributed to the decrease need for re-intubation, significantly shorter lengths of invasive mechanical ventilations, and decreased rates of hospital infections.

Coudroy et al. conducted an observational cohort study to assess and compare outcomes of patients who were immune compromised and treated for ARF using HFNC or NIV over a period of 8 years (Coudroy et al., 2016). All patients who were admitted to a 15-bed ICU in a hospital in France were included in the study. The analysis included 115 patients. Of those, 60 (52%) received HFNC and 55 (48%) received NIV. Findings of this study showed that mortality and ICU stay lengths were significantly lower for the HFNC compared to the NIV group. Additionally, mortality rates of patients who needed intubation were lower for the HFNC compared to the NIV group. The study showed that HFNC was tolerated more than the NIV as indicated by the comfort degree, severity of dyspnea, and respiratory rate.

A systematic review with meta-analysis was conducted to assess the efficacy and safety of HFNC among patients with AHRF (Kundra, Vitheeswaran, Nagappa, & Sistla, 2010). In this review, RCT in which HFNC was used compared to standard O2 therapy were included. The review included 9 RCT with 2093 patients. Findings of this review showed that there were no significant differences in the mortality rates of patients who received HFNC compared to those who received standard O2 therapy (relative risk [RR] 0.94, 95% confidence interval [CI] 0.67-1.31, moderate certainty). On the other hand, the review showed that HFNC decreased the risk of needing tracheal intubation with no effect on mortality rate. The review also reported that HFNC did not impact length of stay in the ICU, length of stay in the hospital, patient reported comfort, or patient reported dyspnea.

Another systematic review with meta-analysis was conducted to determine whether HFNC was superior to standard O2 therapy or NIV among patients with ARF (Zhao, Wang, Sun, Lyu, & An, 2017). The review included 3459 patients of whom 1681 received HFNC. The review reported that HFNC reduced the need for escalation of respiratory support, intubation, and mechanical ventilation compared to standard O2 therapy or NIV. On the other hand, there was no difference in the mortality rates among patients who received HFNC, standard O2 therapy, or NIV.

Koyauchi et al. conducted a study to assess the tolerability and efficacy of HFNC used in the treatment of AHRF patients with interstitial lung disease

in Japan (Koyauchi et al., 2018). In this study, records of 84 patients (HFNC, n = 54; NPPV, n = 30) were reviewed. The focus of this study was to compared in-hospital mortality, 30-day survival, treatment discontinuation, adverse events, oral intake, and communication ability at the end of life. The study showed that there was no significant difference between HFNC and NPPV with regard to 30-day survival (p-value = 0.86) and hospital mortality rates (p-value = 0.78). The study also showed that patients who received HFNC reported less adverse events and discontinuation of therapy compared to those who received NPPV. Patients who received HFNC were able to eat and communicate a brief period before death. The study concluded that HFNC can be used in palliative care.

Another retrospectively study conducted in Korea aimed to evaluate what predicted success of HFNC therapy among patients with AHRF (Hyun Cho et al., 2015). The study included 75 patients with baseline variables and changes in respiratory factors after HFNC treatment at 1 h and 24 h were assessed. Results found that 62.7% of patients successfully avoided intubation, and the physiologic parameters for them, such as PaO2, SaO2, respiratory rate (RR), and heart rate (HR), improved throughout the first 24 h of HFNC therapy with significantly differences. In addition, the other clinical variables as cardiogenic pulmonary edema, PaO2, APACHE II, SOFA, improvement at 1 h and 24 h were associated with treatment success. Also, the mortality rate in the ICU among therapy failure group was associated with using vasopressor and a low PaO2 improvement at 1 h.

Finally, it concluded that HFNC therapy led to improve of the physiologic parameters and good lung compliance for patients with AHRF, also, the failure to ameliorate oxygenation status within 24 h could predict intubation.

Comparing of HFNC therapy and NIV as a modality of treatment in ARF in a retrospective study conducted by Koga et al. (2020) (Koga et al., 2020). The study included 200 patients treated with HFNC and 378 patients with NIV. Results indicated that the management failure rates were higher in the HFNC group compared to NIV group (56% vs. 41%, p-value = 0.001), the rates of 30-day mortality were not significantly different between the 2 groups (29% vs. 32%, p-value = 0.456). Persistent hypoxia in HFNC and NIV groups (74% versus 53%), hypercapnia (14% versus 24%), circulatory instability (8% versus 16%) were less common among the HFNC group. Subgroup analysis showed that patients with mild to moderate hypoxia, cardiogenic pulmonary edema, and hypercapnia were more likely to suffer treatment failure.

A systematic review aimed to observe the outcomes of HFNC compared to standard O2 therapy and NIV among patients with AHRF (Lee et al., 2016). Results showed that in most of the studies, patients who received HFNC reported higher comfort and tolerance compared to patients who received NIV or standard O2 therapy. Additionally, HFNC reduced breathing work compared to other methods. On the other hand, NIV and standard O2 therapy were associated with elevated 90-day mortality rates

compared to HFNC in one study but not in other studies. Additionally, 3 in 4 studies showed a reduction in the need to escalate O2 therapy with HFNC, 6 in 8 studies showed improved oxygenation status with HFNC compared to standard O2 therapy. On the other hand, 2 in 3 studies reported lower oxygenation status with HFNC compared to NIV. The study concluded that HFNC could be superior to standard O2 therapy.

A systematic review with meta-analysis of RCTs was conducted by Huang et al. (2018) to assess the effect of HFNC compared to standard O2 therapy and NIV on the rate of reintubation of adults after extubation (Huang et al., 2018). Findings of the study showed that HFNC was associated with comparable reintubation rates with standard O2 therapy and NIV. In patients who were critically ill, HFNC was associated with lower reintubation rate compared to standard O2 therapy. Qualitative analysis indicated that HFNC could be associated with less complications and higher tolerance and patient comfort. The study also suggested that HFNC might not delay intubations.

Hu et al. (2020) carried out a retrospectively study among patients with COVID-19 treated with HFNC in Wuhan-China aimed to evaluate all clinical outcomes, success rates of HFNC, and other respiratory variables (Hu et al., 2020). The study included 105 hypoxemic patients. Results indicated that 61.9% of the patients had improved oxygenation and were subsequently withdrawn from HFNC. The SpO2/FiO2 ratio, PaO2/FiO2 ratio, and ROX index (SpO2/FiO2*RR) at 6 h, 12 h and 24 h of

HFNC were highly associated with prognosis. SpO2/FiO2*RR (ROX index) after 6 h predicted outcomes of HFNC. Outcomes were also predicted by being of young age, being of female gender, and having lower SOFA score. The study concluded that HFNC was an effective in the treatment of COVID-19 patients with respiratory complications.

Gürün Kaya et al. (2020) showed that using HFNC was more controversial among patients with COVID-19 due to concerns over the merits and risks of aerosol-dispersion (GÜRÜN, 2020). In this review, studies related to the use of HFNC in COVID-19 were reviewed. The study showed that HFNC can provide high concentrations of O2 to the patients who cannot be treated with conventional devices. Also, HFNC can reduce the need of intubation among COVID-19 patients, decrease the length of ICU stay, and complications related to mechanical ventilation. In addition, the use of HFNC can produce aerosols. Finally, it recommended HFNC treatment should be carried out in a negative pressure room.

Chapter Four
Methodology

In this section, the methods used in this study are described. This section includes the subsections: 1) study design, 2) study setting, 3) population, 4) sample size and sampling, 5) study interventions, 6) eligible criteria, 7) variables, 8) data collection, 9) pilot testing, 10) ethical considerations, and 11) analysis of data.

4.1 Study Design

This study was conducted in a retrospective cohort design, all patients with AHRF treated with HFNC and/or NIPPV at the ICU at An-Najah National University Hospital (NNUH) in August 2018 to July 2019. All data were extracted from clinical records via electronic system of the hospital and from the patients' records.

4.2 Study Setting

This study was conducted at NNUH which is an academic non-profit medical institution founded in 2013 in collaboration with the College of Medicine and other Health Sciences at An-Najah National University (NNU), the hospital consists of 120 beds in general and the intensive care units contain 18 beds that receive patients from all regions of the West Bank and Gaza Strip. The hospital is considered the only teaching hospital in Palestine that provides clinical training and education to current and future healthcare professionals.

4.3 Population

This study was performed in all patients with AHRF who were treated with HFNC and / or NIPPV in August 2018 to July 2019 at the ICU (Medical ICU, Surgical ICU) at the NNUH.

4.4 Sample size and Sampling

To calculate the needed sample size to identify differences among two proportions. From the study of Koga, et al (2020), the most frequent cause of therapy failure was long lasting hypoxia in the NIV and HFNC cohorts (53% vs. 74%). We use the ClinCalc calculator to compare two proportions - Sample size. Test share in group HFNC 74% and test share in group NIV 53% with confidence level 95% and study power with 80%. It was shown that we need 162 patients with the smallest sample size needed for each cohort was 81 to identify if the stated differences existed among the two proportions (with the appropriate confidence interval and required power). When we took into consideration the 30-day mortality rate that was significantly higher among the NIV compared to that among the HFNC (56% vs. 28%, P = 0.001) Koga, et al (2020). We use the ClinCalc calculator to compare two proportions - Sample size. Test share in group HFNC 28% and test share in group NIV 56% with confidence level 95% and study power with 80%. It was shown that we needed 96 patients were needed as the smallest sample size, 48 patients in each group to if the said differences existed among the two proportions.

In all cases, we took only 70 patients, as the new modality of HFNC was available at An-Najah National University Hospital only from August 2018 to Dec 2019. We took all patients treated with HFNC modality, there were only 35 patients and compared them with 35 patients treated with non-invasive ventilation during the same period.

The sample was nonprobability- a purposive sample, which includes patients aged ≥ 18 years and ≤60 years. The patients had a PaO2/FIO2 (P/F) ratio of less than 300 following breathing oxygen spontaneously at a rate of 15 L/min for 15 min via a non-rebreathing face mask. The breathing frequency was more than 30 breaths/min (or appearance of signs of respiratory distress) for the patients who received HFNC (HFNC group) or NIV (NIV group) as a first line respiratory support in the time period between August 2018 to July 2019 included 50 patients who were divided into two groups afterwards, 35 patients treated with HFNC and the other 35 patients with NIPPV. The NIV cohort included patients who received a full-face mask with non-invasive continuous positive airway pressure (CPAP). For patients in the HFNC group, the Nasal High Flow system was used.

