UNIVERSITY OF BIRMINGHAM

Extending the use of non-invasive ventilation in ward-based settings: clinical effectiveness outside COPD

by

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Declaration

I Bandar Faqihi confirm that the work presented in this thesis is my own. Where information has been derived from other sources, I confirm that this has been indicated in the thesis.

Signature:

Date:

Abstract

Introduction: Non-invasive ventilation (NIV) has been regarded as an effective method for avoiding the use of endotracheal intubation (ETI) and decreasing mortality in patients with acute hypercapnic respiratory failure (AHRF). It has been considered as an effective care strategy for many years to treat AHRF patients due to acute exacerbations of chronic obstructive pulmonary disease (AECOPD) in critical care and ward settings. However, the clinical effectiveness of NIV in AHRF patients due to aetiologies other than COPD is still questioned and the use of ward-based NIV is not widely established which limits a hospital's ability to design care pathways. Currently, managing patients who require NIV in a critical care setting is resource intensive and in the current economic climate, where healthcare budgets are increasingly limited, maximizing cost-effectiveness by enhancing ward-based care is important.

Aim: To evaluate the clinical effectiveness of NIV in non-COPD patients with AHRF and the clinical effectiveness of using NIV outside COPD in ward-based settings.

Methods: Firstly, a systematic review was conducted to assess the existing literature regarding the clinical effectiveness of bilevel positive airway pressure (BIPAP) in non-COPD patients with AHRF. Next, a retrospective cohort study to evaluate the success and failure rates and predictors associated with NIV application in the ward-based setting for patients with AHRF unrelated to COPD. Finally, a multi-methods study to understand the healthcare professional perspectives on the use of NIV for respiratory failure outside of critical care

units, how the attitudes have changed after the COVID-19 pandemic, and the future of ward-based NIV.

Results: Existing controlled trials that evaluate the clinical effectiveness of NIV for non-COPD patients with AHRF were small (mainly for acute cardiogenic pulmonary oedema (ACPO)) and lack of robust data. Our cohort demonstrated that obesity-related AHRF was the commonest condition, of all non-COPD conditions, used for-ward-based NIV management with the highest rate of survival to hospital discharge. Age, pneumonia on admission, and pre-NIV pH were identified as important predictors of surviving ward-based NIV treatment. Healthcare providers felt positive regarding ward-based NIV especially for AHRF due to COPD and OHS with limited/uncertain use for other conditions. The pandemic emphasizes the role of ward units in the care of different patient conditions (Covid and non-Covid patients) to relieve the pressure from other units. Healthcare providers support the expansion of designated wards, multidisciplinary staff deployment with proper training and competencies to improve the ward-based NIV practice in the future.

Conclusion: Ward-based NIV for AHRF patients unrelated to COPD may be considered a useful and safe management strategy especially for conditions with promising and positive outcomes like OHS but further future robust studies are required to confirm this. A particular challenge is a process of initiating and expanding the ward-based NIV service by expanding the designated wards capacities with more well-trained multidisciplinary staff deployment.

Acknowledgement

I would like to express gratitude to my primary supervisor Professor Alice M. Turner who provided guidance and expertise in developing every section of this work. I would also like to thank my second supervisors Professor Nicola Gale and Dr Dhruv Parekh who provided me with a lot of valuable advice that helped me to overcome hurdles. Besides my supervisors, I would like to thank everyone who shared knowledge, work, and wisdom with me, which made my progress possible.

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Abbreviations

ABG	Arterial Blood Gases
ACE2	Angiotensin-Converting Enzyme 2
ACPO	Acute Cardiogenic Pulmonary Oedema
AECOPD	Acute Exacerbations of Chronic Obstructive Pulmonary Disease
AHI	Apnoea Hypopnea Index
AHRF	Acute Hypercapnic Respiratory Failure
ALS	Amyotrophic Lateral Sclerosis
ARDS	Acute Respiratory Distress Syndrome
ARF	Acute Respiratory Failure
ATS	American Thoracic Society
BIPAP	Bi-Level Positive Airway Pressure
BMI	Body Mass Index

BP	Blood Pressure
BTS	British Thoracic Society
CAT	COPD Assessment Test score
CCU	Critical Care Unit
CI	Confidence Intervals
CO_2	Carbon Dioxide
COPD	Chronic Obstructive Pulmonary Disease
CoV	Coronavirus
CPAP	Continuous Positive Airway Pressure
CPO	Cardiogenic Pulmonary Oedema
CRF	Chronic Respiratory Failure
CSA	Central Sleep Apnoea
CWD	Chest Wall Deformities

DHI	Dynamic Hyperinflation
ERS	European Respiratory Society
ETI	Endotracheal Intubation
FRC	Functional Residual Capacity
FVC	Forced Vital Capacity
GBS	Guillain–Barré Syndrome
GOLD	Global Initiative for Chronic Obstructive Lung Disease
HDU	High Dependency Unit
HR	Heart Rate
ICU	Intensive Care Unit
IMV	Invasive Mechanical Ventilation
IQR	Inter-Quartile Range
LMICs	Low- and Middle-Income Countries

LOS	Length of Stay
MERS-Cov	Middle East Respiratory Syndrome Coronavirus
MG	Myasthenia Gravis
MI	Myocardial Infarction
mMRC	modified Medical Research Council dyspnoea score
MODS	Multiple Organ Dysfunction Syndromes
MV	Minute Ventilation
NCEPOD	National Confidential Enquiry into Patient Outcome and Death
NIS	Nationwide Inpatient Sample
NIV	Non-Invasive Ventilation
NMD	Neuromuscular Disorders
NPPV	Non-Invasive Positive Pressure Ventilation
O_2	Oxygen

OHS	Obesity Hypoventilation Syndrome
OSA	Obstructive Sleep Apnoea
$PaCo_2$	Arterial Partial Pressure of Carbon Dioxide
PaO_2	Arterial Partial Pressure of Oxygen
PEEPi	Intrinsic Positive End-Expiratory Pressure
PPV	Positive Pressure Ventilators
$Ptcco_2$	Transcutaneous Carbon Dioxide Tension
R0	Transmission Rate
RCT	Randomized Controlled Trials
REM	Rapid Eye Movement
RF	Respiratory Failure
RR	Risk Ratio
SARS-Cov	Severe Acute Respiratory Syndrome Coronavirus

SMA	Spinal Muscular Atrophy
UK	United Kingdom
US	United States
VAP	Ventilator-Associated Pneumonia
VC	Vital Capacity
WHO	World Health Organization
WOB	Work of Breathing

1 INTRODUCTION

1.1 Background

Acute respiratory failure (ARF), which is generally a problem resulting from insufficient gas exchange by the respiratory system (1), is a significant disorder that may require invasive mechanical ventilation (IMV), via endotracheal intubation (ETI) for its management (2). In the 1990s, an international review of IMV utilization, done in Argentina, Brazil, Chile, Spain, Uruguay, Canada, Portugal, and the United States of America, demonstrated that acute respiratory failure was the commonest indication for IMV accounting for more than 65% of ventilated patients (2). Despite the high use of IMV and its survival rates (3), IMV, through ETI, can cause many complications. ETI is associated with ventilator-associated pneumonia (VAP) (4), increasing the mortality rate(4, 5), weaning difficulty from IMV, and increased healthcare costs (5). Therefore, non-invasive ventilation (NIV) has been increasingly used for acutely ill patients. NIV has many advantages including reduction of the risk of infection, a greater degree of patient cooperation and ability to communicate (6), as well as improvement in dyspnoea (7). It is possible for NIV to reach the same physiological outcomes of improved gas exchange and reduced work of breathing in some situations when compared to IMV (8). Moreover, NIV can prevent many side effects related to ETI and IMV such as VAP, upper airway injuries, and excessive sedation, thus NIV can show better clinical outcomes (9).

1.2 Respiratory Failure

1.2.1 Mechanisms, Types, and Causes of Respiratory Failure

The lungs, which support pulmonary gas exchange, and the pump that moves the lungs and facilitates airflow are the two major components of the respiratory system. The pump consists of the inspiratory muscles, which are characterized by the intercostal muscles and the diaphragm, and the expiratory muscles, which are characterized by the abdominal wall muscles. Inspiration is considered an active procedure that creates a negative atmospheric pressure for the pressure gradient that moves air into the lungs. This process takes place by the diaphragm and the intercostal muscles contracting (10, 11). Expiration at rest is a passive procedure that provides the recoil forces, generated by the elastic properties of the chest wall and lungs, which allow the lung volume to return to the functional residual capacity (FRC) (12) (See Figure 1.1). In general, respiratory failure results from lung failure, typically causing hypoxemic respiratory failure (Type I RF), or pump failure typically leading to hypercapnic respiratory failure (Type II RF) (1). Overlap between lung and pump failure may also occur; for example, in chronic obstructive pulmonary disease (COPD) the lungs are damaged, but muscle deconditioning is also recognised, such that both elements may contribute to respiratory failure. “Type I (hypoxemic) respiratory failure is defined as arterial partial pressure of oxygen (PaO_2) less than 8 kPa, or 60 mm Hg, on room air breathing with normal arterial partial pressure of carbon dioxide ($PaCO_2$)” (13). Type II (hypercapnic) respiratory failure, less commonly known as ventilatory failure or pump

failure, is defined as PaO_2 less than 8.0 kPa, or 60 mmHg, with an elevated $PaCO_2$ greater or equal to 6.0 kPa, or 45 mm Hg (13).

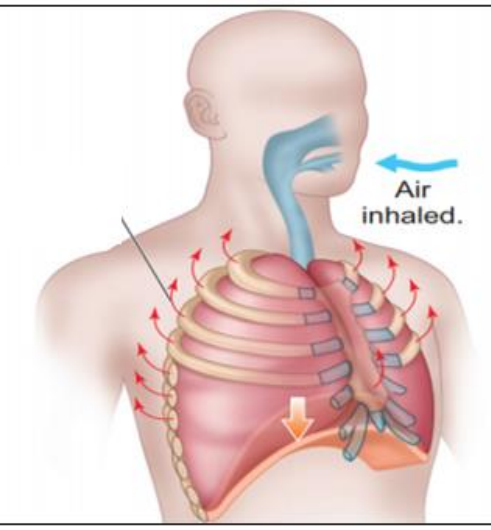
Hypercapnic respiratory failure is a complex clinical condition causing a change of the acid-base balance. Controlling of acid-base balance including the respiratory system, the kidneys, the red blood cells, blood proteins, and the bicarbonate buffering system (See Figures 1.2 and 1.3). Two main approaches are used for acid-base interpretation: (1) a physical-chemical approach; the Strong Ion Difference; or (2) a pathophysiologic approach; the compensation laws. The physio-pathological method is clinically feasible and easier to use as it delivers a quantitative measurement.

The causes of type 1 respiratory failure can result from a ventilation/perfusion (V/Q) mismatch or right-to-left-shunt, whereas the causes of type 2 respiratory failure can result from increased exposure to harmful substances, impaired respiratory control, neurologic disease, or work of breathing (1) (See table 1.1).

Inspiration

Sequence of events

1- Inspiratory muscles contract (diaphragm & intercostal muscles).
2- Thoracic cavity volume increases.
3- Lungs are stretched.
4- Intrapulmonary pressure decreases (-1 mmHg).
5- Air moves into lungs down its pressure gradient until intrapulmonary pressure equal to atmospheric pressure (0 mmHg).



Expiration

Sequence of events

1- Inspiratory muscles relax (diaphragm & intercostal muscles).
2- Thoracic cavity volume decreases.
3- Lungs are recoil passively.
4- Intrapulmonary pressure increases (to +1 mmHg).
5- Air moves out of lungs down its pressure gradient until intrapulmonary pressure equal to atmospheric pressure (0 mmHg).

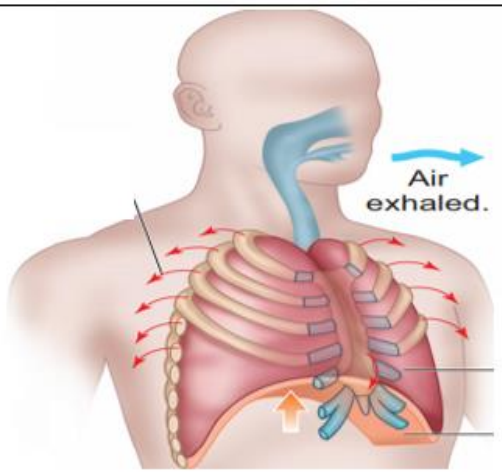


Figure 1.1 The process of inspiration and expiration (12)

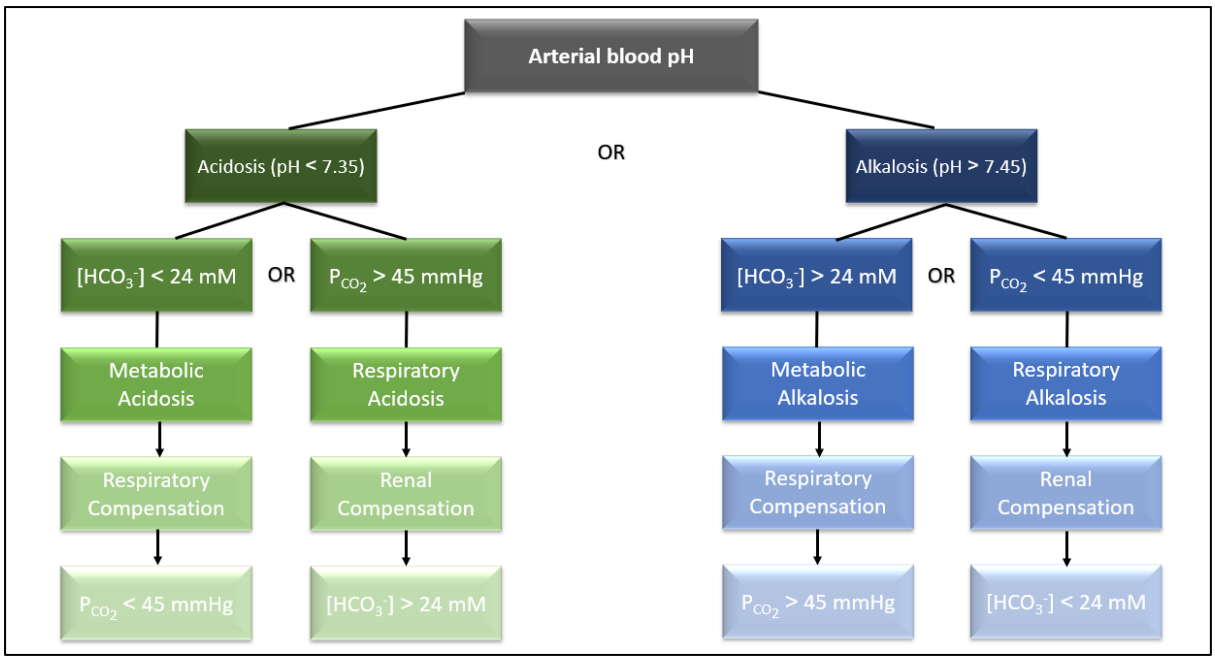


Figure 1.2 Classification, characteristics, and compensation of simple acid–base disorders

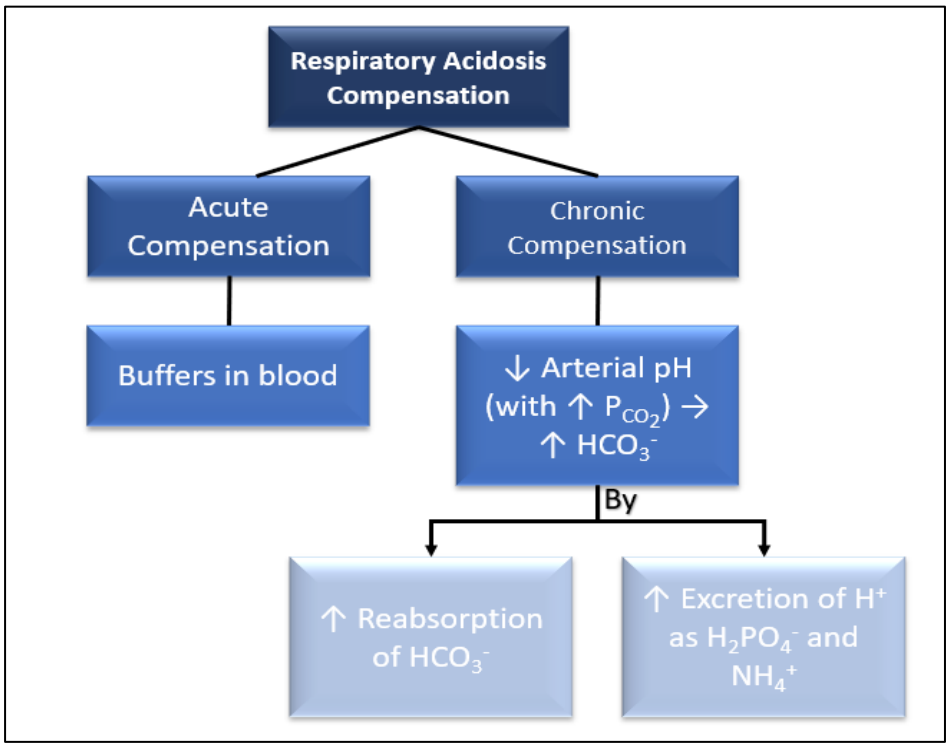


Figure 1.3 Acute and chronic respiratory acidosis compensation

Table 1.1 Causes of Respiratory Failure (1)

Type I (Hypoxemic)	TYPE II (HYPERCAPNIC)			
	Increased Exposure	Impaired Respiratory Control	Neurologic Disease	Work of Breathing
• ARDS • Pulmonary embolism • Pulmonary oedema • Septic shock • Pulmonary infection • Pleural effusion	• Defective CO_2 scrubbers • Occupational exposure • Excess caloric intake	• Drug overdose • Central sleep apnoea • Cheyne-Stokes • Cerebrovascular • accident • Congenital central • hypoventilation • Carotid body resection	• Spinal cord trauma • Amyotrophic lateral • sclerosis • Guillain-Barré • Neuromuscular junction	• COPD • Asthma • Upper airway obstruction • Obesity-hypoventilation • Chest wall disorders • Kyphoscoliosis

1.2.2 Epidemiology of Respiratory Failure

In the United Kingdom, about one-third of admitted patients have respiratory problems, and within these respiratory failure accounts for the most admissions (14). Moreover, approximately 15% of the patients who are admitted to the critical care unit are because of respiratory failure from causes including asthma, chronic obstructive pulmonary disease (COPD), and pneumonia with a relatively high percentage of in-hospital mortality (14-16). In 2003, the incidence of ARF in some European countries was between 77.6 and 88.6 patients per 100,000 patients per year (17). A prospective cohort study done in Brazil that was published in 2011 which assessed the prevalence of ARF concluded that 57% of all patients entering the intensive care units (ICUs) were due to ARF - 49% of the total patients admitted to the ICUs were due to ARF and 8% of all patients developed ARF after admission (18). In a study in the USA, incidence of ARF among hospitalised patients rose at an average annual rate of 11.3% from 1,007,549 in 2001 to 1,917,910 in 2009 (19) (See Figures 1.4 & 1.5). Growth and aging of the US population might explain the increase of the incidence of ARF, as age-adjusted population rate increased by 56% from 2001 to 2009. Additionally, and as the author stated, “the Nationwide Inpatient Sample (NIS) captures data on hospital discharges and not individual patients” which may record patient who may have had multiple admissions.

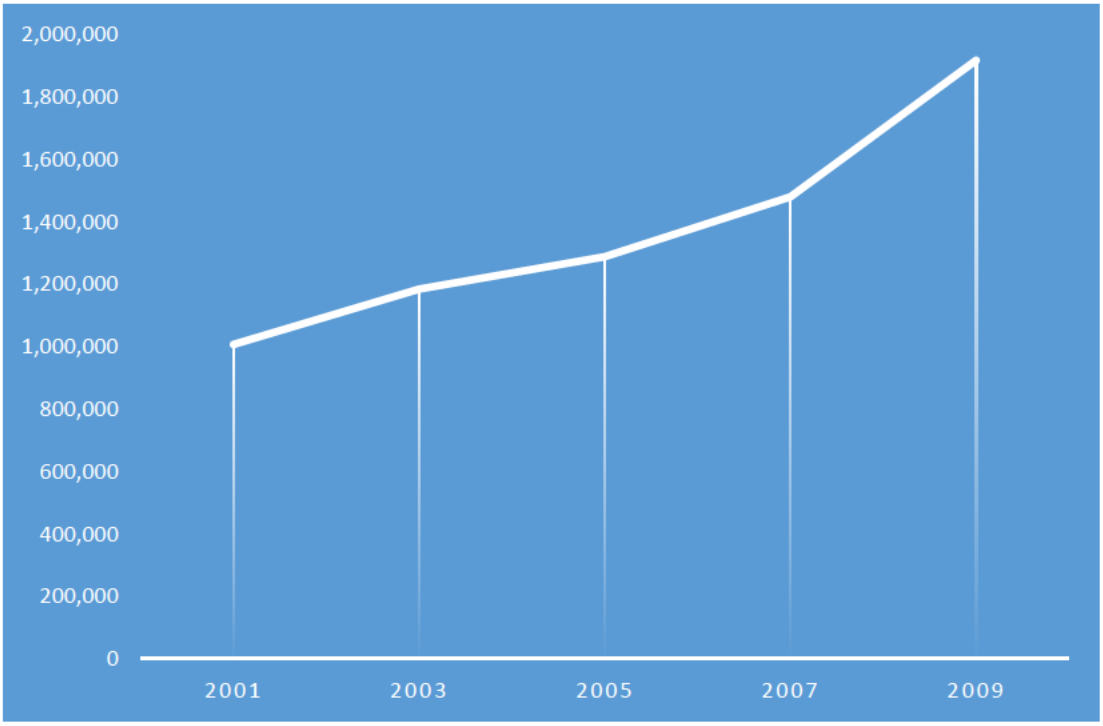


Figure 1.4 Numbers of ARF cases in the United States (19)

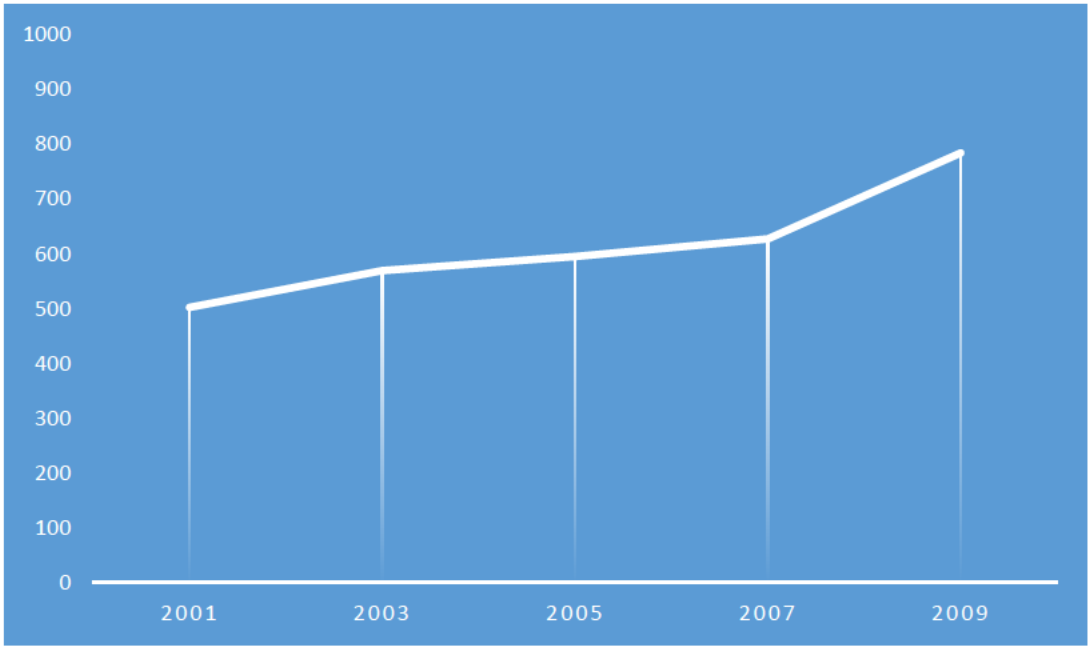


Figure 1.5 Cases of ARF per 100,000 population (19)

1.2.3 Acute and Chronic Respiratory Failure

The main role of the respiratory system is maintaining normal gas exchange, normal oxygen (O_2) delivery and carbon dioxide (CO_2) removal from the blood and tissues. The parenchyma, airways, pulmonary vasculature, and respiratory muscles are the four main components of the respiratory system (20) (See Figure 1.6) and impaired function of any of these four components can cause respiratory failure (RF) (21). Therefore, RF is defined as the "inability to maintain either the normal O_2 delivery and/or the normal CO_2 removal from the tissues" (22). Depending on the speed of onset, RF can be an acute respiratory failure (ARF) or chronic respiratory failure (CRF). ARF is a sudden onset, from hour to days, of respiratory system dysfunction and results in abnormal gas exchange and a change of the patient's baseline condition; sudden oxygenation and/or ventilation failure (23). CRF is a slowly progressive (from days to months) form of respiratory system dysfunction that is caused by a number of underlying conditions and it is generally characterized by low oxygen levels, and (in the case of type 2 CRF) metabolic compensation with a normal to near normal pH and elevated HCO_3 levels (24).

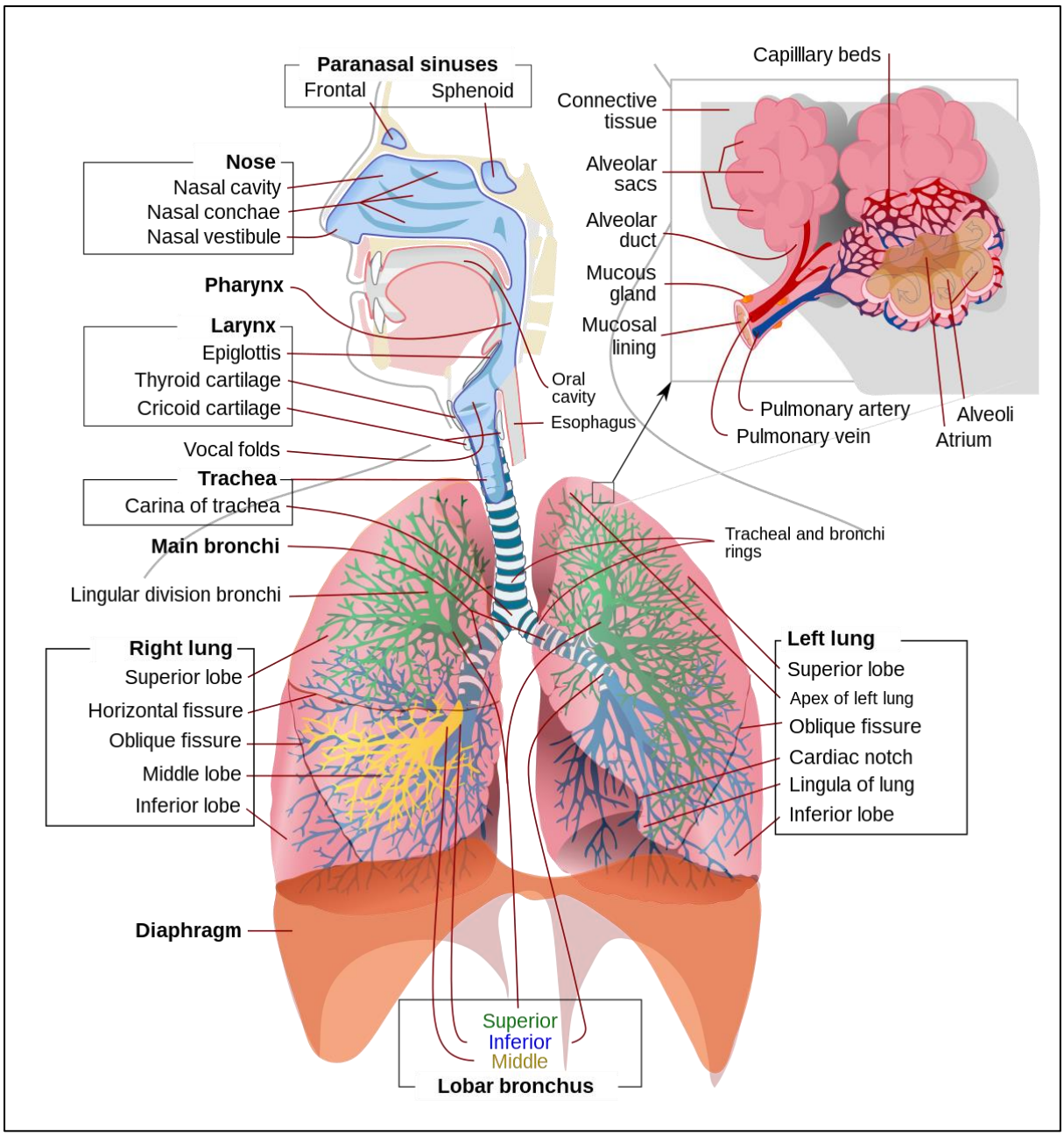


Figure 1.6 Respiratory System (20)

1.2.4 Common Conditions causing Hypercapnic Respiratory Failure

The aetiology that leads to ARF differs between underlying diagnosis and realizing the effect of the changes in physiology is essential for successful NIV treatment.

1.2.4.1 Chronic Obstructive Pulmonary Disease (COPD)

COPD is a chronic inflammatory lung disease that cause expiratory airflow limitation and thereby causes physiological ventilatory dysfunction (25). COPD is diagnosed by pulmonary function testing, when the FEV1/FVC ratio is <0.70, and less than the lower limit of normal for age, after a bronchodilator. In addition, COPD severity classification depend on the FEV1 reduction and compared to predicted values derived from factors which are height, gender, age. The Global Initiative for Chronic Obstructive Lung Disease (GOLD) system categorises COPD severity for patients with FEV1/FVC <0.70 into mild, moderate, severe, very severe (25) (See Table 1.2), though they also use a classification system based on symptoms and exacerbation rate (A, B, C, and D) (26) (See figure 1.7). Emphysema, the loss of elastic tissue support for small airways, and bronchitis, irreversible structural bronchial airway remodelling, are the most common pathologies caused by chronic airway inflammation. In emphysema, elastin breakdown and loss of alveolar integrity are the outcomes of the inflammatory responses. In chronic bronchitis, dysfunction of cilia and elevation of goblet cell size and number are the outcomes of the inflammatory changes which will lead to excessive mucus secretion (27). These changes, combined with

bronchospasm, increase airway resistance, and generate expiratory airflow limitation that leads to hyperinflation caused by incomplete expiration (28) (See Figure 1.8).

Dynamic hyperinflation (DHI) is a condition which occurs when the hyperinflation is exacerbated during times of increased demanding of minute ventilation (MV), like exercise or exacerbation (29-31). DHI generates an intrinsic positive end-expiratory pressure (PEEPi) which elevates the work of breathing (WOB), and thereby respiratory muscle fatigue may result (31). Moreover, inspiratory muscles, mainly the diaphragm, are affected by hyperinflated lungs, which reduce their load-tension capacity. Muscles are also influenced chronically through malnutrition, hypoxia, and steroid use, all of which may cause functional deterioration of muscle tissue (32).

Table 1.2 Classification of severity of COPD by spirometry based on post-bronchodilator FEV1 (25)

GOLD	Class	FEV1
GOLD 1	**Mild**	FEV1≥ 80% predicted
GOLD 2	**Moderate**	50% ≤ FEV1 < 80% predicted
GOLD 3	**Severe**	30% ≤ FEV1 < 50% predicted
GOLD 4	**Very Severe**	FEV1 <30% predicted

COPD: Chronic Obstructive Pulmonary Disease, **GOLD**: Global Initiative for Chronic Obstructive Lung Disease

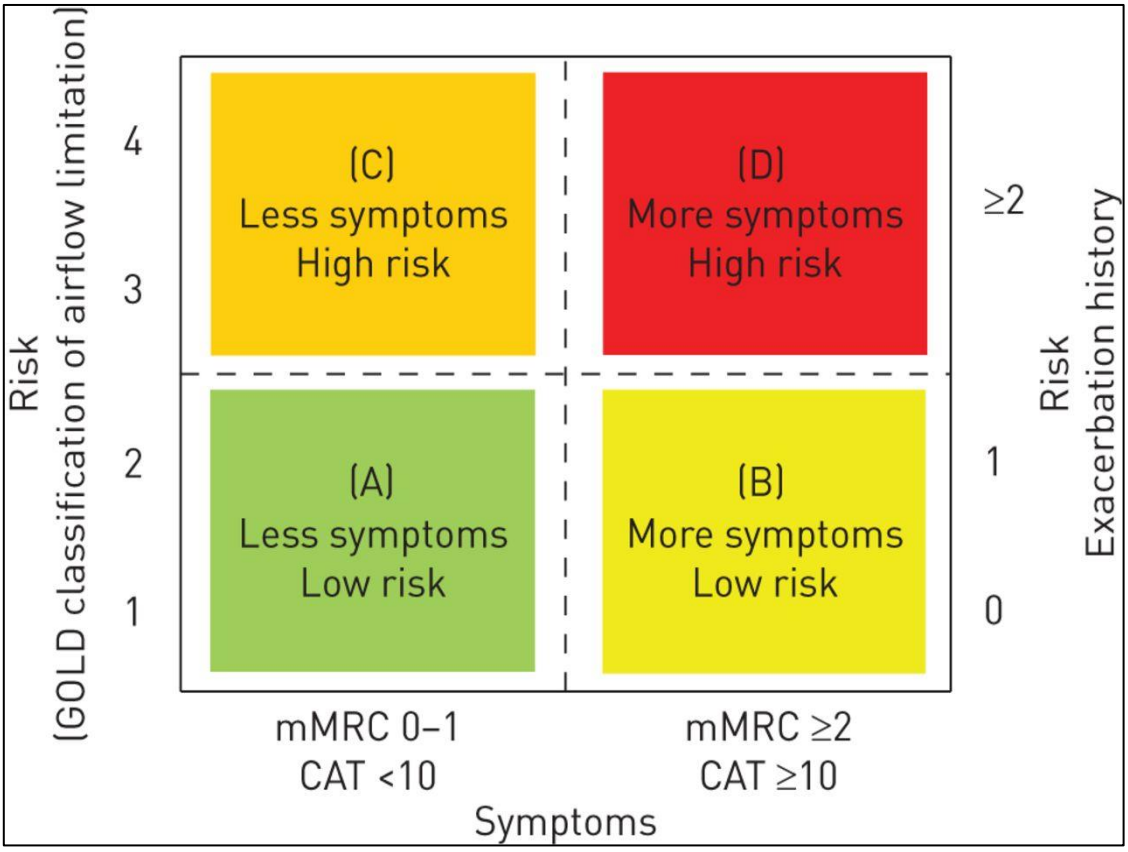


Figure 1.7 Four patient categories resulting from the application of the GOLD assessment proposal (26)

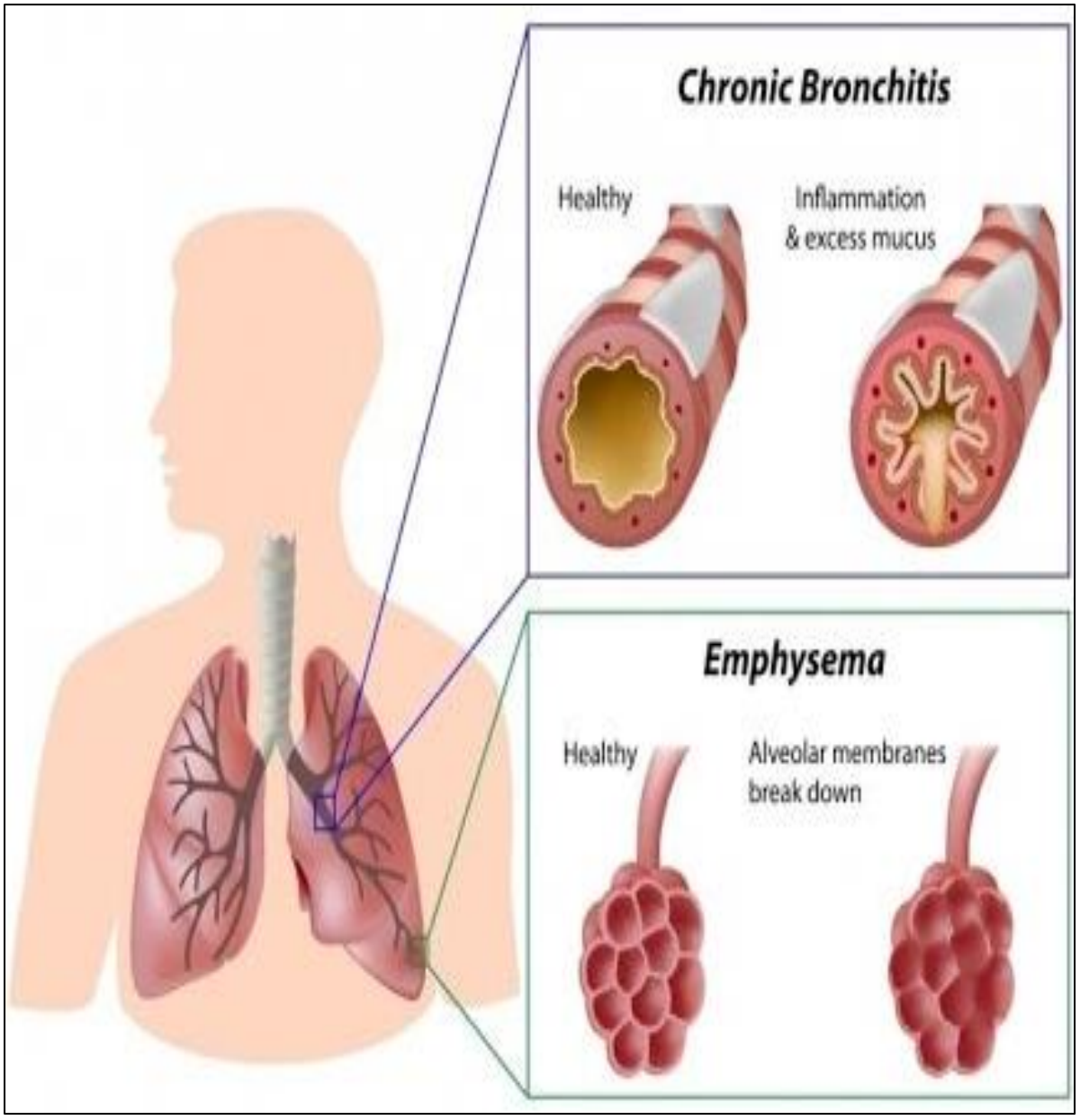


Figure 1.8 Chronic Obstructive Pulmonary Disease (COPD) (28)

1.2.4.2 Obesity Hypoventilation Syndrome (OHS)

OHS is the combination of daytime alveolar hypoventilation (daytime PCO_2 > 6 kPa), obesity (BMI > 30 kg/m^2), and sleep disordered breathing (33). Obesity increases work of breathing (WOB) and impairs lung mechanics. As in CWD, OHS patients have a reduction in lung compliance and breathe at low lung volumes (34). As in COPD, OHS patients have high airway resistance that can lead to expiratory flow limitation and high inspiratory thresholds (35, 36). Moreover, peripheral lung unit collapse occurs leading to V/Q mismatch that may be worsened by a supine position. In addition, sleep disordered breathing, especially obstructive sleep apnoea (OSA), is common in OHS (37). Sleep-disordered breathing is defined as respiration abnormalities that occur during sleep. It includes obstructive sleep apnoea (OSA), central sleep apnoea (CSA), and sleep-related hypoventilation disorders. OSA is the commonest condition of sleep-disordered breathing, and its severity is classified based on the Apnoea Hypopnea Index (AHI) (38) (See Table 1.3). Almost 90% of OHS patients have OSA with AHI ⩾5 events per hour and 70% of patients have OSA with AHI ⩾30 events per hour (39). The European Respiratory Society task force has recommended severity grading for OHS (40) (See Table 1.4).

Overweight and obesity are a global epidemic that influences many people around the world (41, 42). The world health organization (WHO) stated that worldwide obesity has nearly tripled since 1975 with 13% obesity of the global population (43). In the United Kingdom, the WHO summarised that almost two-thirds of the adult population were overweight and almost one-fourth were obese (44). With this epidemic, the prevalence of

OHS is likely to increase. OHS prevalence is as follows: 0.3–0.4% in the global population, 10–20% in patients with sleep-related breathing disorders, and in almost half of admitted patients with BMI > 50 kg/m2 (33, 45).