4.5 Study interventions

High-flow nasal cannula (HFNC) therapy: In this technique, humidified and heated high-flow O2 is delivered through a nasal cannula. It is well-established that HFNC can ameliorate oxygenation status through supplying gas that flows with high inspiratory flow. This ensures high FiO2

(Sim, et al., 2008). Additionally, HFNC generates low level of PEEP that can elevate the end-expiratory lung volume (Corley, et al., 2011). It is noteworthy mentioning that the requirements of minute ventilation are decreased through washout of the anatomic dead space of the upper airways (Frat, et al., 2015). The machine used for HFNC consists of a blender of air/O2 that accurately adjusted FiO2 in the range of 0.21 to 1.0 and deliver gases in a flow rate of 70 L/min that were preheated and humidified. The mixture of gases is routed via a circuit to the patients that is delivered at a temperature of 37 °C and a humidity of 44 mg/L that is delivered through bi-nasal prongs of large-bore. Initially, HFNC was used at a gas flow rate of 50 L/min and FiO2 of 1.0. The FiO2 was set to maintain an SpO2 of 92%. After 1 h of HFNC initiation, blood gases were measured. HFNC was delivered through a Fisher and Paykel Optiflow system. O2 delivery was titrated through adjusting the FiO2 to maintain O2 saturation within the recommended level (90%) on a flow rate of 45 to 50 L/min. Data were collected from the medical records of the patients.

When patients showed alterations in consciousness, hemodynamic instability, seizures, exacerbations of respiratory failure, they were switched to iv after a clinical assessment by an intensivist. Patients who were successfully maintained on face masks or nasal tips were considered as therapeutic success group and those who required iv were considered as treatment failure group. The main therapeutic objective in this study was to keep the SpO2 level > 92% or PaO2 level > 65 mmHg. It is noteworthy mentioning that the parameters like air-O2 mixture flow rate and FiO2

were adjusted in accordance with the individual needs of the patients. ABGs were assessed at 1 h and 24 h post initiation of therapy as well as at the end of the therapy. Therapeutic success was defined as avoidance of intubation and subsequent withdrawal of HFNC. Withdrawal of HFNC was defined as maintaining SpO2 level > 92% or PaO2 level > 65 mmHg no need of HFNC.

NIV: Using this technique, patients received medical gases in while positioned semi-recumbent position and wearing a full-face mask that was linked with an ICU ventilator with a specialized NIV mode that was supported by a heated humidifier. The patients received medical gases via NIV with a pressure support to target an expired tidal volume of 6 to 8 mL/kg and a frequency of breathing of 30 breaths/min. The FiO2 was set to keep the SpO2 > 92% with PEEP of ≥ 4 cm H_2O. The settings of the ventilator were set during NIV with a pressure support of 13 (12–15) cm H_2O, PEEP of 4 (4–5) cm H_2O, and FiO2 of 0.9 (0.6 –1.0). In this group, patients were ventilated for ≥ 6 h either intermittently or continuously during the first 24 h. Between sessions of NIV, the patients were ventilated via standard O2 therapy (at a rate of up to 15 L/min to keep an SpO2 of ≥ 92%).

4.6 Eligibility criteria

4.6.1 Inclusion criteria

The patients who were recruited in this study met the criteria as follows:

1. The age of the patients varies between 18 and 60 years, regardless of gender.

2. Patients diagnosed with AHRF as per the criteria that follows: (respiratory rate > 25 breaths/min, arterial oxygen partial pressure ratio (PaO2) to Fio2 of ≤ 300 mm Hg while breathing O2 at a flow rate of ≥ 10 L/min for at least 15 min, a partial pressure of arterial carbon dioxide (PaCO2) < 45 mm Hg and an absence of clinical history of underlying chronic respiratory failure (Frat, Brugiere, et al., 2015).

3. Patients who received HFNC treatment without switching to NIV or invasive mechanical ventilation and NIPPV without switching to invasive mechanical ventilation (Nagata et al., 2015).

4.6.2 Exclusion criteria

1. Patients who have received treatment with mechanical ventilation.

2. Patients who received treatment with HFNC and / or NIPPV and then switched to mechanical ventilator (NIPPV or HFNC failed).

3. Patients suffering from chronic hypoxemic RF such as COPD.

4.7 Variables

4.7.1 Independent variables

HFNC and NIPPV.

4.7.2 Dependent variables

Respiratory system condition (per and post use HFNC and NIPPV). The scales used to measure the variables with their definitions are shown in Table .

1. ABGs (PaCO2, PaO2, PH, HCO3), a ratio of the partial pressure of arterial oxygen (PaO2) to the FiO2.

2. Hemodynamic parameters (vital signs) including (pulse, blood pressure, O2 saturation (SpO2), respiratory rate, pain, ECG rhythm and body temperature.

3. Signs and symptoms of AHRF. Presenting symptoms of hypoxemia include dyspnoea, cyanosis, restlessness, confusion, tachypnea, tachycardia, and hypertension.

4. Chest x ray and electrocardiography (ECG) every day (Fisher et al., 2017; Shebl & Burns, 2018).

5. Outcomes (mortality at ICU, length of stay in ICU and hospital, level of patients pain, and incidence of endotracheal intubation rate).

6. Sequential Organ Failure Assessment (SOFA) Score using the worst variable within the first 24 h of ICU admission and Acute Physiology and Chronic Health Evaluation (APACHE) II score on admission.

Table 3.1: Scales used to collect the variables with their definitions.

Variable	**Definition**
Numeric pain scale	
0	No pain
1-3	Mild pain
4-6	Moderate pain
7-10	Severe pain
Chest X ray	
1	Unilateral pneumonia
2	Lung Atelectasis
3	Acute respiratory distress syndrome (ARDS)
4	Clear lung (healthy lung)
5	Bilateral pneumonia
Glasgow coma scale (GCS)	
13-15	Mild impairment in level of consciousness
9-12	Moderate impairment in level of consciousness
≤ 8	Severe impairment in level of consciousness
Assessment of respiratory status	
0	Absent (No)
1	Present (Yes)
PaO2/FiO2 Ratio (P/F Ratio)	
200-300	Mild
100-200	Moderate
< 100	Severe
BMI	
< 18.5	Underweight
18.5-24.9	Normal weight
25.0-29.9	Overweight
30.0-34.9	Obese

4.8 Data collection

4.8.1 Procedure

After the critical review of the literature, the researcher for the current study developed a data sheet consisting of five parts. The medical records were reviewed retroactively from the hospital's electronic system next to the patient records. based on file-critical review; the first part consisted of complete socio-demographic information; it contains eight objects for assessing marital status, age, gender, place of residence, and level of education. Previous characteristics in medical and surgical history; any trauma, surgeries or other neurological deficits. In addition to significant data needed to extract the value of participants suffering from AHRF, HFNC and NIPV received. Permissions were obtained from the Institutional Review Board (IRB) of NNU and from the Research Ethics Committee of NNUH.

In this study, settings of the ventilator, blood gases, tolerance, FiO2, and respiratory parameters were measured at the baseline during spontaneous ventilation via a traditional face mask and 1 hour following initiating HFNC and NIV. Pain was assessed using visual analog scale. All variables were collected 1 h after initiating the second session either by HFNC or NIV. O2 therapy using either HFNC or NIV continued until decline of respiratory distress or intubation took place.

For endotracheal intubation, we used the following criteria: 1) persistent hypotension (systolic arterial blood pressure of < 90 mmHg or mean

arterial blood pressure of < 65 mmHg) despite fluid resuscitation or need to administer vasopressors, 2) psychomotor agitation or loss of consciousness that prevented nursing care, 3) an obvious worsening of respiratory distress, 4) frequency of breathing of ≥ 40 breaths/min, 5) excessive secretions, and 6) failure of maintaining an SpO2 level of > 90% or PaO2 level > 60 mmHg. On the other hand, NIV failure was defined as a patient that needs endotracheal intubation.

4.9 Validity of the data sheet

The validation of the data sheet was performed by involving 11 experts. This panel represented a group of experts with adequate expertise in the field involving two intensivists, four ICU nurses including medical and surgical ICUs, two CCU nurses, two researchers and a statistician to obtain expert feedback to evaluate and support data sheet development. Review components and complete a detailed data sheet was performed (Beecham, et al., 2005). This is shown in other's work conducted by Dyba˚ (2000) used 11 experts to carry out its review process, the value of expert knowledge is also recognized in the evaluation which proposes methods for formally capturing expert assessment (Dyba, 2000; Rosqvist, Koskela, & Harju, 2003). Following current results of data sheet validation. We related results to the success criteria to get an impression of strengths and weaknesses. We modified the data sheet based on comments from the expert panel that gives confidence in its representation. The reliability of using expert assessment is shown in other work. For example, Lauesen and

Vinter (2001) found that experts' ability to predict techniques to prevent requirements errors was very high when implemented (Lauesen & Vinter, 2001).

We mimic previous studies as validated improvement of data sheet by inviting an expert panel (Dyba, 2000; El Emam & Birk, 2000). We addressed experts with different backgrounds recommended by previous research (Lauesen & Vinter, 2001). Expert-panelists were recruited from a pool of skilled healthcare providers and researchers in the field. Areas of competencies were represented to make sure that the healthcare providers and the researchers are involved in early development and assessment. We define an expert-panelist in connection with this study as a person who is a researcher (b) has practical experience in the field for several years (Beecham, Hall, Britton, Cottee, & Rainer, 2005).

4.10 Data Collection sheet (appendix 1)

The data sheet includes nine parts, Part I: Demographic data, Glasgow coma scale, and comorbidities (appendix 2). Part II: Observational checklist for the assessment of respiratory status and Vital sign; Part III: Observational checklist for ABG results; Part IV: Observational checklist for pre and post parameters of the HFNC and NIPV period; Part V: Observational checklist for Length of stay in ICU and hospital; Part VI: Observational checklist for CX-Ray; Part VII: Observational checklist for pain assessment; Part VIII: Observational checklist for signs and symptoms

of AHRF; Part IX: Main outcomes of patients with AHRF treated with HFNC and NIV.

The Glasgow coma scale was used to measure the degree of impairments of consciousness in the different types of serious illnesses and traumas. The scale helps in classifying patients based on three responses: eye opening, verbal responses, and motor responses. Collection of these responses can be combined in the Glasgow coma scale to provide a description that is less detailed of the patients that might help in summarizing the overall difficulty the patient is facing. This scale has classically recommended by different guidelines for the assessment of patients who suffer trauma and critical illnesses.

4.11 Pilot testing

The purpose of conducting a pilot testing was to assess, on a limited scale, the steps described in a formerly developed plan that was based on the pilot's results, the plan would then be revised accordingly (Ackerman & Lohnes, 1981) and tested all techniques that used for data collection. In fact, pilot includes a risk-reducing strategy to reduce the risk of failure in a major project. Pilot testing in the current study was conducted to test data collection sheets on five patients. A pilot study was conducted to identify potential problem areas. Two researchers were filled the data sheets, there were no changes to the data sheet, therefore data sheet (No. 5) was included in the large study.

4.12 Ethical considerations

This study was conducted after approval by the IRB of NNU, the Research Ethics Committee of NNUH was approved to conduct this study. In addition, all participants in the study were named with a code to maintain anonymity and confidentiality for all participants. Participation in the study was voluntary. The study follows the World Health Organization's Declaration from Helsinki on Medical Research on Humans (World Medical Association (2013))

4.13 Analysis of data

The data collected in this study were processed in IBM SPSS v.21.0. Kolmogorov Smirnov Statistics were used to investigate if the data were normally distributed. In this study, data were expressed using their medians and interquartile ranges (IQR). Chi-squared/Fisher’s exact test, Kruskal Wallis test, and/or Mann-Whitney U test were used to compare categories. Data were correlated using Spearman’s correlations. Statistical significance was considered when the p value was < 0.5.

Chapter Five

Results

5.1 Baseline demographic and clinical characteristics of the patients

The median age of the patients was 52.5 with an IQR of 16.5 years, the median number of cigarettes smoked was 25 with an IQR of 10 per day, and the median BMI was 25.9 with an IQR of 4.9 kg/m^2. Details of the continuous variables are shown in Table .

Table 5.1: Median and interquartile range of the continuous variables of the patients .

Variable	Q1	Median	Q3
Age (years)	39.8	52.5	56.3
Cigarettes (number/day)	20.0	25.0	30.0
Height (m)	1.6	1.7	1.7
Weight (kg)	65.0	70.0	78.5
BMI (kg/m^2)	23.2	25.9	28.1

Of the patients, 28 (40%) were less than 50 years old and 42 (60%) were 50 years and above, 40 (57%) were male and 30 (43%) were female, 34 (49%) had diabetes, 31 (44%) had hypertension, 27 (39%) were smokers, and 44 (63%) were either overweight or obese. Dichotomous variables of the patients are shown in Table .

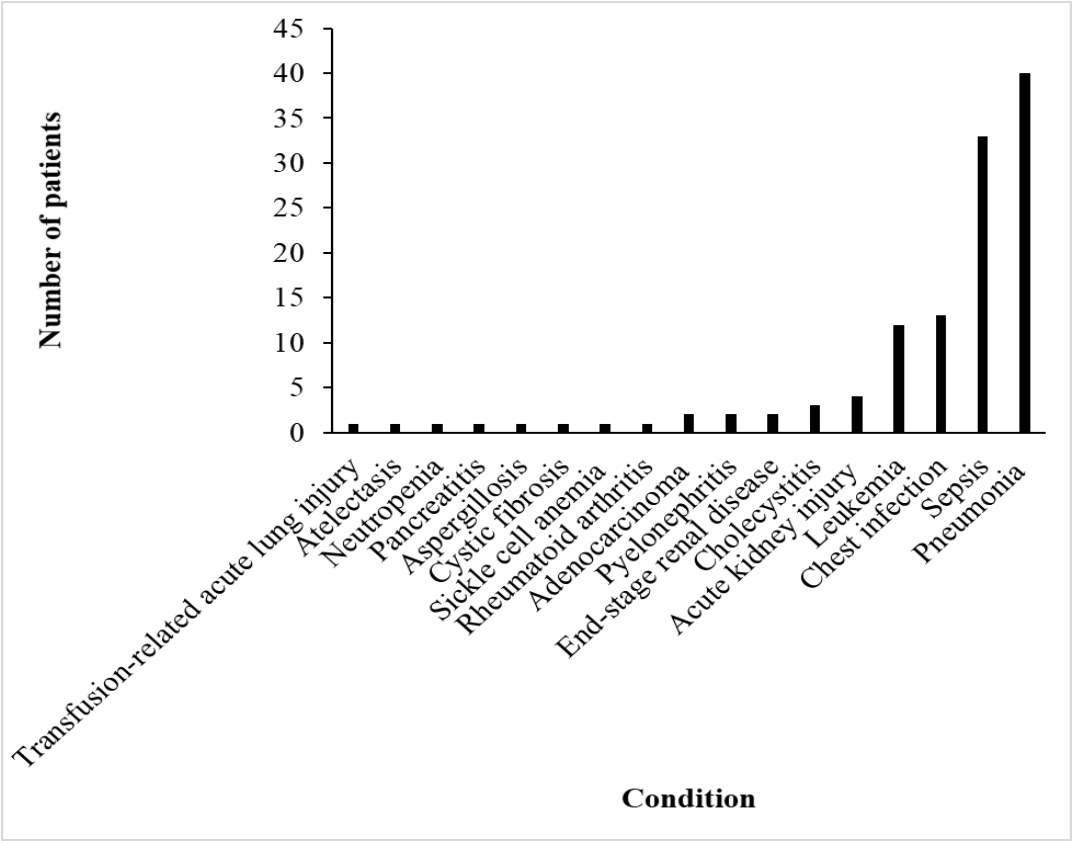
Table 5.2: Dichotomous variables of the patients

Characteristic	n	%
Gender		
Male	40	57.1
Female	30	42.9
Diabetes mellitus		
No	36	51.4
Yes	34	48.6
Hypertension		
No	39	55.7

Characteristic	n	%
Yes	31	44.3
Smoking		
No	43	61.4
Yes	27	38.6

5.1.1 Health conditions of the patients included

Of the patients, 40 (57.1%) had pneumonia and 33 (47.1%) had sepsis. The other health conditions that the patients had included chest infection, leukemia, acute kidney injury, cholecystitis, adenocarcinoma, pyelonephritis, end-stage renal disease, atelectasis, neutropenia, pancreatitis, aspergillosis, cystic fibrosis, sickle cell anemia, rheumatoid arthritis, and transfusion-related acute lung injury. Prevalence of these health conditions is shown in **Error! Reference source not found.**.



Health conditions of the patients included in the study (patients with each condition do not sum to 70)

5.1.2 Baseline stratification of the patients into Glasgow coma scale (GCS)

Using the GCS, 50 (71.4%) patients were classified as having mild impairment in level of consciousness at the baseline. However, 20 (28.6%) patients were stratified as having moderate impairment in level of consciousness. Distribution of the patients into the GCS is shown in Table .

Table 5.3: Baseline stratification of the patients into Glasgow coma scale (GCS).

Treatment day	n	%
Baseline		
Mild impairment in level of consciousness	50	71.4
Moderate impairment in level of consciousness	20	28.6

5.1.3 Baseline vital signs

At the baseline, the median respiratory rate was 30 with an IQR of 6.0 breaths/min. The median heart rate, systolic blood pressure, diastolic blood pressure, and temperature are shown in Table .

Table 5.4: Baseline vital signs.

Vital sign	Q1	Median	Q3
Respiratory rate (breaths/min)	27.0	30.0	33.0
Heart rate (beats/min)	80.0	107.0	112.3
Systolic blood pressure (mmHg)	110.5	125.0	140.8
Diastolic blood pressure (mmHg)	65.3	70.0	74.0
Temperature (ºC)	37.0	38.0	38.7

5.1.4 Baseline oxygenation status

At the baseline, the median PaO2/FiO2 ratio was 116.6 with an IQR of 68.0. The other oxygenation variables like pH, partial pressure of oxygen

(PaO_2), partial pressure of carbon dioxide ($PaCO_2$), bicarbonate (HCO_3), and oxygen saturation (SpO_2) are shown in Table .

Table 5.5: Oxygenation variables at the baseline.

Variable	Q1	Median	Q3
pH	7.3	7.3	7.4
Partial pressure of oxygen (PaO_2)	59.0	60.0	63.0
Partial pressure of carbon dioxide ($PaCO_2$)	26.0	28.0	29.0
Bicarbonate (HCO_3)	18.0	20.0	22.0
Oxygen saturation (SpO_2)	78.0	83.5	86.3
PaO_2/FiO_2 ratio	98.0	116.6	166.0

At the baseline, the majority of the patients 42 (60.0%) were stratified as having moderate acute hypoxemic respiratory failure and 20 (28.6%) were stratified as having severe acute hypoxemic respiratory failure. Stratification of the patients into oxygenation status at the baseline is shown in Table .

Table 5.6: Baseline stratification of the patients into different oxygenation status.

Oxygenation status	n	%
Mild acute hypoxemic respiratory failure	8	11.4
Moderate acute hypoxemic respiratory failure	42	60.0
Severe acute hypoxemic respiratory failure	20	28.6

5.1.5 Baseline chest X ray

At baseline, the majority of the patients, 40 (57.1%) were stratified as having unilateral pneumonia and 8 (11.4%) were stratified as having bilateral pneumonia. Stratification of the patients based on the chest X ray at the baseline is shown in Table .

Table 5.7: Chest X ray at baseline.

Chest X ray	n	%
Unilateral pneumonia	40	57.1
Lung Atelectasis	22	31.4
Bilateral pneumonia	8	11.4

5.1.6 Baseline pain assessment

At baseline, the median pain score was 8.0 with an IQR of 1.0. The majority of the patients, 62 (88.6%) had severe pain. The baseline pain assessment is presented in Table .

Table 5.8: Baseline pain assessment.

Pain	n	%
Moderate pain	8	11.4
Severe pain	62	88.6

5.1.7 Baseline signs and symptoms

At baseline, all (100%) patients had tachypnea and restlessness. Additionally, the majority of the patients had dyspnea, tachycardia, cyanosis, and confusion. Prevalence of these signs and symptoms is shown in Table .

Table 5.9: Prevalence of signs and symptoms at the baseline.

Signs and symptoms	Presence	n	%
Dyspnea	No	3	4.3
	Yes	67	95.7
Tachycardia	No	30	42.9
	Yes	40	57.1
Tachypnea	No	0	0.0
	Yes	70	100.0
Hypertension	No	61	87.1
	Yes	9	12.9
Cyanosis	No	2	2.9
	Yes	68	97.1
Restlessness	No	0	0.0

Signs and symptoms	Presence	n	%
	Yes	70	100.0
Confusion	No	6	8.6
	Yes	64	91.4
Hypotension	No	57	81.4
	Yes	13	18.6

5.2 Outcomes of treatment with HFNC and NIPPV

In this study, half of the patients received HFNC (n = 35) and another half received NIPPV (n = 35) treatment.

5.2.1 Comparison of the demographic and clinical characteristics of the patients.

Patients who received NIPPV were significantly younger compared with those who received HFNC (Pearson's Chi-square = 8.57, p value = 0.007). Details of these associations are shown in

Table . With regard to gender, diabetes, hypertension, smoking, and BMI status were not significantly different between the two groups (p value > 0.05). In general, male patients were significantly younger (Spearman's rho = -0.24, p value = 0.049) than female patients. Male and older patients had more prevalence of diabetes, hypertension, and smoking (p value < 0.05). Diabetes was associated with hypertension and hypertension was associated with smoking.

Table 5.10: Association between variables of the patients and the treatment method.