The pathophysiology of OHS consists mainly of three major mechanisms as follows: 1) changes in the respiratory system caused by obesity; 2) changes in the respiratory drive and 3) breathing abnormalities during sleep (46) (See Figure 1.9).

Changes in the respiratory system caused by obesity

Fat deposits in the abdomen and the chest have the impact on decreasing the lung volume, affecting the diaphragm motion, decreasing lung compliance, and increasing the lower airway resistance (47). Intrinsic positive end-expiratory pressure (PEEPi) will be created by as a result of premature airway closure, with formation of atelectasis (48). Weakness in respiratory muscles will happen due to increase in the work of breathing and impairment in respiratory mechanics.

Changes in the respiratory drive

As a result of the obesity and its following abnormal respiratory workload, respiratory drive will be stimulated to compensate and therefore the obese patient initially remains in eucapnia status; a normal concentration of CO_2 in the blood. Failure to maintain the increase in respiratory drive, hypoventilation will develop. The hypoventilation occurs initially during the rapid eye movement (REM) stage during sleep which will make a

generalised muscle atonia that will affect the normal ventilation by affecting the diaphragm role and reducing the central drive. The repetition of hypoventilation depresses the respiratory centres and causes daytime hypercapnia and obesity hypoventilation syndrome (40).

Breathing abnormalities during sleep

The negative impact of the physiological changes in obese patients is increased during supine position (during sleep). During sleep, these changes (e.g., fat depositions and reduced lung volume, and fluids shifted from lower extremities to the neck) will narrow the upper airway and increase the incidence of airway closure and causes hypercapnia (49). Recurrent high CO_2 during sleep will cause a daytime hypoventilation (50).

Table 1.3 Classification of severity of OSA (38)

Class	AHI
None/Minimal	AHI < 5 per hour
Mild	AHI ≥ 5, but < 15 per hour
Moderate	AHI ≥ 15, but < 30 per hour
Severe	AHI ≥ 30 per hour

AHI: Apnoea Hypopnea Index

Table 1.4 Staging of hypoventilation in obesity (40)

0	At risk	BMI >30 kg·m−2	OSA	No hypercapnia
I	Obesity-associated sleep hypoventilation	BMI >30 kg·m^{-2}	OSA/hypoventilation during sleep	Intermittent hypercapnia during sleep, full recovery during sleep ($PaCO_2$ or $PtcCO_2$ morning∼evening) Serum bicarbonate <27 mmol·L^{-1} during wake
II	Obesity-associated sleep hypoventilation	BMI >30 kg·m^{-2}	OSA/hypoventilation during sleep	Intermittent hypercapnia during sleep ($PaCO_2$ or $PtcCO_2$ morning > evening) Serum bicarbonate ⩾27 mmol·L^{-1} during wake Bicarbonate increased during day
III	Obesity hypoventilation	BMI >30 kg·m^{-2}	OSA/hypoventilation during sleep	Sustained hypercapnia (PCO_2 >45 mmHg) while awake
IV	Obesity hypoventilation syndrome	BMI >30 kg·m^{-2}	OSA/hypoventilation during sleep	Sustained hypercapnia while awake Cardiometabolic comorbidities

BMI: body mass index; **OSA**: obstructive sleep apnoea; **$PaCO_2$**: arterial carbon dioxide tension; **$PtcCO_2$**: transcutaneous carbon dioxide tension; **PCO_2**: carbon dioxide tension.

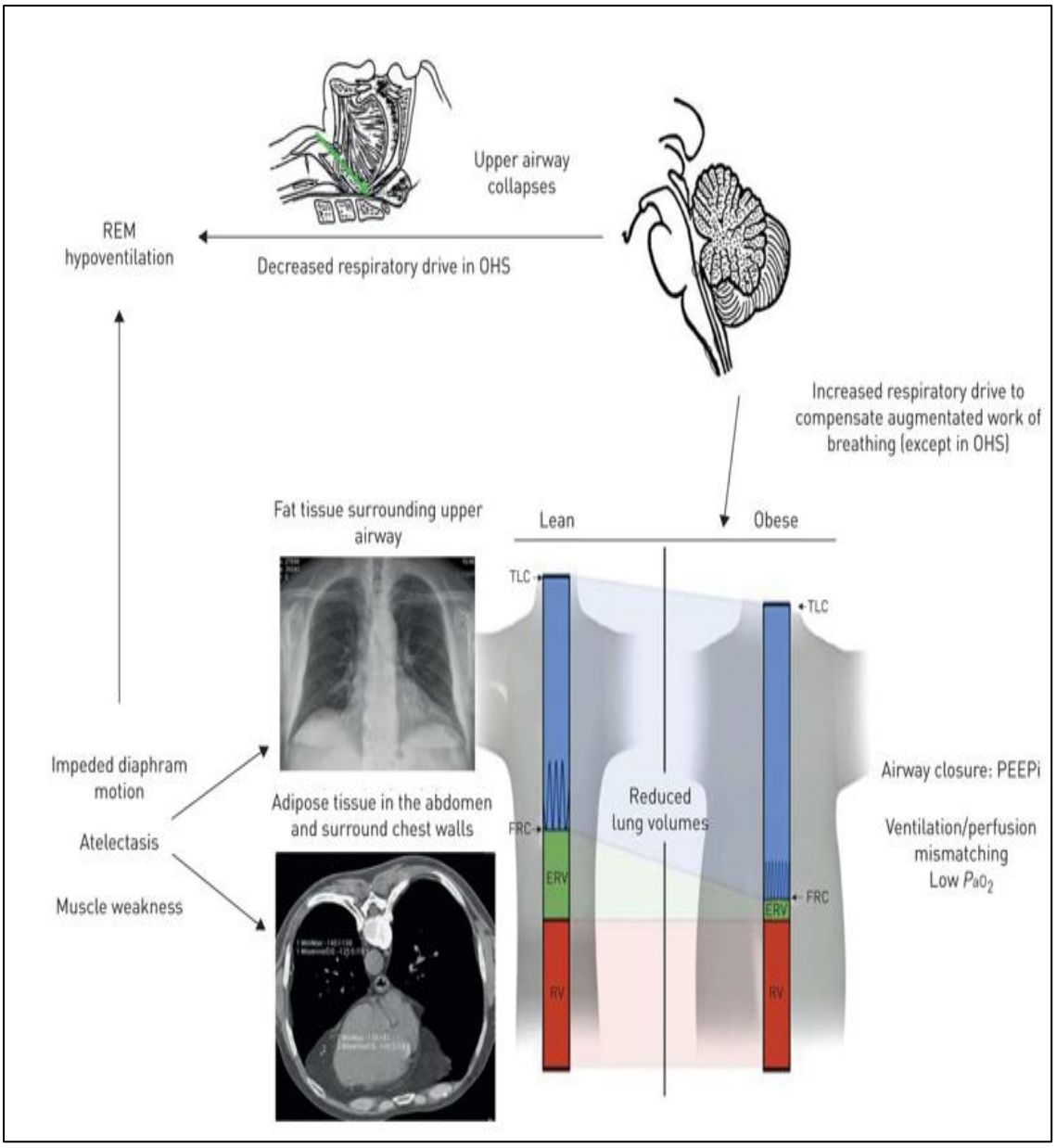


Figure 1.9 Pathophysiology of Obesity Hypoventilation Syndrome (OHS) (46)

1.2.4.3 Cardiogenic Pulmonary Oedema (CPO)

Cardiogenic pulmonary oedema, also called hydrostatic pulmonary oedema, is one of the common causes of acute respiratory failure. It is the result of elevation of venous pressure leading to clinical development of dyspnoea and fluid accumulation within the lungs' alveolar and/or interstitial spaces. Under normal situations, the alveolar membrane is permeable to very small "solutes" as generally the alveolar pressure is higher than interstitial pressure, this change prevents additional alveolar fluid accumulation. In contrast, when the venous hydrostatic pressure increases over the defence mechanisms in the lung, it increases within the lung's interstitial spaces, and alveolar fluid develops. This mechanism is supported by the findings of Conhaim et al who demonstrated that increasing in interstitial fluid pressure contributes to more alveolar fluids its associated respiratory bronchioles and alveolar ducts (51). CPO commonly occurs in clinical practice when heart failure occurs, either acutely, such as in the case of a myocardial infarction, or chronically when the ejection fraction from the left ventricle is reduced (typically by chronic ischaemic heart disease) (52) (See Figure 1.10).

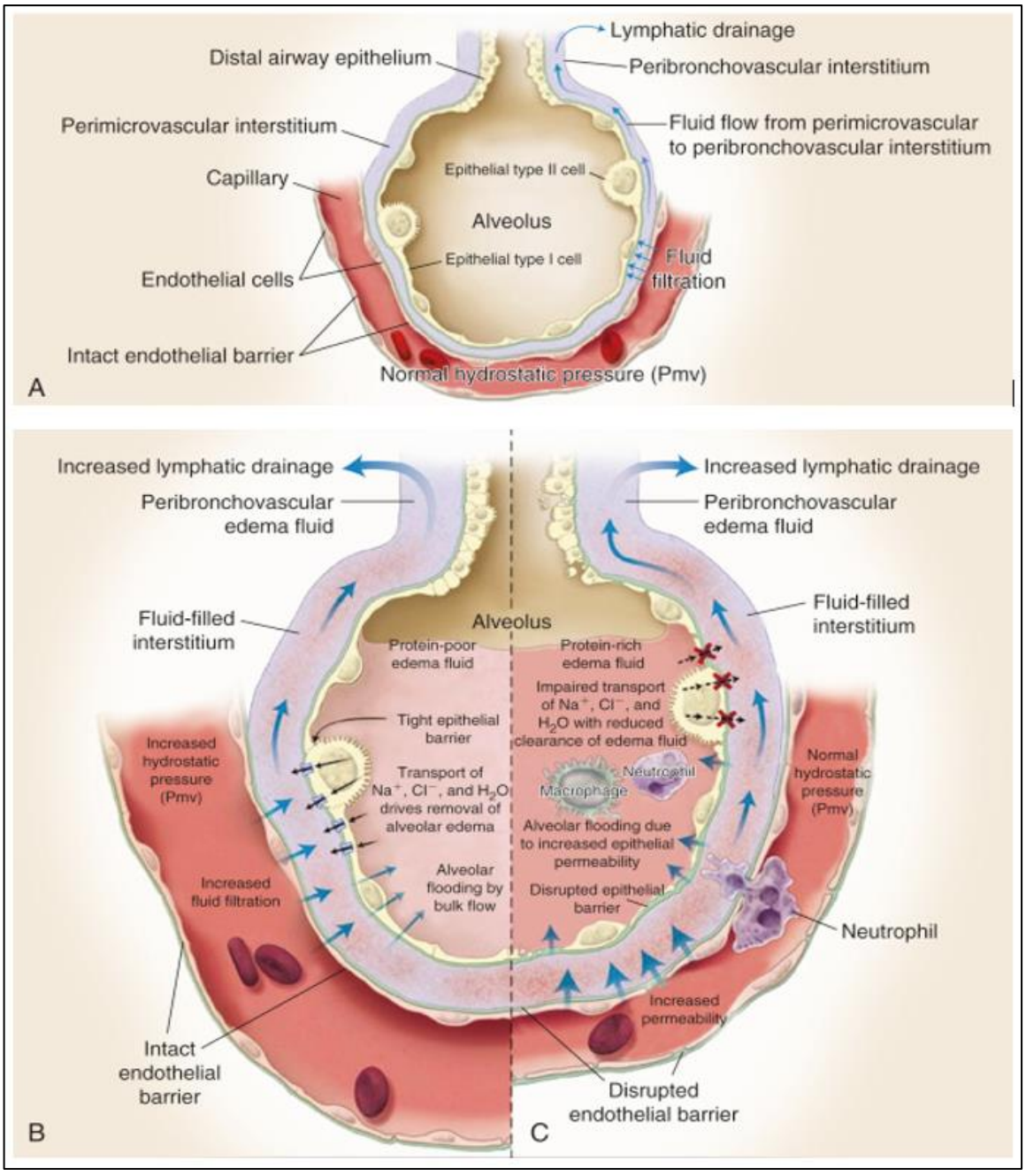


Figure 1.10 (A) Normal Lung, (B) Cardiogenic Pulmonary Oedema, (C) Non-cardiogenic Pulmonary Oedema (52)

1.2.4.4 Neuromuscular Disorders (NMD)

Muscle weakness is the main aspect in the pathophysiology of hypercapnic respiratory failure in NMD. Inspiratory, expiratory, and upper airway muscles are the main muscles in which if weakness arises, it leads to failure in ventilation, airway clearance, and airway protection (53). It also can lead to respiratory infection, with bronchial mucous plugging, that may cause further muscle weakness and reduction in vital capacity (VC) (54, 55). This pathophysiology (increasing load, muscle weakness, and reduction in VC) causes hypoventilation and consequently AHRF, though usually this occurs on a background of chronic deterioration, and might more accurately be called acute on chronic RF. Examples of NMD which cause chronic type 2 RF, and thus potentially AHRF as well are Motor Neurone Disease (e.g., Amyotrophic lateral sclerosis (ALS)), and Muscular dystrophy (e.g., Duchenne).

1.2.4.5 Chest Wall Deformities (CWD)

Chest deformities, like Kyphoscoliosis, generate change in respiratory mechanics. This change in lung mechanics may cause reduce in lung compliance, increase in thoracic impedance, and higher muscle loading and muscle fatigue that leads to hypoventilation and thereby respiratory failure (56). Kyphoscoliosis may be congenital or acquired; a common cause of acquired kyphosis in the UK is osteoporosis of the spine, which generally occurs in older people and is a known co-morbidity in COPD.

1.3 Non-Invasive Ventilation

Non-invasive ventilation (NIV) is a way of delivering ventilatory support without utilizing invasive tools like endotracheal tube (ETT) or tracheostomy tube (1, 57). The evolution of ventilatory support started in 1920s as the first experiment to support patients with breathing disorder came with the introduction of the “iron lung” (58-61). Thereafter, in the 1950s, medicine developed more in various areas: 1) shifting from home medical activities to hospitals; 2) more understanding of the body physiology (including respiratory physiology) and its abnormal conditions; 3) creating the first ICU with new technologies and devices (62). The development of mechanical ventilation in its modern form (positive pressure) was encouraged by studies done in Denmark, and the United States during the polio epidemics that proved its efficacy in saving lives in acute conditions and in apnoeic patients (63-66). Later, mechanical ventilators changed rapidly to become more effective and more advanced in terms of the new modes of support. From that time, it also became apparent that invasive mechanical ventilation is associated with complications (67-71) affecting the patients – this in turn led to led to an interest in less aggressive (i.e., non-invasive) ventilatory support, which might have potential for fewer complications.

NIV, in a non-invasive positive pressure ventilation (NPPV) form, was first used in 1780 as a way of resuscitation by using a bag and mask (72). In 1947, the use of NPPV started to spread clinically by using intermittent positive pressure breathing to deliver aerosolized medications. However, in the mid-1980s, there was a significant decline in using intermittent positive pressure breathing after the advantages of using aerosol medication

delivery with a small volume nebulizer (72, 73). Around that time, NIV was used in different clinical conditions. For instance, nasal mask CPAP was recommended as a treatment for patients with obstructive sleep apnoea (OSA) (74), and nasal mask with positive pressure ventilators (PPV) was used for patients with neuromuscular disorders (75). After the successful application of nasal mask CPAP in obstructive sleep apnoea, there was a new interest of improving patient interfaces. This has started to avoid IMV complications and to meet the patients desire if they refuse to be intubated (76). In 1989, a renewal of interest in NIV began after positive findings of utilizing NPPV in clinical settings; it successfully supported 8 out of 10 patients with ARF (77). From that time, and for the past two decades, NIV has been widely used to treat different clinical conditions as an effective tool to avoid the need for ETI and its complications.

ARF leads to failure in gas exchange that requires ventilatory support. In severe cases, IMV is used for ARF management, which can cause many complications for the patients. Therefore, the goals of using NIV are to:

- Improve gas exchange.
- Avoid intubation.
- Decrease mortality.
- Decrease length of time on mechanical ventilation.
- Decrease length of hospitalization.
- Decrease the incidence of VAP.

- Improve patient-ventilator asynchrony.
- Improve mobility.

Generally, in the acute setting, NIV is used to maintain gas exchange, correct rapid shallow breathing, increasing minute ventilation (MV), by increasing tidal volume (Vt), unloading respiratory muscles, and thereby decreasing WOB, respiratory rate (RR), and dyspnoea (78-80). Typical indications and contraindications for NIV are shown in table 1.5, and predictors of NIV success in acute care settings in table 1.6.

Table 1.5 Indications and contraindications for NIV (73)

Indications for NIV	*At least two or more of the following factors should be present:* Respiratory rate > 25 breaths/min Moderate to severe acidosis: pH <7.35; $PaCO_2$ > 45 mm Hg Use of accessory muscles Moderate to severe dyspnoea Paradoxical breathing
Contraindications for NIV	Respiratory arrest Cardiac arrest Hemodynamic instability Inability to protect the airway/ high risk of aspiration Upper airway obstruction Excessive amount of secretions/ inability to clear secretions Inability to use non-invasive interface due to facial burns or trauma Lack of patient cooperation

Table 1.6 Predictors of NIV success in acute care setting (81)

Predictors of NIV success	Minimal air leak Respiratory acidosis ($PaCO_2$ > 45 mm Hg but <92 mm Hg) pH <7.35 but >7.22 Improvement in gas exchange within 30 minutes to 120 minutes of initiation Improvement in respiratory rate and heart rate Low severity of illness

1.3.1 Types and modes of NIV

NIV is classified into negative pressure NIV and positive pressure NIV. Negative pressure NIV was used in the first half of the 20th century by using the iron lung (82). Positive pressure NIV delivers positive pressure through different types of interfaces such as nasal mask, nasal pillow, oronasal mask, full face mask, or Helmet. These are illustrated in figure 1.11. There are different modes of delivering the positive pressure to a patient like continuous positive airway pressure (CPAP), and bi-level positive airway pressure (BIPAP). CPAP is a mode of non-invasive ventilatory support that provides a constant positive pressure to the patient. CPAP improves the lungs by reducing the work of breathing (WOB), improving lung compliance, recruiting atelectatic alveoli, and improving hemodynamic by reducing preload and afterload (83-85).

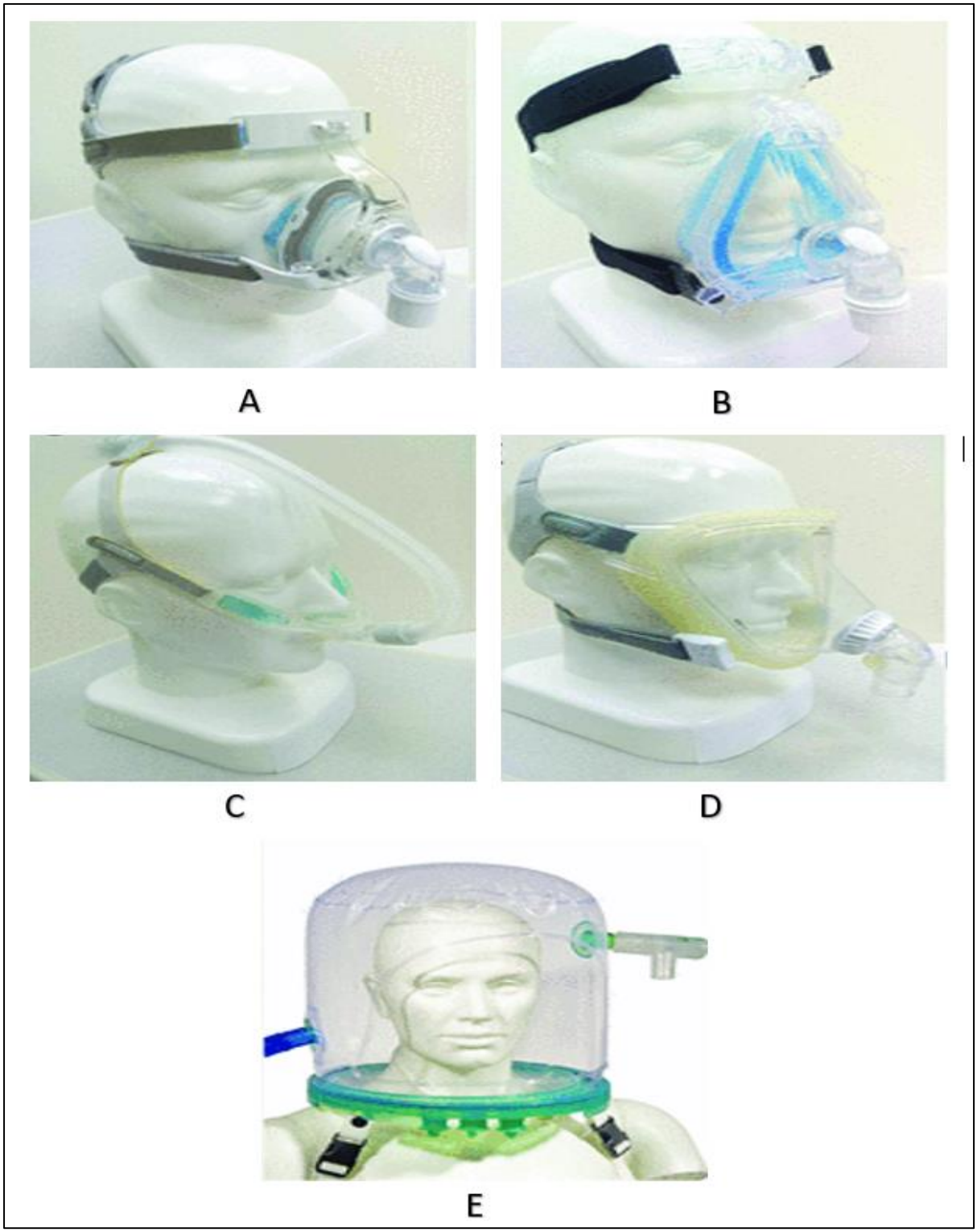


Figure 1.11 Types of NIV interfaces: (A) Nasal Mask, (B) Oro-nasal Mask, (C) Nasal Pillows, (D) Total Face Mask, (E) Helmet (86)

1.3.2 Bi-level positive airway pressure (BIPAP)

BIPAP is a mode of non-invasive ventilatory support with freedom of spontaneous breathing on two positive pressure levels; inspiratory positive airway pressure (IPAP) and an expiratory positive airway pressure (EPAP) (87). In 1988, Professor Benzer and his group presented BIPAP as a mode of ventilation based on their theory of alternating PEEP levels (88). In 1989, M. Baum and H. Benzer published a new approach to ventilatory technique by introducing “Biphasic Positive Airway Pressure” as a mode of ventilation in the Evita ventilator (87). Essentially, BIPAP is a CPAP system with time-cycled alters between two different pressure levels (89) (See figure 1.12). The advantages of BIPAP are improving the gas exchange; improving O_2 and clearing CO_2 and facilitating the exhalation period; exhaling against a lower pressure. BIPAP is commonly used clinically for hypercapnic respiratory failure as it improves the oxygenation and the ventilation whereas CPAP has often been preferred for hypoxemic respiratory failure as it improves the oxygenation alone.

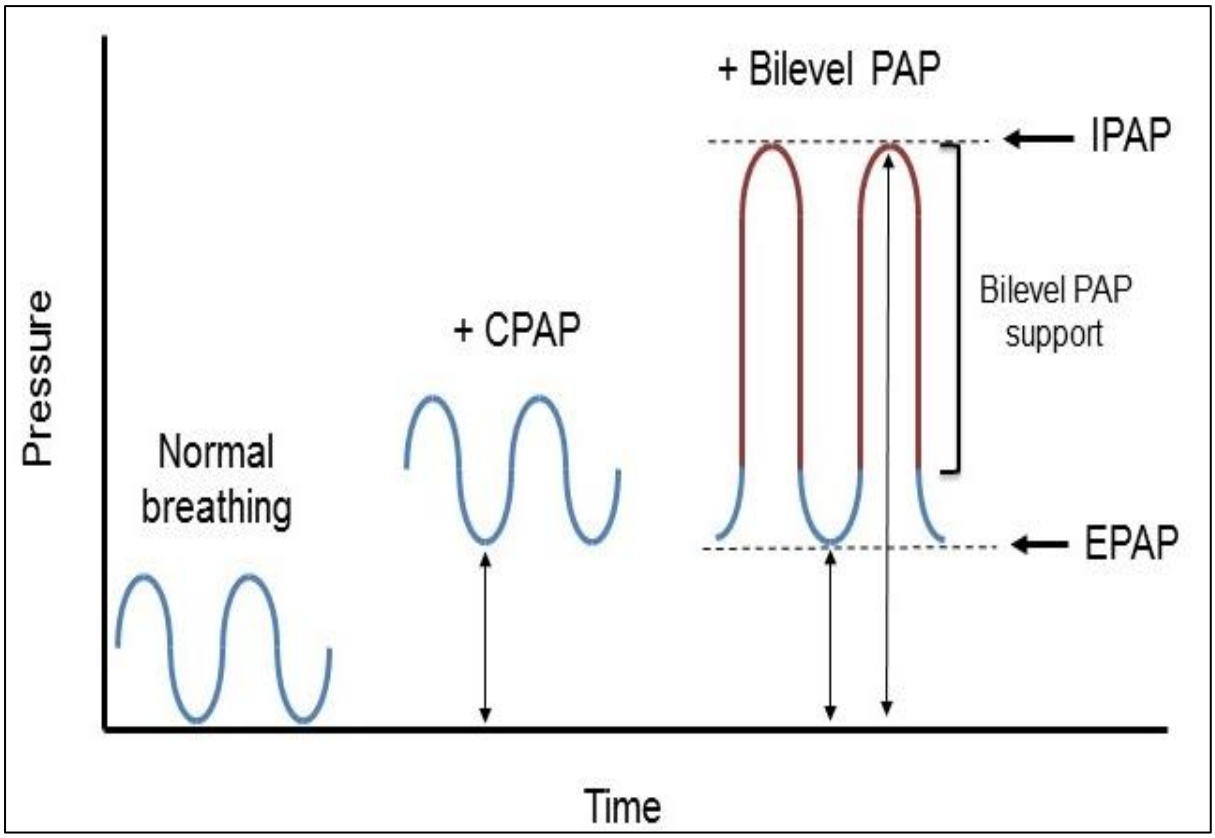


Figure 1.12 Normal breathing vs CPAP vs BIPAP (89)

1.4 Non-Invasive Ventilation & Acute Hypercapnic Respiratory Failure

Non-invasive ventilation (NIV) has been well established for treating AHRF secondary to COPD (90). However, acute exacerbation of COPD (AECOPD) is not the only cause of AHRF that results from the reduced capacity of the respiratory pump and imbalance between the increased resistive and elastic load. Other conditions can cause AHRF which resulting hypercapnia and acidosis, hence, NIV can be used for these conditions. (91).

1.4.1 Acute Exacerbation of COPD

NIV is regarded as the standard of care in managing AHRF patients secondary to AECOPD (92). Brochard et al. showed in the first randomized controlled trial that NIV, when compared to standard medical treatment, significantly lowered the ETI and mortality rates, lowered the complications' frequency, and shortened the mean length of hospital stay among AECOPD patients admitted to an ICU (93). A following study confirmed that NIV was associated with reduced ETI and in-hospital mortality rates (94). In a study evaluating NIV and invasive mechanical ventilation (IMV) in AECOPD patients who failed usual medical care, Conti et al. showed that for severe patients, NIV was shown to be as effective as IMV (95). Furthermore, ICU stays, and 1-year readmission reductions were advantageous for patients who successfully managed with NIV.

In ward-based settings, NIV application has been widely studied in several studies. Plant et al. confirmed in the largest study of its kind to date (236 patients were recruited

from 14 UK hospitals)` that NIV delivery in ward-based area is feasible (96). This multicentre trial showed that early NIV application reduced treatment failure and in-hospital mortality when comparing NIV with standard therapy. Fiorino et al. demonstrated in a prospective cohort study done in ward settings that NIV aided in arterial blood gases (ABG) correction in respiratory acidosis patients (mild and severe) (97). The superiority of NIV over usual medical care has since been proved by numerous randomized controlled trials (RCT) in many care settings and healthcare systems (98). Moreover, several studies demonstrated that the NIV use in managing AECOPD has become widespread in the United States and in Europe (99-101).

Currently, NIV can be utilised safely in different care settings; emergency departments, general wards, high-dependent settings, and critical care settings with the conditions of appropriate resources and well-trained staff to ensure successful outcomes as they are highly dependent on patient selection and the case severity of hypercapnia and/or acidosis as they major predictors of NIV failure (102-104).

ATS/ERS guidelines stated recently a solid evidence resulted from robust data supporting the use of NIV in AHRF patients due to AECOPD (92). For moderately ill patients (pH of 7.25–7.35), NIV can be effective to avoid acidosis progression and the progression to IMV. For the more severely ill patients (pH < 7.25), NIV can be an alternative to IMV instead of being a preventative tool. ATS/ERS guidelines indicated that there is no lower limit of pH to apply NIV; however, from clinical practice, lower pH is associated with high risk of NIV failure. One cohort study in the UK has reported equivalent survival in a ward-based setting

at pH 7.15-7.25, compared to 7.25-7.35 (105) , although further confirmation of this result would aid confidence that it is generalisable. Moreover, compared to IMV, successful NIV application reduces the length of critical care and hospital stay, incidence of ventilator-associated pneumonia, the number of hospital readmissions (95), and the number of tracheostomy procedures (106).

1.4.2 Cardiogenic Pulmonary Oedema

Cardiogenic pulmonary oedema (CPO) is a condition that commonly causes acute respiratory failure (ARF), in some cases associated with acidosis and hypercapnia (107). Around 50% of severe CPO patients have hypercapnia which is considered as a marker of severity of the disease that may require IMV (108). However, in this hypercapnic group, the NIV success rate is very high (96%) (109). NIV and CPAP act as the first choice of care with usual medical care in acute condition of CPO. Since CPAP only provides a constant positive pressure to increase FRC and does not provide support during the inspiratory phase, it is not considered a 'real' form of MV. On the other hand, NIV, or bilevel ventilation with inspiratory and expiratory pressures, is considered a reasonable and real form of ventilation which theoretically more suitable for the hypercapnic group.

In the hypercapnic CPO patients, a multicentre study showed that NIV, compared with usual medical therapy, decreased the ETI and the in-hospital mortality rates (110).

In a study comparing CPAP to NIV, NIV improved patients with CPO faster compared to CPAP. However, NIV was as effective as CPAP in improving the main clinical outcomes (i.e., intubation and mortality rates) for overall CPO patients and for hypercapnic CPO patients (111). Similarly, Bellone et al. demonstrated that NIV wasn't superior to CPAP in the treatment of patients with CPO with hypercapnia (112).

In 2008, a large multicentre study was published by Gray et al. in which >1000 patients were randomized to NIV, CPAP, and usual medical care. The NIV and CPAP groups showed more physiological improvement compared to the group with usual medical care with no variation in ETI and in-hospital mortality rates (113).

Subsequently, a few systematic reviews concluded CPAP is as effective as NIV and that both are superior to standard oxygen therapy in decreasing intubation and mortality rates. However, no clear conclusion regarding which treatment (NIV and CPAP) would be used for hypercapnic patients (114-118). Indeed, these reviews may have had some weaknesses (See also chapter 2), such that further work is still required. Nevertheless, on the basis of these reviews, both NIV and CPAP are recommended for CPO patients with ARF (92). Theoretically, NIV could be the favoured choice in patients with hypercapnia considering its action on alveolar hypoventilation.

1.4.3 Obesity and OHS

Generally, obesity is a condition that is common in the general population and this may include patients who also have COPD, sleep disorders and asthma, however, some obese patients progress to obesity hypoventilation syndrome (OHS), defined by the association between daytime alveolar hypoventilation, sleep disordered breathing, and obesity; (BMI) >30 kg/m^2 (119).

There is limited data regarding NIV application to patients with obesity and OHS, most of the trials are case series with low patient numbers (120-122). Duarte et al. showed that NIV avoided ETI in most of 50 morbidly obese patients with AHRF with lower in-hospital mortality in the successfully managed group with NIV compared to IMV group (123). Similarly, Rabec et al. demonstrated that NIV avoided ETI and improved $PaCO_2$ in the majority of patients with OHS and AHRF (124). Bry et al. concluded that the risk of receiving long-term NIV may occurs to adult subjects with severe obesity and ARF (125). A multicentre randomized controlled trial compared BIPAP versus CPAP for newly diagnosed severe OHS (including patients who presented in acute condition) and concluded that BIPAP and CPAP have similar improvements in ventilatory failure (126). With regards to positive airway pressure therapy, recent clinical practice guidelines for managing OHS have concluded that the use of PAP generally is recommended for stable ambulatory patients with OHS. Moreover, the panel members recommended the use of CPAP for OHS patients in stable ambulatory conditions. However, they lacked certainty on the clinical benefits of initiating CPAP, rather than BIPAP, in patients with hypercapnic OHS as the improvements in

hypercapnia may be achieved more quickly with BiPAP than with CPAP during the initial treatment. The overall quality of evidence was very low; conditional recommendations were based on a very low level of certainty in the evidence. However, future research opportunities are apparent based on this guideline that focuses on the best management strategies after an acute episode of respiratory failure (127).

Carrillo et al. compared results in AHRF patients due to COPD and OHS, managed with NIV using the same ventilation settings, which is different from the usual clinical practice (128). Compared to the COPD group, the OHS group had lower NIV failure and in-hospital mortality, with higher 1-year survival. Although the clinical use of NIV in OHS patients with AHRF is large, there is a lack of RCT in this area and thus there is no clear recommendation given on which modality to use by the ERS/ATS guidelines (92).

1.4.4 Neuromuscular Diseases and Chest Wall Deformities

NMD and CWD can negatively affect the alveolar ventilation, caused by decrease in respiratory muscle strength, and ineffective airway secretion clearance, caused by expiratory muscle weakness which therefore cause hypercapnic respiratory failure (HRF) (129). NMD includes many conditions which is classified based on the onset of AHRF: (1) slowly progressive NMD like spinal muscular atrophy (SMA)and motor neurone diseases and (2) rapidly progressive, reversible, NMD such as Guillain–Barré syndrome (GBS) and myasthenia gravis (MG) (130). The usual medical care in treating patients with HRF due to CWD and NMD is nocturnal NIV with assisted coughing technique (131).

A recent systematic review found no RCT using NIV vs IMV to manage acute respiratory failure patients with NMD and CWD (132). Compared to IMV, Vianello et al. demonstrated that in patients with AHRF due to slowly progressive NMD, NIV with mini-tracheostomy decreased the in-hospital mortality and ICU length of stay (133). Moreover, an observational study showed that NIV has positive effect in avoiding ETI in the majority of enrolled NMD patients (134). Practically, the consensus opinion is to manage NMD and CWD with NIV, and this practice is based on the British Thoracic Society/Intensive Care Society guidelines for the ventilatory management of acute hypercapnic respiratory failure in adults as it is recommended that ''NIV should almost always be trialled in the acutely unwell patients with NMD or CWD with hypercapnia''. The level of evidence was graded D; based on case reports, case series, or expert opinion (135).

1.4.5 Weaning from IMV

Increased ETI and IMV times are linked to many complications (136, 137). Therefore, an approach to speed up the weaning process is essential to minimise the complications and to improve patients' outcomes. In many respiratory failure cases, the withdrawal of IMV was performed after resolving the underlying conditions responsible for ARF. However, some of the ventilated patients, who are with pre-existing conditions and persisting hypercapnia, require more and gradual time for IMV withdrawal. Using NIV for hypercapnic patients who are ventilator-dependent was as effective as IMV as it improves blood gases and respiratory effort (6, 138).

An RCT done for subjects who failed the T-piece trial randomized to a group who were extubated and immediately had NIV versus a group who continued with ETI and IMV. The trial revealed that there is an increased weaning success when using NIV as a weaning technique. Over the following years, many studies were done to assess the NIV efficacy (139). Burns et al. found 16 RCTs that assessed the NIV efficacy as a weaning technique for respiratory failure patients. Compared with traditional weaning techniques, NIV was effective in decreasing the mortality, ICU and hospital length of stay and pneumonia rate (140). As a result from these findings, recent guidelines recommend the use of NIV for AHRF patients to accelerate the weaning process from IMV (92). The weaning from IMV is clearly out of our scope and aims. However, it was included as it is a usual clinical practice and one of the common uses of NIV.

In summary, NIV is regarded as the standard of care in managing AHRF patients secondary to AECOPD. However, it was apparent that there were gaps in the evidence for AHRF patients other than AECOPD as the published guidelines for AHRF management provided conditional and low recommendations, based on a low level of certainty in the evidence, for managing AHRF patients other than COPD by BIPAP. Hence, the effectiveness of NIV in AHRF due to aetiologies other than COPD is still questioned with a lack of robust data and strong recommendations. Moreover, the use of ward-based NIV with exploring factors/predictors of NIV success/failure for AHRF unrelated to COPD is not widely established worldwide due to concerns over its efficacy and safety resulting from unclear and limited evidence. Poor understanding of the role of ward-based care for AHRF unrelated

to COPD limits a hospital's ability to design care pathways and limits guidance for future large-scale and high-quality trials. The detailed aims are presented in the next section.

1.5 Aims of This Thesis

The objective of this thesis was to evaluate the clinical effectiveness of NIV application for AHRF unrelated to COPD

The specific aims were:

1. To systematically review the clinical effectiveness of non-invasive ventilation for non-COPD patients with acute hypercapnic respiratory failure (excluding NIV for weaning). Based on the literature cited in the introduction, NIV was being widely used in different conditions known to cause AHRF without COPD but demonstrated that there may be a lack of trials in some areas. It was also unclear if there were differences between disease areas, such that a review amalgamating all literature in this area might aid hospitals in delivering a pathway. There were also concerns about quality of some of the systematic reviews in the area, which are discussed further in chapter 2, and prompted me to conduct a new review.
2. To explore the outcomes and failure rates, with predictors of mortality, associated with NIV application in the ward-based setting for patients with AHRF unrelated to COPD. There are potential benefits to hospitals and patients from using NIV outside an ICU, however little data exists on using NIV in this setting outside COPD. I

therefore chose to use a cohort study to examine outcomes, and associations of poor outcome, in AHRF patients who did not have COPD. The ultimate aim of this work was to identify factors which might aid design and delivery of a new RCT in areas of the literature identified as most lacking in the systematic review reported in chapter 2.

3. The pandemic made it impossible to deliver a feasibility RCT or any further clinical study using NIV, irrespective of the need identified in chapters 2 and 3. Thus my plans for year 3 were adapted to understand the landscape for NIV use outside the ICU in the during and post-Covid era. The aim was to investigate the healthcare professional attitudes to non-invasive ventilation outside Intensive Care Units post-COVID-19 through a multi-methods study. Ultimately this could inform feasibility and structure of future trials by others in this area.

2 BILEVEL POSITIVE AIRWAY PRESSURE VENTILATION FOR NON-COPD PATIENTS WITH ACUTE HYPERCAPNIC RESPIRATORY FAILURE: A SYSTEMATIC REVIEW AND META-ANALYSIS

A version of this stage of the PhD, formatted as a manuscript, has been published in the Annals of Thoracic Medicine (141) (See Appendix 7).

Published article:

Faqihi BM, Trethewey SP, Morlet J, Parekh D, Turner AM. Bilevel positive airway pressure ventilation for non-COPD acute hypercapnic respiratory failure patients: a systematic review and meta-analysis. Annals of thoracic medicine. 2021 Oct;16(4):306.

B. M. F. was responsible for idea conceptualization, literature search, study methodology, study inclusion, data extraction, data curation, formal data analysis, risk of bias assessment, and manuscript writing (original draft).

2.1 Introduction

For several decades, NIV has been regarded as an effective method for avoiding the use of ETI and decreasing mortality in patients with acute hypercapnic respiratory failure (AHRF). As discussed in section 1.4, there is considerable evidence about the use of NIV and CPAP in a range of conditions including COPD and non-COPD with AHRF, where use is established. However, it was apparent that there were gaps in the evidence for AHRF patients other than AECOPD as the published guidelines for AHRF management provided conditional and low recommendations, based on a low level of certainty in the evidence, for managing AHRF patients other than COPD by BIPAP. In addition, the guidelines recommended CPAP for stable ambulatory patients, however, BIPAP was recommended, with low level of evidence, for patients in acute conditions (127, 142). Hence, the effectiveness of NIV in AHRF due to aetiologies other than COPD is still questioned with lack of robust data and strong recommendations. Moreover, some of the studies of pulmonary oedema did not exclude COPD patients for the analysis (111, 143), so may not have proven NIV efficacy even in this group. This led me to construct a protocol for a new review that overcame these issues by evaluating existing literature and determining the effectiveness of BiPAP for non-COPD patients with AHRF, using the need for ETI and the mortality rate after applying NIV as the primary outcomes.