			Treatment method							
	Total		NIPPV		HFNC		Chi-square/Fisher's exact test		Spearman's correlation	
Variable	**n**	**%**	**n**	**%**	**n**	**%**	**Chi-square**	**p value**	**rho**	**p value**
Age (years)										
< 50	28	40.0	8	22.9	20	57.1	8.57	0.007	-0.35	0.003
≥ 50	42	60.0	27	77.1	15	42.9				
Gender										
Male	40	57.1	21	60.0	19	54.3	0.23	0.809	0.06	0.635
Female	30	42.9	14	40.0	16	45.7				
Diabetes										
No	36	51.4	14	40.0	22	62.9	3.66	0.093	-0.23	0.057
Yes	34	48.6	21	60.0	13	37.1				
Hypertension										
No	39	55.7	18	51.4	21	60.0	0.52	0.631	-0.09	0.478
Yes	31	44.3	17	48.6	14	40.0				
Smoking										
No	43	61.4	23	65.7	20	57.1	0.54	0.461	0.09	0.469
Yes	27	38.6	12	34.3	15	42.9				
BMI										
Under weight	4	5.7	2	5.7	2	5.7	6.11	0.117	0.05	0.674
Normal	22	31.4	14	40.0	8	22.9				
Over weight	30	42.9	10	28.6	20	57.1				
Obese	14	20.0	9	25.7	5	14.3				

5.2.2 Association between treatment method and scores on the Glasgow coma scale (GCS)

When GCS scores were compared between patients treated with NIPPV and those who received HFNC, there was no significant difference in the distribution of patients into the GCS categories.

Similarly, when the GCS scores were compared using Mann-Whitney U test and Spearman's correlations, there was no significant differences between the two treatment methods. Results are shown in Table 5.11 The median difference in the GCS score for NIPPV was -2.0 with an IQR of 2.0 and the median difference for the HFNC was -2.0 with an IQR of 0.0.

Table 5.11: Association between treatment method and score on Glasgow coma scale (GCS).

			Mann-Whitney test				Spearman's correlation	
Treatment day	**Treatment method**	**n**	**Q1**	**Median**	**Q3**	**p value**	**rho**	**p value**
GCS Baseline	NIPPV	35	12.0	13.0	13.0	0.917	0.01	0.917
	HFNC	35	13.0	13.0	13.0			
GCS Day 1 Session 1	NIPPV	35	13.0	14.0	14.0	0.222	-0.15	0.224
	HFNC	35	13.0	13.0	14.0			
GCS Day 1 Session 2	NIPPV	35	14.0	15.0	15.0	0.476	0.09	0.480
	HFNC	35	15.0	15.0	15.0			
GCS Day 1 Session 3	NIPPV	35	15.0	15.0	15.0	0.093	0.2	0.093
	HFNC	35	15.0	15.0	15.0			
GCS Day 2 Session 1	NIPPV	32	15.0	15.0	15.0	0.142	0.18	0.143
	HFNC	34	15.0	15.0	15.0			
GCS Day 2 Session 2	NIPPV	32	15.0	15.0	15.0	0.142	0.18	0.143
	HFNC	34	15.0	15.0	15.0			
GCS Day 2 Session 3	NIPPV	32	15.0	15.0	15.0	0.142	0.18	0.143
	HFNC	34	15.0	15.0	15.0			
GCS Day 3 Session 1	NIPPV	30	15.0	15.0	15.0	0.474	0.09	0.478
	HFNC	34	15.0	15.0	15.0			
GCS Day 3 Session 2	NIPPV	30	15.0	15.0	15.0	0.118	0.2	0.119
	HFNC	34	15.0	15.0	15.0			
GCS Day 3 Session 3	NIPPV	30	15.0	15.0	15.0	0.125	0.19	0.126
	HFNC	34	15.0	15.0	15.0			

5.2.3 Vital signs of the patients during the treatment days (Hypotheses H6 and H7)

During the treatment period, vital signs like respiratory rate, heart rate, systolic blood pressure, diastolic blood pressure, temperature, and rhythmic ECG were recorded at baseline and in three sessions during the three treatment days.

The respiratory and heart rate were significantly higher (p value < 0.05) for patients who received NIPPV compared to patients who received HFNC at the baseline and during the 1^{st}, 2^{nd}, and 3^{rd} sessions of day 1 and day 2 of the treatment. However, patients who received HFNC were more likely to have higher blood pressure and irregular ECG on day 2 and day 3 of the treatment (p value < 0.05) compared to those who received NIPPV. Associations between the vital signs and treatment methods are shown in Table 5-12.

Table 5.12: Association between treatment method and vital signs of the patients.

Treatment day	Session	Vital sign	Treatment	n	Q1	Median	Q3	p value
Day 0	Baseline	Respiratory rate	NIPPV	35	26.0	30.0	33.0	0.002
			HFNC	35	27.0	30.0	33.0	
		Heart rate	NIPPV	35	85.0	110.0	115.0	0.121
			HFNC	35	80.0	97.0	112.0	
		Systolic blood pressure	NIPPV	35	120.0	135.0	150.0	0.011
			HFNC	35	100.0	121.0	131.0	
		Diastolic blood pressure	NIPPV	35	70.0	70.0	80.0	0.037
			HFNC	35	60.0	70.0	70.0	
		Temperature	NIPPV	35	37.0	38.0	38.7	0.272
			HFNC	35	37.5	38.5	38.7	
		Irregular ECG rhythm	NIPPV	35	2.0	2.0	2.0	0.006
			HFNC	35	2.0	2.0	2.0	
Day 1	Session 1	Respiratory rate	NIPPV	35	26.0	28.0	30.0	0.002
			HFNC	35	23.0	26.0	27.0	
		Heart rate	NIPPV	35	90.0	101.0	110.0	0.007
			HFNC	35	83.0	90.0	96.0	
		Systolic blood pressure	NIPPV	35	87.0	120.0	131.0	0.098
			HFNC	35	118.0	125.0	132.0	
		Diastolic blood pressure	NIPPV	35	50.0	67.0	70.0	0.259
			HFNC	35	60.0	70.0	70.0	
		Temperature	NIPPV	35	37.0	37.0	38.0	0.688
			HFNC	35	36.7	37.0	38.0	
		Irregular ECG rhythm	NIPPV	35	2.0	2.0	2.0	0.167
			HFNC	35	2.0	2.0	2.0	
	Session 2	Respiratory rate	NIPPV	35	25.0	26.0	28.0	0.007
			HFNC	35	22.0	25.0	26.0	
		Heart rate	NIPPV	35	80.0	100.0	120.0	0.041
			HFNC	35	80.0	88.0	101.0	

		Systolic blood pressure	NIPPV	35	100.0	100.0	130.0	0.050
			HFNC	35	110.0	125.0	131.0	
		Diastolic blood pressure	NIPPV	35	60.0	67.0	76.0	0.203
			HFNC	35	60.0	70.0	73.0	
		Temperature	NIPPV	35	37.0	37.0	37.5	0.098
			HFNC	35	36.8	37.5	38.0	
		Irregular ECG rhythm	NIPPV	35	2.0	2.0	2.0	0.167
			HFNC	35	2.0	2.0	2.0	
	Session 3	Respiratory rate	NIPPV	35	21.0	22.0	26.0	0.142
			HFNC	35	20.0	23.0	23.0	
		Heart rate	NIPPV	35	80.0	98.0	110.0	0.018
			HFNC	35	72.0	75.0	98.0	
		Systolic blood pressure	NIPPV	35	95.0	100.0	122.0	0.000
			HFNC	35	121.0	125.0	133.0	
		Diastolic blood pressure	NIPPV	35	55.0	60.0	70.0	0.002
			HFNC	35	67.0	70.0	78.0	
		Temperature	NIPPV	35	36.8	37.0	38.0	0.108
			HFNC	35	36.7	37.0	37.3	
		Irregular ECG rhythm	NIPPV	35	2.0	2.0	2.0	0.090
			HFNC	35	2.0	2.0	2.0	
Day 2	Session 1	Respiratory rate	NIPPV	35	20.0	22.0	25.5	0.007
			HFNC	35	18.0	20.0	21.0	
		Heart rate	NIPPV	35	73.0	87.0	95.0	0.791
			HFNC	35	77.0	85.5	98.0	
		Systolic blood pressure	NIPPV	33	101.0	110.0	125.0	0.001
			HFNC	34	121.0	131.0	134.0	
		Diastolic blood pressure	NIPPV	33	60.0	67.0	78.0	0.078
			HFNC	34	67.0	70.0	78.0	
		Temperature	NIPPV	35	36.7	37.0	37.6	0.486
			HFNC	35	36.7	36.8	37.6	
		Irregular ECG rhythm	NIPPV	35	2.0	2.0	2.0	0.167
			HFNC	35	2.0	2.0	2.0	

	Session 2	Respiratory rate	NIPPV	35	20.0	22.0	23.0	0.002
			HFNC	35	17.0	18.0	20.3	
		Heart rate	NIPPV	35	80.0	88.0	97.0	0.078
			HFNC	35	79.3	85.0	87.0	
		Systolic blood pressure	NIPPV	33	104.5	120.0	130.0	0.000
			HFNC	34	122.0	126.5	136.3	
		Diastolic blood pressure	NIPPV	33	60.0	67.0	78.0	0.031
			HFNC	34	69.3	74.0	78.5	
		Temperature	NIPPV	35	36.8	37.0	37.5	0.655
			HFNC	35	36.8	37.0	37.5	
		Irregular ECG rhythm	NIPPV	35	2.0	2.0	2.0	0.048
			HFNC	35	2.0	2.0	2.0	
	Session 3	Respiratory rate	NIPPV	35	18.0	20.0	20.0	0.000
			HFNC	35	15.0	17.5	18.0	
		Heart rate	NIPPV	35	73.0	87.0	97.5	0.491
			HFNC	35	76.0	82.0	90.0	
		Systolic blood pressure	NIPPV	33	100.5	120.0	131.0	0.001
			HFNC	34	123.0	131.0	141.0	
		Diastolic blood pressure	NIPPV	33	60.0	70.0	78.0	0.065
			HFNC	34	67.0	73.0	80.0	
		Temperature	NIPPV	35	36.8	37.0	37.0	0.629
			HFNC	35	36.7	37.0	37.1	
		Irregular ECG rhythm	NIPPV	35	2.0	2.0	2.0	0.048
			HFNC	35	2.0	2.0	2.0	
Day 3	Session 1	Respiratory rate	NIPPV	35	18.0	18.0	20.0	0.720
			HFNC	35	16.0	18.0	20.0	
		Heart rate	NIPPV	35	78.0	85.0	90.0	0.925
			HFNC	35	76.5	80.0	90.0	
		Systolic blood pressure	NIPPV	31	121.0	123.0	125.0	0.329
			HFNC	34	120.5	126.0	135.0	
		Diastolic blood pressure	NIPPV	31	67.0	76.0	78.0	0.438
			HFNC	34	70.0	70.0	78.0	

		Temperature	NIPPV	35	36.7	37.0	37.6	0.558
			HFNC	35	36.6	37.0	37.0	
		Irregular ECG rhythm	NIPPV	35	2.0	2.0	2.0	0.048
			HFNC	35	2.0	2.0	2.0	
	Session 2	Respiratory rate	NIPPV	35	16.0	19.0	20.0	0.331
			HFNC	35	17.8	18.0	20.0	
		Heart rate	NIPPV	35	75.0	80.0	90.0	0.873
			HFNC	35	73.0	84.0	88.0	
		Systolic blood pressure	NIPPV	31	121.0	124.0	131.0	0.295
			HFNC	34	121.0	128.5	135.0	
		Diastolic blood pressure	NIPPV	31	67.0	70.0	76.0	0.529
			HFNC	34	65.0	70.0	78.0	
		Temperature	NIPPV	35	36.6	36.7	37.0	0.125
			HFNC	35	36.7	36.7	37.0	
		Irregular ECG rhythm	NIPPV	35	2.0	2.0	2.0	0.167
			HFNC	35	2.0	2.0	2.0	
	Session 3	Respiratory rate	NIPPV	35	17.0	17.0	19.0	0.573
			HFNC	35	16.0	17.0	18.0	
		Heart rate	NIPPV	35	77.0	88.0	98.0	0.071
			HFNC	35	73.0	77.0	88.0	
		Systolic blood pressure	NIPPV	31	120.0	127.0	132.0	0.625
			HFNC	34	121.0	131.0	136.3	
		Diastolic blood pressure	NIPPV	31	66.0	76.0	78.0	0.047
			HFNC	34	70.0	73.0	80.0	
		Temperature	NIPPV	35	36.7	37.0	37.0	0.206
			HFNC	35	36.7	36.8	37.0	
		Irregular ECG rhythm	NIPPV	35	2.0	2.0	2.0	0.013
			HFNC	35	2.0	2.0	2.0	

5.2.4 Ventilator settings (Fraction of inspired oxygen)

Ventilator settings like pressure support, positive end expiratory pressure, flow rate, and fraction of inspired oxygen at the baseline and during the treatment days were collected.

When the fraction of inspired oxygen was compared between both treatment methods, there was not statistically significant differences except for Day 2, Session 2 (p value < 0.05). Associations between treatment method and fraction of inspired oxygen are shown in Table 5-13.

Table 5.13: Association between treatment method and fraction of inspired oxygen.

Treatment day	Session	Treatment	n	Q1	Median	Q3	p value
Day 0	Baseline	NIPPV	35	80.0	100.0	100.0	0.160
		HFNC	35	60.0	60.0	80.0	
Day 1	Session 1	NIPPV	35	80.0	80.0	100.0	0.214
		HFNC	35	55.0	80.0	80.0	
	Session 2	NIPPV	35	50.0	80.0	80.0	0.824
		HFNC	24	30.0	40.0	50.0	
	Session 3	NIPPV	35	40.0	60.0	80.0	0.260
		HFNC	24	35.0	40.0	45.0	
Day 2	Session 1	NIPPV	25	45.0	50.0	65.0	0.066
		HFNC	10	30.0	30.0	31.3	
	Session 2	NIPPV	25	40.0	50.0	60.0	0.001
		HFNC	10	35.0	35.0	35.0	
	Session 3	NIPPV	25	35.0	45.0	60.0	-
		HFNC	0	35.0	45.0	60.0	
Day 3	Session 1	NIPPV	9	30.0	45.0	50.0	-
		HFNC	0	30.0	45.0	50.0	
	Session 2	NIPPV	9	30.0	30.0	47.5	-
		HFNC	0	30.0	30.0	45.0	
	Session 3	NIPPV	9	25.0	30.0	40.0	-
		HFNC	0	25.0	30.0	35.0	

5.2.5 Oxygenation status of the patients (Hypothesis H5)

During the treatment period, oxygenation status signs like pH, partial pressure of oxygen (PaO2), partial pressure of carbon dioxide (PaCO2), bicarbonate (HCO3), and oxygen saturation (SpO2) were recorded at baseline and in three sessions during the three treatment days.

In general, the pH and bicarbonate were significantly higher (p value < 0.05) for patients who received HFNC compared to patients who received NIPPV at the baseline and during the 1^{st}, 2^{nd}, and 3^{rd} sessions of day 1, day 2, and day 3 of the treatment. Associations between treatment methods and the oxygenation status are shown in Table 5-14.

Table 5.14: Association between treatment method and oxygenation status.

Treatment day	Session	Oxygenation status	Treatment	n	Q1	Median	Q3	p value
Day 0	Baseline	pH	NIPPV	35	7.3	7.3	7.4	0.000
			HFNC	35	7.3	7.4	7.5	
		Partial pressure of oxygen (PaO2)	NIPPV	35	59.0	60.0	63.0	0.434
			HFNC	35	58.0	60.0	60.0	
		Partial pressure of carbon dioxide (PaCO2)	NIPPV	35	26.0	28.0	28.0	0.990
			HFNC	35	26.0	28.0	29.0	
		Bicarbonate (HCO3)	NIPPV	35	17.0	20.0	22.0	0.023
			HFNC	35	20.0	20.0	22.0	
		Oxygen saturation (SpO2)	NIPPV	35	75.0	80.0	86.0	0.175
			HFNC	35	78.0	86.0	87.0	
		PaO2/FiO2 ratio	NIPPV	35	100.0	119.0	166.0	0.526
			HFNC	35	95.0	116.6	135.0	
Day 1	Session 1	pH	NIPPV	35	7.3	7.4	7.4	0.002
			HFNC	35	7.4	7.4	7.5	
		Partial pressure of oxygen (PaO2)	NIPPV	35	80.0	86.0	113.0	0.316
			HFNC	35	87.0	90.0	105.0	
		Partial pressure of carbon dioxide (PaCO2)	NIPPV	35	26.0	28.0	32.0	0.054
			HFNC	35	28.0	30.0	33.0	
		Bicarbonate (HCO3)	NIPPV	35	16.0	22.0	22.0	0.799
			HFNC	35	20.0	21.0	23.0	
		Oxygen saturation (SpO2)	NIPPV	35	91.0	95.0	97.0	0.929
			HFNC	35	91.0	95.0	98.0	
	Session 2	pH	NIPPV	35	7.4	7.4	367.7	0.158
			HFNC	35	7.4	7.4	7.4	
		Partial pressure of oxygen (PaO2)	NIPPV	35	100.0	110.0	117.0	0.924
			HFNC	35	90.0	100.0	117.0	
		Partial pressure of carbon dioxide (PaCO2)	NIPPV	35	30.0	32.0	35.0	0.803
			HFNC	35	26.0	30.0	32.0	

		Bicarbonate (HCO3)	NIPPV	35	16.5	18.0	25.0	0.192
			HFNC	35	18.0	22.0	23.0	
		Oxygen saturation (SpO2)	NIPPV	35	96.0	98.0	100.0	0.802
			HFNC	35	95.0	98.0	100.0	
	Session 3	pH	NIPPV	35	7.3	7.3	7.4	0.246
			HFNC	35	7.4	7.4	7.5	
		Partial pressure of oxygen (PaO2)	NIPPV	35	98.0	98.0	116.0	0.383
			HFNC	35	100.0	105.0	116.0	
		Partial pressure of carbon dioxide (PaCO2)	NIPPV	35	28.0	30.0	45.0	0.991
			HFNC	35	32.0	32.0	34.0	
		Bicarbonate (HCO3)	NIPPV	35	20.0	22.0	24.0	0.610
			HFNC	35	20.0	21.0	22.0	
		Oxygen saturation (SpO2)	NIPPV	35	94.0	98.0	99.0	0.198
			HFNC	35	96.0	97.0	98.0	
Day 2	Session 1	pH	NIPPV	25	7.3	7.4	7.4	0.000
			HFNC	24	7.4	7.4	7.4	
		Partial pressure of oxygen (PaO2)	NIPPV	25	98.0	100.0	109.0	0.323
			HFNC	24	90.0	116.0	118.0	
		Partial pressure of carbon dioxide (PaCO2)	NIPPV	25	27.0	35.0	42.0	0.342
			HFNC	24	32.0	34.0	35.0	
		Bicarbonate (HCO3)	NIPPV	25	17.0	18.0	21.5	0.014
			HFNC	24	20.0	21.0	23.0	
		Oxygen saturation (SpO2)	NIPPV	25	98.0	100.0	100.0	0.217
			HFNC	24	98.0	99.0	100.0	
	Session 2	pH	NIPPV	25	7.4	7.4	7.4	0.001
			HFNC	24	7.4	7.4	7.4	
		Partial pressure of oxygen (PaO2)	NIPPV	25	105.0	110.0	118.5	0.808
			HFNC	24	100.0	118.0	119.0	
		Partial pressure of carbon dioxide (PaCO2)	NIPPV	25	28.0	35.0	45.0	0.763
			HFNC	24	33.0	34.0	35.0	
		Bicarbonate (HCO3)	NIPPV	25	16.0	19.0	21.5	0.476
			HFNC	24	20.0	21.0	22.0	

		Oxygen saturation (SpO2)	NIPPV	25	99.0	99.0	99.0	0.002
			HFNC	24	99.0	100.0	100.0	
	Session 3	pH	NIPPV	25	7.3	7.4	7.4	0.005
			HFNC	24	7.4	7.4	7.5	
		Partial pressure of oxygen (PaO2)	NIPPV	25	95.0	100.0	116.5	0.528
			HFNC	24	100.0	107.0	112.0	
		Partial pressure of carbon dioxide (PaCO2)	NIPPV	25	31.0	35.0	36.5	0.638
			HFNC	24	33.0	35.0	35.0	
		Bicarbonate (HCO3)	NIPPV	25	18.0	20.0	20.5	0.692
			HFNC	24	20.0	21.0	22.0	
		Oxygen saturation (SpO2)	NIPPV	25	97.0	98.0	99.5	0.002
			HFNC	24	99.0	100.0	100.0	
Day 3	Session 1	pH	NIPPV	9	7.4	7.4	7.4	0.002
			HFNC	11	7.4	7.5	7.5	
		Partial pressure of oxygen (PaO2)	NIPPV	9	109.0	109.0	110.0	0.466
			HFNC	11	98.0	107.0	116.0	
		Partial pressure of carbon dioxide (PaCO2)	NIPPV	9	37.0	40.0	42.0	0.082
			HFNC	11	33.0	35.0	35.0	
		Bicarbonate (HCO3)	NIPPV	9	18.0	18.0	21.0	0.126
			HFNC	11	20.0	20.0	21.0	
		Oxygen saturation (SpO2)	NIPPV	9	97.0	100.0	100.0	0.814
			HFNC	11	98.0	100.0	100.0	
	Session 2	pH	NIPPV	9	7.4	7.4	7.4	0.166
			HFNC	11	7.4	7.4	7.4	
		Partial pressure of oxygen (PaO2)	NIPPV	9	103.0	110.0	110.0	0.019
			HFNC	11	90.0	96.0	103.0	
		Partial pressure of carbon dioxide (PaCO2)	NIPPV	9	37.0	40.0	45.0	0.042
			HFNC	11	34.0	35.0	37.0	
		Bicarbonate (HCO3)	NIPPV	9	16.0	18.0	22.0	0.124
			HFNC	11	21.0	21.0	22.0	
		Oxygen saturation (SpO2)	NIPPV	9	97.0	99.0	100.0	0.293
			HFNC	11	99.0	100.0	100.0	

	Session 3	pH	NIPPV	9	7.4	7.4	7.4	0.336
			HFNC	11	7.4	7.4	7.4	
		Partial pressure of oxygen (PaO2)	NIPPV	9	104.5	110.0	110.0	0.044
			HFNC	11	97.0	100.0	104.0	
		Partial pressure of carbon dioxide (PaCO2)	NIPPV	9	35.0	37.0	38.5	0.728
			HFNC	11	36.0	36.0	38.0	
		Bicarbonate (HCO3)	NIPPV	9	18.0	18.0	23.5	0.457
			HFNC	11	20.0	22.0	23.0	
		Oxygen saturation (SpO2)	NIPPV	9	97.0	100.0	100.0	0.823
			HFNC	11	98.0	100.0	100.0	

5.2.6 Chest X ray during the treatment days (Hypothesis H8)

On day 3, there were more acute respiratory distress syndrome and bilateral pneumonia cases in the group who received NIPPV compared to those who received HFNC treatment (p value = 0.004). The chest X ray findings of patients during the treatment days is shown in Table .