2.2 Methods

2.2.1 Criteria for considering studies for this review

2.2.1.1 Types of included studies

Randomised controlled trials (RCTs) that assess the clinical effectiveness of BiPAP on non-COPD acute hypercapnic respiratory failure patients were included. In order to be confident COPD patients were excluded from the study cohorts I examined the studies during the full-text review to make sure that the studies didn't include COPD as the primary diagnosis, didn't have a past medical history of COPD, or didn't include mixed conditions (including COPD) in one analysis.

2.2.1.2 Types of participants

All adult patients with the diagnosis of acute hypercapnic respiratory failure due to a cause other than COPD.

2.2.1.3 Types of interventions

The intervention studied was NIV by BIPAP applied through a facemask or nasal mask. The control group were either O_2 therapy or CPAP. Where the control intervention varied, subgroup analyses were planned, based on the specific comparator presented.

2.2.1.4 Types of outcome measures

The primary outcomes of interest included the need for ETI and the mortality rate after applying NIV. The secondary outcomes of interest, if applicable, were length of intensive care unit (ICU) stay, length of hospital stay, complications from treatment and blood gas following the start of NIV.

2.2.2 Data sources and search strategy

The protocol for this systematic review was prospectively registered on PROSPERO (CRD42018089875). To identify articles for inclusion in this review, the Cochrane Central Register of Controlled Trials (CENTRAL) in the Cochrane Library (Wiley interface), MEDLINE (Ovid interface), EMBASE (Ovid interface) and CINAHL Plus (EBSCO interface) were searched for relevant studies (See Appendix 1 for search lists). In addition, trial registries (clinicaltrials.gov and WHO ICTRP) were used to search for ongoing and completed, but not yet published, clinical trials. The bibliographies of the retrieved articles were reviewed to identify and conduct searches on related articles. Clinical effectiveness was determined by comparison of the rates of the primary outcomes of interest, ETI and mortality, between treatment groups.

2.2.3 Study selection

Study reviewers independently made study selections based on titles and abstracts, which were compared against the inclusion criteria (lead reviewer – B.M.F., second

reviewers – D.P., A.M.T., J.M., S.P.T.). Full texts were obtained after screening the titles and abstracts of potentially includable studies and conducting a similar dual-review process. Discussion between two reviewers and consultation with a third reviewer was done to resolve any concerns regarding the study selections. A spreadsheet was used to record the decision making by individual reviewers.

2.2.4 Data extraction and quality assessment

Two reviewers (B.M.F. and S.P.T.) independently extracted data from the included studies. A third reviewer was consulted to resolve any disagreement regarding data extraction. The extracted information included study participant demographic data, study setting, study methodology, details of NIV used and outcome measures (See Appendix 2 for Data Extraction Form). The form was piloted prior to use on the full review.

2.2.5 Assessment of risk of bias in included studies

The methodological quality of each study was assessed using the risk-of-bias tool in RevMan. This tool consists of the following six domains: random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data and selective reporting. Each domain was graded 'yes', 'no' or 'unclear' to reflect a high or low risk of bias and uncertain bias, respectively. One reviewer (B.M.F.) completed the risk of bias assessment which was checked by a

second reviewer (A.M.T.). Publication bias was planned to be assessed using funnel plots but was not possible because of too few studies obtained.

2.2.6 Statistical analysis

The descriptive analyses are reported, and meta-analysis was performed using RevMan; pooled risk ratios (RR) and 95% confidence intervals (CI) were computed and chi-square test and I^2 statistics were used to assess the heterogeneity of the study results. The heterogeneity was defined as low, moderate, and high with I^2 values of >25%, >50% and >75%, respectively. In the analysis of heterogeneity, a P value <0.05 was considered to be statistically significant.

2.3 Results

2.3.1 Results of the Search

A total of 2485 records were identified through the database search after removing the duplicated articles. 88 articles were identified for full-text assessment after initial title and abstract review excluded the majority as they do not meet the inclusion criteria. Full-text review resulted in exclusion of 82 studies for different reasons as shown in PRISMA diagram in figure 2.1. Six articles were included in the study involving 320 participants (Mehta 1997; Bellone 2005; Moritz 2007; Rusterholtz 2008; Nava 2003; Nava 2013). This included 4 RCTs comparing BIPAP to CPAP and 2 RCTs comparing BIPAP to oxygen therapy.

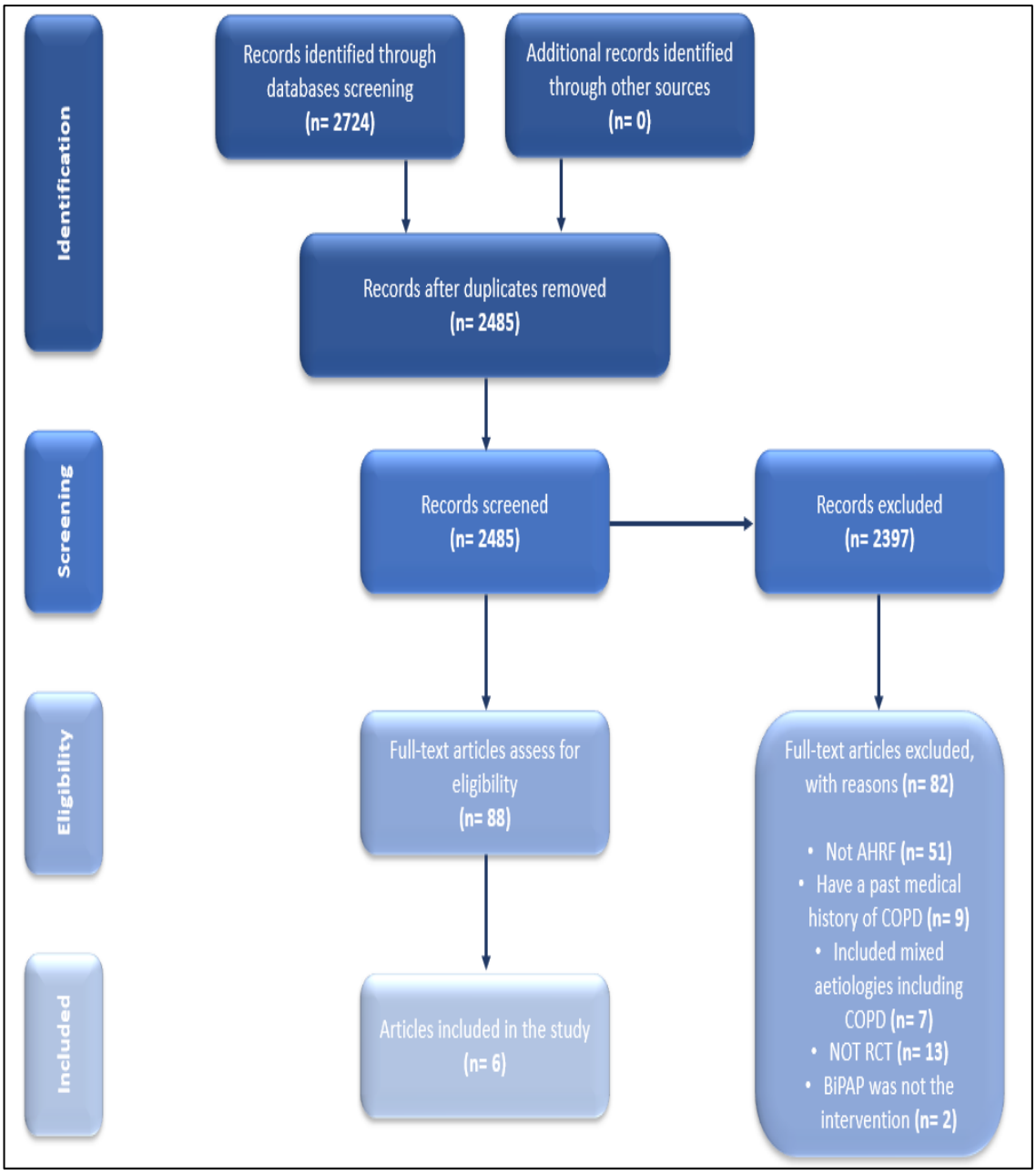


Figure 2.1 PRISMA diagram

2.3.2 Characteristics of the included studies

Six articles were included in the study, involving 320 participants (110, 112, 144-147). These included four RCTs comparing BiPAP to CPAP (112, 144-146) and two comparing BiPAP to oxygen (O_2) therapy (110, 147). All of the studies were RCTs using a parallel-group design. The six studies were done in Italy (110, 112, 147), the United States (144), France (145, 146), Spain (147) and Taiwan (147). Four of the six articles were multicentre studies (110, 145-147). All reported on adult patients with AHRF due to ACPO (110, 112, 144-146) and malignancy (147). The NIV initial application was done in the emergency department for all studies. Three of them reported that the patients were transferred to ICU to continue NIV management (144, 146, 147) and the other three haven't reported any patients transfer neither ICU nor wards (112, 145, 147). The number of patients recruited in each study ranged from 27 to 100 with an average age of participants of 74.3 years; males and females accounted for 52% and 48% of the participants respectively. Five studies reported intervention failure, demonstrated by the need for an ETI outcome, four studies compared intubation between BiPAP and CPAP (112, 144-146) and one study compared intubation between BiPAP and O_2 (110). In-hospital mortality was reported in almost all the studies; except for one study (146), three studies compared mortality between BiPAP and CPAP (112, 144, 145) and two studies between BiPAP and O_2 (110, 147). See table 2.1 for summary of the characteristics of the included studies, table 2.2 that shows the different level of pressures used; inspiratory positive airway pressure (IPAP), expiratory positive

airway pressure (EPAP), and CPAP, O_2 therapy, and the choice of patient-ventilator interface, and table 2.3 for the details of characteristics of included studies.

Table 2.1 Characteristics of the included studies

Study	Disease	Participants	Intervention	Control	Outcomes
Mehta (1997)	ACPO	N = 27	BiPAP = 14	CPAP = 13	ETI Mortality rate LOS: hospital & ICU
Nava (2003)	ACPO	N = 64	BiPAP = 33	O_2 = 31	ETI Mortality rate LOS: hospital
Bellone (2005)	ACPO	N = 36	BiPAP = 18	CPAP = 18	ETI Mortality rate
Moritz (2007)	ACPO	N = 57	BiPAP = 29	CPAP = 28	ETI Mortality rate LOS: hospital
Rusterholtz (2008)	ACPO	N = 36	BiPAP = 17	CPAP = 19	ETI Mortality rate LOS: ICU
Nava (2013)	ESSD	N = 100	BiPAP = 53	O_2 = 47	Mortality rate

ACPO: *Acute Cardiogenic Pulmonary Oedema,* ***BiPAP****: Bi-level Positive Airway Pressure,* ***ETI****: Endotracheal Intubation,* ***LOS****: Length of Stay,* ***ICU****: Intensive Care Unit,* ***CPAP****: Continuous Positive Airway Pressure,* ***ESSD****: End-stage Solid Tumour*

Table 2.2 IPAP, EPAP, and O_2 levels and patient-ventilator interface

Study	Initial NIV settings			Final NIV settings			O_2	Interface	Notes
	IPAP (Cm H2O)	EPAP (Cm H2O)	CPAP (Cm H2O)	IPAP (Cm H2O)	EPAP (Cm H2O)	CPAP (Cm H2O)			
Bellone 2005	15	5	10	-	-	-	N/A	Face mask	All studies followed their NIV protocol in terms of initiation and increasing/decreasing IPAP by 2 cm H2O, until meeting the patient's tidal volume demand and/or patient's tolerance, and increasing/decreasing EPAP by 1 cm H2O, to meet the desired O_2 saturation.
Mehta 1997	14	5	10	14.35±1.73	5	10.08±1.24	N/A	Nasal mask	
Moritz 2007	12	5	10	12±3.2	4.9±0.9	7.7±2.1	N/A	Facemask	
Rusterholtz 2008	14	4	10	14±5	4.2±0.6	9±2	N/A	Face mask	
Nava 2003	15	5	N/A	14.5±21.1	6.1±3.2	-	Not stated	Face mask	
Nava 2013	10	5	N/A	13±3.4	6.5±2.6	-		Face mask	

***IPAP**: Inspiratory Positive Airway Pressure, **EPAP**: Expiratory Positive Airway Pressure **CPAP**: Continuous Positive Airway Pressure*

Table 2.3 Detailed characteristics of included studies

Mehta 1997		
Method	Randomized, controlled, double-blind trial. **Setting**: Emergency department in a university hospital	
Participants	N= 27	
Interventions	Control: CPAP= 13 Intervention: BIPAP= 14	
NIV duration	Not stated	
Outcomes	1. Intubation rate 2. length of time using BIPAP or CPAP 3. Length of ICU and hospital stays 4. Mortality rate 5. BP 6. Heart Rate, 7. Breathing Frequency 8. Arterial Blood Gases 9. Dyspnea Score	
Risk of Bias		
Risk	**Authors' judgement**	**Support for judgement**

Random sequence generation	Low	Patients were randomized … using a computer-generated random number sequence”
Allocation concealment	Unclear	Not reported
Blinding of participants and personnel.	Low	“... physicians, nurses, and patients were blinded to the ventilator mode”
Blinding of outcome assessors	Low	"... but respiratory therapists were unblinded in order to make ventilator adjustments.”
Incomplete outcome data	Low	No missing data mentioned or noticed
Selective reporting	Low	Protocol is available, and all outcomes were reported in a pre-specified way
Other sources of bias	Low	No other sources of bias noticed

Nava 2003		
Method	A Multicentre Randomized Trial. **Setting**: Five emergency departments	
Participants	N= 64	
Interventions	Control: O_2= 31 Intervention: BIPAP= 33	
NIV duration	11.4 hours	
Outcomes	1. Endotracheal intubation 2. In-hospital Mortality 3. Arterial blood gases 4. Respiratory Rate 5. Systolic and diastolic blood pressure 6. Heart Rate 7. Dyspnoea 8. The duration of hospital stays 9. Cardiac enzymes	
Risk of Bias		
Risk	**Authors' judgement**	**Support for judgement**
Random sequence generation	Low	"... patients were randomly assigned to receive standard

		medical treatment plus O_2 or standard treatment"
Allocation concealment	Unclear	Not reported
Blinding of participants and personnel	Unclear	Not reported
Blinding of outcome assessors	Unclear	Not reported
Incomplete outcome data	Low	No missing data mentioned or noticed
Selective reporting	Low	Protocol is available, and all outcomes were reported in a pre-specified way
Other sources of bias	Low	No other sources of bias noticed

Bellone 2005		
Method	Controlled prospective randomized study. **Setting**: The Niguarda Hospital Emergency Department	
Participants	N= 36	
Interventions	Control: CPAP= 18 Intervention: BIPAP= 18	
NIV duration	3 hours	
Outcomes	1. Endotracheal intubation 2. In-hospital Mortality 3. Arterial blood gases 4. Respiratory Rate 5. Resolution Time	
Risk of Bias		
Risk	**Authors' judgement**	**Support for judgement**
Random sequence generation	Low	"Randomization used a computer-generated random number sequence,"
Allocation concealment	Low	"and assignments were placed in closed envelopes with

		identification numbers that were stored in the Emergency Room.”
Blinding of participants and personnel.	Unclear	Not reported
Blinding of outcome assessors	Unclear	Not reported
Incomplete outcome data.	Low	No missing data mentioned or noticed
Selective reporting	Low	Protocol is available, and all outcomes were reported in a pre-specified way
Other sources of bias	Low	No other sources of bias noticed

Moritz 2007		
Method	Prospective multicentre randomized study. **Setting**: Three Emergency Departments	
Participants	N= 57	
Interventions	Control: CPAP= 28 Intervention: BIPAP= 29	
NIV duration	3 hours	
Outcomes	1. Endotracheal intubation 2. In-hospital Mortality 3. Arterial blood gases 4. Respiratory Rate 5. The duration of hospital stays	
Risk of Bias		
Risk	**Authors' judgement**	**Support for judgement**
Random sequence generation	Low	"Allocation to treatment was stratified for centres and based on block randomization of 10 consecutive study numbers as either CPAP or Bilevel PAP"

Allocation concealment	Low	“Each of the 3 study centres had blocks of sealed envelopes.”
Blinding of participants and personnel.	Unclear	Not reported
Blinding of outcome assessors	Low	"Data collection and analysis were performed independently of clinical investigations"
Incomplete outcome data.	Low	No missing data mentioned or noticed
Selective reporting	Low	Protocol is available, and all outcomes were reported in a pre-specified way
Other sources of bias	Low	No other sources of bias noticed

Rusterholtz 2008		
Method	A prospective multicentre randomized study. **Setting**: Three medical ICUs of three teaching hospitals	
Participants	N= 36	
Interventions	Control: CPAP= 19 Intervention: BIPAP= 17	
NIV duration	'The minimal ventilation duration was 1 h'.	
Outcomes	1. Endotracheal intubation 2. In-hospital Mortality 3. Arterial blood gases 4. Respiratory Rate 5. The duration of ICU stays	
Risk of Bias		
Risk	**Authors' judgement**	**Support for judgement**
Random sequence generation	Low	".. the study enrolled 36 patients. Randomization to receive … used a computer-generated random number sequence"

Allocation concealment	Low	“with stratification by centre; assignments were placed in sealed envelopes available in each centre.”
Blinding of participants and personnel.	Unclear	Not reported
Blinding of outcome assessors	Unclear	Not reported
Incomplete outcome data.	Low	No missing data mentioned or noticed
Selective reporting	Low	Protocol is available, and all outcomes were reported in a pre-specified way
Other sources of bias	Low	No other sources of bias noticed

Nava 2013		
Method	Multicentre, stratified, randomised feasibility study. **Setting**: Five respiratory intensive care units and two critical care units of emergency departments	
Participants	N= 100	
Interventions	Control: O_2= 47 Intervention: BIPAP= 53	
NIV duration	23 hours	
Outcomes	1. In-hospital Mortality 2. Arterial blood gases 3. Respiratory Rate 4. Heart Rate	
Risk of Bias		
Risk	**Authors' judgement**	**Support for judgement**
Random sequence generation	Low	"We used a computer-generated randomisation sequence, which was generated by an independent biostatistician who was not otherwise involved in the trial."

Allocation concealment	Low	“Patients were randomly assigned to one of the two treatment groups using opaque, sealed, numbered envelopes.”
Blinding of participants and personnel.	High	“We could not blind patients or investigators to treatment because a sham ventilation was not feasible."
Blinding of outcome assessors	Low	The incomplete blinding and outcomes are unlikely to be influenced.
Incomplete outcome data.	Low	The missing data not huge and don’t have a clinical effect.
Selective reporting	Low	Protocol is available, and all outcomes were reported in a pre-specified way
Other sources of bias	Low	No other sources of bias noticed

2.3.3 Excluded studies

Eighty-two studies were excluded. Most were excluded because they did not study AHRF (n = 51), have a past medical history of COPD (n= 9), included mixed aetiologies including COPD (n = 7), BiPAP was not the intervention (n = 2), or are not RCT (n = 13). Refer to Table 2.4 for the details of specific excluded studies.

Table 2.4 Excluded studies with reasons for exclusion

Study	Reason for exclusion
Antonelli 2000	Not AHRF
Auriant 2001	
Belenguer-muncharz 2017	
Borel 2012	
Bourke 2006	
Celikel 1998	
Chadda 2002	
Coimbra 2007	
Confalonieri 1999	
Cuomo 2004	
Doshi 2018	
Eman 2015	
Esteban 2004	
Fartoukh 2010	
Ferrer 2006	
Ferrer 2009	
Goodcare 2010	
Gruis 2006	
Gupta 2010	
Hanekom 2012	
Hazenberg 2016	
Hetzenecher 2016	
Holley 2001	
Howard 2017	
Hu 2011	
Hui 2013	
Iwama 2002	
Jabber 2016	
Jacobs 2016	
Javaheri 2011	
Jaye 2009	
Kiehl 1996	
Lee 2016	
Lemiale 2015	
Levitt 2001	
Lopez-jimenez 2016	
Luo 2014	
Masa 2015	
Masa 2016	
Masa 2016	
Momomura 2015	
Moraes 2017	

Moran 2003 Murphy 2012 Park 2001 Pinto 1995 Piper 2008 Roessler 2012 Sharon 2000 Soroksky 2003 Wysocki 1995	
Abou-shala 1996 Coudroy 2016 Dumas 2017 Figueiredo 2016 Gonzalez 2014 Hannan 2017 Ho 2006 Jing 2013 Lechtzin 2010 Li 2013 Perazzo 2015 Udekwu 2017 Wermke 2012	Not RCT
Belenguer-muncharz 2017 Bellone 2004 Crane 2004 Cross 2003 Ferrari 2007 Ferrari 2010 Gray 2009 Liesching 2014 Masip 2000	Have a past medical history of COPD
Honrubia 2005 Kramer 1995 Martin 2000 Nava 2011 Nouira 2011 Park 2004 Thys 2002	Included mixed aetiologies including COPD
Brandao 2009 Lellouche 2014	BiPAP was not the intervention

2.3.4 Risk of bias in included studies

Figures 2.2 and 2.3 illustrate the summary of risk of bias of the included articles.

2.3.4.1 Allocation

Risk of bias due to selection procedures was low or unclear for all studies. Almost all the studies used a computer-generated random number sequence for the random sequence generation. The allocation was adequately concealed in four studies (112, 145-147) and unclear in two studies (110, 144).

2.3.4.2 Blinding

In four trials, the blinding of participants was not reported (110, 112, 145, 146). Adequate participants' blinding was reported in one study (144), and inadequate participants' blinding was reported in one study (147). The blinding of the assessors was adequate in half of the studies (110, 112, 146) and not reported in the other half (144, 145, 147).

2.3.4.3 Incomplete outcome data

Four studies had a low risk of bias because of adequate completeness of outcome data (110, 112, 146, 147). Mehta et al. (144)reported that 25% of randomised patients lost due to pneumonia and delayed informed consent; and Moritz et al. (145) reported that 9%

of patients were withdrawn from the study due to no informed consent and lost to follow-up.

2.3.4.4 Selective reporting

Almost all the studies had low risk of selective reporting as the studies' protocols were reported and planned outcomes were analysed.

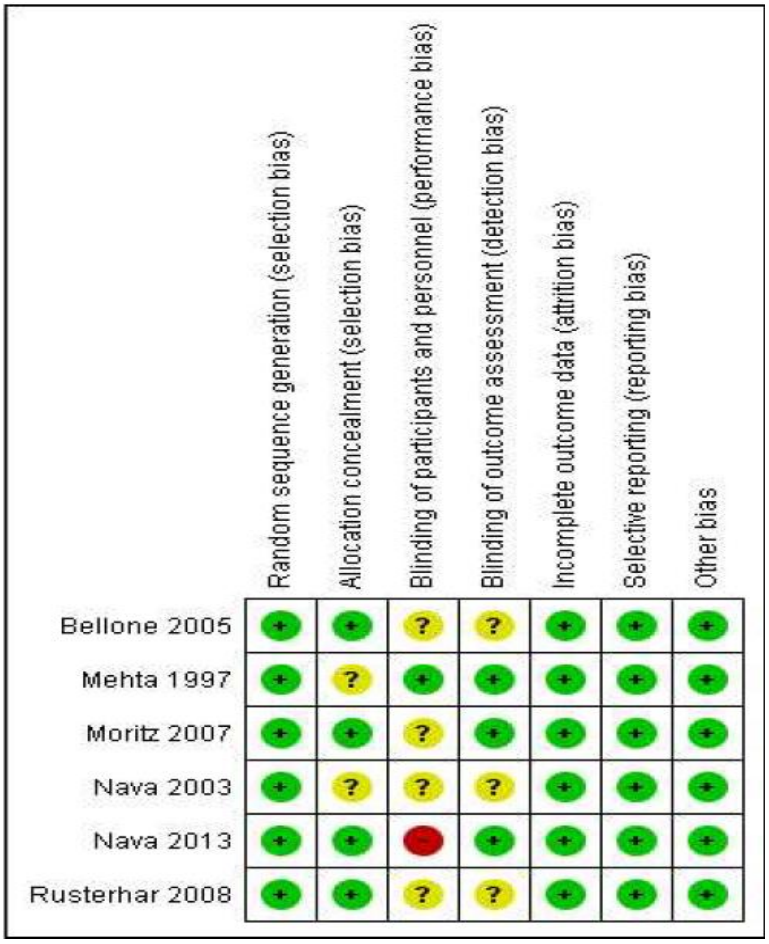


Figure 2.2 Risk of bias summary: review authors' judgements about each risk of bias item for each included study

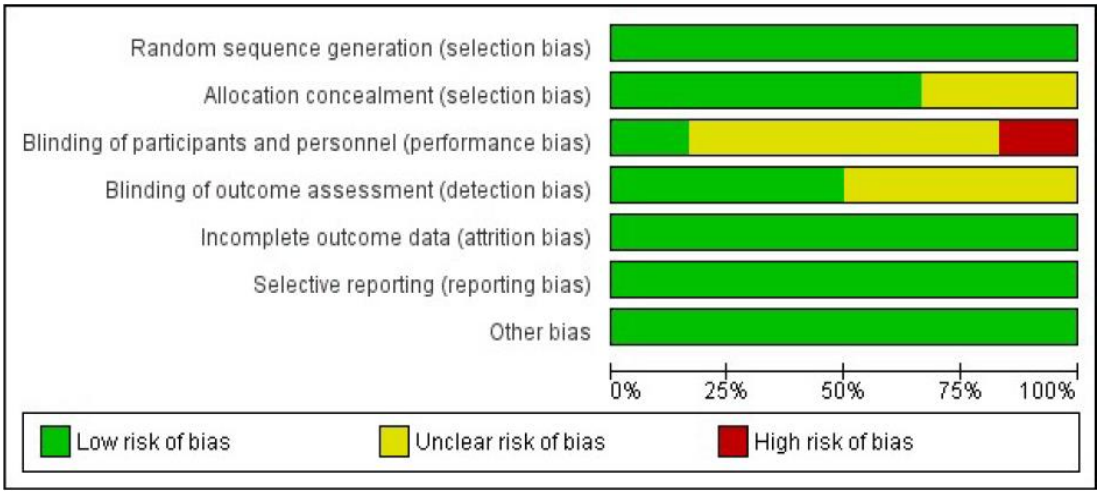


Figure 2.3 Risk of bias graph: review authors' judgements about each risk of bias item presented as percentages across all included studies

2.3.5 Outcomes

2.3.5.1 Endotracheal intubation (ETI)

The results from four trials in ACPO (156 patients) were available for examining the effects of BiPAP vs CPAP on the incidence of ETI. A low level of heterogeneity was found among the identified comparisons (I^2 = 0%; P = 0.97). Pooled analysis showed that the use of BiPAP was as effective as the control (CPAP) group with regards to the rate of intubation in hypercapnic respiratory failure patients, with no statistically significant difference between treatment groups (RR = 1.49; 95% CI: 0.62–3.62; P = 0.37) (See Figure 2.4). One study reported the effect of BiPAP vs O_2 with respect to ETI; this study showed that the percentage of patients with BiPAP needing intubation was significantly lower in a hypercapnic sub-group (110).

2.3.5.2 In-hospital mortality

In-hospital mortality was reported in three trials (120 patients) examining the effects of BiPAP vs CPAP on the incidence of in-hospital mortality in ACPO. A low level of heterogeneity was found (I^2 = 0%; P = 0.75). Pooled analysis showed that BiPAP had no superior effect over CPAP with regard to the rate of in-hospital mortality (RR = 0.71; 95% CI: 0.25–1.99; P = 0.51) (See Figure 2.5). In malignancy, patients with BiPAP had a better expected survival than patients receiving O_2 alone (147).

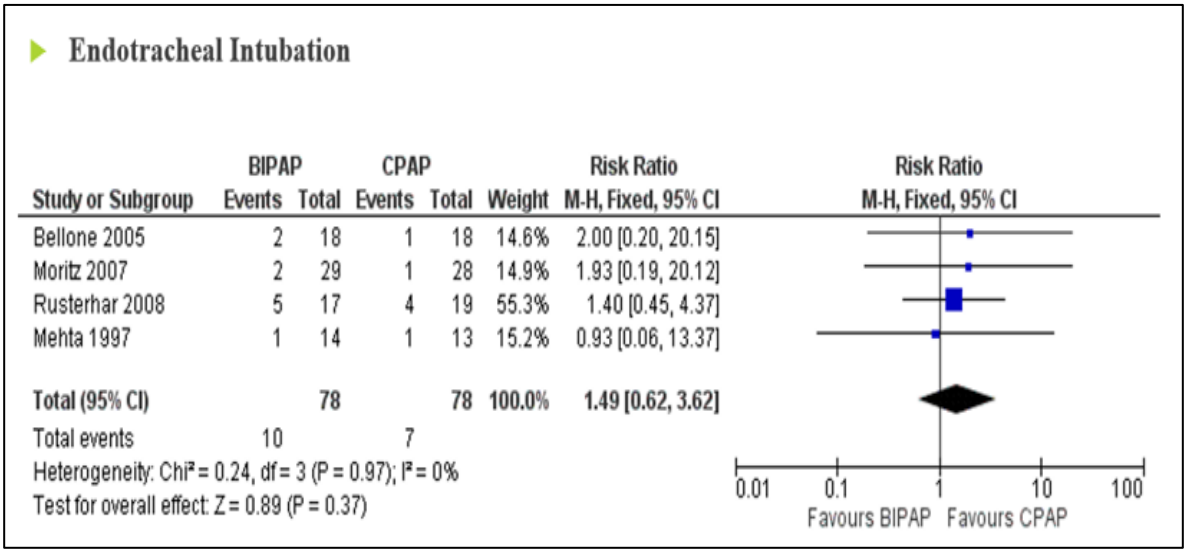


Figure 2.4 Forrest plot comparing ETI rates in AHRF patients treated with BiPAP compared to CPAP

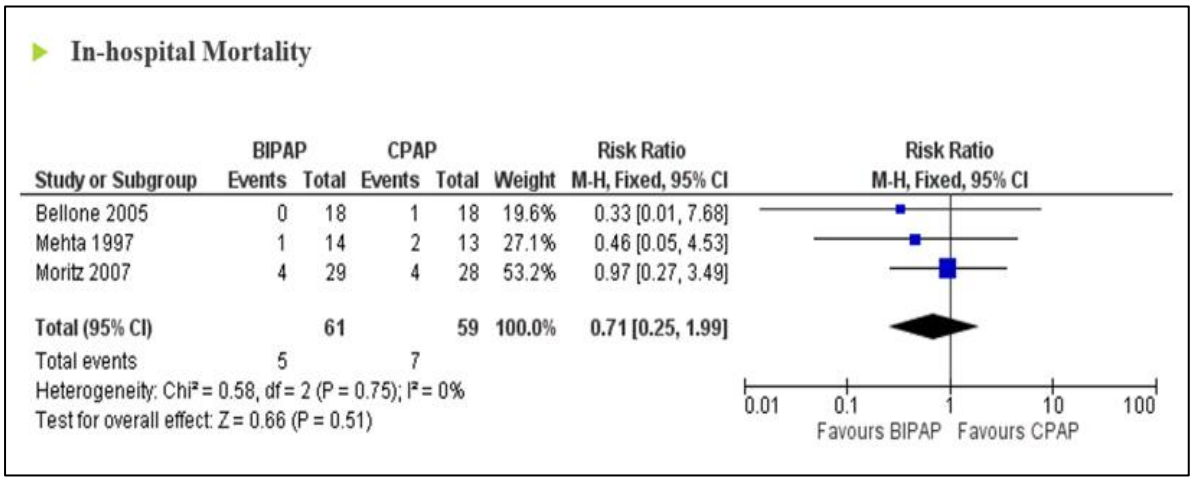


Figure 2.5 Forrest plot comparing in-hospital mortality rates in AHRF patients treated with BiPAP compared to CPAP

2.3.6 Other outcomes

Two studies of BiPAP vs CPAP reported hospital length of stay as an outcome (144, 145). There were no significant differences in hospital length of stay observed between treatment groups in these studies. Bellone et al. (112) reported that there was significant decrease in $PaCO_2$ for both groups, however other studies reported that the BiPAP group had greater reductions and significantly greater improvement in $PaCO_2$ compared to the control group (110, 144, 147). Improvements in other physiological markers like heart rate (HR), blood pressure (BP), pH, respiratory rate (RR), and SpO_2 were similar in trials comparing BIPAP to CPAP (112, 145, 146) and more significant in the BIPAP group when compared to O_2 group (110, 147). Since the main condition included for the analysis was mainly ACPO cohort, information on myocardial infarction (MI), which is an important cause of ACPO, was an important element to assess in our review. The Mehta et al. study presented a higher rate of MI with BiPAP. However, the incidence of MI in the other studies was similar and showed no significant differences between the BiPAP and CPAP treatment groups.

2.4 Discussion

The aim of this systematic review and meta-analysis was to assess the clinical effectiveness of using BiPAP in non-COPD patients with AHRF. The difference between BiPAP and CPAP or O_2 was investigated, with regard to ETI and in-hospital mortality, and included studies generally showed little heterogeneity, perhaps due to our strict inclusion criteria. Six studies of generally low or uncertain risk-of-bias, were included involving 320 participants with acute cardiogenic pulmonary oedema and malignant tumours. Four studies compared BiPAP to CPAP and two compared BiPAP to O_2 therapy. Although the overall point estimate showed no significant differences between BiPAP ventilation and CPAP, the point estimates of the included studies showed that the efficacy of BiPAP tends to be more than CPAP in reducing the ETI and mortality rates for AHRF patients due to ACPO. We were surprised to find that we were only able to meta-analyse studies of hypercapnic patients with ACPO, and that all studies in other conditions did not adequately exclude COPD. The number of studies using the treatment in ACPO was also lower than might be at first expected because many of the studies claiming to be treating a pulmonary oedema population, and included in prior systematic reviews (117, 148), in fact included high numbers of patients with coexistent COPD (149-157). After observing the articles about ACPO and NIV, many patients have coexistent diseases with ACPO and rarely have a single pathology. Therefore, our results are not superior to the results that have coexistent diseases with ACPO in terms of the outcomes' generalization for clinical practice.

The European Society of Cardiology and the American Heart Association have recommended the use of NIV in the treatment of acute heart failure (158), so it would be beneficial to identify which of the ventilation modalities offers the optimal therapeutic benefit in patients with AHRF. Physiologically, BiPAP has a potential advantage over CPAP in reducing dyspnoea and exhaustion by assisting the respiratory muscles in ACPO patients (159). These physiological benefits were translated into improved primary outcomes in our meta-analysis, which found that the efficacy of BiPAP tends to be more than CPAP in reducing the ETI and mortality rates with the need for more research to increase the precision of the point estimates and overall results. Moreover, hypercapnic patients, due to physiological reasons, were expected to benefit from BiPAP based on favourable results in some of the studies using BiPAP (110, 160). However, and based on the overall results, in hospitals where BiPAP is not available, CPAP could be a viable alternative although BIPAP would be optimal when we look also at the broader picture of NIV management for other outcomes like $PaCO_2$ and other vital signs (140).

The studies' findings (except Mehta et al. study) were consistent with the other RCTs, as there were no differences between either technique on the incidence of MI (149, 154, 161). This suggests that irrespective of the aetiology of ACPO, whether it is due to MI or not, CPAP is equally effective as BiPAP and is safe to use. With regards to Mehta et al. study, the prolonged high intrathoracic pressure plays a major role in the incidence of MI as a result of ventilators with no expiratory triggering system that increase the inspiratory time at the presence of air leak (144). This weakness has now been solved with ventilators with

new technologies. Nevertheless, it is advised to use the positive airway pressure cautiously in patients with acute coronary syndrome (142).

The IPAP, EPAP, and CPAP pressure levels are not different from previous reviews on different hypercapnic conditions or the same condition but with different inclusion criteria. All studies followed their NIV protocol in terms of initiation and increasing/decreasing IPAP by 2 cm H2O, until meeting the patient's tidal volume demand and/or patient's tolerance, and increasing/decreasing EPAP by 1 cm H2O, to meet the desired O_2 saturation. In addition, with regards to the NIV interfaces, most of the included studies used face mask interface and all studies used face mask and nasal mask interfaces which are consistent with the previous systematic reviews that reports positive outcomes on hypercapnic respiratory failure patients (98, 117, 162, 163).

2.4.1 Strengths and limitations

The strengths of this meta-analysis are as follows: (1) following Cochrane guidance to ensure the methodology was robust and systematic, (2) using predefined and robust inclusion criteria of RCTs and exclusion criteria of COPD patients such that we can be confident of the results with respect to conditions other than COPD, (3) using a broad search strategy and multiple data sources, (4) no language restrictions hence all available evidence was considered, (5) performing a manual search from reference list of retrieved studies, and (6) the risk-of-bias tool for RCTs was used to assess the risk of bias and quality of evidence. However, it also has limitations. First, the sample size of the trials included in the meta-

analysis was small, providing wide CI which could have underpowered our analysis of BiPAP compared to CPAP with regard to ETI, mortality, and other outcomes. Second, the AHRF conditions outside COPD were limited to ACPO with lack of RCTs for other condition. Third, a publication bias test; funnel plot, was not performed due to the low number of included trials, and so these results should be viewed with caution.

2.4.2 Conclusion

Existing controlled trials that evaluate the clinical effectiveness of NIV for non-COPD patients with AHRF were small (mainly for ACPO) and lack of robust data. Based on the point estimates of the included trials, the efficacy of BiPAP tends to be more than CPAP in reducing the ETI and mortality rates for AHRF patients due to ACPO. However, further trials are needed to increase the precision of the estimate. The NIV management using BIPAP may aid patient flow through the hospital by opening up more locations in which such patients can be safely managed with taking in consideration healthcare providers' experience and confidence with the management of acute respiratory failure. Moreover, further research is needed in this area which includes various other conditions which can cause AHRF, in particular obesity-hypoventilation as it is considered the second most common indication (after COPD) for NIV treatments among AHRF patients (164-166). No RCTs of NIV in obesity-hypoventilation-related AHRF were seen, yet cohort studies suggest a beneficial effect (128) and sufficiently good in-hospital mortality (167) such that management in a ward based setting may be preferable to the more costly and resource intensive ICU setting.

3 WARD-BASED NON-INVASIVE VENTILATION FOR ACUTE HYPERCAPNIC RESPIRATORY FAILURE UNRELATED TO CHRONIC OBSTRUCTIVE PULMONARY DISEASE

A version of this chapter has been accepted for publication in the Canadian Respiratory Journal (168) (See Appendix 8).

Published article:

Faqihi BM, Parekh D, Trethewey SP, Morlet J, Mukherjee R, Turner AM. Ward-Based Noninvasive Ventilation for Acute Hypercapnic Respiratory Failure Unrelated to Chronic Obstructive Pulmonary Disease. Canadian respiratory journal. 2021 Dec 21;2021.

B. M. F. was responsible for idea conceptualization, study methodology, data curation, formal data analysis, and manuscript writing (original draft).

3.1 Introduction

3.1.1 Background

Non-invasive ventilation (NIV) has been widely used in intensive care units (ICUs) for many years to treat conditions such as acute exacerbations of chronic obstructive pulmonary disease (COPD) and is regarded as effective for avoidance of endotracheal intubation (169) and decreasing mortality in patients with acute hypercapnic respiratory failure (AHRF). Moreover, managing patients who require NIV in an ICU setting is resource intensive and in the current economic climate, where healthcare budgets are increasingly limited, maximizing cost-effectiveness by enhancing ward-based care is important. However, the use of ward-based NIV for AHRF unrelated to COPD is not widely established, perhaps due to concerns over its efficacy and safety. In addition, poor understanding of the role of ward-based care for AHRF unrelated to COPD limits a hospital's ability to design care pathways.

In COPD, findings from a randomised controlled trial "YONIV trial" (Yorkshire Non-Invasive Ventilation trial) conducted in 2000 supported the use of ward-based NIV for patients with acute exacerbation of COPD outside ICUs (in wards-based settings) as it improved the mortality rate (10% vs. 20%, $p < 0.05$) and reduced the need for invasive mechanical ventilation (15% vs. 27%, $p = 0.02$) (96). Since the YONIV trial, numerous other studies have supported the use of NIV outside of the critical care environment for AECOPD group with AHRF (97, 164, 170-178). Additionally, a prospective study done in

the UK demonstrated that ward-based NIV was an efficient treatment for severely AHRF patients due to AECOPD (105). The predictor of in-hospital mortality was the main endpoint, and its risk was significant in patients with pre-NIV pH < 7.15 with a mortality rate equal to 37.5%. However, no significant in-hospital mortality rates differences were noted for patients with pre-NIV pH > 7.25 compared to pre-NIV pH 7.16–7.25 with mortality rate equal 21% and 20% respectively. Moreover, the study outcomes were not affected by the NIV initiation/delivery location (ward VS critical care settings), supporting the safety of using ward-based NIV for moderate to severe hypercapnic patients.