Table 5.15: Chest X ray findings during the treatment days

Treatment day	Chest X ray	NIPPV	HFNC	Chi/Fisher	p-value
Day 1	Unilateral pneumonia	20	14	2.07	0.354
	Lung Atelectasis	11	15		
	Bilateral pneumonia	4	6		
Day 2	Unilateral pneumonia	2	10	8.99	0.061
	Lung Atelectasis	10	8		
	Acute respiratory distress syndrome	3	0		
	Bilateral pneumonia	5	4		
Day 3	Unilateral pneumonia	0	2	20.93	0.004
	Lung Atelectasis	1	1		
	Acute respiratory distress syndrome	7	0		
	Bilateral pneumonia	5	0		

5.2.7 Pain during the treatment days (Hypothesis H3)

During the treatment days, some patients progressed from severe or moderate pain to mild pain/no pain. Stratification of the patients into the different pain categories is shown in Table .

Table 5.16: Pain during the treatment days.

Treatment day	Session	Pain	n	%
Day 1	Session 1	Mild pain	4	5.7
		Moderate pain	32	45.7
		Severe pain	34	48.6
Day 1	Session 2	No pain	4	5.7
		Mild pain	19	27.1
		Moderate pain	19	27.1
		Severe pain	28	40.0
Day 1	Session 3	No pain	8	11.4
		Mild pain	24	34.3
		Moderate pain	17	24.3
		Severe pain	21	30.0
Day 2	Session 1	No pain	19	27.1
		Mild pain	19	27.1
		Moderate pain	22	31.4
		Severe pain	6	8.6
Day 2	Session 2	No pain	25	35.7
		Mild pain	18	25.7
		Moderate pain	18	25.7
		Severe pain	5	7.1
Day 2	Session 3	No pain	35	50.0
		Mild pain	15	21.4
		Moderate pain	10	14.3
		Severe pain	6	8.6
Day 3	Session 1	No pain	52	74.3
		Mild pain	8	11.4
		Moderate pain	2	2.9
		Severe pain	1	1.4
Day 3	Session 2	No pain	55	78.6
		Mild pain	4	5.7
		Moderate pain	3	4.3
		Severe pain	1	1.4
Day 3	Session 3	No pain	55	78.6
		Mild pain	7	10.0
		Severe pain	1	1.4

In general, patients who received NIPPV were more likely (p value < 0.05) to progress from severe pain to moderate and mild pain during the treatment days compare to patients who received HFNC. Associations are shown in Table .

Table 5.17: Association between treatment and pain scores.

Treatment day	Session	Treatment	n	Q1	Median	Q3	p value
Day 0	Baseline	NIPPV	35	7.0	8.0	8.5	0.044
		HFNC	35	7.0	7.0	8.0	
Day 1	Session 1	NIPPV	35	7.0	7.0	8.0	0.000
		HFNC	35	5.0	5.0	6.0	
Day 1	Session 2	NIPPV	35	6.0	7.0	8.0	0.000
		HFNC	35	3.0	3.0	4.0	
Day 1	Session 3	NIPPV	35	5.5	6.0	7.5	0.000
		HFNC	35	0.8	2.0	3.0	
Day 2	Session 1	NIPPV	32	3.5	5.0	6.0	0.000
		HFNC	34	0.0	1.0	2.0	
Day 2	Session 2	NIPPV	32	3.0	4.0	6.0	0.000
		HFNC	34	0.0	0.0	1.3	
Day 2	Session 3	NIPPV	32	0.0	3.0	4.0	0.000
		HFNC	34	0.0	0.0	0.3	
Day 3	Session 1	NIPPV	29	0.0	0.0	1.0	0.123
		HFNC	34	0.0	0.0	0.0	
Day 3	Session 2	NIPPV	29	0.0	0.0	0.5	0.012
		HFNC	34	0.0	0.0	0.0	
Day 3	Session 3	NIPPV	29	0.0	0.0	0.5	0.011
		HFNC	34	0.0	0.0	0.0	

5.2.8 Signs and symptoms during the treatment days

Patients who received NIPPV were more likely (p value < 0.05) to report tachycardia, tachypnea, cyanosis, restlessness, and confusion compared to patients who received HFNC during the treatment days (p value < 0.05). Results are shown in Table 5.18.

Table 5.18: Association between treatment and signs and symptoms.

Treatment day	Session	Signs and symptoms	Presence	NIPPV	HFNC	Chi/Fisher	p-value
Baseline	Baseline	Dyspnea	No	2	1	0.35	0.551
			Yes	33	34		
		Tachycardia	No	10	20	5.83	0.016
			Yes	25	15		
		Tachypnea	No	35	35	-	-
			Yes	35	35		
		Hypertension	No	28	33	3.14	0.076
			Yes	7	2		
		Cyanosis	No	0	2	2.03	0.154
			Yes	35	33		
		Restlessness	No	35	35	-	-
			Yes	35	35		
		Confusion	No	4	2	0.72	0.397
			Yes	31	33		
		Hypotension	No	31	26	2.33	0.127
			Yes	4	9		
Day 1	Session 1	Dyspnea	No	5	12	3.75	0.053
			Yes	30	23		
		Tachycardia	No	13	27	11.27	0.001
			Yes	22	8		
		Tachypnea	No	16	31	14.36	0.000
			Yes	19	4		
		Hypertension	No	24	34	9.53	0.002
			Yes	8	0		
		Cyanosis	No	26	34	6.91	0.009
			Yes	6	0		
		Restlessness	No	28	34	4.46	0.035
			Yes	4	0		
		Confusion	No	28	34	2.30	0.129

			Yes	2	0		
		Hypotension	No	26	34	4.76	0.029
			Yes	4	0		
	Session 2	Dyspnea	No	26	34	4.76	0.029
			Yes	4	0		
		Tachycardia	No	19	21	0.23	0.632
			Yes	16	14		
		Tachypnea	No	18	27	4.97	0.026
			Yes	17	8		
		Hypertension	No	23	27	1.10	0.293
			Yes	12	8		
		Cyanosis	No	29	31	0.01	0.938
			Yes	3	3		
		Restlessness	No	28	33	2.12	0.146
			Yes	4	1		
		Confusion	No	28	34	4.46	0.035
			Yes	4	0		
		Hypotension	No	30	34	-	-
			Yes	30	34		
	Session 3	Dyspnea	No	30	34	-	-
			Yes	30	34		
		Tachycardia	No	30	34	-	-
			Yes	30	34		
		Tachypnea	No	2	7	3.14	0.076
			Yes	33	28		
		Hypertension	No	2	16	14.45	0.000
			Yes	33	19		
		Cyanosis	No	19	29	6.53	0.011
			Yes	16	6		
		Restlessness	No	22	33	9.37	0.002
			Yes	10	1		
		Confusion	No	26	33	4.28	0.039
			Yes	6	1		

		Hypotension	No	28	34	4.46	0.035
			Yes	4	0		
Day 2	Session 1	Dyspnea	No	28	34	2.30	0.129
			Yes	2	0		
		Tachycardia	No	26	34	4.76	0.029
			Yes	4	0		
		Tachypnea	No	26	34	4.76	0.029
			Yes	4	0		
		Hypertension	No	35	33	2.03	0.154
			Yes	0	2		
		Cyanosis	No	33	32	0.21	0.645
			Yes	2	3		
		Restlessness	No	33	34	0.34	0.558
			Yes	2	1		
		Confusion	No	32	32	0.18	0.669
			Yes	3	2		
		Hypotension	No	35	33	1.03	0.310
			Yes	0	1		
	Session 2	Dyspnea	No	35	31	3.18	0.074
			Yes	0	3		
		Tachycardia	No	33	34	-	-
			Yes	33	34		
		Tachypnea	No	33	34	-	-
			Yes	33	34		
		Hypertension	No	33	34	-	-
			Yes	33	34		
		Cyanosis	No	11	34	32.45	0.000
			Yes	24	1		
		Restlessness	No	32	34	1.05	0.307
			Yes	3	1		
		Confusion	No	32	34	1.05	0.307
			Yes	3	1		
		Hypotension	No	32	34	-	-

			Yes	32	34		
	Session 3	Dyspnea	No	30	34	2.16	0.142
			Yes	2	0		
		Tachycardia	No	30	34	2.16	0.142
			Yes	2	0		
		Tachypnea	No	30	34	-	-
			Yes	30	34		
		Hypertension	No	28	34	2.30	0.129
			Yes	2	0		
		Cyanosis	No	28	34	2.30	0.129
			Yes	2	0		
		Restlessness	No	2	26	33.80	0.000
			Yes	33	9		
		Confusion	No	14	34	26.14	0.000
			Yes	21	1		
		Hypotension	No	23	34	11.27	0.001
			Yes	12	1		
Day 3	Session 1	Dyspnea	No	25	35	8.42	0.004
			Yes	7	0		
		Tachycardia	No	26	35	7.10	0.008
			Yes	6	0		
		Tachypnea	No	28	35	4.58	0.032
			Yes	4	0		
		Hypertension	No	28	35	2.37	0.124
			Yes	2	0		
		Cyanosis	No	26	35	4.90	0.027
			Yes	4	0		
		Restlessness	No	24	35	7.59	0.006
			Yes	6	0		
		Confusion	No	14	34	26.14	0.000
			Yes	21	1		
		Hypotension	No	23	34	11.27	0.001
			Yes	12	1		

	Session 2	Dyspnea	No	27	34	6.16	0.013
			Yes	8	1		
		Tachycardia	No	28	35	4.58	0.032
			Yes	4	0		
		Tachypnea	No	28	35	4.58	0.032
			Yes	4	0		
		Hypertension	No	26	35	7.10	0.008
			Yes	6	0		
		Cyanosis	No	28	35	2.37	0.124
			Yes	2	0		
		Restlessness	No	28	35	2.37	0.124
			Yes	2	0		
		Confusion	No	27	35	3.61	0.057
			Yes	3	0		
		Hypotension	No	20	27	3.13	0.077
			Yes	15	8		
	Session 3	Dyspnea	No	19	32	12.03	0.001
			Yes	16	3		
		Tachycardia	No	24	34	9.91	0.002
			Yes	11	1		
		Tachypnea	No	21	35	4.14	0.042
			Yes	11	0		
		Hypertension	No	29	35	3.38	0.066
			Yes	3	0		
		Cyanosis	No	26	35	7.10	0.008
			Yes	6	0		
		Restlessness	No	26	35	4.90	0.027
			Yes	4	0		
		Confusion	No	26	35	4.90	0.027
			Yes	4	0		
		Hypotension	No	26	35	4.90	0.027
			Yes	4	0		

5.2.9 Hospital and ICU stay

The median hospital stay was 10.0 with an IQR of 5.0 days and the median ICU stay was 5.0 with an IQR of 4.0 days. Patients who received NIPPV were more likely (p value = 0.009) to have a longer hospital stay compare to those who received HFNC. Associations between treatment method and length of stay are shown in Table .

Table 5.19: Association between treatment method and length of stay.

Length of stay	Treatment	n	Q1	Median	Q3	p value
ICU	NIPPV	35	5.0	6.0	10.0	0.072
	HFNC	35	4.0	5.0	7.0	
Hospital	NIPPV	35	10.0	12.0	15.0	0.009
	HFNC	35	7.0	8.0	12.0	

5.2.10 Evaluation

The median SOFA score was 9.0 with an IQR of 1.0 and the median APACHE score was 19.0 with an IQR of 7.25. Patients who received NIPPV were more likely (p value = 0.017) to have higher SOFA scores compare to those who received HFNC. Associations between treatment method and SOFA and APACHE scores are shown in Table .

Table 5.20: Association between treatment and SOFA and APACHE scores.

Evaluation	Treatment	n	Q1	Median	Q3	p value
SOFA	NIPPV	35	9.0	10.0	10.0	0.017
	HFNC	35	8.0	9.0	10.0	
APACHE	NIPPV	35	15.0	19.0	23.0	0.255
	HFNC	35	14.0	19.0	21.0	

5.2.11 Outcomes of the treatments in relation to death, complete recovery, receiving vasopressors, and intubation (Hypotheses H1, H2, and H4)

There was no statistical difference between the number of patients who died, completely recovered in 24 h, 48 h, and 72 h in relation to the treatment method. However, patients who received NIPPV were more likely to be intubated (p value = 0.021) and receive vasopressors (p value = 0.002) compared to those who received HFNC. Associations between treatment method and death, complete recovery, receiving vasopressors, and intubation are shown in Table 5.21.

Table 5.21: Association between treatment and death, complete recovery, receiving vasopressors, and intubation.

		Treatment					
Outcome		**NIPPV**	**HFNC**	**Chi/Fisher**	**p value**	**rho**	**p value**
Death	No	31	34	1.91	0.356	-0.17	0.169
	Yes	4	1				
Complete recovery (24 h)	No	28	25	0.70	0.578	0.10	0.410
	Yes	7	10				
Complete recovery (48 h)	No	24	21	0.56	0.618	0.09	0.462
	Yes	11	14				
Complete recovery (72 h)	No	27	26	0.08	1.000	0.03	0.784
	Yes	8	9				
Total recovery (24h, 48h, and 72h)	No	4	1	1.91	0.356	0.17	0.169
	Yes	31	34				
Intubation	No	26	33	5.29	0.045	-0.28	0.021
	Yes	9	2				
Vasopressor	No	17	29	9.13	0.005	-0.36	0.002
	Yes	18	6				
Referred to other treatment	No	35	35	-	-	-	-
	Yes	0	0				

Chapter Six
Discussion

This study was conducted to describe and compare the demographic and clinical variables like health conditions, severity of injury, vital signs, oxygenation status, pain, symptoms, length of hospital and ICU stays, SOFA and APACHE scores, recovery, and death among AHRF patients who were treated with HFNC or NIPPV at the ICU of An-Najah National University Hospital (NNUH) during the period of August 2018 to July 2019. Health conditions of AHRF patients were assessed in different healthcare settings around the globe (Chang et al., 2020; Y. N. Ni et al., 2017; Shen & Zhang, 2017; Zhao et al., 2017). Additionally, recovery and mortality among AHRF patients treated with different methods were also compared elsewhere (Chang et al., 2020; Y. N. Ni et al., 2017; Zhao et al., 2017). To our knowledge, this study is the first to be conducted in Palestine comparing these clinical variables, recovery, and mortality among AHRF patients treated in a Palestinian hospital.

In this study, the AHRF patients included and compared were diverse in relation to their gender, age groups, smoking status, and body characteristics like weight, height, BMI, and comorbidities. The diversified sample should have increased the validity of the findings of this study (Lachin, 2004). The diversity of the clinical variables of the AHRF patients who were included in the study mirrored the clinical diversity of the AHRF patients previously reported in the literature (Y. N. Ni et al., 2017; Zhao et al., 2017).

Findings of this study indicated the majority of the patients were 50 years and older, male, and overweight/obese. These findings were consistent with what was reported on AHRF patients in previous studies (Chang et al., 2020; Tiruvoipati, Lewis, Haji, & Botha, 2010). The majority of the patients who were included in this study had mild impairment in level of consciousness, moderate or severe acute hypoxemic respiratory failure, unilateral pneumonia, severe pain, tachypnea, and restlessness at the baseline.

6.1 Effects of the treatment methods on the clinical variables of the patients

The patients who were allocated to either NIPPV or HFNC were similar in terms of their baseline GCS scores. Additionally, the patients who received NIPPV or HFNC were similar in terms of gender, diabetes, hypertension, smoking, and BMI status. Such similarity might improve the validity of the comparison investigated in this study.

Findings of this study showed that patients who received HFNC reported lower SOFA scores compared to the patients who received NIPPV. Additionally, results of this study indicated that there was no significant difference between the effects of the two methods in terms of patient progress from severe/moderate impairment in level of consciousness to mild impairment in level of consciousness/discharge. These findings were consistent with those reported in previous studies as improved delivery of oxygen can improve progress of patients from severe to mild stages (Frat,

Brugiere, et al., 2015; Frat et al., 2019; Frat, Thille, et al., 2015; Tiruvoipati et al., 2010). Previous studies also showed that HFNC and NIPPV were superior to conventional oxygen therapy in improving patient outcomes (Y. N. Ni et al., 2017; Zhao et al., 2017).

6.2 Effect of the treatment method on the vital signs

Results of this study showed that patients who received HFNC had lower respiratory rates at the baseline and during the 1st, 2nd, and 3rd sessions of day 1 and day 2 of the treatment compared to those who received NIPPV. Previous studies among AHRF patients showed that improved delivery of oxygen improved vital signs and health outcomes of patients (Hernández et al., 2016; Rittayamai, Tscheikuna, Praphruetkit, & Kijpinyochai, 2015). Additionally, patients who received HFNC were more likely to report higher blood pressure and irregular ECG compared to patients who received NIPPV. Findings of this study were consistent with those reported in previous studies in which patients in the ICU were at an increased risk of ECG changes (Routsi, Stanopoulos, Kokkoris, Sideris, & Zakynthinos, 2019). This could be due to the fact that assisted ventilation can increase the intrathoracic pressure. This can reduce the venous return and left ventricular preload and after load. These hemodynamic changes might contribute to the incidence of cardiac arrythmias that can be detected by ECG (Luce, 1984).

Findings of this study showed that the patients who received NIPPV progressed from severe/moderate to mild/no pain compared to patients who received HFNC. Additionally, results of this study showed that patients who received HFNC reported less tachycardia, tachypnea, cyanosis, restlessness, and confusion compared to patients who received NIPPV. Moreover, patients who received NIPPV had lower pressure support and less positive end respiratory pressure compared to patients who received HFNC. These findings were consistent with the nature of the delivery methods used in this study (Antonelli et al., 1998; Chang et al., 2020; Y. N. Ni et al., 2017; Shen & Zhang, 2017; Tiruvoipati et al., 2010; Zhao et al., 2017).

In this study, the patients who received NIPPV had lower pH and bicarbonate levels compared to the patients who received HFNC. These findings are interesting in allowing comparison of the oxygenation status of the patients included and providing more insights into the outcomes of both methods (Ruangsomboon et al., 2020).

6.3 Effects of the treatment methods on the length of hospital and ICU stay, recovery, and death

Findings of this study showed that patients who received HFNC stayed less days in the hospital compared to the patients who received NIPPV. However, there was no significant differences between the length of the ICU stay between both methods. Additionally, results of this study showed that there was no difference in the outcomes of both methods in terms of

death, complete recovery in 24 h, 48 h, and 72 h. However, the patients who received NIPPV were more likely to be intubated and receive vasopressors compared to those who received HFNC. These findings are interesting and consistent with what was previously reported in systematic reviews with meta-analysis of studies comparing both methods (Chang et al., 2020; Y. N. Ni et al., 2017; Shen & Zhang, 2017; Zhao et al., 2017). Although studies have shown that both methods were superior to conventional oxygen therapy, the systematic review with meta-analysis of Ni et al (2018) demonstrated that HFNC could improve prognosis and patient outcomes when it was compared with NIPPV and conventional oxygen therapy (Y. N. Ni et al., 2017).

6.4 Strengths and limitations

There were a number of strengths and limitations associated with this study. The strengths of this study were:

- This study was the first to be conducted among AHRF patients treated in Palestine. Exposing clinical characteristics of patients treated in different healthcare systems, particularly, those in developing countries could be interesting to communicate to the international scientific community.

- Outcomes of two treatment methods: NIPPV and HFNC were compared among AHRF patients. Recently, there has been a growing interest in comparing different methods of treatments in terms of outcomes.

Findings of such studies might help clinicians decide on the best treatment methods for particular patients.

The limitations of this study include:

- The design used in this study was retrospective. Prospective studies are known to produce more reliable findings.
- The sample size in this investigation was limited. Large sample sizes are known to produce more reliable findings.
- Associations between mortality rates and treatment methods were not possible due to the limited sample size.
- This study was a single center study.
- In this study, a third control group was not used.

6.5 Conclusion

Our results indicated that HFNC and NIPPV might be effective in improving prognosis and clinical outcomes of AHRF patients. Both methods were similar in terms of patient progress from severe/moderate impairment in level of consciousness to mild impairment in level of consciousness/discharge, death, ICU length of stay, and complete recovery in 24 h, 48 h, and 72 h. However, patients who received HFNC stayed less days in the hospital compared to the patients who received NIPPV. Findings of this study were comparable to those reported in different

healthcare settings around the world. Future studies are still needed to determine recovery and mortality rates among both treatment methods.