In the past years, however, patients with AHRF caused by conditions other than COPD are excluded from many hospitals' pathways of ward-based NIV based on unclear and limited evidence regarding their prognosis or utility of treatment outside critical care settings. Over time, based on the BTS guideline published in 2002, NIV was recognized to be an accepted treatment beyond COPD and in the following years, better evidence has accumulated for the use of NIV in non-COPD diseases but with weak recommendations due to low level of certainty in the evidence (135). In the past decade, OHS is the second most common indication (after COPD) for NIV treatments among AHRF patients (164-166).

With regards to the studies related to the conditions other than COPD, there are limited studies about the NIV use, most of the data arise from cohort studies. In OHS for example, which is considered one of the most common indication (after COPD) for NIV

treatments among AHRF patients, Rabec et al. and Duarte et al. demonstrated that NIV treatment was successful for AHRF patients due to OHS as it improved the $PaCO_2$, avoided ETI, and lowered the mortality rate (123, 124). Carillo et al. evaluated the results of patients managed by NIV who were suffering from AHRF due to either COPD or OHS. Patients with OHS had a lower rate of NIV failure and in-hospital mortality, and a higher 1-year survival rate (128). Systematic reviews of the RCTs in this field, including our work that presented in the 2nd chapter, shows that there is a lack of robust data.

3.1.2 Rationale and Significance of the study

Findings from this study will help to design a care pathway. The study of the effects of various factors/predictors will help in identifying risk factors associated with in-hospital mortality and/or NIV failure. Moreover, the findings will provide helpful information about the conditions that have positive clinical outcomes which can guide for future large-scale and high-quality trials.

3.1.3 Research Goal

The main goal of this study was:

1) To evaluate outcomes and failure rates associated with NIV application in the ward-based environment for patients with AHRF unrelated to COPD. We further chose to analyse efficacy based on pre-NIV pH thresholds in order to inform care pathway design.

3.1.4 Research Objectives

The research objectives addressed in this study were:

1) Explore factors/predictors associated with in-hospital mortality.
2) Explore factors/predictors associated with NIV failure.
3) Demonstrate the different non-COPD conditions that used NIV in ward-based care settings.
4) Investigate the NIV duration (days) and compare it with the recommendations.
5) Explore factors that may affect the NIV duration.
6) Investigate the time from the diagnosis of AHRF to the application of NIV.
7) Explore factors that may affect the time from diagnosis to application.

3.1.5 Research Questions

The research questions addressed in this study were:

1) What are the factors/predictors that associated with in-hospital mortality?
2) What are the factors/predictors that associated with NIV failure?
3) What are the percentages of the different conditions that indicate the use of NIV in ward-based care settings?
4) What is the NIV duration (days) and how it is close/different from the recommendations?
5) What are the relationships between the NIV duration and other factors?

6) What is the time from the diagnosis of AHRF to the application of NIV?
7) What are the relationships between the time from diagnosis to application and other factors?

3.2 Methods

This section describes the methodology used in the study. It is divided into the following sections: study design, data source, inclusion and exclusion criteria, study independent and dependent variables, and data analysis. The methodology is based on the research objectives of the study.

3.2.1 Study Design

This was a multicentre, retrospective cohort study of patients with AHRF unrelated to COPD treated by NIV in ward-based settings during the study period between February 2004 and December 2018.

3.2.2 Data Source

Data were collected prospectively as part of service evaluation and were analysed retrospectively. It was conducted in Queen Elizabeth Hospital Birmingham (QEHB), Birmingham Heartlands Hospital (BHH), and Good Hope Hospital (GHH) in the United Kingdom. In total, 479 subjects were enrolled using the NIV databases of the QEHB, BHH, and GHH between February 2004 and December 2018, including all patients

receiving ward-based NIV where the cause of AHRF was not COPD. Analysis of data collected was deemed part of service evaluation by the local R&D department, such that ethical approval was not required (the study was approved by both clinical and research departments within the hospital as being a study of routinely collected data for which no external approvals were required, beyond the local ones which they granted). (179).

3.2.3 Inclusion and exclusion Criteria

All adult patients managed with ward-based NIV for AHRF unrelated to COPD at the time of admission were enrolled in this study. All patients enrolled had a pre-NIV pH <7.35 and pCO_2 > 6.0 kPa. The exclusion criteria were as follows: COPD patients (primary diagnosis or with previous or new clinical diagnosis of COPD), patients <18 years old, pre-NIV pH >7.35 or a lack of pre-NIV blood gas.

3.2.4 Study Independent and Dependent Variables

The independent variables available in the data were age, gender, continuous pre-NIV pH, pre-NIV pH thresholds, and conditions.

The dependent variables classified into primary outcome which is in-hospital mortality and secondary outcomes including NIV failure (defined by progression to endotracheal intubation), NIV duration (days), and time from diagnosis to NIV application (minutes). During obtaining the database, there were missing data for some secondary outcomes. These missing data were extracted with the help from the healthcare providers

by the hospitals' medical records such that missing elements were <1% of cases after medical record review.

3.2.5 Data Analysis

The statistical analyses were performed using IBM SPSS Statistics Version 24. Statistical significance was taken as a p-value <0.05. Visual assessment (using histograms figures) and the Kolmogorov-Smirnov test were used to determine data normality. Data including pre-NIV pH, age, NIV duration and time from diagnosis to NIV application were non-parametric and therefore expressed as median [inter-quartile range (IQR)] and compared between outcome groups by using the Mann-Whitney and Kruskal Wallis tests. Number (percentage) was used to present categorical data, such as aetiology of AHRF, and Chi-Square test was used for analyses of associations between categorical variables and outcomes. Factors/predictors associated with in-hospital mortality and NIV failure were assessed initially using univariable analysis and then using a multivariable model to determine independent associations. Sub-group analyses according to the different conditions necessitating the use of NIV in ward-based care settings were also completed. Multivariable analysis was then performed using binary logistic regression (backward stepwise Wald) for categorical dependent variables and poisson regression for count dependant variables if the factors were significant in a univariable analysis to identify independent predictors of in-hospital mortality and NIV failure. The Kaplan-Meier estimator, presented visually by the Kaplan-Meier curve, was used to estimate the survival function and to show what the survival is at a certain time interval (days).

3.3 Results

3.3.1 Patients' Characteristics

In total, 479 patients were included in the study. Patients' baseline characteristics split by diagnostic conditions; obesity-related AHRF and non-obesity related AHRF, are summarised in Table 3.1. The split decision was made as obesity-related AHRF group accounted for almost 40% of the total included patients in the study. Overall, almost 20% of the included patients died in the hospital. Patients' underlying conditions were as follows: obesity-related AHRF, pneumonia, bronchiectasis, neuromuscular disease, fluid overload (included pulmonary oedema, heart failure, and metabolic/renal failure), and other (e.g. asthma, post-operative RF) (Table 3.2). Obesity-related AHRF had the lowest in-hospital mortality rate (6.91%) compared to other diagnosis conditions. The mortality of pneumonia, bronchiectasis, neuromuscular disease, and fluid overload were 32.08%, 25.00%, 25.88%, and 27.08%, respectively. The characteristics of obesity-related AHRF and non-obesity related AHRF are shown in tables 3.3 and 3.4.

Table 3.1 Participant baseline characteristics

Characteristic	Median [IQR] OR n (%)			P
	Total n= 479	Obesity-related AHRF n=188	Non-obesity related AHRF n=291	
Age (years)	73 [62-81]	69 [60-75]	76 [65.75-84]	<0.001
Male	192 (40.08)	66 (35.11)	126 (43.30)	<0.001
Female	287 (59.92)	122 (64.89)	165 (56.70)	0.01
Survival to discharge	384 (80.17)	175 (93.09)	209 (71.82)	0.08
In-hospital mortality	95 (19.83)	13 (6.91)	82 (28.18)	<0.001
Pre-NIV pH	7.27 [7.21-7.31]	7.27 [7.23-7.31]	7.26 [7.20-7.31]	0.04
Pre-NIV pH thresholds:				
pH <7.15	61 (12.73)	16 (8.51)	45 (15.46)	<0.001
pH 7.15 – 7.25	138 (28.81)	50 (26.60)	88 (30.24)	0.00
pH >7.25	280 (58.46)	122 (64.89)	158 (54.30)	0.03
NIV failure	101 (21.09)	15 (7.98)	86 (29.55)	<0.001
Subgroup (BHH):				
Duration of NIV (days)	5 [3-9]	6 [4-10]	4 [2-9]	0.02
RF to NIV (minutes)	123 [63.5 – 302.5]	123 [63.5 – 302.5]	122 [60.0 – 316.0]	0.69
Domiciliary NIV	44 (18.60)	27 (14.40)	17 (5.80)	0.13

**Obesity-related AHRF patients due to obesity hypoventilation syndrome.*
***IQR**, inter-quartile range; **BHH**, Birmingham Heartlands Hospital; **NIV**, non-invasive ventilation; **RF**, respiratory failure; **AHRF**: acute hypercapnic respiratory failure.*

Table 3.2 Prevalence of conditions causing AHRF

Diagnosis	Total n (%)	Survived to discharge	In-hospital mortality
Pneumonia	53 (11.06)	36 (67.92)	17 (32.08)
Bronchiectasis	40 (8.35)	30 (75.00)	10 (25.00)
Obesity-related AHRF	188 (39.25)	175 (93.09)	13 (6.91)
Neuromuscular disease	85 (17.75)	63 (74.12)	22 (25.88)
Fluid Overload	48 (10.02)	35 (72.92)	13 (27.08)
Other	65 (13.57)	45 (69.23)	20 (30.77)
Total	479 (100)	384 (80.17)	95 (19.83)

AHRF: Acute Hypercapnic Respiratory Failure

Table 3.3 Participant baseline characteristics (Obesity-related AHRF)

	Median [IQR] or *n (%)*			
	Total	Survival to discharge	In-hospital mortality	
Characteristic	n = 188	n = 175	n = 13	P value
Age (years)	69 [60-75]	69 [60-75]	72 [66-77]	0.21
Male	*66 (35.11)*	*63 (95.45)*	*3 (4.55)*	<0.001
Female	*122 (64.89)*	*112 (91.80)*	*10 (8.20)*	<0.001
Pre-NIV pH	7.27 [7.23-7.31]	7.27 [7.24-7.31]	7.17 [7.14-7.27]	<0.001
Pre-NIV pH groups				
pH < 7.15	16 (8.51)	12 (75.00)	4 (25.00)	0.05
pH 7.15 – 7.25	50 (26.6)	46 (92.00)	4 (8.00)	<0.001
pH > 7.25	122 (64.89)	117 (95.90)	5 (4.10)	<0.001
NIV failure	15 (7.99)	4 (26.67)	11 (73.33)	0.07
Subgroup (BHH)				
Duration of NIV (days)	6 [4-10]	6 [4-10]	5 [3.5-5]	0.04
RF to NIV (minutes)	123 [63.5 – 302.5]	123 [69.0 – 288.5]	145 [69.0 – 277.5]	0.54
Domiciliary NIV	27 (14.4)	27 (100)	0 (0.00)	<0.001

***IQR**, inter-quartile range; **BHH**, Birmingham Heartlands Hospital; **NIV**, non-invasive ventilation; **RF**, respiratory failure; **AHRF**: acute hypercapnic respiratory failure.*

Table 3.4 Participant baseline characteristics (non-obesity related and non-COPD AHRF)

	Median [IQR] or *n (%)*			
	Total	Survival to discharge	In-hospital mortality	
Characteristic	n = 291	n = 209	n = 82	P value
Age (years)	76 [65.75-84]	74.5 [61-83]	81 [70.75-87]	<0.001
Male	*126 (43.30)*	*89 (70.63)*	*37 (29.37)*	<0.001
Female	*165 (56.70)*	*120 (72.73)*	*45 (27.27)*	<0.001
Condition				
Pneumonia	*53 (18.21)*	*36 (67.92)*	*17 (32.08)*	0.01
Bronchiectasis	*40 (13.75)*	*30 (75.0)*	*10 (25.0)*	0.00
NMD	*85 (29.21)*	*63 (74.12)*	*22 (25.88)*	<0.001
Fluid Overload	*48 (16.49)*	*35 (72.92)*	*13 (27.08)*	0.00
Other	*65 (22.34)*	*45 (69.23)*	*20 (30.77)*	0.00
Pre-NIV pH	7.26 [7.20-7.31]	7.27 [7.21-7.31]	7.23 [7.17-7.29]	0.01
Pre-NIV pH groups				
pH < 7.15	45 (15.46)	30 (66.67)	15 (33.33)	0.03
pH 7.15 – 7.25	88 (30.24)	57 (64.77)	31 (35.23)	0.01
pH > 7.25	158 (54.30)	122 (77.22)	36 (22.78)	<0.001
NIV failure	86 (29.55)	18 (20.93)	68 (79.07)	<0.001
Subgroup (BHH)				
Duration of NIV (days)	4 [2-9]	7 [4-10]	5 [3.5-5]	0.03
RF to NIV (minutes)	122 [60.0 – 316.0]	120 [60.0 – 321.0]	136.5 [73.5 – 297.75]	0.48
Domiciliary NIV	17 (11.10)	16 (94.10)	1 (5.90)	<0.001

***IQR**, inter-quartile range; **BHH**, Birmingham Heartlands Hospital; **NIV**, non-invasive ventilation; **RF**, respiratory failure; **AHRF**: acute hypercapnic respiratory failure; **NMD**, Neuromuscular diseases.*

3.3.2 Normality tests

Figure 3.1 shows the histograms that have been done on pre-NIV pH, age, NIV duration, and time from diagnosis to NIV application. The p-values of the Kolmogorov-Smirnov test were significant, which rejected the null hypothesis, and the results (D statistic, p-value) are as follows: pre-NIV pH (0.122, <0.001), age (0.125, <0.001), NIV duration (0.235, <0.001), time from diagnosis to NIV application (0.366, <0.001).

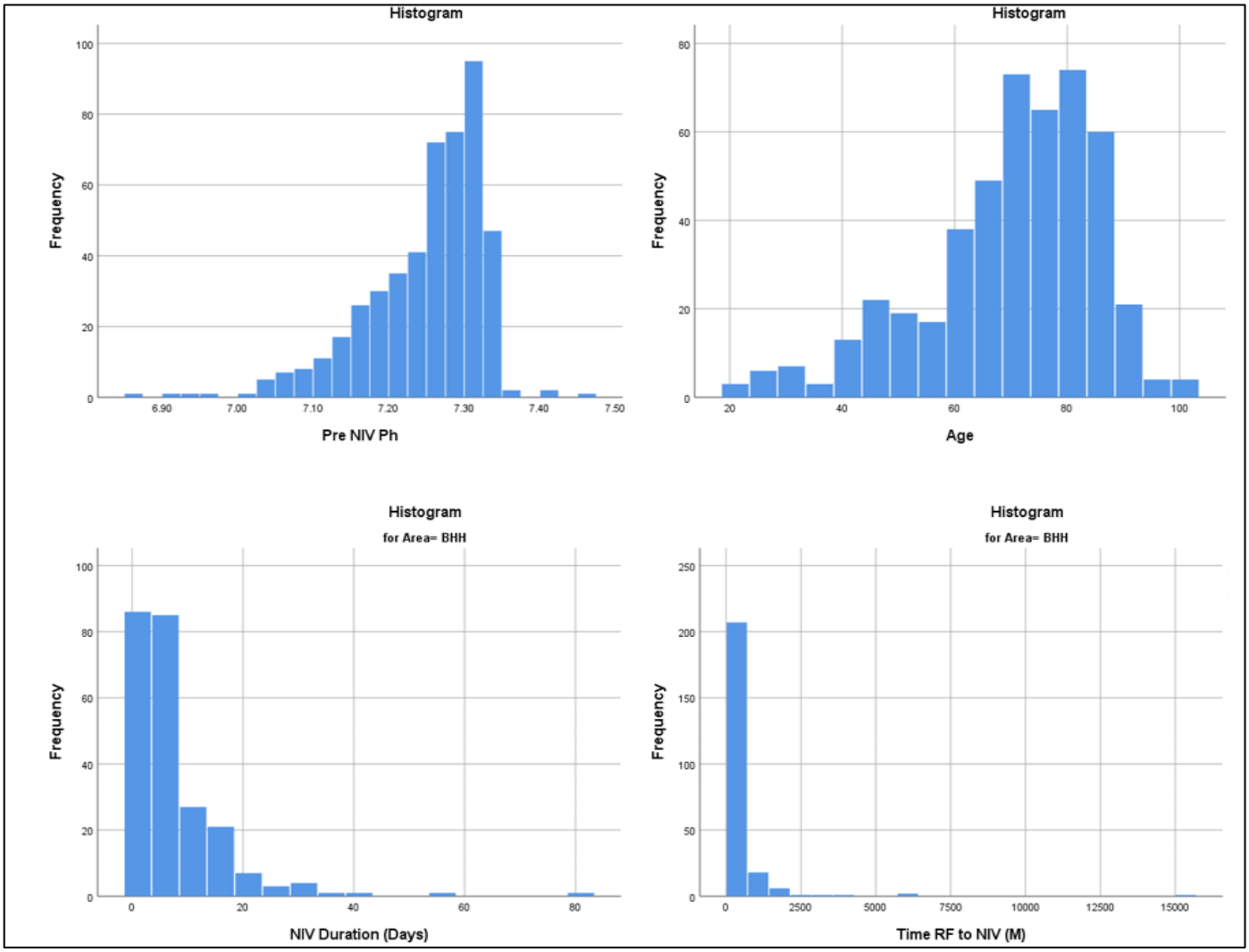


Figure 3.1 Normality tests analysis

3.3.3 Univariable analyses

In the univariable analysis for the two subgroups (obesity & non-obesity related AHRF), the patients who died in-hospital were older than those who survived to discharge. There were significant differences between survivors and those who died with regards to the underlying diagnosis. Pre-NIV pH was higher in the survived to discharge group compared to the in-hospital mortality group. More than two-thirds of the in-hospital mortality group had NIV failure. In one of the included hospitals (BHH, n=237) more data was available, which enabled additional analyses in this subgroup. There were significant differences between the groups (survived vs. died) in the number of days using NIV and the proportion of patients who were treated with domiciliary NIV. No significant differences were noted between the two groups in the time from diagnosis to NIV application (See tables 3.3 and 3.4).

3.3.4 Multivariable analyses

In multivariable logistic regression, significant predictors of in-hospital mortality and NIV failure were pre-NIV pH<7.25, increased age and underlying cause of AHRF, whereby the aetiology with the best prognosis was obesity-related AHRF (See Tables 3.5 & 3.6). This condition was taken as the reference value and hazard ratios for death relative to this were calculated in the regression models. In the obesity-related AHRF group, pre-NIV pH of below 7.15 was associated with a significant increase in mortality (OR 7.80, (95% 1.84-33.01), P=0.01) but not between 7.15-7.25 (OR 2.04, (95% 0.52-7.92), P=0.31) and was associated with a significant increase in NIV failure (OR 10.64, (95% 2.66-42.50), P=0.00) but not between 7.15-7.25 (OR 2.60, (95% 0.72-9.41), P=0.15). Within the BHH sub-group, where additional data was available, we were also able to assess the contribution of domiciliary NIV to the model; receipt of this appeared to be protective (See Tables 3.5 & 3.6). A Kaplan Meier curve was constructed comparing in-hospital mortality in groups split by aetiology of AHRF (obesity-related AHRF vs not obesity-related AHRF) (See Figure 3.2). The pH thresholds included are pH > 7.25 and pH 7.15 - 7.25 as pH < 7.15 demonstrated a significant predictor of in-hospital mortality and NIV failure for obesity-related AHRF and not obesity-related AHRF.

Table 3.5 Multivariable logistic regression demonstrating the predictors of in-hospital mortality

Variable		Odds Ratio	P
Total non-COPD AHRF			
pre-NIV pH <7.25	pH <7.15	2.22[a] (1.13-4.38)	0.02
	pH 7.15-7.25	1.87[a] (1.09-3.19)	0.02
Pre-NIV pH*		0.01 (0.00-0.06)	<0.001
Pneumonia on admission		5.31[b] (2.33-12.13)	<0.001
Bronchiectasis on admission		4.24[b] (1.68-10.68)	0.00
NMD on admission		4.04[b] (1.89-8.64)	0.00
Fluid Overload on admission		3.74[b] (1.56-8.97)	0.02
Age		1.03 (1.01-1.05)	<0.001
Subgroup (BHH): Domiciliary NIV		0.07 (0.01-0.49)	0.01
Subgroup: Obesity-related AHRF			
pre-NIV pH <7.25	pH <7.15	7.80[a] (1.84-33.01)	0.01
	pH 7.15-7.25	2.04[a] (0.52-7.92)	0.31
Age		1.03 (0.98-1.08)	0.23
Subgroup: Non-obesity related AHRF			
pre-NIV pH <7.25	pH <7.15	4.54[a] (1.69-9.35)	0.00
	pH 7.15-7.25	1.84[a] (1.04-3.27)	0.04
Age		1.03 (1.01-1.05)	0.01

[a]The odd ratio is against the reference group: pH>7.25, [b]The odd ratio is against the reference group: Obesity-related AHRF

** The pre-NIV pH analysed as continuous variable*

Table 3.6 Multivariable logistic regression demonstrating the predictors of NIV failure

Variable		Odds Ratio	P
Total non-COPD AHRF			
pre-NIV pH <7.25	pH <7.15	2.52[a] (1.30-4.90)	0.01
	pH 7.15-7.25	2.03[a] (1.20-3.44)	0.01
Pre-NIV pH*		0.01 (0.00-0.04)	<0.001
Pneumonia on admission		5.15[b] (2.32-11.44)	<0.001
Bronchiectasis on admission		1.11[b] (1.23-7.82)	0.02
NMD on admission		3.15[b] (1.49-6.65)	0.00
Fluid Overload on admission		5.43[b] (2.40-12.27)	<0.001
Age		1.03 (1.01-1.06)	<0.001
Subgroup (BHH): Domiciliary NIV		0.00 (0.00- -------)	0.99
Subgroup: Obesity-related AHRF			
pre-NIV pH <7.25	pH <7.15	10.64[a] (2.66-42.50)	0.00
	pH 7.15-7.25	2.60[a] (0.72-9.41)	0.15
Age		1.02 (0.98-1.07)	0.30
Subgroup: Non-obesity related AHRF			
pre-NIV pH <7.25	pH <7.15	1.96[a] (1.11-3.46)	0.02
	pH 7.15-7.25	1.80[a] (0.89-3.68)	0.11
Age		1.03 (1.01-1.05)	<0.001

[a]The odd ratio is against the reference group: pH>7.25, [b]The odd ratio is against the reference group: Obesity-related AHRF

** The pre-NIV pH analysed as continuous variable*

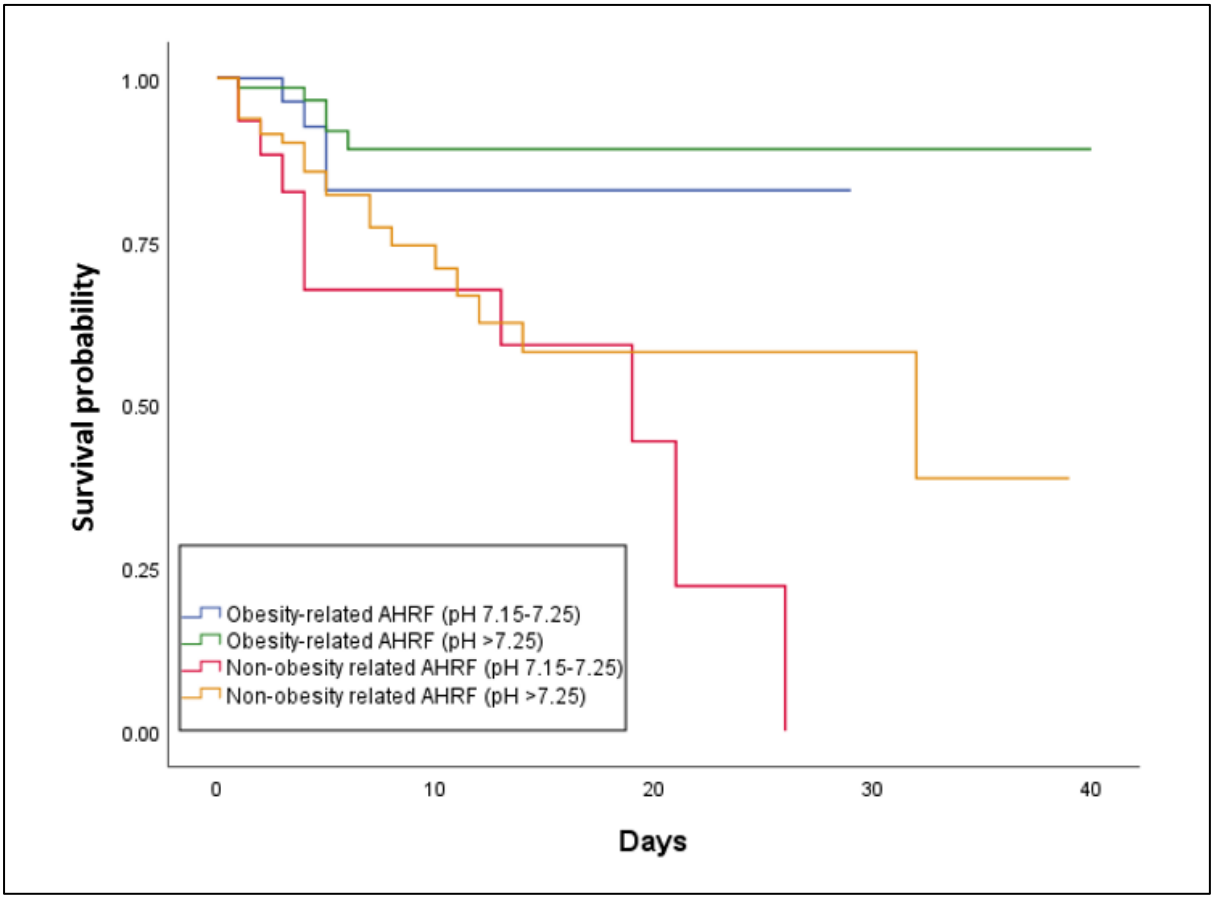


Figure 3.2 Kaplan Meier curves illustrating in-hospital mortality in patients stratified by diagnostic condition (Obesity-related RF VS Not obesity-related RF) (log-rank: p=0.001)

In multivariable poisson regression, age and pre-NIV pH have an impact on the NIV duration & the time from diagnosis to NIV application. For NIV duration (days), the days on NIV increases for every unit increase in Pre NIV pH (OR 2.50, (95% 1.25-4.50), P=0.01), and the days on NIV decreases for every unit increase in Age (OR 0.99, (95% 0.98-0.99), P= <0.001). For time from diagnosis to NIV application, the time increases for every unit increase in Pre NIV pH (OR 1.65, (95% 1.50-1.82), P=<0.001), and the time increases for every unit increase in Age (OR 1.01, (95% 1.00-1.01), P=< 0.001) (See Table 3.7).

Table 3.7 Multivariable poisson regression demonstrating the effect of age and pre-NIV pH on NIV duration & time from diagnosis to NIV application

Variable	Odds Ratio	95% Confidence Interval		P-value
		Lower	Upper	
Days on NIV				
pre-NIV pH	2.50	1.25	4.50	0.01
Age	0.99	0.98	0.99	<0.001
Time from diagnosis to NIV application				
pre-NIV pH	1.65	1.50	1.82	<0.001
Age	1.01	1.00	1.01	<0.001

NIV: *Non-invasive ventilation*

3.4 Discussion

Our study has shown that patients with obesity-related AHRF have a high rate of survival to hospital discharge (93.6%) than other conditions when managed in ward-based settings. We have also shown that patients in this group with a pre-NIV pH between 7.15 and 7.25 exhibit similar prognosis to patients with a higher pre-NIV pH, unlike in other conditions causing AHRF. This suggests that obesity-related AHRF can be safely managed outside the ICU at pre-NIV pH levels down to 7.15. However, in other conditions reported in our paper patients with a pre-NIV pH <7.25 might require management in the ICU setting due to their poor prognosis. The exception to this would be if there was a ceiling of treatment set, defined here as the predetermined highest level of care (ward-based) as the medical team will do the usual care in medical wards without patients' escalation to ICU regardless of how unwell they become, whereby it was decided that escalation beyond the ward environment was inappropriate.

3.4.1 Survival rates when managed with ward-based NIV

Overall, 80.2% of patients survived to hospital discharge, which is greater than the survival rate reported in non-COPD AHRF patients by Carter et al and in the UK national audit of AHRF patients who had COPD (79.55% and 75%, respectively) (167, 180). This suggests that hospitals could consider modifying their NIV care pathways to accept more non-COPD AHRF cases into ward-based settings, as their prognosis is equal or better than those already routinely managed in this setting (COPD). Whilst rates of in-hospital mortality

in other studies appear higher than the landmark randomised controlled trial in COPD (96), this may be related to the selection of patients who were not expected to survive, either due to their condition and its severity or due to co-morbid disease (181).

The in-hospital mortality rate of 6.9% for patients with obesity-related AHRF was significantly lower than for other conditions which strongly suggests that NIV should be considered for use in obesity-related AHRF in ward-based settings, given that their risk of a poor outcome is lower. This finding is consistent with the results of a study of patients managed in a critical care setting, in which mortality was found to be lower in obesity-related respiratory failure patients compared to COPD patients managed with NIV (128). Moreover, this is consistent with a recent study that reported a 15% mortality rate for the obesity-related respiratory failure group which was lower compared to the other diagnostic groups (167).

Patients with pneumonia had the highest rate of in-hospital mortality (32.1%), with a high odds ratio of mortality when compared to obesity-related AHRF patients (5.313, $P<0.0001$) and other diagnostic groups. This finding is in line with the National Confidential Enquiry into Patient Outcome and Death (NCEPOD) data, which indicated that patients with pneumonia experienced higher in-hospital mortality (181). Moreover, the British Thoracic Society/Intensive Care Society guidelines for the ventilatory management of acute hypercapnic respiratory failure in adults already recommend against the use of ward-based NIV in patients with pneumonia (135). The higher in-hospital mortality rate noticed in patients with pneumonia emphasises the importance of the NCEPOD recommendation that

“Early senior review and escalation planning is essential to ensure these patients receive appropriate treatment in the correct location.” (181).

This study showed that a higher proportion of the in-hospital mortality group had NIV failure compared to the discharged group (83.2% vs. 5.7%, P<0.0001). One possible explanation for this is that most of them may have received NIV as a ceiling treatment, which is not fully reported in the database; this might explain why they were being treated in ward-based setting, instead of critical care settings with advanced treatment.

3.4.2 Predictors of in-hospital mortality and NIV failure

Pre-NIV pH was a significant predictor of in-hospital mortality and NIV failure when it was analysed as a continuous variable and when it was grouped by thresholds. The importance of pre-NIV pH seen in our study was consistent with the findings of the UK national audit of COPD patients treated with NIV (180) where pre-NIV pH < 7.15 and 7.15-7.25 were associated with a higher risk of mortality and NIV failure (2.223, P=0.021 and 1.865, P=0.023, respectively). However, in contrast to the findings seen in COPD patients in the national audit, we were able to show that there was no difference in rate of in-hospital mortality between obesity-related AHRF patients with pre-NIV pH 7.15-7.25 compared to those with pre-NIV pH>7.25, and that this effect was driven by low death rates in the obesity sub-group at lower pH levels. This suggests that a pre-NIV pH threshold of 7.15-7.25 could be chosen for managing obesity-related AHRF patients in lower intensity settings

(outside the ICU). The thresholds pre-NIV pH appears to be superior to continuous pre-NIV pH as it is quick, feasible, and easy to use in clinical situations.

Age was also an important predictor of in-hospital mortality in non-COPD AHRF patients treated with NIV. This is consistent with studies done on AHRF due to COPD (105, 182) and AHRF unrelated to COPD (167). It was expected that a relation between age and mortality could be found since age is not necessarily a restriction to the treatment and in general older age is associated with worse prognosis. The time from AHRF to NIV application was not different in the in-hospital mortality group. The British Thoracic Society 'Quality standards for acute NIV in adults' notes "Patients who meet evidence-based criteria for acute NIV should start NIV within 60 minutes of the blood gas result associated with the clinical decision to provide NIV and within 120 minutes of hospital arrival for patients who present acutely" (183). This is because delays in treatment have been associated with reduced survival, however it is also notable that some patients with COPD deteriorate late, and these also represent a poor prognostic group (182). A longer wait for NIV application could result from high numbers of emergency hospital admissions, poor NIV capacity, or inadequate clarity within the hospital's NIV pathway. Notably, the time from diagnosis to NIV application was generally at or close to the national standard of 120 mins (120 v 140 minutes, survived v died) in our group which may have reduced power to detect differences based on this factor.

3.4.3 Strengths and limitations

The key strengths of this study include the multiple centres with a large cohort size, which is larger than other recent cohort studies targeting the same population (167), and the detailed data available particularly at BHH, which allowed assessment of the impact of timing of acute NIV treatment as well as the impact of previous domiciliary NIV. It includes a 'real world' dataset as the patients were unselected. Moreover, the study can be used as one of the initial steps and insights studies generating hypotheses to be studied further by larger and more controlled trials. The limitations of the study's findings are as follows. First, it was limited by the uncontrolled and retrospective cohort design (pre-recorded dataset) which produced a selection bias as some of the independent variables, such as some vital signs, were missing in the data set. Those missing variables limit us from recording potential confounding factors and testing more NIV success/failure predictors tools that have been used in COPD such as NIVO or HACOR scores. Second, despite the larger cohort size, compared to other cohort studies, the findings revealed wide confidence intervals which can underpower and limit the generalization of the findings.

3.4.4 Conclusion

In summary, pre-NIV pH and age have been identified as important predictors of surviving ward-based NIV treatment. These findings support the use of NIV in ward-based settings for obesity-related AHRF patients with pre-NIV pH thresholds from 7.15 upwards. Although the study showed promising outcomes for the obesity-related AHRF group, these outcomes represented with wide confidence intervals which can underpower and limit the generalization of the findings. Therefore, future studies with larger cohort size and future controlled trials are required to prove the clinical effectiveness of using NIV outside critical care settings for obesity-related AHRF. In addition, based on the difficulty in ascertaining from the database the important variables such as vital signs, which patients had NIV as ceiling of treatment, and what were the comorbidities, from April 2019 the trust's databases have been upgraded to capture this information in real time.

4 Investigation of healthcare professionals' attitudes on managing acute hypercapnic respiratory failure patients with non-invasive ventilation outside Intensive Care Units pre and post COVID-19: a multi-methods study

4.1 Introduction

4.1.1 Background

4.1.1.1 How Covid-19 affected the original plan for this thesis

Chapters 2&3 showed that there was an evidence gap regarding the OHS group in terms of the lack of RCTs assessing the effectiveness of NIV for the OHS group despite positive and promising outcomes from cohort retrospective and prospective studies which prevent strong recommendations from international guidelines, so the plan was to do a feasibility study to address this evidence gap. The predictions were to prepare the ethical approval documents, apply for the IRAS form to get the ethic approval, and start a clinical trial along with writing some of the thesis chapters. The process started on preparing and obtaining ethical approval for the feasibility study. It was started by writing the study protocol followed by IRAS form and the study required documents like consent forms and information sheet (See appendix 3). The ethical approval process was in the final amendment that was required from the sponsor (University of Birmingham). However, at the time that I was due to submit my ethics for this study, the Covid-19 pandemic began which had three main impacts on achieving this aim (1) ICU and ward-based ventilation

would be in short supply due to Covid-19 patients, thus reducing feasibility during my PhD timescale, (2) All NHS Trusts stopped research outside Covid-19, thus making it impossible to set up my study in my PhD timescale (3) Clinician attitudes to the ventilation of hypercapnic patients in wards in the absence of RCT data seemed likely to change markedly due to Covid-19, potentially negating the requirement for a trial of the type II respiratory failure had proposed, as obese patients with AHRF might be much more acceptable in ward-based environments in the post Covid-19 world. I, therefore, decided to conduct a multi-methods study to explore the third impact in more details, which would be feasible in my PhD timescale and complementary to all my prior work.

4.1.1.2 Ward-based NIV for AHRF (COPD and non-COPD)

COPD is a chronic inflammatory lung disease that causes expiratory airflow limitation and thereby causes physiological ventilatory dysfunction (25). COPD is one of the leading causes of mortality worldwide. Many COPD patients will experience an acute exacerbation of COPD (AECOPD) which is defined by the Global Initiative for Chronic Obstructive Lung Disease (GOLD) as “an acute worsening of respiratory symptoms that results in additional therapy.” (184, 185). Around 20% of AECOPD patients will subsequently develop acute hypercapnic respiratory failure (AHRF)(180).

Importantly, development of AHRF in AECOPD is associated with worse outcomes, including in-hospital and post-discharge mortality as the European COPD audit analysed clinical outcomes for almost 16,000 patients admitted with AECOPD and found that the risk

of in-hospital and 90-day mortality was significantly higher for hypercapnic patients (acidosis) compared to non-hypercapnic patients (186).

NIV is an evidence-based treatment for AHRF patients with AECOPD. A systematic review of RCTs found that treatment with NIV, in addition to standard care, compared to standard care alone (which was defined by the trial authors that it involved a combination of supplemental oxygen, antibiotics, bronchodilators, steroids, respiratory stimulants, and/or other suitable medical interventions (e.g., diuretics, methylxanthines) for AHRF with AECOPD was associated with reductions in the mortality rate and need for intubation of 46% and 65%, respectively (98). NIV using is supported by international guidelines that published is 2016 and 2017 recommending its use in selected patients. The European Respiratory Society/American Thoracic Society guidelines and the British Thoracic Society/Intensive Care Society guideline for the ventilatory management of AHRF in adults recommends the use of NIV in AHRF patients secondary to AECOPD (92, 135, 187).

With regards to the area of NIV management, the use of NIV for respiratory failure in AECOPD has grown rapidly over the past two decades particularly in ward-based settings (188). In 2000, the Yorkshire Non-Invasive Ventilation trial showed a significant reduction in need for intubation and in-hospital mortality for the use of early ward-based NIV for mild-to-moderate AHRF secondary to AECOPD (96). Since 2000, numerous studies with the same aim have presented evidence in favour of ward-based NIV delivery for AHRF secondary to AECOPD (97, 165, 170, 171, 173-178, 189) even for COPD patients with severe AHRF (105). Dave et al. (105) used prospectively collected data for AHRF patients secondary to COPD

who were managed by NIV between 2004 and 2009 at a single centre in the UK. The authors analysed predictors of in-hospital mortality and need for intubation and found that severe acidosis patients on admission (pH < 7.15) have higher risk of in-hospital mortality (in-hospital mortality rate = 37.5%). Moreover, the authors found no differences in terms of in-hospital mortality between patients with pH > 7.25 and patients with pH 7.16–7.25 on admission (in-hospital mortality rate= 21% vs. 20% respectively), suggesting that patients with moderate to severe acidosis can be safely managed on a ward-based settings with consideration of close monitoring for severe AHRF patients. In a retrospective study of AHRF patients secondary to COPD treated with NIV in ward-based settings, Yalcinsoy et al. (190) found that there were no differences in the rate of ICU admission, in-hospital mortality, or length of hospital stay between patients grouped according to severity of admission pH ((7.20 < pH < 7.25 vs. 7.26 < pH < 7.30), suggesting that ward-based NIV is safe in patients with moderate to severe AHRF due to COPD.

When the wise use of hospital's resources is a necessity, the ward-based NIV application is expected by policymakers and healthcare providers in the healthcare system as it appeared to be a cost-effective alternative to critical care admission (178, 191). In 2018, the Yorkshire Non-Invasive Ventilation trial demonstrated that ward-based NIV application was associated with a reduction in treatment costs, compared to critical care application, of £521 per patient and the cost-savings were mainly due to reduced utilisation of ICUs resources. The cost-saving of ward-based NIV is very important especially for low-income and middle-income countries with limited access to critical care resources (192).

However, patients with AHRF caused by conditions other than COPD are excluded from many hospitals' pathways of ward-based NIV based on unclear and limited evidence regarding their prognosis or utility of treatment outside critical care settings. Over the last decade, NIV was used in several clinical conditions such as in patients immuno-compromised from haematological diseases, in restrictive lung diseases and in obesity hypoventilation syndrome (OHS) (135). In the past decade, OHS is the second most common indication (after COPD) for NIV treatments among hospitalized patients with AHRF (164, 165).

With regards to the studies related to the conditions other than COPD, there is limited data regarding the use of NIV in obese patients, most of the data arise from cohort studies. In OHS for example, Rabec et al. and Duarte et al. showed in their retrospective cohort studies that patients with AHRF due to OHS were successfully treated with NIV, improved in $PaCO_2$ and avoided ETI, and lowered the mortality rate with sample size of 50 and 41 respectively (123, 124). Carillo et al., using a prospective cohort study, compared the outcomes of patients treated with NIV who were suffering from AHRF due to either COPD or OHS. Patients with OHS had a lower rate of NIV failure and hospital mortality, and a higher 1-year survival (128). Systematic review of the RCTs in this field shows that there is a lack of robust data.

The qualitative literature regarding NIV is focused on different aspects such as HCPs attitudes toward NIV guidelines and use for patients with acute respiratory failure, HCPs experiences of NIV in critical care units including the effect of NIV simulation program on

wards nurses' knowledge, HCPs and patients' experiences of domiciliary NIV including using modems and telehealth, and patients' experiences of NIV due to AHRF.

Sinuff et al. reported in their qualitative study the importance of the NIV guideline as it defines HCPs' responsibilities, increases patient safety, reduces practice variability, avoids clinical conflict, and is used as an educational resource to improve guideline awareness (193). In addition, Green et al. concluded in their review that nurses generally believe NIV is a useful clinical therapy, however, the application of NIV is associated with issues around limited and non-standardised education provision, clinical communication considerations, and variable use of guidelines (194). Another qualitative study was conducted to describe the experienced nurses' actions of caring ARF patients with NIV. The experienced nurses demonstrated practical wisdom in managing ARF patients with NIV by achieving NIV adaptation, ensuring effective ventilation, and responding attentively to patients' perceptions of NIV (195). Using a simulation program, the findings from a qualitative study confirmed that the NIV simulation program is an effective method for improving the knowledge of NIV nursing and self-efficacy and will be helpful in developing educational methods and strategies related to NIV nursing for general ward nurses (196). A qualitative study was conducted aimed to explore the nursing experience with NIV for AECOPD patients. The study authors concluded that interprofessional team communication and collaboration and NIV guidelines implementation are important aspects of nursing education and novice nurses' clinical support which will improve nursing clinical decisions (197). From a patient perspective, a qualitative study, using a semi-structured interview,

was conducted to explore the COPD patient's journey while being managed with NIV and plan for NIV tolerance. Trust in the HCPs and understanding the importance and how NIV works are aspects that promote NIV tolerance, however, being misinformed and physical and psychological discomfort with the NIV treatment are aspects that deterred NIV tolerance (198).

With the current clinical practice of NIV management, there are qualitative evidence gaps regarding the ward-based NIV management for AHRF that will be addressed in this study. For example, there are gaps in addressing the current clinical practice of ward-based NIV for AHRF due to not only COPD but non-COPD diseases, the HCPs' perspectives and opinions of AHRF diseases that can be managed in ward-based settings with NIV, the barriers to the expansion of ward-based NIV services, the factors that aid the improvement of ward-based NIV, and the effect of Covid-19 on managing AHRF patients with NIV in terms of guidelines/protocol application and resources availability.

4.1.1.3 Covid-19

This section includes a general overview of Covid-19 and its effect on the hospitals' beds capacity (especially critical care beds) which may have changed the HCPs' attitudes toward managing AHRF outside critical care units. Therefore, exploring the attitudes could be an important aspect of understanding behaviour and impact on medical services long-term and could inform feasibility and structure of future trials by others in this area.

Definition & History

Coronaviruses (CoVs) are a group of RNA viruses that mostly cause respiratory tract infection for humans. Severe Acute Respiratory Syndrome Coronavirus (SARS-CoV) was first identified in 2002-2003 in the Guangdong Province of China. Following this outbreak, in 2012, a highly pathogenic respiratory tract infection mainly in Saudi Arabia and other middle east countries was detected which became another novel human CoV called Middle East Respiratory Syndrome Coronavirus (MERS-CoV) (199-201). On December 8th, 2019, Chinese health authorities recognized an unexplained SARS-like disease in some patients in Wuhan. Diseases have been tracked to the South China Seafood Wholesale Market in Wuhan, that trades fish and a variety of other live species including chickens, bats, marmots and snakes (201). This tracking process concluded that most patients who acquired this virus had some form of contact with this market. On January 7th, 2020, the Chinese Centre for Disease Control and Prevention (CDC) examined the patients by throat swab and the World Health Organization (WHO) has officially named the disease as the coronavirus disease 2019

(Covid-19), which is currently also named Severe Acute Respiratory Syndrome Coronavirus-2 (SARS-CoV-2) (202). Due to its outbreak and rapid spreading concerns, the WHO announced a global emergency on January 31st, 2020, and listed as a pandemic on March 11th, 2020 (203). As of December 2021, COVID-19 has been recognized in 190 countries with approximately 250 million laboratory-confirmed cases. Almost 2.1% global deaths and 68% global recovery were reported from the total laboratory-confirmed cases.

Pathophysiology & Pathogenesis

In 2020, Zhou. et al. reported that SARS-CoV-2 is the same as SARS-CoV in terms of enzyme cellular entry receptor (204). It is characterised by a lung injury with increased infiltrations of monocyte, macrophage, and neutrophil into the lungs and increased levels of pro-inflammatory cytokines and chemokines. Thus, the combination of these elevations may explain the clinical exacerbation of SARSCoV-2 infection. Constant stimulation by the virus creates increases in plasma cytokines and chemokines called “cytokine storm” with immunological reactions that can damage the cells and tissues extensively and results acute respiratory distress syndrome (ARDS) and multiple organ dysfunction syndromes (MODS) (205, 206).

Clinical presentation & Diagnosis

COVID-19 is an infectious disease that is transmitted by respiratory droplets and contact routes (207, 208). While most affected patients have mild symptoms (mainly fever and cough) or even no symptoms (asymptomatic), some patients with chronic comorbidities may develop serious illness such as ARDS, respiratory failure, sepsis, septic shock, or multiple organ failure (209, 210). A Ground-glass opacification and lungs consolidation are the most common presentation in chest x-ray and CT scan (211).

Clinical symptoms, serum test, clinical diagnosis, and epidemiological history are the important procedures of considering a patient is affected by covid-19 (212).

4.1.1.4 Effect of covid-19 on critical care beds

Data obtained from 182 countries showed that ICU beds ranging from 0 to 60 per 100.000 population with more than 50% of the countries have <5 ICU beds per 100,000 population (213). Globally, the ICU beds range is 5-60 per 100,000 population in high-income countries (HICs) and 0-21 per 100,000 population in low- and middle-income countries (LMICs) (213). In European countries, the ICU beds per 100,000 ranged between 5 to 35.3 (See Table 4.1 for most European countries' ICU beds). In China, the Chinese Society of Critical Care Medicine reported that there is major insufficiency in ICU beds as the ICU beds per 100,000 population is 3.5 which make the country face serious challenges during the pandemic outbreak (214). Moreover, with the current estimation of 0.1 to 2.5 ICU beds per 100,000 population in some of LMICs, LMICs are at high risk of failure to manage the surge of severe COVID-19 patients who need critical care management (215).

Table 4.1 ICU beds by country (216)

Country	Total ICU Bed	ICU Beds Per 100,000 Population
Germany	28,031	35.3
Estonia	483	33.5
Austria	2,369	26.4
Slovenia	539	24.2
Lithuania	644	22.7
Romania	4,574	21.4
Luxembourg	130	21.1
Belgium	1,755	15.9
Slovakia	814	14.4
Hungary	1,374	13.8
Bulgaria	913	12.2
Czech Republic	1,227	11.6
Cyprus	92	11.4
Poland	4,391	11.1
Malta	49	9.9
Spain	4,479	9.7
Latvia	217	9.7
Slovakia	500	9.2
Croatia	396	9
France	5,671	8.2
Italy	5,184	8.1
England	3,999	7
Ireland	289	6.5
Netherlands	1,065	6.4
Denmark	382	6.4
Finland	329	6.1
Greece	680	6
Sweden	522	5
Portugal	451	4.2

ICU: *Intensive care unit*

Since the identification of SARS-CoV-2 in December 2019 in China, COVID-19 has caused more than 250 million confirmed cases across 190 countries. Despite the governmental and public health agencies' regulations and efforts to contain the Covid-19 outbreak, there is concern regarding the hospital resources to manage Covid-19 patients admitted to hospitals (217). A recent study systematically reviewed studies regarding to ICU admission rate done in the first half of 2020; first-wave outbreak, and revealed that one-third ICU beds were occupied by of coronavirus patients (218).

Despite good numbers of ICU beds in some countries overall, some areas within these countries struggle with ICU beds availabilities. In Brazil, some areas have no ICU beds despite the number of ICU beds per 100,000 population; 12.9. Furthermore, north-eastern region of Brazil faced a serious ICU beds shortages as after one and a half months of the first Covid-19 case was discovered, around 60% of Covid-19 cases required ICU admission and 55% required mechanical ventilation support (219, 220).

In United States, a study done a scenario analysis based on the self-isolation variations. Without self-isolation, 3.8 times more ICU beds were needed than the number that existed in the United States to manages severe Covid-19 cases. On the other hand, self-isolation from the symptoms' onset will decrease the number of ICU beds needed by 48% (221, 222).

In Italy, the ICU beds per 100,000 population is far below the European Union average. After the COVID-19 outbreak, 10% of the confirmed cases had severe Covid-19

requiring critical care management and mechanical ventilation. This outbreak has saturated the ICU beds availability of many areas in Italy, which negatively affected the healthcare systems beside the dramatic decisions from physicians regarding patient's selection priorities (223).

In the United Kingdom, as of Dec 2021, the total confirmed Covid-19 cases exceeded 9.5 million with transmission rate (R0) of 1.1-1.5. The admitted Covid-19 patients around 550,000 patients with 6,500 patients currently hospitalised. With the second covid-19 wave now increasing, more hospital admissions for Covid-19 patients is expected as the first wave in UK showed a 72% bed occupancy in general and critical care beds (224). On October 2020, NHS Wales reported that general and critical care beds went back to 87% bed occupancy (225, 226).

4.1.2 Rationale & Purpose of the Study

Establishing attitudes to an intervention are vital to a feasibility study anyway, but exploring how they are formed in more detail, and moreover how they have changed with Covid-19 could be an important aspect of understanding behaviour and impact on medical services long term. Therefore, the purpose of this multi-methods study is to understand healthcare professional perspectives on the use of non-invasive ventilation for respiratory failure outside of Intensive Care Units.

4.1.3 Research Questions

1. What are the experiences and perceptions of healthcare professionals on the use of NIV for respiratory failure outside critical care?
2. What is the effect of the pandemic on NIV management and how the perceptions have changed before and after the COVID-19 pandemic?
3. What are the enablers and barriers to the expansion of NIV treatment for respiratory failure outside of critical care settings?
4. What factors would be important to maintain or improve NIV services in ward-based setting?

4.2 Methods

The aim of this section is to set out the methodological approach undertaken to understand healthcare professional perspectives on the use of non-invasive ventilation for respiratory failure outside of Intensive Care Units and the effect of the pandemic on ward-based NIV management. This section will present the aim of this research, the methodological approach adopted, research design and ethical considerations, the sample that was selected, the instrument used in data collection, and the process of data analysis.

4.2.1 Study design

A multi-methods approach was chosen for this study. It involves the collection of empirical data which will gives more understanding and clarification for various observations (227).

4.2.2 Ethical considerations

A research proposal was submitted to the University of Birmingham Research Ethical Review Committee. Ethical approval was granted prior to commencement of the research (ERN_20-0528). The study was undertaken with the willingness and knowledge of the participants, and informed consent. It was clear to all participants that their participation was voluntary, and they were free to withdraw from the study at any time. Participants were given advanced notice prior to the interview with a broad outline of the subject to be discussed (participant information sheet).

4.2.3 Sampling and selection of Participants

Participants were sought through scoping surveys followed by in-depth interviews. The sample of participants was recruited by a purposive sampling method for the surveys and the interviews. We aimed to conduct 15 interviews based on prior research on the same type of interviewees (healthcare professionals) as they have shown this sufficient to gain meaningful insights (228-230) and data saturation as determined by continuous data analysis. The inclusion criterion was healthcare professionals who have experience in

managing respiratory failure patients by non-invasive ventilation in healthcare settings. The interviewer (B.M.F.), a PhD candidate, was not known to participants prior to the study, had qualitative research courses as part of his research degree and was mentored by N.K.G. and A.M.T. during the process.

4.2.4 Data Collection and Instruments Used in Data Collection

Data collection took place in 2021. This was a multi-methods study using sequential methods: a scoping survey; to mainly recruit participants and to have a general idea of NIV management for acute hypercapnic respiratory failure patients, followed by in-depth qualitative interviews. The online scoping survey was circulated to relevant professional organisations groups such as British Thoracic Society, Intensive Care Society, local Trust newsletters, via Birmingham Health Partners, Midlands Thoracic Society, and West Midlands Physicians Association, with a mixture of closed, Likert and open text questions. After the scoping survey, in-depth, semi-structured interviews were conducted with a series of questions in the general form of an interview schedule which was prepared in advance by B.M.F., N.K.G. and A.M.T. to help with the structure and flow of the interview. Interviews were undertaken face-to-face, via video conference or telephone according to the preference of the interviewee. The scoping survey and interview schedule were structured to cover the following sections:

- participant's demographics
- their general views on NIV and NIV management for AHRF due various conditions,

- their opinion on factors that affect the decision for which AHRF patients be managed with NIV in ward-based settings
- their view on Covid-19's effect on the healthcare services in general and the use of NIV in ward-based settings.

A pilot survey and interview were carried out prior to the commencement of the actual research to resolve any difficulties with the wording of the questions and the structure.

4.2.4.1 Survey

An online survey composed of 19 items was developed and validated by an expert panel, which included consultant respiratory physicians, critical care and respiratory medicine consultant, and a reader in health sociology and policy. Face and content validity were assessed after piloting this survey to 4 HCPs from different specialities. The questionnaire contained multiple-choice and Likert scale responses in two main sections. Section one included items regarding the NIV management for acute hypercapnic respiratory failure patients (e.g., management site, who conduct or lead NIV management, the presence of NIV protocol for AHRF, the presence of ward-based NIV for AHRF and factors affect the decision of ward-based NIV, and the effect of NIV management after Covid-19). Section two included participants' demographic information (e.g., education level, working role and area, and years of current work experience) (See appendix 4).

4.2.4.2 Interview

Semi-structured interviews were performed for this research study, which provided more flexibility to the participants than structured interviews to answer questions in their own words and elaborate them to develop an in-depth understanding of their experiences and perceptions in relation to the research questions. Five open-ended interview questions aligned with the research questions. In designing the interview questions, the goal was to explore and understand the general NIV management for AHRF patients. In addition, these interview questions addressed the participant's experience and opinion of which AHRF disease can be managed safely with NIV in ward-based settings, factors that affect the decision for managing this group in ward-based settings, and effect of Covid-19 on NIV management for AHRF patients (See appendix 4).

4.2.5 Procedures Used in Data Analysis

The Statistical Package for the Social Sciences (SPSS) version 24 was used to analyse the participants' data. The scoping survey was analysed using descriptive statistics, by measuring frequencies and percentages to summarize the demographic data of the sample and by measuring mean scores and standard deviation for the approximate beds' availabilities in the participant's hospital. Furthermore, the survey's Likert scale was converted to numerical scale with 1 being strongly disagree and 5 being strongly agree. Chi-square was used to present comparisons between groups. A p-value of ≤0.05 was considered statistically significant.

Interviews were transcribed *verbatim* (word-by-word) and analysed using qualitative content analysis which defined as a systematic process of coding to interpret the content of text data. Specifically, the framework method (231), which belongs to the qualitative content analysis family, was used for analysis. The framework method was chosen because it is characterized as a highly systematic method of categorizing and organizing qualitative data, provides clear steps to follow, produces highly structured outputs of summarised data, and seeks to draw descriptive and/or explanatory conclusions clustered around themes. The framework method provides a framework into which the researcher can systematically summarise the data and analyse it by matrix output; rows (cases) and columns (codes) (232). The procedure of the framework analysis is summarised into steps as follows: (1) Transcription; (2) Familiarisation with the interview; (3) Coding (See Figure 4.1); (4) Developing a working analytical framework; (5) Applying the analytical framework; (6) Charting data into the framework matrix; (7) Interpreting the data (231). Without using a qualitative data analysis software, inductive coding was applied to transcripts, line-by-line, independently by both B.M.F and N.K.G and then summarised in a matrix. Key findings were reported with illustrative quotes using an anonymous identifier: HCPs [HCP#]. Table 4.4 listed the major and minor themes derived from the procedure of analysis.

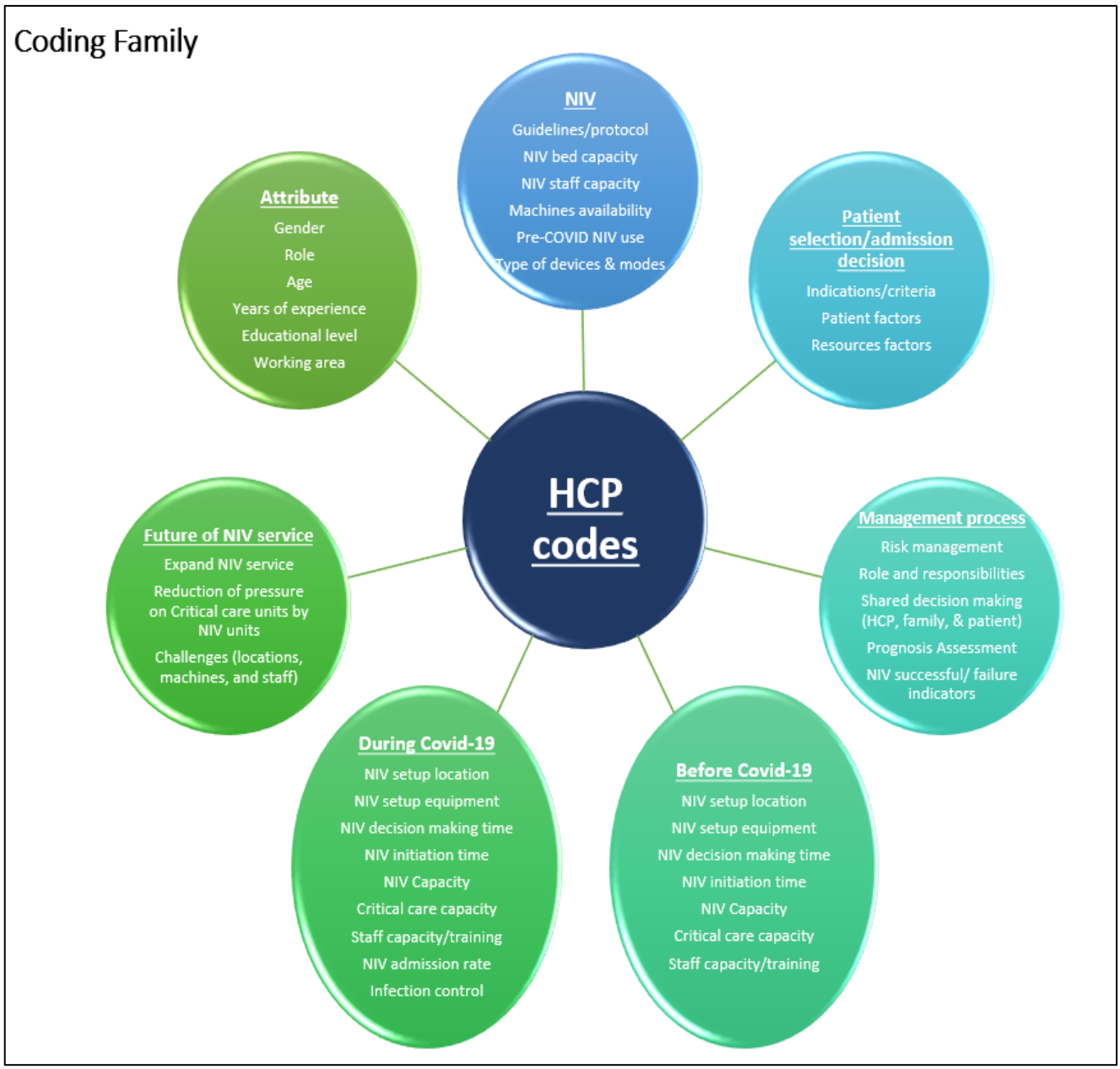


Figure 4.1 Coding Framework used in data analysis

4.3 Results

4.3.1 Scoping Survey

4.3.1.1 Participant characteristics

In all, 48 HCPs participated in the survey from different hospitals/health organizations around the United Kingdom such as Queen Elizabeth Hospital Birmingham, Birmingham Heartlands Hospital, Royal Free hospital, Royal Sussex County Hospital, South Tyneside District Hospital, and Royal Liverpool University Hospital. Characteristics of the participants are shown in Table 4.2. Almost two-thirds of the participants had a bachelor's degree as their highest qualification; more than half of the participants were physiotherapists, and the majority were working in ward-based settings.

4.3.1.2 NIV management for AHRF patients

In terms of HCPs responsibilities, almost two-thirds of the participants responded that the physiotherapists conduct day to day NIV management, and the majority agreed that doctors lead the daily NIV management decisions. With regards to the current clinical practice of the area of NIV management for common AHRF; COPD, OHS, and CPO, more than ninety percent of the participants responded that ward-based settings are the first place of care for COPD and OHS. However, two-thirds of the HCPs tend to manage CPO in critical-care settings. The most common factors that affect the acceptance of offering ward-based NIV to a patient with AHRF are as follows: cause of AHRF, initial blood gasses,

beds/staff availabilities, the hospital's protocol, and patient with comorbidities (See figure 4.3). Moreover, the HCPs' level of agreement (the HCPs' views and opinions) about managing AHRF with NIV in ward-based settings was different depending on the main cause of AHRF. For COPD, OHS, and NMD, more than half of the participants had an agreement of offering NIV in ward-based setting. For CPO, although half of the participants felt positive about offering NIV in ward-based settings, one-third of the HCPs were uncertain about offering NIV management in ward-based settings. For pneumonia, the majority disagreed that a ward-based setting was suitable for NIV (See figure 4.4). The figures 4.3 and 4.4 are presented in table format (See appendix 5).

Table 4.2 Characteristics of the participants

	n	%
Total	48	100.0
Gender		
Male	19	39.6
Female	29	60.4
Age (years)		
20-29	4	8.3
30-39	22	45.8
40-49	19	39.6
50-59	3	6.3
Ethnicity		
White	26	54.2
Asian / Asian British	18	37.5
Black / African / Caribbean / Black British	4	8.3
Highest qualification		
Bachelor's degree	30	62.5
Master's degree	15	31.3
PhD degree	3	6.3
Working role		
Consultant	2	4.2
Respiratory specialist	14	29.2
Physiotherapist	26	54.2
Nurse	6	12.5
Working area		
Wards	45	93.8
Critical care	2	4.2
Outpatient	1	2.1
Work experience (Years)		
<5	4	8.3
5-10	26	54.2
11-15	8	16.7
>15	10	20.8

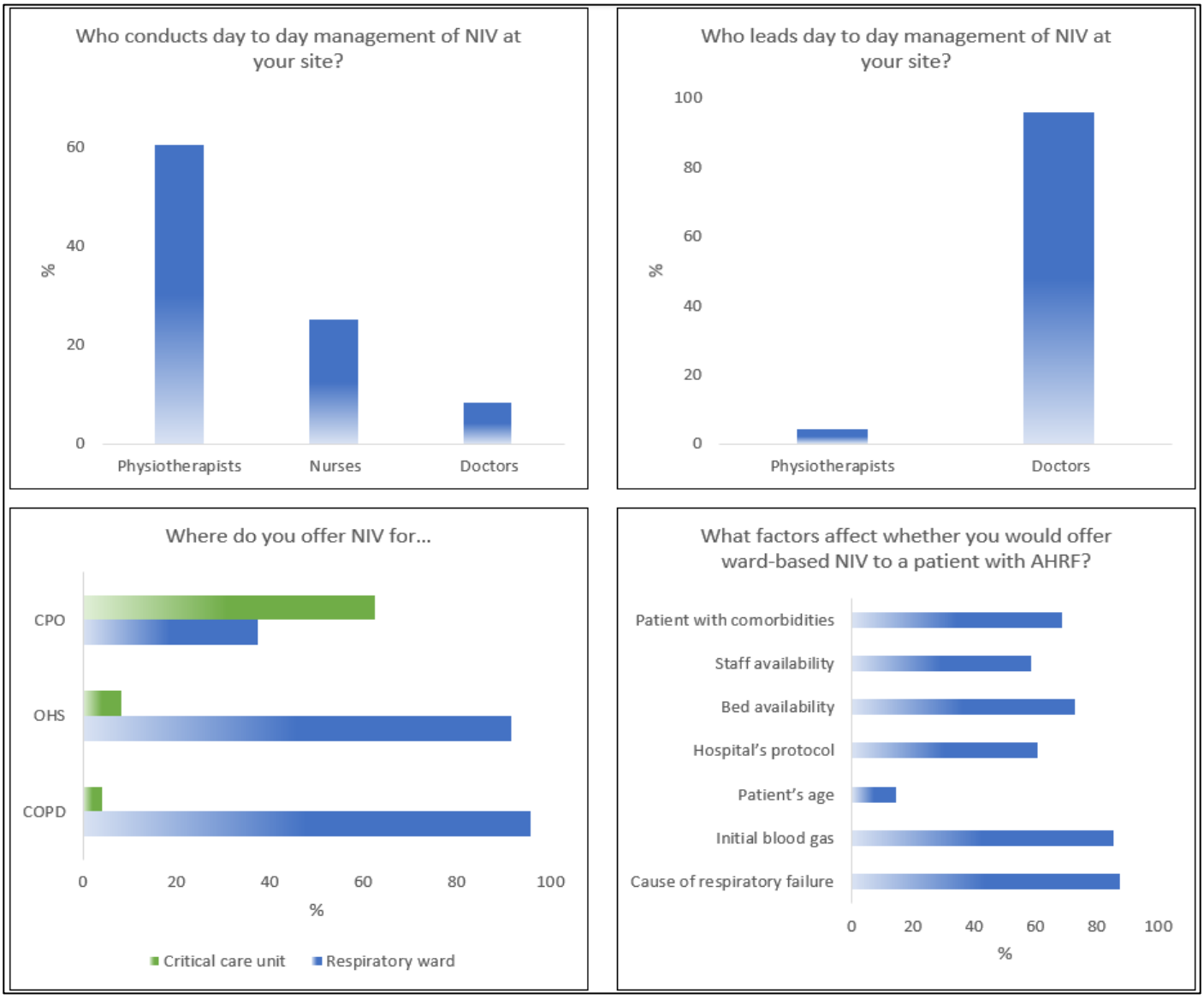


Figure 4.2 Clinical responsibilities of HCPs on managing AHRF with NIV

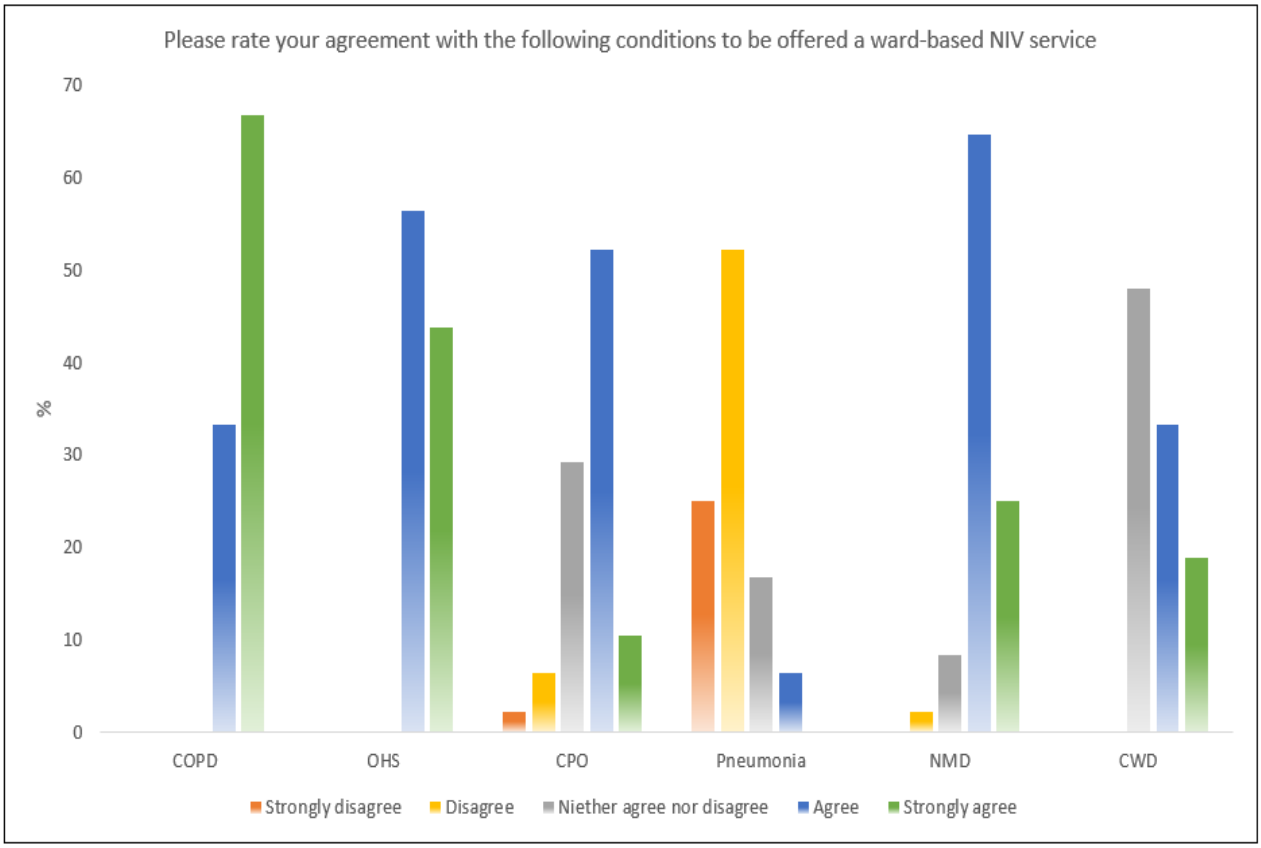


Figure 4.3 HCPs agreement on managing AHRF with NIV in ward-based settings

4.3.2 Interview study

4.3.2.1 Participant characteristics

In total, 15 HCPs were recruited for the qualitative interview study from different hospitals around the United Kingdom. Characteristics of the HCPs are shown in Table 4.3. The recruited HCPs comprised 9 physiotherapists, 5 physicians, and 1 nurse. Interview duration averaged 35 (range 20 – 45).

Table 4.3 Table of characteristics

Characteristic	n (%)
Gender	
Male: female	6 (40.0): 9 (60.0)
Age (years)	
20-29	1 (6.7)
30-39	8 (53.3)
40-49	4 (26.7)
50-59	1 (6.7)
60 and above	1 (6.7)
Ethnicity	
White	9 (60.0)
Asian / Asian British	4 (26.7)
Black / African / Caribbean / Black British	2 (13.3)
Educational level	
Bachelor's degree	9 (60.0)
Master's degree	3 (20.0)
PhD degree	3 (20.0)
Current role	
Physiotherapist	9 (60.0)
Nurse	1 (6.7)
Respiratory specialist	3 (20.0)
Consultant	2 (13.3)
Experience (years)	
<5	1 (6.7)
5-10	8 (53.3)
11-15	1 (6.7)
>15	5 (33.3)
Working area	
Wards	15 (100.0)
Critical care	0 (0.0)

The analysis of the interviews provided 40 free codes (See Appendix 6). Major and minor themes were generated after carefully reviewing the 40 codes (See table 4.4). Table 4.4 provides a list of clinical actions, grouped thematically, and provides illustrative quotes. It demonstrates, in some minor themes, clearly how experiences of HCPs have changed before and during/after Covid-19. Table 4.5 shows areas that emerged from the analysis to aid initiation and improving ward-based NIV services in the future.

4.3.2.2 Major theme 1: Clinical aspects of the delivery of NIV

Before COVID-19

Addressing the protocol

There is consensus among the HCPs with regards to the main protocol for using NIV for AHRF patients as it is based on the BTS guidelines (HCP2, HCP5, HCP8).

Addressing the clinical indications

From the HCPs' experiences, some of them feel that COPD, OHS, NMD, CWD, and bronchiectasis can be managed safely in ward-based settings (*HCP2, HCP6, HCP8, HCP12*). However, some HCPs have experienced only COPD and OHS patients, so they are more confident in managing those patients in ward-based settings and other conditions are discussed first with the consultant (*HCP3, HCP4, HCP5, HCP7, HCP11*). With regards to the

AHRF due to pneumonia, the HCPs emphasized that ward-based NIV is not the right decision for treatment (*HCP4, HCP6*).

Factors affecting the decision making

Based on the HCPs views, the factors affecting the decision making for initiating NIV concluded to two main factors: patients' factors and resource factors. The patient factors are as follows: whether the patient fits the protocol in terms of the underlying condition, patient's history, and patient's pre-existing conditions (*HCP2, HCP3, HCP5*). The resource factors focus mainly on staff and beds, and they are as follows: the nursing staff availability, the staff to patient ratio, the staff knowledge and confidence in terms of NIV management, and the beds' availability in the ward (*HCP2, HCP3, HCP5, HCP11, HCP13*).

After COVID-19

Addressing the protocol

During Covid-19, HCPs reported that the protocol has changed due to infection control procedures, and these changes mainly in NIV set-up location and equipment (*HCP2*).

NIV admission rate

The AHRF patients' numbers who require NIV dropped significantly during the pandemic. The HCPs suggested that human factors (e.g., patients were shielding which may

reduce the community transmission of respiratory viruses and pollution) played an important role in this reduction (*HCP2, HCP4, HCP5, HCP6, HCP8, HCP12*). However, some HCPs reported some other factors in this reduction like '...*or they don't want to come to not get the virus, or they've actually picked up COVID and then pass away*' (*HCP5*).

4.3.2.3 Major theme 2: Technical aspects of the delivery of NIV

Before COVID-19

NIV decision making & initiation time

In general, hospitals acknowledge the importance of initiation time, and the HCPs reported trying to initiate the NIV within an hour to two hours (*HCP8*).

HCPs roles and responsibility

Regarding the HCPs' NIV responsibilities, the interviewees agreed on the pathway of ward-based NIV management; the consultant (or medical registrar) lead the NIV by assessing the admitted patient and ordering the NIV, the physiotherapist perform the NIV initiation with the proper parameters and proper equipment, and the nurse do the basic NIV management and troubleshooting when the patient admitted to the ward (*HCP2, HCP3, HCP5, HCP8, HCP10, HCP14*). However, some HCPs reported a different pathway as the nurse only, without the physiotherapist, does the NIV initiation and management based on the consultant order (*HCP4, HCP11*).

After COVID-19

NIV decision making time & door to mask time

After the pandemic, the HCPs reported that the decision-making time for AHRF and other conditions is much quicker due to increasing experience for the HCPs with a high number of admitted patients (*HCP2, HCP7, HCP8, HCP13*). However, the time from door to mask for AHRF has increased above the time suggested by guidelines during Covid-19, and this increment is due to side rooms availability and infection control procedures (*HCP2, HCP5, HCP11*).

4.3.2.4 Major theme 3: Logistical aspects of the delivery of NIV

Before COVID-19

NIV setup location

The set-up location before the pandemic has no restrictions, it would be initiated anywhere in the hospital whenever the NIV was a need whether it is in A&E or wards (*HCP2, HCP6, HCP8, HCP13*).

NIV setup equipment

Before Covid-19, HCPs use the vented mask as it is safer for the patients, better in terms of ventilation, and more comfortable (*HCP2, HCP7)*.

Beds capacity

Only a few HCPs interviewees reported that bed availability is always an issue and a challenge in every acute hospital (*HCP15*).

Staff capacity/training

In terms of the staff capacity before Covid-19, the HCPs' views divided into 3 main points. First, they had no staff availability challenges as they have enough and well-trained staff, whether they are nurses or physiotherapists. Second, they have enough and well-trained nurses, however, out of hours nurses lack confidence due to inadequate training and uncompleted competencies. Finally, they don't have any specialist nurses or specialist physiotherapists for NIV management as they have one nurse per bay (*HCP7, HCP11, HCP12, HCP15*).

After COVID-19

NIV setup location

The set-up location during Covid-19 has some restrictions, to align with the infection control policies, as the majority of the HCPs reported that the NIV should be initiated in a single side room either in A&E or respiratory wards (*HCP2, HCP3, HCP7, HCP11, HCP12, HCP13*).

NIV setup equipment

During the pandemic, the main changes to the NIV equipment are the types of equipment and the supply chain. The types of equipment have changed to non-vented masks and circuits with additional filters to limit the virus aerosolization (*HCP2, HCP5, HCP7, HCP12*). Some hospitals had a supply chain shortage with the consumables like so circuits, masks, oxygen ports, and sometimes they faced issues in having enough oxygen (*HCP14, HCP15*).

Beds capacity

During the first wave of the pandemic, most of the hospitals faced huge bed capacity issues because of the huge numbers that suddenly needed hospital beds. After that, and during the second wave, some hospitals cope with the surge by increasing the bed capacity (opening extra ITU and extra wards) (*HCP2, HCP3, HCP4, HCP5, HCP8*).

Staff capacity/training

During covid-19, most of the hospitals have struggled in terms of staffing capacity. The main reasons for the staff capacity issues are staff who got Covid-19 and/or staff who were isolated for suspected Covid-19. Thereby, the hospitals faced another issue in terms of recruiting more staff with proper confidence and competence (*HCP2, HCP4, HCP6, HCP7, HCP11, HCP12*).