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Appendices

Appendix 1: Data collection sheet

Part I : Demographic data	
Name	
Age	
Sex (female , male)	
History of Diabetes (yes, no)	
History of Hypertension (yes, no)	
History of Smoking (yes, no)	
If Yes, How many cigarette per day	
Diagnosis	
Weight	
Height	
BMI	
Other	

Appendix 2: Glasgow coma scale (GCS)

Glasgow coma scale (GCS)				
	Baseline	**Day 1**	**Day2**	**Day 3**
First Time				
Second Time				
Third Time				

Appendix 3: Observational check list to assess vital signs

	Baseline	**DAY1**			**DAY2**			**DAY3**		
Observation		1st	2nd	3rd	1st	2nd	3rd	1st	2nd	3rd
Respiratory rate										
Heart rate										
Blood Pressure										
Temperature										
ECG sinus (yes, no)										
ECG rhythm (regular , irregular)										

Appendix 4: Checklist for Oxygenation Status (ABGs)

	OXYGENATION STATUS patient on HFNC									
Observation	**Baseline**	**DAY1**			**DAY2**			**DAY3**		
		1st	2nd	3rd	1st	2nd	3rd	1st	2nd	3rd
PH										
PaO2										
PaCO2										
HCO3										
SPO2										
Day 1 (first time)										
Pao2/FIO2										

Appendix 5: Patient on HFNC the ventilator settings

Ventilator setting	Baseline	Day 1			Day 2			Day 3		
		1st	2nd	3 rd	1st	2nd	3 rd	1st	2nd	3 rd
Flow rate										
Fraction of inspired oxygen										

Appendix 6: Patient on NIPV the ventilator siting

Ventilator siting	Baseline	Day 1			Day 2			Day 3		
		1st	2nd	3 rd	1st	2nd	3 rd	1st	2nd	3 rd
Pressure support (Ps)										
Positive end expiratory pressure (PEEP)										
Fraction of inspired oxygen										

Appendix 7: Checklist for Length of Stay

LENGHTH OF STAY	
	Number of Day's
ICU Length of Stay	
Hospital length of stay	.

Appendix 8: Checklist for Chest X ray

CX Ray	Baseline	Day 1	Day 2	Day 3
HFNC				
NIPV				

Appendix 9: Checklist for Pain Assessment

PAIN ASSESSMENT patient												
	Baseline			**DAY1**			**DAY2**			**DAY3**		
Pain (VAS)	1st	2nd	3 rd	1st	2nd	3 rd	1st	2nd	3 rd	1st	2nd	3 rd

Appendix 10: OBSERVATIONAL CHECK LIST TO ASSESS RESPIRATORY STATUS: RESPIRATORY STATUS

- A **score of (0)** mark will be given for each ***normal*** (**Absent**) findings.
- A **score of (1)** marks will be given for each ***altered*** (**Present**) findings.

Observation		ASSESS RESPIRATORY STATUS										
	Baseline			**DAY1**			**DAY2**			**DAY3**		
	1st	2nd	3 rd	1st	2nd	3 rd	1st	2nd	3 rd	1st	2nd	3 rd
Dyspnea												
Tachycardia												
Tachypnea												
Hypertension												

cyanosis												
restlessness,												
confusion,												
Hypotension												

Appendix 11: Main outcomes of patients with AHRF treated with HFNC and NIPV

OUTCOME	HFNC	NIPV
Death		
Complete recovery of respiratory function after 24 hours		
Complete recovery of respiratory function after 48 hours		
Complete recovery of respiratory function after 72 hours		
No recovery of respiratory function, pt. need intubation		
Switch to another device		

Appendix 12: SOFA and APACHE II scores

	SCORE
SOFA Score	
APACHE II Score	

Appendix 13: Use of vasopressor

Use of vasopressor	
Yes	No

جامعة النجاح الوطنية

كلية الدراسات العليا

تأثير قنية الأنف عالية التدفق مقارنة مع التهوية بالضغط الإيجابي لدى المريض المصاب بالفشل التنفسي الناجم عن نقص الأكسجين الحاد

إعداد

إسراء سريس

إشراف

د. عايدة القيسي

د. وائل صدقة

قدمت هذه الاطروحة استكمالاً لمتطلبات الحصول على درجة الماجستير في برنامج تمريض العناية المكثفة، بكلية الدراسات العليا، في جامعة النجاح الوطنية، نابلس–فلسطين.

2021

تأثير قنية الأنف عالية التدفق مقارنة مع التهوية بالضغط الإيجابي لدى المريض المصاب بالفشل التنفسي الناجم عن نقص الأكسجين الحاد

إعداد

إسراء سريس

إشراف

د. عايدة القيسي

د. وائل صدقة

الملخص

الخلفية: الفشل التنفسي الحاد (ARF) هو حالة صحية خطيرة يمكن أن تترافق مع مضاعفات مميتة تتطلب التدخل الطبي الفوري وترتبط بنسبة عالية من 30 ٪ من المرضى الذين تم إدخالهم إلى وحدة العناية المركزة. تُستخدم التهوية غير الباضعة بالضغط الإيجابي (NIPPV) وقنية الأنف عالية التدفق (HFNC) بشكل شائع بين المرضى الذين يعانون من فشل الجهاز التنفسي في وحدة العناية المركزة (ICU). أجريت هذه الدراسة لتقييم آثار NIPPV وHFNC بين المرضى الذين يعانون من فشل تنفسي حاد لنقص تأكسج الدم (AHRF) في وحدة العناية المركزة في مستشفى جامعة النجاح الوطني.

الطريقة: كانت هذه الدراسة عبارة عن دراسة جماعية بأثر رجعي ، حيث تم علاج جميع المرضى الذين يعانون من AHRF باستخدام HFNC و/ أوNIPPV في وحدة العناية المركزة في مستشفى جامعة النجاح الوطني (NNUH) في أغسطس 2018 إلى يوليو 2019. تم استخراج جميع البيانات من السجلات السريرية عبر الإنترنت نظام المستشفى ومن سجلات المرضى.

النتائج: كان متوسط عمر المرضى 52.5 بمعدل معدل ذكاء يبلغ 16.5 عامًا، وكان متوسط عدد السجائر التي يتم تدخينها 25 بمعدل معدل ذكاء 10 يوميًا، وكان متوسط مؤشر كتلة الجسم 25.9 بمعدل معدل ذكاء يبلغ 4.9 كجم/ م 2. من بين المرضى، كان 40 (57.1٪) مصابين بالالتهاب الرئوي و33 (47.1٪) لديهم تعفن الدم. كان المرضى الذين تلقوا NIPPV أصغر سناً

بشكل ملحوظ مقارنة مع أولئك الذين تلقوا HFNC (مربع تشي بيرسون = 8.57، قيمة p = 0.007). كان معدل ضربات القلب والجهاز التنفسي معنويا.

أعلى (قيمة p <0.05) للمرضى الذين تلقوا NIPPV مقارنة بالمرضى الذين تلقوا HFNC في الأساس وخلال الجلسات الأولى والثانية والثالثة من اليوم الأول واليوم الثاني من العلاج. ومع ذلك، كان المرضى الذين تلقوا HFNC أكثر عرضة لارتفاع ضغط الدم وتخطيط القلب غير المنتظم في اليوم 2 واليوم 3 من العلاج (قيمة p <0.05) مقارنة مع أولئك الذين تلقوا NIPPV. عندما تمت مقارنة جزء الأكسجين الملهم بين طريقتي العلاج، لم تكن هناك فروق ذات دلالة إحصائية باستثناء اليوم 2، الجلسة 2 (قيمة p <0.05). بشكل عام، كان الرقم الهيدروجيني والبيكربونات أعلى بشكل ملحوظ (قيمة p <0.05) للمرضى الذين تلقوا HFNC مقارنة بالمرضى الذين تلقوا NIPPV في الأساس وخلال الجلسات الأولى والثانية والثالثة من اليوم الأول واليوم الثاني واليوم 3 من العلاج. في اليوم الثالث، كان هناك متلازمة الضائقة التنفسية الحادة وحالات الالتهاب الرئوي الثنائي في المجموعة التي تلقت NIPPV مقارنة مع أولئك الذين تلقوا العلاج HFNC (القيمة p = 0.004). بشكل عام، كان المرضى الذين تلقوا NIPPV أكثر احتمالًا (قيمة p <0.05) للتقدم من الألم الشديد إلى الألم المعتدل والخفيف خلال أيام العلاج مقارنةً بالمرضى الذين تلقوا HFNC. كان المرضى الذين تلقوا NIPPV أكثر احتمالاً (قيمة p <0.05) للإبلاغ عن تسرع القلب، وتسرع النفس، والزرقة، والأرق، والارتباك مقارنةً بالمرضى الذين تلقوا HFNC خلال أيام العلاج (قيمة p <0.05). كان متوسط الإقامة في المستشفى 10.0 مع معدل الذكاء الذي يبلغ 5.0 أيام ومتوسط الإقامة في وحدة العناية المركزة كان 5.0 بمعدل معدل ذكاء يبلغ 4.0 أيام. كان المرضى الذين تلقوا NIPPV أكثر احتمالا (قيمة p =0.009) للحصول على إقامة أطول في المستشفى مقارنة بأولئك الذين تلقوا HFNC. كان متوسط درجة SOFA 9.0 مع معدل الذكاء 1.0 وكان متوسط درجة APACHE 19.0 مع معدل الذكاء 7.25. كان المرضى الذين تلقوا NIPPV أكثر احتمالًا (قيمة p = 0.017) للحصول على درجات أعلى في SOFA مقارنة بأولئك الذين تلقوا HFNC. لم يكن هناك فرق إحصائي بين عدد المرضى الذين ماتوا وتعافوا تمامًا خلال 24 ساعة و48 ساعة و72 ساعة فيما يتعلق

بطريقة العلاج. ومع ذلك، كان المرضى الذين تلقوا NIPPV أكثر عرضة للتنبيب (قيمة p = 0.021) وتلقي مقابض الأوعية الدموية (قيمة p = 0.002) مقارنة مع أولئك الذين تلقوا HFNC.

الخلاصة: أشارت نتائجنا إلى أن HFNC وNIPPV قد يكونان فعالين في تحسين التشخيص والنتائج السريرية لمرضى AHRF. كانت كلتا الطريقتين متشابهتين من حيث تقدم المريض من إصابة حادة/ معتدلة في الرأس إلى إصابة / إفرازات خفيفة في الرأس، والوفاة، ومدة الإقامة في وحدة العناية المركزة، والتعافي التام في 24 ساعة و48 ساعة و72 ساعة. ومع ذلك، فإن المرضى الذين تلقوا HFNC مكثوا أيامًا أقل في المستشفى مقارنة بالمرضى الذين تلقوا NIPPV. كانت نتائج هذه الدراسة قابلة للمقارنة مع تلك التي تم الإبلاغ عنها في أماكن رعاية صحية مختلفة حول العالم. لا تزال هناك حاجة لدراسات مستقبلية لتحديد معدلات الشفاء والوفيات بين طريقتين العلاج.

الكلمات المفتاحية: فشل تنفسي حاد، التنبيب الرغامي، قنية أنفية عالية التدفق، تهوية بالضغط الإيجابي غير الغازي.