Table 4.4 Experiences of ward-based NIV by themes

	Before Covid-19	During/after Covid-19
Clinical	***Addressing the protocol*** • 'we stick to a strict protocol. It was originally derived from the BTS 2012 guidelines. And then it just has now developed in 2016 guidelines' **HCP2** • 'for initiating NIV there is a protocol for COPD type two, decompensated type two RF to follow the standard sort of BTS guidelines' **HCP5** • 'there's the hospital protocol, which is based broadly on the BTS criteria'**HCP8** ***Addressing the clinical indications*** • 'NIV is provided to patients who have acute hypercapnic respiratory failure and have a background of respiratory disease with the following: COPD, CWD, bronchiectasis, NMD' **HCP2** • 'From my experience with the COPD patients who could be managed safely on a ward basis for the type 2 RF.... we didn't see NMD, CPO, OHS on our unit. Maybe those went to intensive care in most cases, but largely we saw the type 2 RF in COPD patients' **HCP3** • 'So, we use NIV for acute hypercapnic respiratory failure for exacerbations of COPD is probably about 90% of our use, and we see OHS, NMD as well. The use for pneumonia, I think is not a good use and I think this patient should be intubated and ventilated. I	***Addressing the protocol*** • 'And obviously since then, protocols have changed in terms of NIV set-up location and equipment because of the infection control' **HCP2** ***NIV admission rate*** • 'our numbers have actually had a decrease whether that's because people are shielding or older people are away from sort of breathing through traditional respiratory viruses because they're staying inside because of the restriction' **HCP2** • 'So but essentially basically the numbers that have been admitted and normally go NIV have dropped by I'd say about 50% patients compared to previous year' **HCP4** • 'And I think we've had very little of that over the last 12 months through the COVID period. And I think that's primarily all of our COPD patients have shielding. As a result of shielding, they haven't got as many exacerbations as they may usually have' **HCP4** • 'I think it's probably decrease. I haven't seen a decompensated type two like before, I don't know whether that's because COPD patients are shielding, and they're not being exposed. or they don't want to come to not get the virus, or they've actually picked up COVID and then pass away' **HCP5**

	personally don't feel it's a good mode of ventilation' **HCP4** • 'NIV it was generally for COPD exacerbations with decompensated type two respiratory failure who met the criteria for Ward based NIV… and obviously there's OHS, causing type two failure. I think most likely that probably can be managed safely on the wards' **HCP5** • 'I think they can all be managed quite safely, and I think the only time there are issues, it tends to be around neuromuscular weaknesses. However, I would never, start bipap at all on pneumonia patient' **HCP6** • 'NIV bi level ventilation which we offer mostly for COPD. So, if there's somebody outside the indications of COPD, an increasingly obesity hyperventilation tends to get accepted. So certainly, outside COPD and obesity hyperventilation, then it's a question with the consultant on the call' **HCP7** • 'We use NIV for essentially for acute hypercapnic respiratory failure due to either COPD, OHS, NMD, or CWD' **HCP8** • 'So, COPD patients get a lot of our main cohort, and we struggle with anything outside of that in our area… and we get the OHS patients very rarely' **HCP11** • 'it's sort of based upon the categories of the underlying conditions of COPD, bronchiectasis, OHS, or any NMDs or any sort of CWDs. So as long as they fit into one of those five categories, and as long as they're in acute	• 'With COVID, the main thing we've noticed is actually we weren't needing bilevel it was all CPAP. In fact, I don't think we've had any patient come with type 2 RF And I think it's to do a lot with human factors and sharing viruses' **HCP6** • 'we had fewer people needing NIV in general than say the period the year before, which I guess it's to do with reduced community transmission of respiratory viruses and pollution dropping and people staying in their home' **HCP8** • 'So in the tight six months prior to COVID, we'd treated 118 patients in type two RF with Ward based NIV, and over the same period a year later, which was sort of during the second and third waves of COVID, we've only treated 44, Ward based NIV. So we'd have a significant reduction in numbers' **HCP12**

type 2 respiratory failure, and we will set them up' **HCP12**

Factors affecting the decision making

- 'it's sort of multifactorial. So you're looking obviously at the protocol, do they fit the protocol in terms of the respiratory conditions as listed within the BTS, and we look at that age, history, physical ability and have advanced discussions with the patient themselves and the family members to ensure that the patient is comfortable with receiving or happy to receive' **HCP2**
- 'In terms of nursing resources, that's the limiting factor, so if we have, say, more patients with NIV who are acute, and in that stage if we don't have the nursing staff availability to look after that patient that will be a limiting factor' **HCP2**
- 'It is basically the safety aspect of whether they had other pre-existing conditions that would prevent them being on a ventilator type like NIV' **HCP3**
- 'In the relevant ward area, sometimes the staff sectors would make decisions difficult for patients to be admitted to the unit' **HCP3**
- 'There are a lot of factors. So I think from a medical point of view, whether they fit the criteria for the trust ward based care. And then there's nursing factors where there's an appropriate nursing staff in the ward, whether people are trained. And then there's in terms of staffing to patient ratios, so NIV should be, ideally

	two to one nursing care. And finally, if there's not the beds available, then there wouldn't be suitable to go to ward-based care. And they have to remain in a place of safety until an appropriate bed can be found' **HCP5** • 'Nursing confidence is a big thing as well. So a lot of our nurses are quite Junior. And there isn't such a robust training scheme at the moment for our nurses' **HCP11** • 'to be honest, most of the time, the NIV patients only went to critical care when there was no other bed. Capacity' **HCP13**	

Technical	***NIV decision making & initiation time*** • 'It is so important, and we generally try to get NIV on within **an hour** to **two hours** of the recognition of type two respiratory failure' **HCP8** ***HCPs roles and responsibility*** • 'In terms of HCP, you've got the consultants who takes the lead on NIV as well as specially trained nurses. In terms of who will initiate NIV that will be conducted by the physiotherapist who are all trained to initiate NIV safely and in line with a protocol' **HCP2** • 'The patients will be seen by the respiratory consultants and then calling the respiratory physiotherapist who would go and see the patients in an A&D and then start treatment there before they are transferred to the ward where they were handed over to the nurses would manage them until recovery' **HCP3** • 'so the people who turn on the machines, put the patient on the BIPAP are the nursing staff on the ward. So the changes are led by the doctors, a registrar or consultant basically. So then nurses do all the basic all the patient interface stuff and manage the machines on a day to day running and the changes are led by the doctors' **HCP4** • 'So the initial sort of identification of the patients with RF who would be suitable for NIV will be the medical registrar on call. And then usually they will call the respiratory physiotherapist to set up NIV And then on the wards there are NIV trained nurses who are able to	***NIV decision making time*** • 'Decision making is much better. And I think probably because people are making the advanced decisions of whether for escalation or not. So if they are for escalation, that decision is made quickly enough' **HCP2** • 'So I think since COVID, the inpatient decision making was much more quickly' **HCP7** • 'In COVID, the aim has not changed in that we would still try and get it on quickly if somebody with type two respiratory failure. But in terms of getting people into different wards and beds, it's slightly slower' **HCP8** • 'The time has decreased. Obviously, it's quicker now. Because most areas where people are being managed on the machines more experienced in getting these patients to get started. And decisions obviously made a lot quicker because they know if someone is sick, they need that ventilation as quickly as possible. Yeah, it seems a bit quicker' **HCP13** ***Door to mask…*** • 'There is always a dedicated side room available for patients requiring NIV and our door to mask or referral to mask time has increased as a result of the A&E admission, the A&E transfer, the availability of beds, and also the time it takes for people to use the correct PPE' **HCP2** • 'I think during COVID, with the increased sort of capacity and the increased numbers, I would probably still meet the one hour target to start NIV' **HCP5**

	do basic troubleshooting; mask leak mask fitting, starting and stopping the NIV machines to allow patients to have breaks for eating and drinking' **HCP5** • 'I guess management is led generally by the doctors in terms of the decisions about commencing NIV. But the setup of the NIV equipment is led principally by the physiotherapists occasionally. A senior nurse might help the physios out but it's generally done by the physiotherapists' **HCP8** • 'Usually, the patient will come to A&E, where usually the registrar consults medical management, then the physio would come out and see the patient and put the NIV on. And then they try and get into the respiratory Ward as soon as they can ready' **HCP10** • 'So it's mainly doctor lead and nurses start and monitor the NIV, but we are currently looking to become more involved in that pathway from a physiotherapy point of view. And looking at whether we're the ones to start the treatment, but currently, currently the nurses do that' **HCP11** • 'the medical registrar or the consultant will refer to the physio service. And from that they will then be set up in whichever department they were in prior' **HCP12** • 'if they're admitted by a&e, they would be reviewed by the doctors, including typically taken an ABG. If they were found to be in type two RF, the doctors deem them appropriate, then the physio would be called for to set up NIV' **HCP14**	• 'But given the fact that we now have to wait for a side room, the times probably gone up, because we severely lacks side rooms' **HCP11**

Logistical	***NIV setup location*** • 'The usual process pre Covid was they would be started anywhere in the hospital, whether that's A&E, and trauma & orthopaedic Ward, wherever any part of the hospital, and then they will transfer to the ward' **HCP2** • 'Although pre COVID obviously got started in different areas, and they obviously moved to the respiratory ward' **HCP6** • 'what would normally have happens pre COVID is that if somebody comes into the emergency department, and they need NIV, the emergency department would have called the physiotherapists who would have come in to set them up on NIV and that would normally have happened either in the emergency department or the acute medical unit pretty quickly' **HCP8** • 'Yeah, we in this hospital because the physios set up NIV, the patients prior to COVID could almost be settled anywhere, really. And we were trying not to set the patients on NIV in an area where the nurses were not trained to look after the patient' **HCP13** ***NIV setup equipment*** • 'So prior to that, we would use a vented mask, which essentially has an inbuilt co2 port. And, and therefore is a little bit safer for those patients. And it's much better in terms of ventilation' **HCP2** • 'But before that, we would use the vented masks just because they tended to be better tolerated and then more comfortable' **HCP7**	***NIV setup location*** • 'the key changes for NIV start with the setup, to align with infection control policies and to mitigate the risk of infections, we now only set up NIV within side rooms' **HCP2** • 'with ventilation of this type, NIV, the masks give off a gas. So they're obviously presumed to release aerosol into the atmosphere, isn't it? So patients had to be nesting in single rooms, which obviously it's a limited resource, which is difficult' **HCP3** • 'in terms of cohorting, it's made decisions in where they get placed. So there's the person who's COVID, negative, but potentially does have COVID, clinically, or radiologically. and based, the main thing is that we've ended up needing a lot more side rooms. than we ever had before, that that's certainly caused a lot of difficulty' **HCP7** • 'now post COVID we don't have any side rooms so they don't have any space for aerosol generating so they're all initiated when they're up on the ward' **HCP11** • 'because of COVID and because it's an aerosol generating procedure, the policies that the patients must be set up within a side room on the respiratory wards' **HCP12** • 'Since COVID, we're quite restricted now to where we can set the patients up' **HCP13** ***NIV setup equipment*** • 'circuits have changed, And now we've gone to sort of non vented circuits with a filter at the mask end. we've got a

	Beds capacity • 'And beds is always an issue in every acute hospital. I would say it's an issue every day where everybody's always on the brink of regular divert and all of that. So there's this you can't ring fenced the beds because there's never enough Bed Availability' **HCP15** ***Staff capacity/training*** • 'if it's not an COVID, there are just about enough' **HCP7** • 'Staff wise, we don't have any specialist nurses or specialist physios for the NIV role at the minute. So, nursing wise, it tends to be one nurse per Bay. And that six beds. And then physio wise, we've got pre COVID we had one, one band six on each side' **HCP11** • 'So it was it's never one to two nurses per NIV patient' **HCP12** • 'The staff availability isn't really a problem. We've got trained staff and they've completed their competencies in general. But we've sometimes had issues out of hours with the nursing staff. That's been more around commitment from the nursing leadership team to release staff to do the training. So we've had periods where we've got not got very many trained staff, because the nursing management haven't allowed the staff to attend that training to complete their competencies' **HCP15**	mask filter, oxygen tubing, and an exhalation port to essentially make sure there is co2 washed out' **HCP2** • 'And we were using non vented masks on the unit because if the rescue aerosolization from COVID' **HCP5** • 'the circuits, as you know, have all changed since COVID, with filters in and then non ported masks' **HCP7** • 'I think we had to add additional filters to our machine. So previously, we just had the one filter machine And now we've got to have two filters, we've had to change our masks, as well. And that is it's sort of an additional cost because we've had to buy exhalation ports for all of our machines' **HCP12** • 'We went through some shortages during COVID. And which alternatives were brought in like different models of like tube and masks. The only addition really that was included for the patient was over HME filter. Well, that that has persisted post COVID, we still have to include that now' **HCP14** • 'And we had supply chain issues with all the consumables, so circuits, masks, oxygen ports, and we had issues with having enough oxygen' **HCP15** ***Beds capacity*** • 'if there was potentially like a lack of beds, because the ICU has their own pressures, you know, my centre at the moment is facing it almost like a 300% capacity. So you know those patients you can understand that why they're not getting into ICU or C or M or HDU because there simply isn't the space resources, the capacity' **HCP2**

	• 'It's been very difficult to see because of the huge numbers all of a sudden needing hospital beds. So people had to be moved around some areas which were not used originally for ventilating patients there had to be adapted to accommodate more patients' **HCP3** • 'I see double. So they open up as we open up a second ITU. And they had to go into you know, just use ward they repurposed as an ITU. So we opened up a lot more. two extra wards. and you know, pretty much our respiratory Ward was converted into an HDU. So huge implications on bed capacity. Really, really, any space was being used for beds, as you can imagine, so it was it was hard. It was hard really hard' **HCP4** • 'So post COVID has been less of an issue because the capacity for NIV has been expanded quite a lot. But pre COVID, there's there have been issues with beds..... From a respiratory point of view, obviously, the hospital workout we've changed from having five, sometimes if we were able to staff at six NIV beds to having 17' **HCP5** • 'we've got a new respiratory support unit that's opening is in the process of being opened, which is partly due to the COVID response that that was that was made' **HCP8** ***Staff capacity/training*** • 'At the moment, it's a difficult task to recruit the number of nurses to ensure that we can essentially look after 11 acute patients on NIV' **HCP2** • 'And training, we've had to do a lot of training. staff has done quite a few webinars, but training has been one in

	ensuring that the nurses are trained effectively. The physiotherapists are all trained' **HCP2** • 'And nurses were spread thin. So you know, since then the staff struggled because they got COVID or whatever reason, then you haven't got enough staff. Patients already there. So yeah, it's a huge, huge resource struggle' **HCP4** • 'the main issue comes down to training of the nursing staff actually. for example, our Ward recently have just lost quite a lot of long term staff. And, you know, staff who are very experienced. And I think that's partly because they want to break and partly because they want to move on to new things, but we're not getting the flow coming in, which I think is the shame and I don't know why that is the case in this trust' **HCP6** • 'The illness that staff have had caused a lot of difficulty because they've been off the times that bays or wards have had to be closed, because it's not being very frequent' **HCP7** • 'So within the first stage a year ago, a lot of our NIV patients were on the ward, but they were going down to intensive care a lot sooner than they did in the second stage, mainly just because of the effect of nursing confidence and competence with the NIV systems' **HCP11** • 'staffing, So obviously COVID had a big impact on staffing, whether you've had COVID yourself and how to isolate or whether among family members been, like had COVID, and you've had to isolate, we've just had a lot of members of staff off multiple times this year having to isolate which

	obviously impacts the number of patients that we can care for' **HCP12**

***NIV**: Non-invasive ventilation, **BTS**: British thoracic society, **HCP**: Healthcare provider, **COPD**: Chronic obstructive pulmonary disease, **RF**: Respiratory failure, **CWD**: Chest wall deformity, **NMD**: Neuromuscular disease, **CPO**: Cardiogenic pulmonary oedema, **OHS**: Obesity hypoventilation syndrome, **CPAP**: Continuous positive airway pressure, **BIPAP**: Bilevel positive airway pressure.*

Table 4.5 Emerging themes and suggestions generated after the interviews to aid initiation and improving ward-based NIV.

Clinical aspects of the delivery of NIV	Clarity regarding ward-based NIV effectiveness
Technical aspects of the delivery of NIV	Clarity regarding NIV set-up, management, troubleshooting
Logistical aspects of the delivery of NIV	Expand NIV service: • Designated wards/beds capacity • More staff capacity/training

***NIV**: Non-invasive ventilation*

4.4 Discussion

The data demonstrate the HCPs' attitudes toward ward-based NIV and the effect of Covid-19 that is informed by clinical, technical, and logistical evidence. The study has shown with regards to the ward-based NIV pathway that doctors lead the NIV management decisions, physiotherapists initiate and conduct day to day NIV management, and nurses perform the basic NIV management and troubleshooting. From the HCPs' experiences and views, COPD, OHS, NMD, CWD, and bronchiectasis can be managed safely in ward-based settings. However, the current clinical practice revealed that ward-based NIV is the first place of care for COPD and OHS patients more than other conditions. Patients' factors and resources' factors are determining the decision making for initiating ward-based NIV. Covid-19 has affected the hospitals normal process and ultimately the NIV management process. The NIV management protocol in the hospitals has changed in terms of NIV set-up location and equipment due to infection control procedures. The decision-making time for AHRF and other conditions is much quicker due to increasing experience for the HCPs. However, the time from door to mask for AHRF has increased above the time suggested by guidelines due to side rooms availability and infection control procedures. The types of equipment have changed to non-vented masks and circuits with additional filters to limit the virus aerosolization. Most of the hospitals have struggled in terms of beds and staffing capacity due to huge number of admitted patients. HCPs strongly suggested that understanding the NIV management and expanding the ward-based services with more staff capacity/training could lead to more initiations and improvements in the ward-based NIV.

4.4.1 Clinical issues including clinical effectiveness and patient choice

There is consensus among the HCPs with regards to the main protocol used which is driven from the BTS guidelines. However, there are different pathways reported in terms of the admitted conditions and patient choice. Some hospitals tend to manage in ward-based settings milder hypercapnic respiratory failure patients due to COPD, OHS, NMD, CWD, and bronchiectasis while other hospitals manage mainly COPD and OHS patients. The reports that manage COPD and OHS only by NIV are supported by different studies. For example, numerous studies have supported the use of NIV outside of the critical care settings for AECOPD group with AHRF (97, 164, 170-178), and was an effective treatment in moderate to severe acidosis patients due to AECOPD (105). Moreover, other cohort studies demonstrated that NIV treatment was successful for AHRF patients due to OHS as it improved the $PaCO_2$, avoided ETI, lowered the mortality rate, and improved a 1-year survival rate (123, 124, 128).

The clinical and resources factors such as the lack of robust data to support the use of NIV, the lack of multidisciplinary team availability, and the lack of experienced and confident nurses to deal with NIV management are the main factors that affect the acceptance of the AHRF patient chosen to be managed by NIV in ward-based settings which create different clinical pathways among hospitals. For example, HCP11 reported that they struggle with conditions outside the area of COPD, and this was linked to the lack of nurses' availability (one nurse per bay), lack of a complete team for the management (no physiotherapists), and lack of specialist nurses (mainly junior nurses).

During Covid-19, the protocol has slightly changed mainly for the delivery of care as NIV use was limited to side-rooms due the infection control and to limit the virus aerosolization. However, before the pandemic, the 'BTS/ICS Guidelines for the Ventilatory Management of AHRF in Adults' and the 'BTS National Audit Report: Adult NIV Audit 2019' reported that the NIV most common initiation locations are emergency department and respiratory ward without any restrictions due to infection control (166, 233). Therefore, the pandemic has affected the process of NIV by increasing the time of NIV application due to infection control.

For the admission rate, the HCPs reported that the number of patients who require NIV dropped significantly during the pandemic, and this was in line with the published studies which concluded that the in-hospital admissions for the non-Covid-19 condition groups were substantially decreased during the lockdown compared to the pre-pandemic period (234-238). The national lockdown and the social distancing may play important roles in the in-hospital admission rate reduction.

4.4.2 Technical issues including NIV management procedure

Before the pandemic, most of the hospitals try to commence NIV within 2 hours from the admission which was reinforced by the findings of the 'National Asthma and Chronic Obstructive Pulmonary Disease Audit Programme' (NACAP) (239). However, the 'BTS National Audit Report: Adult NIV Audit 2019' reported that the door to mask within 2 hours only met by 24% of the audit's cohort. The reasons for the delay in order of

magnitude were as follow: not identifying the need for NIV > patient transfer delay > blood gas results delay > lack of beds > lack of required equipment (166). After the pandemic, the HCPs highlighted that the initiation time has increased and the lack of beds (side rooms) due to infection control procedures play a big role in this increment.

There are variations among the hospitals with regards to the HCPs roles and responsibilities. Some hospitals follow the BTS/ICS Guidelines as they have a complete designated team (physicians, physiotherapists, nurses) for the NIV management while other hospitals have physicians and nurses only for the NIV management and this is (233). These variations play an important role in generating variations in the hospitals' clinical pathways.

4.4.3 Logistical issues

Due to the pandemic, and to limit the virus spread, NIV initiation has been changed in terms of set-up location and set-up equipment. NIV is now started in side-rooms with non-vented masks and circuits with additional filters. The isolation rooms are mainly in emergency departments and designated wards as in the UK, the National Confidential Enquiry into Patient Outcome and Death (NCEPOD) report recommended that the emergency department (ED) is considered to be the best place to start acute NIV for acute patients(240). Although these procedures are important in limiting the spread of the virus, they have affected particularly the NIV initiation process by increasing the decision to mask time in hospitals with limited side rooms (238) as the BTS stated that early initiation of NIV helps in reducing the intubation rates, improving the clinical outcomes, and shortening the

in-hospital stay (183). This delay probably reflects the strict infection control procedures and the recommendations for side rooms with 10–12 air changes per hour or the limited number of side rooms in some hospitals. Since then, new ways have been founded by different hospitals to overcome the side rooms limitations by converting some of the wards' rooms into side rooms using dehumidifier exhausts (241). However, future broad restructuring might be required, given the fact of the global impact of COVID-19 on hospitals (241, 242).

During the pandemic, the hospitals faced beds capacity challenges to admit the patients, mostly Covid patients. These challenges were affected most countries' hospitals either HICs or LMICs (243-246) and were associated with Covid-19 mortality (247). To cope with bed capacity challenges, many hospitals in the UK were in line with other hospitals around the world in terms of expanding the bed capacity by either opening new critical care beds or transforming existing beds into critical care beds or high dependency beds (245).

Another important challenge was the staff capacity and training which was raised before the pandemic, for-ward-based NIV, and during the pandemic, for the pandemic surge and the hospitals' responses by increasing the beds capacity. In the UK, the hospitals' adaptations done by several interventions to meet the demands resulted by the pandemic. One of the main interventions was recruiting more staff by the deployment of newly HCPs or final year students, and the redeployment of former HCPs (248). However, the success of the staff deployment, to ensure positive clinical outcomes, is associated with proper staff trainings and competencies (248-251).

4.4.4 Strengths and limitations

The key strengths of the study are as follows. First, it lies in the novelty of the data provided which includes a focus on emerging themes to aid the initiation and improving ward-based NIV as qualitative studies have addressed mechanical ventilation (IMV and NIV) in critical care settings, however, to the best of our knowledge, no prior studies have used qualitative methods to study the attitudes of HCPs toward the use of ward-based NIV for AHRF. Second, the multidisciplinary HCPs with NIV experience were interviewed to provide data required for emerging themes to aid the initiation and improving ward-based NIV. Third, the multidisciplinary HCPs were sampled and interviewed until achieved saturation of themes by continuous data analysis. Finally, the interviews were conducted at multiple institutions and hospitals which reflect the different NIV management procedures of patients with AHRF in ward-based settings and provide the range of perspectives collected, across HCP types and geographical areas. There are several limitations to the study. First, the study includes the perspectives of HCPs including doctors, nurses, and respiratory physiotherapists using NIV. However, it was not possible, due to time and resource limitations, to interview emergency department doctors who may initiate the NIV, hospital managers, or policymakers whose perspectives would also be important and would add other dimensions to the data. Second, the findings are based on interview data and reflect the subjective views of the interviewees. Third, the study only sought to explore the experiences and perspectives of HCPs about the use of NIV for AHRF, and not to assess their knowledge and skills, which may impact on optimal use of ward-based NIV.

4.4.5 Conclusions

The HCPs actively expressed their positive views regarding ward-based NIV especially for AHRF due to COPD and OHS diseases with limited and/or uncertainty use for other conditions. The pandemic emphasizes the role of the ward units in the care of different patient conditions (Covid and non-Covid patients) as the HCPs in ward-based settings were at the frontline against this pandemic to relieve the pressure from the CCUs. To improve the ward-based NIV practice in the future, it is important that designated wards should be expanded alongside multidisciplinary staff deployment with proper training and competencies to aid clarity regarding ward-based NIV effectiveness for different hypercapnic conditions and clarity regarding NIV process (set-up, management, and troubleshooting). Additionally, the HCPs' views may support the feasibility of performing future randomized controlled trials for conditions that had already beneficial effects resulting from previous cohort studies like OHS, and this support comes from the HCPs' confidence and positive views on managing AHRF patients in ward-based settings that derived from the familiarity with the protocols and HCPs responsibilities and acknowledging the importance of expanding the ward-based NIV services. The HCPs' views were understood within the context of clinical, technical, and logistical factors on the reasons of delivering and not delivering NIV in ward-based settings in the current clinical practice with themes to aid the initiation and improvement of the ward-based NIV services.

5 Conclusion and suggested future studies

In this last chapter I have summarised the main findings of this PhD and included some suggestions for future work. The key findings of this PhD could be summarised as:

1. Systematic review

- Previous RCTs examining the clinical effectiveness of BIPAP for non-COPD AHRF patients are small (mainly for ACPO) and lack of robust data.
- Based on the point estimates of the included trials, the efficacy of BiPAP tends to be more than CPAP in reducing the ETI and mortality rates for AHRF patients due to ACPO. However, further trials are needed to increase the precision of the estimate.

2. Cohort retrospective study

- Obesity-related AHRF was the commonest indication for-ward-based NIV management of all non-COPD conditions with the highest rate of survival to hospital discharge.
- Increased age, pneumonia on admission, pre-NIV pH <7.15 (for obesity-related AHRF), and pre-NIV pH <7.25 (for non-obesity-related AHRF) have been identified as important predictors of surviving ward-based NIV treatment.

3. Qualitative study

- Healthcare professionals felt positive regarding ward-based NIV especially for AHRF due to COPD and OHS with limited/uncertain use for other conditions.
- The pandemic emphasizes the role of ward units in the care of different patient conditions (Covid and non-Covid patients) to relieve the pressure from other units.
- Healthcare professionals felt that more designated wards, multidisciplinary staff deployment with proper training and competencies are important factors to improve the ward-based NIV practice in the future.

Discussion and future work suggestions

Based on the findings from this thesis we have identified gaps that need to be addressed about the clinical effectiveness of NIV for non-COPD AHRF patients such as OHS, which has promising positive outcomes from cohort studies, and NMD as they lack controlled trials and robust data. Currently, the number of patients diagnosed with OHS is increasing as a result of increasing obesity globally. Moreover, managing patients who require NIV in critical care settings is resource-intensive and maximizing the cost-effectiveness by enhancing ward-based care is important to overcome the current economic climate where healthcare budgets are increasingly limited, and to overcome the future pandemics that might affect the healthcare systems. Consequently, the application of ward-based NIV will help the healthcare systems not only in the low and middle-income countries but even in the high-income countries as the pandemic, for example, has negatively affected the critical care beds capacity. Therefore, future studies should focus on conducting high-quality randomized trials on a large scale to assess the clinical effectiveness of ward-based NIV for non-COPD AHRF patients and assessing these trials against clinically important outcome measures such as NIV success/failure and in-hospital mortality. The healthcare systems should consider expanding the ward-based NIV service by expanding the designated wards capacities with more well-trained multidisciplinary staff deployment.

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Appendices

Appendix 1

Search lists

Medline Search List

1. randomized controlled trial.pt.
2. randomized controlled trial.ti.
3. controlled clinical trial.pt.
4. randomized.ab.
5. trial.ab.
6. groups.ab.
7. 1 or 2 or 3 or 4 or 5 or 6
8. exp animals/ not humans/
9. 7 not 8
10. exp Respiratory Insufficiency/
11. respiratory failure.ti,ab.
12. Hypercapnia/
13. acute hypercapnic respiratory failure.mp.
14. type II respiratory failure.mp.
15. (hypercap* or hypercarb* or pco2 or paco2).mp.
16. Neuromuscular Diseases/
17. neuromuscular disease*.ti,ab.

18. exp Muscular Dystrophies/

19. Muscular Disease*.mp. or exp Muscular Diseases/

20. (neuromuscular adj 2 Disease*).mp. or exp neuromuscular junction Diseases/

21. exp Motor Neuron Disease/

22. amyotrophic lateral sclerosis.ti,ab.

23. (Charcot disease or Lou Gehrig's disease).ti,ab.

24. (charcot syndrome or Lou Gehrig's syndrome).ti,ab.

25. exp Thoracic Diseases/ or chest wall disorder*.ti,ab.

26. IMMUNOSUPPRESSION/

27. exp IMMUNOCOMPROMISED HOST/

28. Acquired Immunodeficiency Syndrome/ or HIV Infections/ or Immunologic Deficiency Syndromes/

29. IMMUNOSUPPRESSIVE AGENTS/

30. (immunocompromised or immunosuppressive or Immunodeficien* or immunosuppressed).mp.

31. exp ASTHMA/

32. Respiratory Sounds/ or wheez*.mp.

33. Bronchoconstriction/ or bronchoconstrict*.mp.

34. Obesity Hypoventilation Syndrome/

35. obesity hypoventilation.ti,ab.

36. Pickwickian.mp.

37. OBESITY/

38. exp Sleep Apnea, Obstructive/

39. cardiogenic pulmonary edema.ti,ab.

40. Pulmonary Edema/

41. (cardiogenic adj 2 edema*).ti,ab.

42. (pulmonary edema* or pulmonary oedema*).ti,ab.

43. wet lung.mp.

44. 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30 or 31 or 32 or 33 or 34 or 35 or 36 or 37 or 38 or 39 or 40 or 41 or 42 or 43

45. NONINVASIVE VENTILATION/

46. NIV.mp.

47. Intermittent Positive-Pressure Ventilation/ or Positive-Pressure Respiration/

48. positive pressure ventilation.mp.

49. positive airway pressure.mp.

50. bipap.mp.

51. bilevel positive airway pressure.mp.

52. bi-level positive airway pressure.mp.

53. bilevel pressure ventilation.mp.

54. bi-level pressure ventilation.mp.

55. bilevel ventilation.mp.

56. bi-level ventilation.mp.

57. nippv.mp.

58. nppv.mp.

59. 45 or 46 or 47 or 48 or 49 or 50 or 51 or 52 or 53 or 54 or 55 or 56 or 57 or 58

60. (chronic obstructive pulmonary disease or chronic obstructive airway disease or copd).t

61. 9 and 44 and 59

62. 61 not 60

EMBASE Search List

1. randomized controlled trial.tw.
2. randomized controlled trial.ti.
3. controlled clinical trial.tw.
4. randomized.ab.
5. trial.ab.
6. groups.ab.
7. 1 or 2 or 3 or 4 or 5 or 6
8. exp animals/ not humans/
9. 7 not 8
10. exp Respiratory Insufficiency/
11. respiratory failure.ti,ab.
12. Hypercapnia/
13. acute hypercapnic respiratory failure.mp.
14. type II respiratory failure.mp.
15. (hypercap* or hypercarb* or pco2 or paco2).mp.
16. Neuromuscular Diseases/
17. neuromuscular disease*.ti,ab.
18. exp Muscular Dystrophies/
19. Muscular Disease*.mp. or exp Muscular Diseases/
20. (neuromuscular adj 2 Disease*).mp. or exp neuromuscular junction Diseases/
21. exp Motor Neuron Disease/

22. amyotrophic lateral sclerosis.ti,ab.

23. (Charcot disease or Lou Gehrig's disease).ti,ab.

24. (charcot syndrome or Lou Gehrig's syndrome).tw.

25. exp Thoracic Diseases/ or chest wall disorder*.ti,ab.

26. IMMUNOSUPPRESSION/

27. exp IMMUNOCOMPROMISED HOST/

28. Acquired Immunodeficiency Syndrome/ or HIV Infections/ or Immunologic Deficiency Syndromes/

29. IMMUNOSUPPRESSIVE AGENTS/

30. (immunocompromised or immunosuppressive or Immunodeficien* or immunosuppressed).mp.

31. exp ASTHMA/

32. Respiratory Sounds/ or wheez*.mp.

33. Bronchoconstriction/ or bronchoconstrict*.mp.

34. Obesity Hypoventilation Syndrome/

35. obesity hypoventilation.ti,ab.

36. Pickwickian.mp.

37. OBESITY/

38. exp Sleep Apnea, Obstructive/

39. cardiogenic pulmonary edema.ti,ab.

40. Pulmonary Edema/

41. (cardiogenic adj 2 edema*).ti,ab.

42. (pulmonary edema* or pulmonary oedema*).ti,ab.

43. wet lung.mp.

44. 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30 or 31 or 32 or 33 or 34 or 35 or 36 or 37 or 38 or 39 or 40 or 41 or 42 or 43

45. NONINVASIVE VENTILATION/

46. NIV.mp.

47. Intermittent Positive-Pressure Ventilation/ or Positive-Pressure Respiration/

48. positive pressure ventilation.mp.

49. positive airway pressure.mp.

50. bipap.mp.

51. bilevel positive airway pressure.mp.

52. bi-level positive airway pressure.mp.

53. bilevel pressure ventilation.mp.

54. bi-level pressure ventilation.mp.

55. bilevel ventilation.mp.

56. bi-level ventilation.mp.

57. nippv.mp.

58. nppv.mp.

59. 45 or 46 or 47 or 48 or 49 or 50 or 51 or 52 or 53 or 54 or 55 or 56 or 57 or 58

60. (chronic obstructive pulmonary disease or chronic obstructive airway disease or copd).ti.

61. 9 and 44 and 59

62. 61 not 60

63. remove duplicates from 63

Cochrane Search List

Cochrane Controlled Register of Trials (CENTRAL)

#1 MeSH descriptor: [Respiratory Insufficiency] explode all trees

#2 ("respiratory failure") (Word variations have been searched) in Trials

#3 MeSH descriptor: [Hypercapnia] explode all trees

#4 (acute hypercapnic respiratory failure) (Word variations have been searched) in Trials

#5 MeSH descriptor: [Neuromuscular Diseases] explode all trees

#6 (Neuromuscular Disease) (Word variations have been searched) in Trials

#7 MeSH descriptor: [Muscular Dystrophies] explode all trees

#8 MeSH descriptor: [Muscular Diseases] explode all trees

#9 MeSH descriptor: [Neuromuscular Junction Diseases] explode all trees

#10 MeSH descriptor: [Motor Neuron Disease] explode all trees

#11 MeSH descriptor: [Amyotrophic Lateral Sclerosis] explode all trees

#12 (Charcot Disease) (Word variations have been searched) in Trials

#13 (Gehrig's disease) (Word variations have been searched) in Trials

#14 MeSH descriptor: [Thoracic Diseases] explode all trees

#15 MeSH descriptor: [Immunocompromised Host] explode all trees

#16 ("immunocompromised") (Word variations have been searched) in Trials

#17 MeSH descriptor: [Acquired Immunodeficiency Syndrome] explode all trees

#18 MeSH descriptor: [Asthma] explode all trees

#19 MeSH descriptor: [Obesity Hypoventilation Syndrome] explode all trees

#20 ("obesity hypoventilation") (Word variations have been searched) in Trials

#21 ("Pickwick Syndrome") (Word variations have been searched) in Trials

#22 MeSH descriptor: [Sleep Apnea, Obstructive] explode all trees

#23 (cardiogenic pulmonary edema) (Word variations have been searched) in Trials

#24 (#1 or #2 or #3 or #4 or #5 or #6 or #7 or #8 or #9 or #10 or #11 or #12 or #13 or #14 or #15 or #16 or #17 or #18 or #19 or #20 or #21 or #22 or #23) in Trials

#25 MeSH descriptor: [Noninvasive Ventilation] explode all trees

#26 (NIV) (Word variations have been searched) in Trials

#27 MeSH descriptor: [Respiration, Artificial] explode all trees

#28 ("non-invasive ventilation") (Word variations have been searched) in Trials

#29 ("positive pressure ventilation") OR ("positive pressure respiration") (Word variations have been searched) in Trials

#30 ("positive airway pressure") (Word variations have been searched) in Trials

#31 ("bilevel positive airway pressure") OR ("bi-level positive airway pressure"):ti,ab,kw (Word variations have been searched) in Trials

#32 ("NIPPV") OR (nppv):ti,ab,kw (Word variations have been searched) in Trials

#33 (#25 or #26 or #27 or #28 or #29 or #30 or #31 or #32) in Trials

#34 (#24 AND #33) in Trials

CINAHL Plus Search List

1. S1 (MH "Respiratory Failure")
2. S2 (MH "Hypercapnia")
3. S3 "acute hypercapnic respiratory failure"
4. S4 (MH "Neuromuscular Diseases")
5. S5 (MH "Muscular Dystrophy, Duchenne")
6. S6 (MH "Muscular Diseases")
7. S7 (MH "Neuromuscular Junction Diseases")
8. S8 (MH "Motor Neuron Diseases")
9. S9 (MH "Amyotrophic Lateral Sclerosis") OR "ALS"
10. S10 "charcot disease"
11. S11 "gehrig's disease"
12. S12 (MH "Thoracic Diseases") OR "chest wall disorders"
13. S13 (MH "Immunosuppression") OR (MH "Immunosuppressive Agents")
14. S14 (MH "Immunocompromised Host")
15. S15 (MH "Acquired Immunodeficiency Syndrome") OR "AIDS"
16. S16 (MH "Asthma")
17. S17 (MH "Pickwickian Syndrome") OR "obesity hypoventilation syndrome"
18. S18 (MH "Obesity")
19. S19 (MH "Sleep Apnea, Obstructive")
20. S20 (MH "Pulmonary Edema, Acute Cardiogenic") OR (MH "Pulmonary Edema") OR "cardiogenic pulmonary edema"

21. S21 S1 OR S2 OR S3 OR S4 OR S5 OR S6 OR S7 OR S8 OR S9 OR S10 OR S11 OR S12 OR S13 OR S14 OR S15 OR S16 OR S17 OR S18 OR S19 OR S20
22. S22 (MH "Pressure Support Ventilation") OR (MH "Positive Pressure Ventilation") OR (MH "Noninvasive Procedures") OR "noninvasive ventilation"
23. S23 "non invasive ventilation" OR "non-invasive ventilation" OR "NIV"
24. S24 (MH "Intermittent Positive Pressure Ventilation")
25. S25 "bipap or nippv or bilevel positive airway pressure or noninvasive ventilators or mechanical ventilation or noninvasive positive pressure ventilators or respiration, artificial or pressure"
26. S26 "bilevel positive airway pressure" OR "bi-level positive airway pressure" OR "bipap" OR "nippv" OR "nppv"
27. S27 S22 OR S23 OR S24 OR S25 OR S26
28. S21 AND S27

Appendix 2

Data Extraction Form adapted from the Cochrane Collaboration

Reviewer ID	
Identification	
Study details	
Title	
COUNTRY	
SETTING	
Author's contact details	
NAME	
INSTITUTION	
EMAIL	
ADDRESS	
Additional data	
YEAR	
Methods	
DESIGN	
GROUP	
STUDY DESIGN	
Population	
INCLUSION CRITERIA	
EXCLUSION CRITERIA	

GROUP DIFFERENCES	
Interventions and Comparisons	
Interventions	
Comparisons	
Outcomes	
Results & Conclusion	
Primary Outcomes	
Outcome names	Description
Secondary Outcomes	
Outcome names	Description

Data analysis						
Outcome:						
Result	Intervention			Comparison		
	Mean/ Event	SD / %	Total No.	Mean/ Event	SD / %	Total No.
Note:						

Risk of Bias		
Risk	**Authors' judgement**	**Support for judgement**
Random sequence generation		
Allocation concealment		
Blinding of participants and personnel		
Blinding of outcome assessors		
Incomplete outcome data		
Selective reporting		
Other sources of bias		

Appendix 3

Randomised controlled trial's ethical documents

Patient Consent Form

Ward based versus critical care NIV for obesity-related AHRF: a feasibility study

Participant Study ID:

1. I confirm that I have read and understand the information sheet (version number 1.1 dated 01 March 2020) for the above study. I have had the opportunity to consider the information, ask questions and have had these answered satisfactorily. ☐

2. I understand that my participation is voluntary and that I am free to withdraw at any time without giving any reason, without my medical care or legal rights being affected. If I withdraw from the study research data collected up to the point that I withdraw will be kept for research purposes and no further data would be collected or any other research procedures carried out on or in relation to me. ☐

3. I understand that relevant sections of my medical notes and data collected during the study may be looked at by individuals from the University of Birmingham and Heartlands Hospital part of University Hospitals NHS Foundation Trust and from regulatory authorities, where it is relevant to my taking part in this research. I give permission for these individuals to have access to my records. ☐

4. I agree to my GP being involved and/or informed of my participation in the study. ☐

5. I give permission for my anonymized data to be included in the publication of the study results. ☐

6. I agree to take part in the above study. ☐

……

Name of Participant Date Signature

……

Name of Person taking consent Date Signature

1 original for participant; 1 original for researcher site file; 1 copy to be kept in medical notes.

Retrospective Patient Consent Form

Ward based versus critical care NIV for obesity-related AHRF: a feasibility study

Participant Study ID:

1. I confirm that I have read the information sheet (version 1.1 dated 01 March 2020) for the above study. I have had the opportunity to consider the information, ask questions and have had these answered satisfactorily. ☐

2. I understand that my participation is voluntary and that I am free to withdraw at any time without giving any reason, without my medical care or legal rights being affected. If I withdraw from the study research data collected up to the point that I withdraw will be kept for research purposes and no further data would be collected or any other research procedures carried out on or in relation to me. ☐

3. I understand that relevant sections of my medical notes and data collected during, the study may be looked at by individuals from the University of Birmingham, from regulatory authorities or from the NHS Trust, where it is relevant to my taking part in this research. I give permission for these individuals to have access to my records. ☐

4. I understand that the information collected from me may be used to support other research in the future and may be shared anonymously with other researchers. ☐

5. I understand that if after agreeing to take part I lose capacity to consent during the study I will continue to be included in the study. ☐

6. I agree to take part in the above study. ☐

……

Name of Participant Date Signature

……

Name of Person taking consent Date Signature

1 original for participant; 1 original for researcher site file; 1 copy to be kept in medical notes.

Personal Consultee Declaration Form

Ward based versus critical care NIV for obesity-related AHRF: a feasibility study

Participant Study ID:

1. I …… have been consulted about ……'s participation in this research project. I have read the patient information sheet (version number 1.1 dated 01 March 2020) and have had the opportunity to ask questions about the study and understand what is involved. ☐

2. In my opinion he/she would have no objection to taking part in the above study. ☐

3. I understand that I can request he/she is withdrawn from the study at any time, without giving any reason and without his/her care or legal rights being affected. If he/she withdraw from the study research data collected up to the point that he/she withdraw will be kept for research purposes and no further data would be collected or any other research procedures carried out on or in relation to the participant. ☐

4. I understand that relevant sections of his/her care record and data collected during the study may be looked at by responsible individuals from The University of Birmingham or from regulatory authorities, where it is relevant to their taking part in this research. ☐

5. I agree to their GP or other care professional being informed of their participation in the study. ☐

……

Name of Consultee & relationship Date Signature

……

Name of Person taking consent Date Signature

1 original for participant; 1 original for researcher site file; 1 copy to be kept in medical notes.

Professional Consultee Declaration Form

Ward based versus critical care NIV for obesity-related AHRF: a feasibility study

Participant Study ID:

Regarding patient (please write the patients name here)……

This form should be completed by a doctor unconnected to this research study only in situations when the patient is unable to provide informed consent for himself or herself, and if there is no Personal Consultee (a next of kin for the patient) willing and capable to act as his or her legal representative.

If there is no person available and willing to act as a Personal Consultee, the doctor primarily responsible for the medical treatment provided to the patient can act as a Professional Consultee for the patient – as long as they are not connected with the conduct of this study.

1. I Dr. …….. as the clinician with overall responsibility for this patient declare by signing this form that I have read the professional consultee information sheet dated 01 October 2019/V1.0 and have no objection for this patient to be entered into this research study. ☐

2. I also understand that should the patient regain consciousness they will be informed of the decision to enter them into this research study and consent will be sought from them for their continued participation. ☐

3. I agree that this patient's decision will override my consent when the patient is able to give informed consent. ☐

…….

Name of designated consultee Date Signature

…….

Name of Person taking consent Date Signature

1 original for participant; 1 original for researcher site file; 1 copy to be kept in medical notes.

PATIENT INFORMATION SHEET

STUDY TITLE: WARD BASED VERSUS CRITICAL CARE NIV FOR OBESITY-RELATED AHRF: A FEASIBILITY STUDY

- We would like to invite you to take part in our research study. Before you decide we would like you to understand why the research is being done and what it would involve for you. One of our team will go through the information sheet with you and answer any questions you have. We'd suggest this should take about 15 minutes
- Talk to others about the study if you wish.
- Part 1 tells you the purpose of this study and what will happen to you if you take part.
- Part 2 gives you more detailed information about the conduct of the study.
- Ask us if there is anything that is not clear.

PART 1

What is the purpose of the study?

The main purpose of the study is to assess whether the study is applicable in terms of performing a randomised controlled trial of ward-based versus critical care NIV for a patient who suffers from breathing problems caused by obesity.

We also want to compare the clinical outcomes of using non-invasive ventilation in ward-based setting with intensive care unit setting for patients with breathing problems caused by obesity.

What is non-invasive ventilation?

Non-invasive ventilation is a machine that helps you breathe when you have a breathing problem. The machine does not breathe for you but offers gentle help with each breath you take.

Why do I need NIV?

Your condition can affect your breathing and lead to high levels of carbon dioxide (waste gas) in your blood and not enough oxygen. NIV supports your breathing, giving your breathing muscles a rest and removing the carbon dioxide.

What does NIV involve?

We will fit a tight mask to your face, over your nose and mouth. It will be held in place with straps around your head. This mask will connect via tubing to the machine.

We will ask you to breathe as normally as possible and with each breath, the machine will provide air into your lungs at a set pressure. As you breathe out you will notice a little resistance. This is to help keep your lungs open.

Why have I been invited?

You have been invited because you have a breathing difficulty resulting from the weight during the enrolment period of this study.

Do I have to take part?

It is up to you to decide to join the study. We will describe the study and go through this information sheet. If you agree to take part, we will then ask you to sign a consent form. You are free to withdraw at any time, without giving a reason. Declining to join the study, or withdrawing at a later date, will not affect the standard of care you receive in any way. If the participant withdraw from the study research data collected up to the point that the participant withdraw will be kept for research purposes and no further data would be collected or any other research procedures carried out on or in relation to the participant.

What are the benefits, disadvantages and risks of taking part?

We cannot promise the study will help you but the information we get from this study will help improve the treatment of people with obesity-related AHRF. We do not expect any harm to come to you as a result of taking part.

What happens when the research study stops?

Throughout the study, and when it ends, your hospital doctor and general practitioner will continue to monitor you as normal.

What if there is a problem?

Any complaint about the way you have been dealt with during the study or any possible harm you might suffer will be addressed. The detailed information on this is given in Part 2.

Will my taking part be kept confidential?

Yes. We will follow ethical and legal practice and all information about you will be handled in confidence. The details are included in Part 2.

This completes part 1. If the information in Part 1 has interested you and you are considering participation, please read the additional information in Part 2 before making any decision.

PART 2

What if relevant new information becomes available?

If any new information becomes available, we will review our study methods and if we think changes are needed we will discuss them with you.

What will happen if I don't want to carry on with the study?

You can withdraw at any time. No specific action will be taken however information collected may still be used. Declining to join the study, or withdrawing at a later date, will not affect the standard of care you receive in any way. If you withdraw from the study research data collected up to the point that you withdraw will be kept for research purposes and no further data would be collected or any other research procedures carried out on or in relation to you.

Complaints

If you have a concern about any aspect of this study, you should ask to speak to the researchers who will do their best to answer your questions; their contact details are at the end of this sheet.

If you wish to make a formal complaint you can contact the local NHS Patient Services Department at Heartlands Hospital or Queen Elizabeth Hospital by any of the following methods:

Heartlands Hospital:

1.Telephone Hotline: 0121 424 0808 (manned 09:00 – 14:00, 24 hour voicemail facility)

2.E-mail: bhs-tr.complaints-concernsandcompliments@nhs.net

Queen Elizabeth Hospital:

1.Telephone: 0121 371 4400 (09:00 – 17:00, Monday to Friday)

2.E-mail: PALS@uhb.nhs.uk

Will my taking part in this study be kept confidential?

All information which is collected about you during the course of the research will be kept strictly confidential, and any information about you which leaves the hospital will have your name and address removed so that you cannot be recognized. Personal data will be stored for 6-12 months after the end of the study. If you decide to take part you will need to allow access to your medical records. They may be looked at by the doctors carrying out the research, by the hospital research and development department and by regulatory authorities who check that the study is being carried out properly.

The information collected will be stored on a secure computer, but your name will not. This is known as linked anonymised data, meaning that only the lead researching doctor will

have access to your details. They will have sole access to a written record of your information, stored in a secure facility at the clinical site only. All the data collected will be coded with a number. Research data generated by the study will be stored for 10 years.

The results of the study may be published in a medical journal, but your identity will not be revealed. The results may be used in statistical tests, research and development of new treatments, diagnostic tests and medical aids.

Will my GP be involved?

Yes, your GP will be closely involved in the study and will have already been involved in the design of this study.

What will happen to the results of the study?

We would like to publish our results in medical journals, to help other doctors to learn, and patients to benefit. If we are successful with this it will be in an anonymous manner, so you cannot be identified. If you would like to know the results of the research we are happy to provide you with a summary. Please let the research team know when you sign this form.

Who is organizing and funding the research?

The research is being organized by a research team at University of Birmingham part of University Hospitals Birmingham NHS Foundation Trust, headed by Dr Dhruv Parekh. It is funded by the Royal Embassy of Saudi Arabia granted to the PhD student at the University of Birmingham (Bandar Faqihi) as a part of his PhD research. The University of Birmingham is the sponsor for the study. The university has in force a Public Liability Policy and/or Clinical Trials policy which provides cover for claims for "negligent harm" and the activities here are included within that coverage.

Who has reviewed the study?

All research in the NHS is looked at by independent group of people, called a Research Ethics Committee, to protect your interests.

Further information and contact details for the research team

In the first instance any concerns or questions should be addressed to either your GP or hospital doctor. If you have further concerns you can contact

Dr Dhruv Parekh

Tel: [redacted]

[redacted]

Outside the hours of 9-5pm, in the event of an emergency you should call your local NHS services, but we ask that you contact us as soon as possible the next working day.

Personal Consultee Information Leaflet

Ward based versus critical care NIV for obesity-related AHRF: a feasibility study

- We would like your relative/friend to take part in a research study. However, we feel your relative/friend is unable to decide for himself/herself whether to participate in this research.
- To help decide if he/she should join the study, we'd like to ask your opinion whether or not they would want to be involved. We'd ask you to consider what you know of their wishes and feelings, and to consider their interests. Please let us know of any advance decisions they may have made about participating in research. These should take precedence.
- If you decide your relative/friend would have no objection to taking part we will ask you to read and sign the consultee declaration. We'll then give you a copy to keep. We will keep you fully informed during the study so you can let us know if you have any concerns or you think your relative/friend should be withdrawn.
- If you decide that your friend/relative would not wish to take part it will not affect the standard of care they receive in any way.
- If you are unsure about taking the role of consultee you may seek independent advice. We will understand if you do not want to take on this responsibility.
- If you have further questions either now or at any time subsequently, please feel free to contact Dr. Dhruv Parekh (Tel: [redacted]), the doctor leading the study.
- Alternatively you can also contact the Patient Advice and Liaison Service (PALS) on (0121) 371 3280 between 9am and 5pm Monday to Friday.
- The following information is the same as would have been provided to your relative/friend. Thank you for your time in considering this request.

Professional Consultee Information Leaflet

Ward based versus critical care NIV for obesity-related AHRF: a feasibility study

- We would like to invite this patient to take part in a research study while he/she is a patient in this hospital. We feel that he/she does not have the capacity to decide for him/herself whether or not to participate. There is also no personal consultee available to discuss the study with (i.e. a person who cares for the patient or is interested in the patient's welfare but is not doing so for remuneration or acting in a professional capacity).
- Therefore, we ask if you could read the Patient Information Leaflet that follows carefully and give your opinion as to whether or not you think that this patient should be enrolled into this study.
- The patient information sheet is exactly the same as would be given to the patient.
- You are being asked to advise on the views and feelings you believe the patient would have towards participation in this study. You are free to decide whether you wish to provide this advice or not.
- If and when this person has regained capacity to give informed consent, we will explain the study to them and seek his/her permission to use the data we have collected retrospectively. If they decline consent, then we will not collect any further data or samples from them.
- If you have further questions either now or at any time subsequently, please feel free to contact Dr. Dhruv Parekh ([redacted]), the doctor leading the study.
- Alternatively you can also contact the Patient Advice and Liaison Service (PALS) on (0121) 371 3280 between 9am and 5pm Monday to Friday.

Thank you for your time in considering this request.

GP INFORMATION SHEET

STUDY TITLE: WARD BASED VERSUS CRITICAL CARE NIV FOR OBESITY-RELATED AHRF: A FEASIBILITY STUDY

Your patient (……) has consented to take part in this research study. This letter is sent for information so that you are aware of the study and what it involves.

This study is designed to perform a feasibility randomised controlled trial of ward based versus critical care NIV for obesity-related acute hypercapnic respiratory failure (AHRF).

Who is organizing and funding the research?

The research is being organized by a research team at University Hospitals Birmingham NHS Foundation Trust, headed by Dr Dhruv Parekh. It is funded by the Royal Embassy of Saudi Arabia granted to the PhD student at the University of Birmingham (Bandar Faqihi) as a part of his PhD research. The University of Birmingham is the sponsor for the study.

Who has reviewed the study?

All research in the NHS is looked at by independent group of people, called a Research Ethics Committee, to protect patients' interests. This study has been reviewed and given favourable opinion by ……..

Further information and contact details for the research team

If you have further questions or need to report a problem you can contact us using the details below

Yours sincerely,

Dr Dhruv Parekh

Consultant in Critical Care &Respiratory Medicine

Tel: [redacted]

[redacted]

Study protocol

Full/long title of the study

Ward based versus critical care NIV for obesity-related AHRF: a feasibility study

Short study title/acronym

Ward NIV-OHS

Protocol version number and date

Version 1.0, 01 October 2019

Research reference numbers

IRAS Number	272326
Sponsor reference number	ERN_19-1228, RG_19-171
ISRCTN number	
REC reference number	

Signature page

- The undersigned confirm that the following protocol has been agreed and accepted and that the Chief Investigator agrees to adhere to the signed University of Birmingham's Sponsorship CI declaration.
- I agree to ensure that the confidential information contained in this document will not be used for any other purpose other than the evaluation or conduct of the investigation without the prior written consent of the Sponsor
- I also confirm that I will make the findings of the study publically available through publication or other dissemination tools without any unnecessary delay and that an honest accurate and transparent account of the study will be given; and that any discrepancies from the study as planned in this protocol will be explained.

Chief Investigator:

Signature: .....Date: ...../...../.....

Name: (please print):.....

Key study contacts

Chief Investigator: Dr Dhruv Parekh

Institute of Inflammation and Ageing, University of Birmingham, B15 2WB

Tel: [redacted] Email: [redacted]

Study Co-ordinator: Dr Alice M Turner

Institute of Applied Health Research, University of Birmingham, B15 2TT AND

Heartlands Hospital, part of University Hospitals Birmingham NHS Foundation Trust, Birmingham, B9 5SS

Tel: [redacted], Email: [redacted] OR

[redacted]

PhD student: Bandar Faqihi

The PhD student's role will be mainly working with the principal investigator or appropriately trained and delegated member of the research team at the local study site in the process of eligibility screening, randomization, gathering and storing data during the study, and data analysis.

Study Sponsor / Funder(s): Royal Embassy of Saudi Arabia

Study summary

Study Title: Ward based versus critical care NIV for obesity-related AHRF: a feasibility study

Internal ref. no. (or short title): Ward NIV-OHS

Study Design: RCT (Feasibility study)

Study Participants: Subjects with AHRF due to Obesity Hypoventilation Syndrome (OHS)

Planned Study Period: 1 Year

Research Question/Aim(s): To estimate the feasibility of performing a randomised controlled trial of ward based versus critical care Non-invasive Ventilation (NIV) for obesity-related acute hypercapnic respiratory failure (AHRF).

Funding and support in kind

FUNDER(S)	**FINANCIAL AND NON FINANCIALSUPPORT GIVEN**
Saudi Arabian *Cultural Bureau*	The support for this study is part of the student's PhD project

Role of study sponsor and funder

The sponsor has no input to study design or analysis.

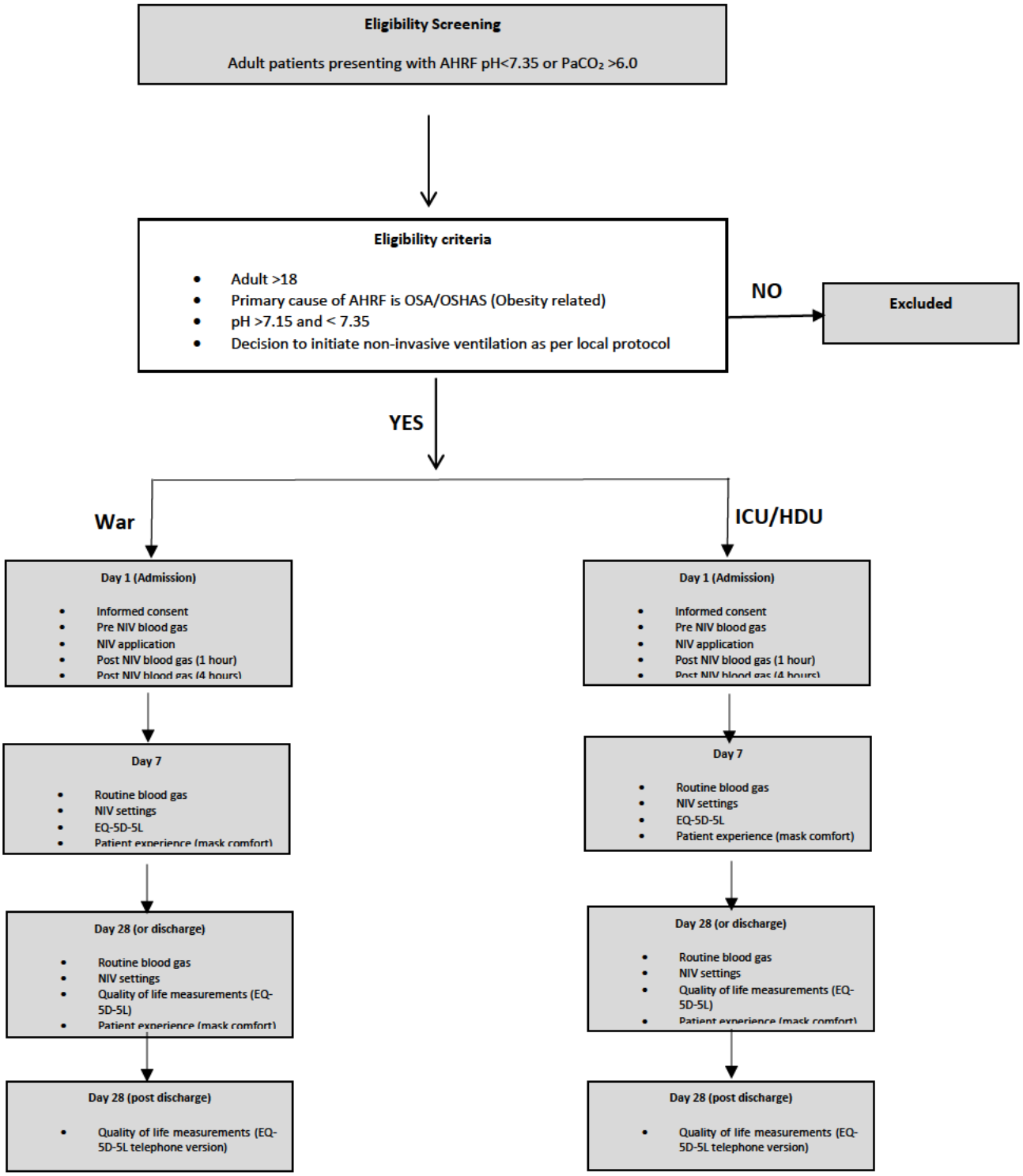
Roles and responsibilities of study management committees/groups and individuals

There are no study management committees. BF will recruit patients in conjunction with site teams, and analyse all data.

Protocol contributors

DP, AMT, BF

Study flow chart



Study protocol

Ward based versus critical care NIV for obesity-related AHRF: a feasibility study

Background :

Overweight and obesity are a global epidemic that influences many people around the world (1, 2). The world health organization (WHO) stated that worldwide obesity has nearly tripled since 1975 with 13% obesity of the global population (3). In the United Kingdom, the WHO summarised that almost two-thirds of the adult population were overweight and almost one-fourth were obese (4). The incidence of Obesity Hypoventilation Syndrome (OHS) increases as the prevalence of obesity increases. OHS prevalence is as follows: 0.3–0.4% in the global population, 10–20% in patients with sleep-related breathing disorders, and in almost half of admitted patients with BMI > 50 kg/m^2 (5,6).

Multiple complications may arise from obesity affecting the endocrine, cardiovascular, and respiratory systems. One of the respiratory complications is obesity hypoventilation syndrome (OHS), defined by a combination of body mass index (BMI) >30 kg/m^2, alveolar hypoventilation leading to awake daytime hypercapnia, $PaCO_2$ >6 kPa, and breathing disorder during sleep (7-9). The pathophysiology of OHS arise from various interactions in sleep breathing disorders, decreased thoraco-abdominal compliance that increases the work of breathing (WOB), and ventilatory drive change. Moreover, stiffness of the respiratory system in OHS patients leads to development of low lung volume which increases the airway resistance, expiratory flow limitation, and gas trapping (8,10,11).

Over the past two decades, non-invasive ventilation (NIV) has been regarded as an effective method for avoiding the use of endotracheal intubation (ETI) and decreasing mortality in patients with acute hypercapnic respiratory failure (AHRF). Evidence supports the main role of NIV in both patients with chronic obstructive pulmonary disease (COPD) exacerbation and patients with acute cardiogenic pulmonary oedema (ACPO) (12,13). Over time, NIV was used in several clinical conditions such as in patients immuno-compromised

from haematological diseases, in restrictive lung diseases and in obesity hypoventilation syndrome (14). In the past decade, OHS is the second most common indication (after COPD) for NIV treatments among AHRF patients (15,16).

The studies related to the conditions other than COPD were limited and most of the data arise from cohort studies. Rabec et al. and Duarte et al. demonstrated that NIV treatment was successful for AHRF patients due to OHS as it improved the $PaCO_2$, avoided ETI, and lowered the mortality rate (17,18). Carillo et al. evaluated the results of patients managed by NIV who were suffering from AHRF due to either COPD or OHS. Patients with OHS had a lower rate of NIV failure and in-hospital mortality, and a higher 1-year survival rate (19). Systematic review of the RCTs in this field shows that there is a lack of robust data. Our own cohort study data shows that 80.2% of the included patients from various diagnoses were survived to discharge and obesity-related AHRF patients have the highest percentage of surviving to discharge (93.1%). Pre-NIV Ph was higher in the survived to discharge group compared to the in-hospital mortality group. There were significant predictors of in-hospital mortality in pre-NIV pH < 7.25, increased age, and all underlying diagnoses except obesity-related AHRF. Moreover, the study's outcomes suggest that NIV can be used safely in ward-based settings for obesity-related AHRF patients with pH thresholds >7.25 and 7.16-7.25. This implies that OHS patients have a good prognosis and might therefore be safe to manage in a lower intensity setting.

Rationale

Managing patients who require NIV in an ICU setting is resource intensive, and in the current healthcare climate where budgets are increasingly tight maximizing cost-effectiveness by enhancing ward-based care is important. However, at present poor understanding and limited studies (with no RCT) exploring the role of ward-based care for AHRF due to OHS limits the ability to design care pathways and limits the European Respiratory Society (ERS)/ American Thoracic Society (ATS) guidelines to provide a clear recommendation. Therefore, the aim is to perform a feasibility randomised controlled trial of ward based versus critical care NIV for obesity-related AHRF.

Research question/aims

Objectives

- The primary objectives are to estimate the feasibility outcomes of conducting a clinical trial to establish if the setting of patients' hospital care (ward or ICU/HDU) affects the clinical outcome.
- The secondary objectives are to explore clinical outcome measures of safety, efficacy and cost-effectiveness across the whole trial population and per treatment group and will be used to inform any future definitive trial.

Outcome

Feasibility outcomes:

1. Rate of eligible patients.
2. Proportion and rate of recruitment (patient willingness to participate and clinician willingness to recruit).
3. Adherence to the protocol.
4. Proportion of trial arm cross-over (proportion of ward NIV arm admitted to critical care).
5. Retention and data completeness at 28 days.
6. Follow-up rates.

Clinical outcomes:

1. Rates of endotracheal intubation (proportion undergoing ETI by 28 days).
2. Mortality 28-day (proportion).
3. Mean and median hospital length of stay.
4. Blood gas pH pre NIV, 1 hour and 4-hour post NIV.
5. Time to initiation of NIV and liberation from NIV.
6. NIV – NIV machine used, Maximum NIV pressure and oxygen delivery.
7. Mean change in quality of life, measured with EQ-5D-5L – mask comfort (by VAS).

8. Health resource use up to 28 days (ICU/HDU length of stay, ward length of stay, hospital length of stay, major interventions received in hospital).

Study design and methods of data collection

This is a feasibility randomised controlled trial of ward based versus critical care NIV for obesity-related AHRF

Data collection:

- Baseline data will be collected including demographics, medical history, co-morbid conditions, body mass index, and baseline blood gas.
- Post NIV blood gas (1 & 4hours)
- NIV information will be collected including NIV machine used, NIV interface, initial and maximum NIV pressure and oxygen delivery.
- EQ-5D-5L will be used to assess the mean change in quality of life
- VAS will be used to assess the patient experience regarding the face mask

Study setting

The study will be performed at 2 sites in the UK, namely Birmingham Heartlands Hospital (PI Dr Alice Turner) and Queen Elizabeth Hospital Birmingham (PI Dr Dhruv Parekh).

Participant recruitment

Eligibility Criteria

Eligibility for screening: Adult patients presenting to emergency department (ED) or the Acute Medical Unit with AHRF pH<7.35 or $PaCO_2$ >6.0

Inclusion criteria

- Adult aged 18 and over
- Primary cause of AHRF is OHS (Obesity related)
- pH >7.15
- Decision to initiate non-invasive ventilation as per local protocol
- BMI>30

Exclusion criteria

- More than one organ failure requiring organ support
- Immediate need for critical care admission for invasive ventilation
- Not deemed a candidate for admission to intensive care
- pH<7.15 or $paCO_2$ <6.0
- GCS <8 or likely not to tolerate NIV
- COPD or pneumonia as primary cause of admission

Recruitment target

Size of recruitment target

The sample size is 40 participants.

Recruitment technique

All consecutive patients deemed eligible and who are interested in the study will be approached.

Recruitment

Participant identification

Patients will be identified by clinical teams within the hospital, including (but not limited to) respiratory physicians, critical care physicians and physiotherapists managing the NIV service. After initial identification by the clinical team the research team will approach the patient.

Consent

- **Patients with capacity**: the patient will be provided with a written 'Patient Information Sheet'. A member of the research team with relevant GCP training will provide verbal information and answer any questions. If the patient chooses to be enrolled in the study, they will sign a 'Patient Consent Form'. The patient may withdraw consent at any stage.
- **Patients lacking capacity**: many patients will be unable to give informed consent due to the effects of being acutely unwell, raised CO_2 and respiratory acidosis. Consent will ideally be taken from a Personal Legal Representative (PerLR) prior to randomisation. A

trained authorised staff member/researcher will describe the study to the individual and provide them with a PerLR Information Sheet. In the event that a PerLR is not available to provide assent, an independent doctor not involved with the patient's care (Professional Legal Representative (ProfLR)) will be consulted and will be informed about the trial by an authorised staff member/researcher and given a copy of the Information Sheet. If the independent doctor agrees, the authorised staff member/researcher will recruit the patient into the trial. In the event that a patient is randomised in the study via an independent doctor, the PerLR will be informed at the earliest opportunity and consent to continue will be sought.

- Once a patient who initially lacks capacity, regains capacity, they will be informed about the trial and invited to consent to continue in the trial. If the patient chooses to continue to be part of the study they will sign a consent form; if the patient does not wish to consent to continue, they will be withdrawn from the study but consent gained for the data collected to that point to be
- retained. In the event that the patient never regains capacity or dies then he/she will remain in the study and their data will be included in the analysis.
- Informed consent will be taken by an appropriately trained individual in accordance with GCP who has been delegated to do so by the PI.

Data analysis:

The data analyses will be performed using IBM SPSS Statistics Version 24. Statistical significance will be taken as p>-value 0.05 and Kolmogorov-Smirnov test will be used for testing the normality. Baseline and demographic characteristics will be analysed by descriptive analysis and Chi-Square test will be used for analyses of associations between categorical variables. Multivariate analysis will be performed to identify predictors of in-hospital mortality.

Ethical and regulatory considerations

Research Ethics Committee (REC) and other Regulatory review & reports

Before the start of the study, approval will be sought from a REC for the trial protocol, informed consent forms and other relevant documents e.g. advertisements and GP information letters. Substantial amendments will be reviewed by the sponsor first, and the substantial amendments that require review by REC will not be implemented until the REC grants a favourable opinion for the study. All correspondence with the REC will be retained in the Trial Master File/Investigator Site File. An annual progress report (APR) will be submitted to the REC and the sponsor within 30 days of the anniversary date on which the favourable opinion was given, and annually until the trial is declared ended. The CI (or delegate) will produce the annual reports as required and notify the REC and the sponsor of the end of the study. If the study is ended prematurely, the CI will notify the REC and the sponsor, including the reasons for the premature termination. The CI will submit a final report with the results, including any publications/abstracts, to the REC and the sponsor.

Regulatory Review & Compliance

Before enrolling patients into the study, the CI or designee will apply for NHS permission from the site's Research & Development (R&D) department. For any amendment that will potentially affect a site's NHS permission, the CI or designee will confirm with that site's R&D department that NHS permission is ongoing (note that both substantial amendments, and amendments considered to be non-substantial for the purposes of REC and/or MHRA may still need to be notified to NHS R&D).

Amendments

The CI will be responsible for the decision to make any amendments to the study protocol and the University of Birmingham Research Governance Team will decide whether an amendment is substantial or non-substantial.

Amendments will be tracked in Appendix 3 of the study protocol to identify the most recent protocol version.

A Notification of Amendment will be completed and submitted for review and approval by the Funder, National Co-ordinating Centre, REC and HRA as appropriate. No amendments will be implemented until all relevant approvals have been obtained.

Protocol compliance

The procedures and assessments detailed in the study protocol should be followed at all times, however, accidental protocol deviations can happen and they must be adequately documented on the relevant forms and reported to the Chief Investigator and Sponsor immediately. Deviations from the protocol which are found to frequently recur are not acceptable, will require immediate action and could potentially be classified as a serious breach.

A “serious breach” is a breach which is likely to effect to a significant degree –

(a) the safety or physical or mental integrity of the subjects of the trial; or
(b) the scientific value of the trial

The National Co-ordinating Centre will be notified immediately of any case where the above definition applies during the trial study.

Data protection and patient confidentiality

All investigators and study site staff will comply with the requirements of the Data Protection Act 1998 with regards to the collection, storage, processing and disclosure of personal information and will uphold the Act’s core principles.

All data will be de-identified before being stored electronically on secure NHS servers. All source documents will be stored according to University of Birmingham SOPs and the Trial Master File (TMF) and Investigator Site File (ISF) will be stored in a secure office location by the trial co-ordinator.

Indemnity

If research activities are taking place at the NHS sites, NHS indemnity will apply. The University has in force a Public Liability Policy and/or Clinical Trials policy which provides cover for claims for "negligent harm" and the activities here are included within that coverage.

End of study and archiving

After the final report has been sent, study documents will be archived for 10 years from the end of the study, as per the University of Birmingham guidelines https://intranet.birmingham.ac.uk/mds/documents/public/RKTO/CRCT-Docs/UoB-CLN-ARC-SOP-001

Access to the final study dataset

Direct access will be granted to authorised representatives from the University of Birmingham, host institution, Global Sponsor, and the regulatory authorities to permit trial-related monitoring, audits and inspections.

Dissemination policy

Results of the study will be published in the form of conference abstracts and manuscript preparation.

Authorship eligibility guidelines and any intended use of professional writers

The CI will be the senior author on the final study report. Those individuals who have also made a significant contribution to the study will be eligible for authorship as per guidelines produced by The International Committee of Medical Journal Editors criteria, known as the Vancouver Protocol.

Appendix 4

Qualitative study ethical documents

Consent Form

Investigation of healthcare professional attitude on managing acute hypercapnic respiratory failure patients with non-invasive ventilation outside Intensive Care Units pre and post COVID-19: a qualitative study

Participant Study ID:

Please initial box:

1. I confirm that I have read and understand the information sheet (version number 1.1 dated 01 July 2020) for the above study. I have had the opportunity to consider the information, ask questions and have had these answered satisfactorily. ☐

2. I understand that my participation is voluntary and that I am free to withdraw (up to one month from the interview) without giving a reason. ☐

3. I give permission for my anonymized data to be included in the publication of the study results.
   : ☐

4. **Please INITIAL the box Yes/No for the following question. It is entirely optional whether to consent and if you answer "No", it will not influence your participation in the study.** I give permission for my data to be used for teaching purposes or to support other research in the future and may be shared anonymously for those purposes only. Yes ☐ No ☐

5. I agree to take part in the above study. ☐

Name of Participant	Date	Signature
Name of Person taking consent	Date	Signature

1 original for participant; 1 original for researcher site file

PARTICIPANT INFORMATION SHEET

Study Title: Investigation of healthcare professional attitude On managing acute hypercapnic respiratory failure patients with non-invasive ventilation outside Intensive Care Units pre and post COVID-19: a qualitative study

Thank you for taking the time to look at this information sheet. I would like to invite you to take part in our research study. Before you decide, I would like you to understand why the research is being done and what it would involve for you. If you are interested in finding out more, I will be happy to telephone you to discuss the information sheet and answer any questions that you may have.

The information sheet will tell you the purpose of this study and what will happen to you if you take part and gives you more detailed information about the conduct of the study.

What is the purpose of the study?

The purpose of this study is to understand the experiences and perceptions of healthcare professionals on the use of NIV for respiratory failure conditions outside of Intensive Care Units and how these perceptions have changed before and after the COVID-19 pandemic.

Why have I been invited?

You have been invited because you are a healthcare professional who has experience with non-invasive ventilation and its management in a healthcare setting.

Do I have to take part?

It is up to you to decide to join the study. We will describe the study and go through this information sheet. If you agree to take part, we will then ask you to sign a consent form. You are free to withdraw (up to one month from the interview) without giving a reason. If you withdraw from the study, your data can be destroyed if you wish.

What will the interview involve?

During the interview, you will be asked questions related to your perception of using non-invasive ventilation for respiratory failure outside critical care unites and whether your perception changed after Covid-19 pandemic. The questions will mostly focus on:

- Non-invasive ventilation (NIV) management in ICU/ward settings
- Covid-19 pandemic and its effect on healthcare management including managing patients with respiratory failure with non-invasive ventilation.
- The enablers and barriers to the expansion of NIV treatment for respiratory failure outside of critical care settings.

What are the possible benefits of taking part?

Although this study does not intend to provide any specific benefits to individuals taking part, it is hoped that the information we gain could help to understand healthcare professional perspectives on the use of non-invasive ventilation for respiratory failure outside of Intensive Care Units and how they have changed with Covid-19 because this will help to understand behaviour and the impact on medical services afterwards.

What if there is a problem?

If you experience any problems due to taking part in the study, I would be happy to discuss these with you. However, contact details for other people involved in the research are available in Section Two, and they can also help with any problems or complaints.

Will my participation in the study be kept confidential?

Yes. We will follow ethical and legal practice and all information about you will be handled in confidence.

What will happen if I do not want to carry on with the study?

You can withdraw at any time during the interview and for up to one month from the date of the interview without giving a reason. If you withdraw from the study, your data can be destroyed if you wish.

Will my taking part in this study be kept confidential?

Yes, all information which is collected about you during the course of the research will be kept strictly confidential.

- Your interview will be recorded and the recording will be stored on a password protected and encrypted computer or audio recording device. It may also be listened to by my research supervisor.
- I will type up the interview to create a 'transcript' of what we said. I will remove all information, such as names or places, that could potentially identify you. Anonymized transcripts will be stored electronically on a password protected and encrypted computer.
- Your anonymized transcript will be seen by members of the research team only, unless you give permission in the consent form to be used anonymously to support other research or teaching in the future.
- Once the research is completed, electronic copies of the transcript will be stored securely on the university network until the point of secure disposal.
- The results of the study may be published in a medical journal, but your identity will not be revealed.

What will happen to the results of the study?

As the study is part of my PhD research, it will be submitted to the University for marking. I also hope to publish the findings of this study in a relevant journal and perhaps present this at a conference. A brief report of the findings will be sent to interested participants. Participants will not be identified within any of these publications, but anonymous quotes from your interview may be included.

Who is organizing and funding the research?

The research is being organized by a research team at University of Birmingham part of University Hospitals Birmingham NHS Foundation Trust, headed by Dr Alice Turner. It is funded by the Royal Embassy of Saudi Arabia granted to me (Bandar Faqihi) as a PhD student at the University of Birmingham as a part of my PhD research.

Who has reviewed the study?

All research in the UoB is looked at by independent group of people, called a Research Ethics Committee, to protect your interests.

Further information and contact details for the research team

If you have a concern about any aspect of this study, I am happy to discuss this with you and do my best to answer your questions.

If you have further concerns, you can contact:

Dr Bandar Faqihi

[redacted]

[redacted]

Other contact details:

Dr Nicola Gale (Qualitative Supervisor)

Tel: [redacted]

[redacted]

Prof Alice Turner (Lead Supervisor)

Tel: [redacted]

[redacted]

Thank you for taking the time to read this information sheet.

Scoping survey

Qualitative Study

Investigation of healthcare professional attitude on managing acute hypercapnic respiratory failure patients with non-invasive ventilation outside Intensive Care Units pre and post COVID-19: a qualitative study

Dear participant,

We would like to invite you to participate in this questionnaire to explore the nature of managing patients with acute hypercapnic respiratory failure.

1Working site name:

----

2 What is your role at this site? Tick all that apply.

Clinical Service Lead

Consultant

Respiratory specialist

Critical care specialist

Physiotherapist

Nurse

Manager

Other (please specify)

----

3 Working area:

Critical care settings

Wards settings

Other (please specify)

----

4 Years of current work experience

<5 years

5-10 years

10-15 years

>15 years

5 Who conducts day to day management of NIV at your site? Tick one only.

Physiotherapists

Nurses

Doctors

Other (please specify)

---

6 Who leads (overall management type decisions) day to day management of NIV at your site? Tick one only.

Physiotherapists

Nurses

Doctors

Other (please specify)

---

7 Does the hospital you work in have a protocol for managing acute hypercapnic respiratory failure?

Yes

No

I don't know

Do you have ward-based NIV?

Yes

No

I don't know

8 Where do you offer NIV for Chronic obstructive pulmonary disease (COPD)? Tick all that apply.

Respiratory ward

Acute Medical ward

Critical Care Unit

Other (please specify)

---

9 Where do you offer NIV for Obesity Hypoventilation Syndrome (OHS)? Tick all that apply.

Respiratory ward

Acute Medical ward

Critical Care Unit

Other (please specify)

---

10 Where do you offer NIV for Cardiogenic Pulmonary Oedema (CPO)? Tick all that apply.

Respiratory ward

Acute Medical ward

Critical Care Unit

Other (please specify)

---

11 What factors affect whether you would offer ward-based NIV to a patient with AHRF?

Cause of respiratory failure

Initial blood gas

Patient's age

Hospital's protocol

Bed availability

Patient with comorbidities

Others (please specify)

---

12 Should patients be offered ward based NIV (non ICU) for the following:

Disease	Strongly disagree	Disagree	Neutral	Agree	Strongly Agree
COPD					
CPO					
OHS					
Pneumonia					
NMD					

CWD					

13 Has the respiratory failure management been changed after the Covid-19?

Yes, Covid-19 has a huge change on the respiratory failure management

Yes, Covid-19 has a minimal change on the respiratory failure management

No

I don't know

14 In your hospital / unit, approximately how many…..

Number of beds in the wards ----------

Number of beds in the ICU/HDU ----------

Number of beds in the ICU/HDU post Covid-19 ----------

Number of beds in the hospital ----------

15 Age:

20-29

30-39

40-49

50-59

60 and above

16 Gender:

Male

Female

Other (please specify)

Prefer not to answer

17 Ethnicity:

White

Asian / Asian British

Black / African / Caribbean / Black British

Middle Eastern / Arab

Other (please specify)

Prefer not to answer

18 Level of education:

Associate degree

Bachelor's degree

Graduate Diploma

Master's degree

PhD degree

Prefer not to answer

Thank you for completing the survey.

Your participation in this survey is **anonymous** (we do not take your contact details). However, we intend to conduct some in-depth interview to explore the issues raised by the survey in more detail. If you would be happy to be contacted by the research team to discuss what is involved in these interviews and possible participate, please provide your contact details below:

The contact details will be treated as **confidential** in all study stages. If you consent to participate, the interview will be conducted according to your preference (face-to-face, video conference, or by telephone) and should not last more than 1-hour.

Email: ----------

Other contact: ----------

Interview questions

Investigation of healthcare professional attitude on managing acute hypercapnic respiratory failure patients with non-invasive ventilation outside Intensive Care Units pre and post COVID-19: a qualitative study

Thank you for letting me interview you today. Before I start the interview, I will briefly explain the aim of this project. By conducting this research, I am hoping to understand the healthcare professional perspectives on the use of non-invasive ventilation for respiratory failure outside of Intensive Care Units and how they have changed with Covid-19. This will help Understanding behaviour and impact on medical services afterwards. I want to ask you a few questions about your experience of bilevel positive pressure ventilation for type 2 respiratory failure patients.

1. Can you tell me how NIV is used on your ward/ICU?

PROMPT- if needed ask about

- ventilation devices & modes,
- management procedures,
- HCPs responsibilities,
- who runs the machine,
- who leads its management?

2. In your experience and opinion, which hypercapnic respiratory failure disease can be managed safely with non-invasive ventilation (NIV) in ward-based settings, and why?

PROMPT- if needed ask about

- what the inclusion / exclusion criteria is for NIV,
- whether they would offer NIV to specific groups

3. What do you think the factor/s that effect the decision for which hypercapnic respiratory failure patients be managed with non-invasive ventilation (NIV) in ward-based settings?

PROMPT- if needed ask about

- patient factors,
- clinical factors,
- resource factors.

4. What effect has Covid-19 had on the healthcare services in general in the hospital you work in and the use of NIV on your ward / ICU?

PROMPT- if needed ask about

- factors/reasons that play a role in the effect.
- what patients were you offering / not offering NIV to (and why)
- what do you think the type 2 respiratory failure patients should be managed safely in ward-based settings during Covid-19 and why.
- environment of care for respiratory patients during a pandemic.
- The capacity during the pandemic (beds, staff, machines)

5. Is there anything you want to add regarding AHRF management, NIV treatment in ward-based settings, or the effect Covid-19?

That is the end of the interview, thank you very much for taking time out of your busy schedule to let me interview you.

Recruitment advertisement

Will COVID-19 forever change our view on what conditions can be managed outside of critical care?

If you are a healthcare provider who has experience with non-invasive ventilation, you may be eligible to participate in a research study.

We are looking for healthcare professionals to understand their perspectives and perceptions on the use of non-invasive ventilation for acute hypercapnic respiratory failure outside of critical care units and how have these changed in the last year before and after the COVID-19 pandemic.

Participants will be asked to participate in:

- Online survey
- Interview based on the participant preference (face-to-face, video conference, or by telephone).

If you are unsure if you meet the requirements, call or email a member of the study team:

- Dr Bandar Faqihi
- bxf755@student.bham.ac.uk
- +44 (0)7378637746

Application for Ethics Review Form

Guidance Notes:

What is the purpose of this form?

This form should be completed to seek ethics review for research projects to be undertaken by University of Birmingham staff, PGR students or visiting/emeritus researchers who will be carrying out research which will be attributed to the University.

Who should complete it?

For a staff project – the lead researcher/Principal Investigator on the project.

For a PGR student project – the student's academic supervisor, in discussion with the student.

Students undertaking undergraduate projects and taught postgraduate (PGT) students should refer to their Department/School for advice

When should it be completed?

After you have completed the University's online ethics self-assessment form (SAF), IF the SAF indicates that ethics review is required. You should apply in good time to ensure that you receive a favourable ethics opinion prior to the commencement of the project and it is recommended that you allow at least 60 working days for the ethics process to be completed.

How should it be submitted?

An electronic version of the completed form should be submitted to the Research Ethics Officer, at the following email address: aer-ethics@contacts.bham.ac.uk.

What should be included with it?

Copies of any relevant supporting information and participant documentation, research tools (e.g. interview topic guides, questionnaires, etc) and where appropriate a health & safety risk assessment for the project (see section 10 of this form for further information about risk assessments).

What should applicants read before submitting this form?

Before submitting, you should ensure that you have read and understood the following information and guidance and that you have taken it into account when completing your application:

- The information and guidance provided on the University's ethics webpages (https://intranet.birmingham.ac.uk/finance/accounting/Research-Support-Group/Research-Ethics/Ethical-Review-of-Research.aspx)

- The University's Code of Practice for Research (https://www.birmingham.ac.uk/Documents/university/legal/research.pdf)
- The guidance on Data Protection for researchers provided by the University's Legal Services team at https://intranet.birmingham.ac.uk/legal-services/What-we-do/Data-Protection/resources.aspx.

Section 1: Basic Project Details

Project Title: Investigation of healthcare professional attitude on managing acute hypercapnic respiratory failure patients with non-invasive ventilation outside Intensive Care Units pre and post COVID-19: a qualitative study

Is this project a:

University of Birmingham Staff Research project ☐

University of Birmingham Postgraduate Research (PGR) Student project ☒

Other (Please specify below) ☐

Details of the Principal Investigator or Lead Supervisor (for PGR student projects):

Title: Dr

First name: Nicola

Last name: Gale

Position held: Health Services Management Centre, Reader in Health Sociology and Policy College, Director of Postgraduate Research

School/Department School of Social Policy, HSMC

Telephone: [redacted]

Email address: [redacted]

Details of any Co-Investigators or Co-Supervisors (for PGR student projects):

Title: Dr

First name: Alice

Last name: Turner

Position held: Professor of Respiratory Medicine, Honorary Consultant Respiratory Physician

School/Department Institute of Applied Health Research

Telephone: [redacted]

Email address: [redacted]

Title: Dr

First name: Dhruv

Last name: Parekh

Position held: Clinical Lecturer in Respiratory Medicine

School/Department Institute of Inflammation and Ageing

Telephone: [redacted]

Email address: [redacted]

Details of the student for PGR student projects:

Title: Mr

First name: Bandar

Last name: Faqihi

Course of study: PhD in applied health research

Email address: [redacted]

Project start and end dates:

Estimated start date of project: 15/09/2020

Estimated end date of project: 01/04/2021

Funding:

Sources of funding:

Section 2: Summary of Project

Describe the purpose, background rationale for the proposed project, as well as the hypotheses/research questions to be examined and expected outcomes. This description should be in everyday language that is free from jargon - please explain any technical terms or discipline-specific phrases. Please do not provide extensive academic background material or references.

Background:

The use of non-invasive ventilation (NIV) for acute hypercapnic respiratory failure (AHRF) unrelated to COPD in medical wards rather than critical care remains controversial.

Previous studies have shown that:

(a) A systematic review and meta-analysis of the literature demonstrated that the efficacy of BiPAP (bi-level positive airway pressure) appears similar to CPAP (continuous positive airway pressure) in reducing rates of endotracheal intubation and mortality in patients with AHRF due to acute cardiogenic pulmonary oedema. This implies that these patients can be safely managed with CPAP, which is available in more non-ICU settings than BiPAP in most countries.

(b) A multicentre, retrospective cohort study of patients with AHRF unrelated to COPD treated with ward-based NIV demonstrated that NIV can be used safely in ward-based settings for obesity-related AHRF patients with pre-NIV pH thresholds down to 7.15. Future controlled trials are required to confirm the clinical effectiveness of NIV use outside critical care settings for obesity-related AHRF.

It has been the intention of the study team to conduct a feasibility trial for a study that randomises patients with a form of respiratory failure to either non-invasive ventilation on intensive care or the same on a medical ward. However, ventilation anywhere will be in short supply due to Covid-19 and so this study will effectively be impossible during the next 4 months, if at all. Equally the attitudes of staff and the about using this type of treatment outside an intensive care department will probably change during Covid-19, simply through necessity.

Therefore, the team have discussed to perform a qualitative study on acceptability of the intervention outside ITU. Establishing attitudes to an intervention are vital to a feasibility study anyway (which we had planned to do using a simple questionnaire), but exploring how they are in more detail, and moreover how they have changed with Covid-19 could be an important aspect of understanding behaviour and impact on medical services afterwards - indeed if attitudes change a lot it could be that the feasibility study itself becomes moot, should clinicians now feel that they would manage all the proposed patient group outside ITU (thus randomisation would be impossible because equipoise would not exist).

Study Aim:

To understand healthcare professional and perspectives on the use of non-invasive ventilation for respiratory failure outside of Intensive Care Units.

Research Questions:

1. What are the experiences and perceptions of healthcare professionals on the use of NIV for different respiratory conditions (including respiratory failure) outside critical care?
2. How have these changed before and after the COVID-19 pandemic?
3. What are the enablers and barriers to the expansion of NIV treatment for respiratory failure outside of critical care settings?
4. What factors would be important to maintain or improve NIV services in ward-based setting?

Section 3: Conduct and location of Project

Conduct of project

Please give a description of the research methodology that will be used. If more than one methodology or phase will be involved, please separate these out clearly and refer to them consistently throughout the rest of this form.

This is a multi-methods study using sequential methods: a scoping survey, followed by in-depth qualitative interviews.

Methods for scoping survey:

- Access and recruitment: A link to the survey will be circulated to relevant professional organisations groups.
- Sampling: We will use convenience Sampling.
- Data collection: We will use an online survey, with a mixture of closed, Likert and open text questions.
- Data analysis: Closed and Likert scales will be analysed using descriptive statistics. Qualitative data from open text questions will be analysed using qualitative content analysis.

Methods for in-depth interview study:

- Access and recruitment: Participants for the interview study will be recruited via the scoping survey – those willing to be contacted to discuss their answers further will provide an email address or other contact details.
- Sampling: Maximum diversity sample (a kind of the purposive sample) will be sought for the target population.
- Data collection: In-depth, semi-structured interviews will be conducted face-to-face, by video conference, or by telephone (according to the preference of the interviewee).

- Data analysis: Qualitative data will be analysed using the Framework method.

Geographic location of project

State the geographic locations where the project and all associated fieldwork will be carried out. If the project will involve travel to areas which may be considered unsafe, either in the UK or overseas, please ensure that the risks of this (or any other non-trivial health and safety risks associated with the research) are addressed by a documented health and safety risk assessment, as described in section 10 of this form.

It is a UK-based study

Section 4: Research Participants and Recruitment

Does the project involve human participants?

Note: 'Participation' includes both active participation (such as when participants take part in an interview) and cases where participants take part in the study without their knowledge and consent at the time (for example, in crowd behaviour research).

Yes ☒

No ☐

If you have answered NO please go on to Section 8 of this form. If you have answered YES please complete the rest of this section and then continue on to section 5.

Who will the participants be?

Describe the number of participants and important characteristics (such as age, gender, location, affiliation, level of fitness, intellectual ability etc.). Specify any inclusion/exclusion criteria to be used.

Healthcare professionals who have experience with non-invasive ventilation in healthcare settings.

How will the participants be recruited?

Please state clearly how the participants will be identified, approached and recruited. Include any relationship between the investigator(s) and participant(s) (e.g. instructor-student). Please ensure that you attach a copy of any poster(s), advertisement(s) or letter(s) to be used for recruitment.

The Scoping survey will be circulated for recruitment to relevant professional organisations and societies like British Thoracic Society, Intensive Care Society, local Trust newsletters, via Birmingham Health Partners, Midlands Thoracic Society, and West Midlands Physicians Association.

Section 5: Consent

What process will be used to obtain consent?

Describe the process that the investigator(s) will be using to obtain valid consent. If consent is not to be obtained explain why. If the participants are under the age of 16 it would usually be necessary to obtain parental consent and the process for this should be described in full, including whether parental consent will be opt-in or opt-out.

Scoping survey: The participant will read the introductory statement and if the participant read and agreed to participate and complete the survey, he/she will click "complete the survey" button.

Interview: If the participants are willing to be interviewed to discuss their answers further after the scoping survey, they will provide an email address or other contact details so they will receive the participant information sheet and informed consent prior to the interview. In addition, before starting the interview, the participant can ask any question regarding the PIS to have an adequate verbal explanation of the research.

Please be aware that if the project involves over 16s who lack capacity to consent, separate approval will be required from the Health Research Authority (HRA) in line with the Mental Capacity Act.

Please attach a copy of the Participant Information Sheet (if applicable), the Consent Form (if applicable), the content of any telephone script (if applicable) and any other material that will be used in the consent process.

Note: Guidance from Legal Services on wording relating to the Data Protection Act 2018 can be accessed at https://intranet.birmingham.ac.uk/legal-services/What-we-do/Data-Protection/resources.aspx.

Use of deception?

Will the participants be deceived in any way about the purpose of the study?

Yes ☐

No ☒

If yes, please describe the nature and extent of the deception involved. Include how and when the deception will be revealed, and the nature of any explanation/debrief will be provided to the participants after the study has taken place.

Section 6: Participant compensation, withdrawal and feedback to participants

What, if any, feedback will be provided to participants?

Explain any feedback/ information that will be provided to the participants after participation in the research (e.g. a more complete description of the purpose of the research, or access to the results of the research).

After participation in the research, access to the results of the research will be provided to the participants (if they wish and request to know this information).

What arrangements will be in place for participant withdrawal?

Describe how the participants will be informed of their right to withdraw from the project, explain any consequences for the participant of withdrawing from the study and indicate what will be done with the participant's data if they withdraw.

Participants will be reassured that their participation is entirely voluntary, that they can withdraw (up to one month from the interview) without providing reason and that their data can be destroyed if they wish.

Please confirm the specific date/timescale to be used as the deadline for participant withdrawal and ensure that this is consistently stated across all participant documentation. This is considered preferable to allowing participants to 'withdraw at any time' as presumably there will be a point beyond which it will not be possible to remove their data from the study (e.g. because analysis has started, the fin dings have been published, etc).

Participants can withdraw from the interview up to one month from completing the interview without providing reason and that their data can be destroyed if they wish

What arrangements will be in place for participant compensation?

Will participants receive compensation for participation?

Yes ☐

No ☒

If yes, please provide further information about the nature and value of any compensation and clarify whether it will be financial or non-financial.

Section 7: Confidentiality/anonymity

Will the identity of the participants be known to the researcher?

Will participants be truly anonymous (i.e. their identity will not be known to the researcher)?

Yes ☒

No ☐

In what format will data be stored?

Will participants' data be stored in identifiable format, or will it be anonymised or pseudo-anonymised (i.e. an assigned ID code or number will be used instead of the participant's name and a key will kept allowing the researcher to identify a participant's data)?

The participants' data from the survey will be anonymous and the data from the in-depth interview will be in a pseudo-anonymised format for data storing and analysis. The transcripts from the interviews will be anonymized.

Will participants' data be treated as confidential?

Will participants' data be treated as confidential (i.e. they will not be identified in any outputs from the study and their identity will not be disclosed to any third party)?

Yes ☒

No ☐

If you have answered no to the question above, meaning that participants' data will not be treated as confidential (i.e. their data and/or identities may be revealed in the research outputs or otherwise to third parties), please provide further information and justification for this:

Section 8: Storage, access and disposal of data

How and where will the data (both paper and electronic) be stored, what arrangements will be in place to keep it secure and who will have access to it?
Please note that for long-term storage, data should usually be held on a secure University of Birmingham IT system, for example BEAR (see https://intranet.birmingham.ac.uk/it/teams/infrastructure/research/bear/index.aspx*).*

Each participant's demographic form and consent form will be stored separately in the secure location of the university computers.

Audio data will be removed from the audio device as soon as it is possible, encrypted, password protected and stored securely.

Transcription will be carried out in a private space. All personal identification information will be removed or changed immediately after transcription is completed.

When transcriptions are completed, they will be handled with caution, stored in the secure location of the university computers and the full transcripts will only be accessible to the researchers.

Data retention and disposal

The University usually requires data to be held for a minimum of 10 years to allow for verification. Will you retain your data for at least 10 years?

Yes ☒
No ☐

If data will be held for less than 10 years, please provide further justification:

Click or tap here to enter text.

What arrangements will be in place for the secure disposal of data?

Click or tap here to enter text.

Section 9: Other approvals required

Are you aware of any other national or local approvals required to carry out this research?

E.g. clearance from the Disclosure and Barring Service (DBS), Local Authority approval for work involving Social Care, local ethics/governance approvals if the work will be carried out overseas, or approval from NOMS or HMPPS for work involving police or prisons? If so, please provide further details:

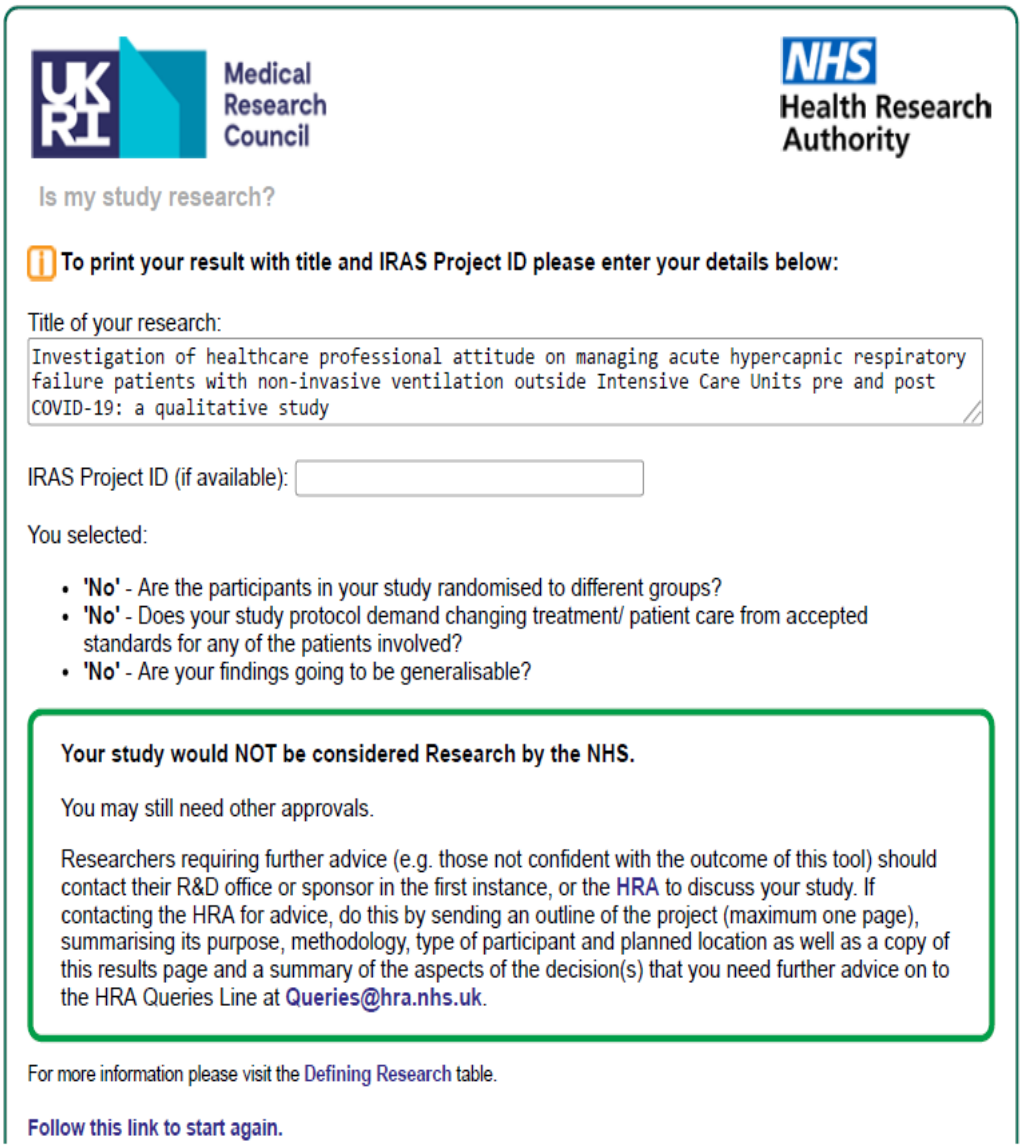
Click or tap here to enter text.

<u>For projects involving NHS staff</u>, is approval from the Health Research Authority (HRA) needed in addition to University ethics approval?

If your project will involve NHS staff, please go to the HRA decision tool at http://www.hra-decisiontools.org.uk/research/ to establish whether the NHS would consider your project to be research, thus requiring HRA approval in addition to University ethics approval. Is HRA approval required?

Yes ☐
No ☒

Please include a print out of the HRA decision tool outcome with your application.



Medical Research Council

NHS Health Research Authority

Is my study research?

To print your result with title and IRAS Project ID please enter your details below:

Title of your research:

Investigation of healthcare professional attitude on managing acute hypercapnic respiratory failure patients with non-invasive ventilation outside Intensive Care Units pre and post COVID-19: a qualitative study

IRAS Project ID (if available):

You selected:

- **'No'** - Are the participants in your study randomised to different groups?
- **'No'** - Does your study protocol demand changing treatment/ patient care from accepted standards for any of the patients involved?
- **'No'** - Are your findings going to be generalisable?

Your study would NOT be considered Research by the NHS.

You may still need other approvals.

Researchers requiring further advice (e.g. those not confident with the outcome of this tool) should contact their R&D office or sponsor in the first instance, or the HRA to discuss your study. If contacting the HRA for advice, do this by sending an outline of the project (maximum one page), summarising its purpose, methodology, type of participant and planned location as well as a copy of this results page and a summary of the aspects of the decision(s) that you need further advice on to the HRA Queries Line at **Queries@hra.nhs.uk**.

For more information please visit the Defining Research table.

Follow this link to start again.

Section 10: Risks and benefits/significance

Benefits/significance of the research

Outline the potential significance and/or benefits of the research

The study will help to understand healthcare professional perspectives on the use of non-invasive ventilation for respiratory failure outside of Intensive Care Units and how they have changed with Covid-19. This this will help us understand behaviour and the impact on medical services afterwards. Moreover, the qualitative results may accelerate the process for randomized controlled trials of ward-based versus critical care NIV for hypercapnic respiratory conditions that have positive outcomes because managing patients who require NIV in an ICU setting is resource-intensive, and in the current healthcare climate where budgets are increasingly tight maximizing cost-effectiveness by enhancing ward-based care is important and the poor RCTs for these groups limits hospital's ability to design care pathways and limits the ERS/ATS guidelines to provide a clear recommendation.

Risks of the research

Outline any potential risks (including risks to research staff, research participants, other individuals not involved in the research, the environment and/or society and the measures that will be taken to minimise any risks and the procedures to be adopted in the event of mishap.) Please ensure that you include any risks relating to overseas travel and working in overseas locations as part of the study, particularly if the work will involve travel to/working in areas considered unsafe and/or subject to travel warnings from the Foreign and Commonwealth Office (see https://www.gov.uk/foreign-travel-advice). Please also be aware that the University insurer, UMAL, offers access to Risk Monitor Traveller, a service which provides 24/7/365 security advice for all travellers, and you are advised to make use of this service (see https://umal.co.uk/travel/pre-travel-advice/).

The outlining of the risks in this section does not circumvent the need to carry out and document a detailed Health and Safety risk assessment where appropriate – see below.

There might be a risk of Covid-19 transmission if the participant preferred a face-to-face way for the interview, but we'll assure the participant that the face-to-face interview will occur under strict precautions to prevent the incidence of virus transmission besides providing other forms of the interview (e.g., online visual interview, or telephone interview). The participant will be aware that speaking about personal or experiences can be an emotional process, however, we do not anticipate that the participant will experience any distress as the participant will be encouraged to take a break whenever necessary during the interview and can decide to stop the interview at any point.

University Health & Safety (H&S) risk assessment

For projects of more than minimal H&S risk it is essential that a H&S risk assessment is carried out and signed off in accordance with the process in place within your School/College and you must provide a copy of this with your application. The risk may be non-trivial

because of travel to, or working in, a potentially unsafe location, or because of the nature of research that will carried out there. It could also involve (irrespective of location) H&S risks to research participants, or other individuals not involved directly in the research. Further information about the risk assessment process for research can be found at https://intranet.birmingham.ac.uk/hr/wellbeing/worksafe/policy/Research-Risk-Assessment-and-Mitigation-Plans-RAMPs.aspx.

Please note that travel to (or through) 'FCO Red zones' requires approval by the University's Research Travel Approval Panel, and will only be approved in exceptional circumstances where sufficient mitigation of risk can be demonstrated.

Section 11: Any other issues

Does the research raise any ethical issues not dealt with elsewhere in this form?

If yes, please provide further information:

Do you wish to provide any other information about this research not already provided, or to seek the opinion of the Ethics Committee on any particular issue?

If yes, please provide further information:

Section 12: Peer review

Has your project received scientific peer review?

Yes ☐

No ☒

If yes, please provide further details about the source of the review (e.g. independent peer review as part of the funding process or peer review from supervisors for PGR student projects):

Section 13: Nominate an expert reviewer

For certain types of project, including those of an interventional nature or those involving significant risks, it may be helpful (and you may be asked) to nominate an expert reviewer for your project. If you anticipate that this may apply to your work and you would like to nominate an expert reviewer at this stage, please provide details below.

Section 14: Document checklist

Please check that the following documents, where applicable, are attached to your application:

Recruitment advertisement ☒

Participant information sheet ☒

Consent form ☒

Questionnaire ☒

Interview/focus group topic guide ☒

Please proof-read study documentation and ensure that it is appropriate for the intended audience before submission.

Section 15: Applicant declaration

Please read the statements below and tick the boxes to indicate your agreement:

I submit this application on the basis that the information it contains is confidential and will be used by the University of Birmingham for the purposes of ethical review and monitoring of the research project described herein, and to satisfy reporting requirements to regulatory bodies. The information will not be used for any other purpose without my prior consent. ☒

The information in this form together with any accompanying information is complete and correct to the best of my knowledge and belief and I take full responsibility for it. ☒

I undertake to abide by University Code of Practice for Research (https://www.birmingham.ac.uk/Documents/university/legal/research.pdf) alongside any other relevant professional bodies' codes of conduct and/or ethical guidelines. ☒

I will report any changes affecting the ethical aspects of the project to the University of Birmingham Research Ethics Officer. ☒

I will report any adverse or unforeseen events which occur to the relevant Ethics Committee via the University of Birmingham Research Ethics Officer. ☒

Please now save your completed form and email a copy to the Research Ethics Officer, at aer-ethics@contacts.bham.ac.uk. As noted above, please do not submit a paper copy.

Appendix 5

Clinical responsibilities of HCPs on managing AHRF with NIV

Characteristics	Count	%
Who conducts day to day management of NIV at your site?		
Physiotherapists	29	60.4
Nurses	12	25.0
Doctors	4	8.3
Who leads (overall management type decisions) day to day management of NIV at your site?		
Physiotherapists	2	4.2
Doctors	46	95.8
Does the hospital you work in have a protocol for managing acute hypercapnic respiratory failure?		
Yes	41	85.4
No	0	0.0
I don't know	7	14.6
Do you have ward-based NIV?		
Yes	48	100.0
No	0	0.0
I don't know	0	0.0
Where do you offer NIV for Chronic obstructive pulmonary disease (COPD)?		
Respiratory ward	46	95.8
Critical Care Unit	2	4.2
Where do you offer NIV for Obesity Hypoventilation Syndrome (OHS)?		
Respiratory ward	44	91.7
Critical Care Unit	4	8.3
Where do you offer NIV for Cardiogenic Pulmonary Oedema (CPO)?		
Respiratory ward	18	37.5
Critical Care Unit	30	62.5
What factors affect whether you would offer ward-based NIV to a patient with AHRF?		
Cause of respiratory failure	42	87.5
Initial blood gas	41	85.4
Patient's age	7	14.6
Hospital's protocol	29	60.4
Bed availability	35	72.9
Staff availability	28	58.3
Patient with comorbidities	33	68.8

HCPs agreement on managing AHRF with NIV in ward-based settings

Characteristics	Count	%
Please rate your agreement with the following conditions to be offered ward-based NIV service: COPD		
Strongly disagree	0	0.0
Disagree	0	0.0
Neither agree nor disagree	0	0.0
Agree	16	33.3
Strongly agree	32	66.7
Please rate your agreement with the following conditions to be offered ward-based NIV service: CPO		
Strongly disagree	1	2.1
Disagree	3	6.3
Neither agree nor disagree	14	29.2
Agree	25	52.1
Strongly agree	5	10.4
Please rate your agreement with the following conditions to be offered ward-based NIV service: OHS		
Strongly disagree	0	0.0
Disagree	0	0.0
Neither agree nor disagree	0	0.0
Agree	27	56.3
Strongly agree	21	43.8
Please rate your agreement with the following conditions to be offered ward-based NIV service: Pneumonia		
Strongly disagree	12	25.0
Disagree	25	52.1
Neither agree nor disagree	8	16.7
Agree	3	6.3
Strongly agree	0	0.0
Please rate your agreement with the following conditions to be offered ward-based NIV service: NMD		
Strongly disagree	0	0.0
Disagree	1	2.1
Neither agree nor disagree	4	8.3
Agree	31	64.6
Strongly agree	12	25.0
Please rate your agreement with the following conditions to be offered ward-based NIV service: CWD		
Strongly disagree	0	0.0
Disagree	0	0.0
Neither agree nor disagree	23	47.9
Agree	16	33.3

Strongly agree	9	18.8

Appendix 6

CODES

1. Guidelines/protocol
2. Indications/criteria
3. NIV bed capacity
4. NIV staff capacity
5. Pre-COVID NIV use
6. Impact of Covid on protocol
7. NIV- type of devices & modes
8. Impact of COVID on NIV setup
9. NIV- type of devices & modes
10. Nurse/operator skills/training
11. Risk management
12. Role and responsibilities
13. NIV protocol
14. NIV management
15. NIV protocol
16. Patient factors
17. Shared decision making – HCP-family-patient
18. Availability of machines
19. Staff availability
20. NIV protocol
21. Shared decision making – HCP-family-patient
22. NIV successful/ failure indicators
23. Prognosis Assessment
24. NIV protocol
25. NIV experience

26. NIV successful/ failure indicators
27. Prognosis Assessment
28. Impact of covid (NIV setup location)
29. Impact of covid (infection control)
30. Impact of covid (NIV initiation time)
31. Impact of covid (NIV setup equipment)
32. Impact of covid (NIV decision making time)
33. Impact of covid (training)
34. Impact of Covid (NIV bed capacity)
35. Impact of Covid (ITU capacity)
36. Impact of COVID (NIV Capacity)
37. Impact of COVID (NIV admission)
38. Future of NIV service
39. Reduction of pressure on ICU by NIV units
40. Future of NIV service (challenges) like NIV device resource, NIV staffing resource).

Appendix 7

TP15. TP015 UPDATES IN ADHERENCE AND TREATMENT OF LUNG DISEASE

Bilevel Positive Airway Pressure Ventilation for Non-COPD Patients with Acute Hypercapnic Respiratory Failure: A Systematic Review and Meta-Analysis

B. Faqihi[1], D. Parekh[2], S.P. Trethewey[1], A.M. Turner[1]
https://doi.org/10.1164/ajrccm-conference.2021.203.1_MeetingAbstracts.A1627

First Page PDF

Bilevel Positive Airway Pressure Ventilation for Non-COPD Patients with Acute Hypercapnic Respiratory Failure: A Systematic Review and Meta-Analysis

B. Faqihi[1], D. Parekh[2], S. P. Trethewey[3], A. M. Turner[1]; [1]Institute of Applied Health Research, University of Birmingham, Birmingham, United Kingdom, [2]Department of Clinical Respiratory Science, University of Birmingham, Birmingham, United Kingdom, [3]University Hospitals Birmingham, NHS Foundation Trust, Birmingham, United Kingdom.

Background: The effectiveness of bilevel positive airway pressure (BIPAP) in patients with acute hypercapnic respiratory failure (AHRF) due to aetiologies other than chronic obstructive pulmonary disease (COPD) is unclear. Therefore, the aim of this study is to systematically review the evidence regarding the effectiveness of BIPAP in non-COPD patients with AHRF. Methods: The Cochrane Library, MEDLINE, EMBASE and CINAHL Plus were searched according to pre-specified criteria (PROSPERO-CRD42018089875). Randomised controlled trials (RCTs) assessing the effectiveness of bilevel positive airway pressure (BIPAP) versus continuous positive airway pressure (CPAP), invasive mechanical ventilation (IMV), or oxygen therapy in adults with non-COPD AHRF were included. The primary outcomes of interest were rates of endotracheal intubation (ETI) and mortality. Risk-of-bias assessment was performed, and data were synthesized and meta-analysed where appropriate. Results: 2485 records were identified after removing duplicates. 88 articles were identified for full-text assessment of which 82 articles were excluded. 6 studies, of generally low or uncertain risk-of-bias, were included involving 320 participants with acute cardiogenic pulmonary oedema (ACPO) and end-stage solid tumours. No significant differences were seen between BIPAP ventilation and CPAP with regards to the rate of progression to ETI (RR= 1.49, 95% CI, 0.63-3.62, p=0.37) and in-hospital mortality rate (RR= 0.71, 95% CI, 0.25-1.99, p=0.51) in patients with AHRF due to ACPO. Conclusion: The efficacy of BIPAP appears similar to CPAP in reducing rates of ETI and mortality in patients with AHRF due to ACPO. Further trials on other non-COPD conditions which commonly cause AHRF such as obesity hypoventilation syndrome (OHS) are needed.

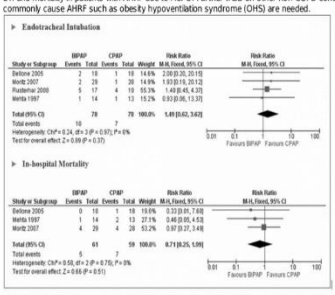


Figure 1: Forrest plot comparing ETI and in-hospital mortality rates in AHRF patients treated with BIPAP compared to CPAP

This abstract is funded by: None

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Internet address: www.atsjournals.org
Online Abstracts Issue

TP19. TP019 QUALITY, PROCESS, AND OUTCOMES IN ACUTE AND CRITICAL CARE

Ward-Based Non-Invasive Ventilation for Acute Hypercapnic Respiratory Failure Unrelated to Chronic Obstructive Pulmonary Disease

B. Faqihi[2], D. Parekh[1], A.M. Turner[2]

https://doi.org/10.1164/ajrccm-conference.2021.203.1_MeetingAbstracts.A1693

First Page PDF

TP019 QUALITY, PROCESS, AND OUTCOMES IN ACUTE AND CRITICAL CARE / Thematic Poster Session

Ward-Based Non-Invasive Ventilation for Acute Hypercapnic Respiratory Failure Unrelated to Chronic Obstructive Pulmonary Disease

B. Faqihi[2], D. Parekh[2], A. M. Turner[1]; [1]Institute of Applied Health Research, University of Birmingham, Birmingham, United Kingdom, [2]Department of Clinical Respiratory Science, University of Birmingham, Birmingham, United Kingdom.

Background: The use of non-invasive ventilation (NIV) for acute hypercapnic respiratory failure (AHRF) conditions unrelated to chronic obstructive pulmonary disease (COPD) outside critical care remains controversial. The aim of this study is to evaluate the outcomes associated with NIV application in the ward-based setting for patients with AHRF unrelated to COPD.Methods: This is a multi-centre cohort study of patients with AHRF unrelated to COPD treated by NIV in ward-based settings between February 2004 and December 2018. Exclusion criteria included COPD patients, pre-NIV pH <7.35, lack of pre-NIV blood gas. Pre-NIV pH was grouped by thresholds (> 7.15, 7.15-7.25) and was compared to pH <7.25. Factors (pre-NIV pH, age, condition) were assessed in a multivariable regression model. Results are shown for the multivariable analysis as (OR, 95% CI, p-value).Results: 479 subjects were included in the analysis. 80.2% of the included patients survived to discharge. Obesity-related AHRF was the indication for 39.2% of all episodes with the highest proportion of survivors (93.1%). Increased age and pneumonia on admission were associated with a higher risk of mortality (1.034, 1.017 - 1.051, P > 0.001) and (5.313, 2.326 - 12.131, P > 0.001) respectively. In the obesity-related AHRF group, pre-NIV pH of below 7.15 was associated with a significant increase in mortality (7.800, 1.843 - 33.013, P = 0.005) but not between 7.15 - 7.25 (2.035, 0.523 - 7.915, P = 0.305).Conclusion: Our outcomes suggest that NIV can be used safely in ward-based settings for obesity-related AHRF patients with pH thresholds down to 7.15. Future controlled trials are required to prove the effectiveness of using NIV outside critical care settings for obesity-related AHRF.

Review Article

Bilevel positive airway pressure ventilation for non-COPD acute hypercapnic respiratory failure patients: A systematic review and meta-analysis

Bandar M. Faqihi[1,4], Samuel P. Trethewey[2], Julien Morlet[2], Dhruv Parekh[2,3], Alice M. Turner[1,2]

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Abstract:

The effectiveness of bi-level positive airway pressure (BiPAP) in patients with acute hypercapnic respiratory failure (AHRF) due to etiologies other than chronic obstructive pulmonary disease (COPD) is unclear. To systematically review the evidence regarding the effectiveness of BiPAP in non-COPD patients with AHRF. The Cochrane Library, MEDLINE, EMBASE, and CINAHL Plus were searched according to prespecified criteria (PROSPERO-CRD42018089875). Randomized controlled trials (RCTs) assessing the effectiveness of BiPAP versus continuous positive airway pressure (CPAP), invasive mechanical ventilation, or O_2 therapy in adults with non-COPD AHRF were included. The primary outcomes of interest were the rate of endotracheal intubation (ETI) and mortality. Risk-of-bias assessment was performed, and data were synthesized and meta-analyzed where appropriate. Two thousand four hundred and eighty-five records were identified after removing duplicates. Eighty-eight articles were identified for full-text assessment, of which 82 articles were excluded. Six studies, of generally low or uncertain risk-of-bias, were included involving 320 participants with acute cardiogenic pulmonary edema (ACPO) and solid tumors. No significant differences were seen between BiPAP ventilation and CPAP with regard to the rate of progression to ETI (risk ratio [RR] = 1.49, 95% confidence interval [CI], 0.63–3.62, $P = 0.37$) and in-hospital mortality rate (RR = 0.71, 95% CI, 0.25–1.99, $P = 0.51$) in patients with AHRF due to ACPO. The efficacy of BiPAP appears similar to CPAP in reducing the rates of ETI and mortality in patients with AHRF due to ACPO. Further research on other non-COPD conditions which commonly cause AHRF such as obesity hypoventilation syndrome is needed.

Keywords:

Acute hypercapnic respiratory failure, bi-level positive airway pressure, endotracheal intubation, meta-analysis, mortality, noninvasive ventilation, systematic review

Acute respiratory failure (ARF), which generally results from insufficient gas exchange by the respiratory system,[1] is a significant disorder that can require invasive mechanical ventilation (IMV) through endotracheal intubation (ETI) for its management.[2] In the 1990s, ARF was the most common indication for IMV among eight countries, accounting for more than 65% of ventilated patients.[2] Despite the high use of IMV due to improved survival rates,[3] IMV can cause many complications. ETI is associated with ventilator-associated pneumonia (VAP),[4] increased mortality rate,[4,5] IMV weaning difficulties, and increased health-care

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costs.[5] Therefore, noninvasive ventilation (NIV) has been increasingly used for acutely ill patients. NIV has many advantages, including a reduction in the risk of infection, a greater degree of patient co-operation and an increased ability to communicate,[6] as well as improvement in dyspnea.[7] Compared with IMV, NIV can achieve the same physiological outcomes of improved gas exchange and reduced work in breathing.[8] Moreover, NIV has a reduced incidence of side effects related to ETI and IMV, such as VAP, upper airway injuries, and excessive sedation. Thus, NIV has the potential to provide better clinical outcomes in certain patient groups.[9]

For several decades, NIV has been regarded as an effective method for avoiding the use of ETI and decreasing mortality in patients with acute hypercapnic respiratory failure (AHRF). Evidence supports the suggestion that the inclusion of NIV in a standard care strategy may enhance the outcomes in both patients with chronic obstructive pulmonary disease (COPD) exacerbation and patients with hypoxemic acute cardiogenic pulmonary edema (ACPO).[10,11] However, the effectiveness of bi-level positive airway pressure (BiPAP) in AHRF due to etiologies other than COPD is still questioned. For instance, some of the studies of pulmonary edema did not exclude COPD patients,[12,13] so may not have proven NIV efficacy even in this group. Therefore, we performed a systematic review to determine the effectiveness of BiPAP in non-COPD patients with AHRF, using the need for ETI and the mortality rate after applying bi-level ventilation as the primary outcomes.

Methods

Data sources and search strategy

The protocol for this systematic review was prospectively registered on PROSPERO (CRD42018089875). To identify the articles for the inclusion in this review, the Cochrane Central Register of Controlled Trials in the Cochrane Library (Wiley interface), MEDLINE (Ovid interface), EMBASE (Ovid interface), and CINAHL Plus (EBSCO interface) were searched for relevant studies. In addition, trial registries (clinicaltrials.gov and WHO ICTRP) were used to search for ongoing and completed, but not yet published clinical trials. The bibliographies of the retrieved articles were reviewed to identify and conduct searches on related articles. Search terms are shown in the supplementary file [Appendix 1]. In brief, the inclusion criteria were randomized controlled trials (RCTs) which compared the effectiveness of BiPAP ventilation versus continuous positive airway pressure (CPAP), IMV, or oxygen therapy in adults with non-COPD AHRF. Effectiveness was determined by the comparison of the rates of the primary outcomes of interest, ETI, and mortality, between treatment groups.

Study selection

The reviewers independently made study selections based on titles and abstracts, which were compared against the inclusion criteria (lead reviewer – B. M. F., second reviewers – D. P., A. M. T., J. M., S. P. T.). Full texts were obtained after screening the titles and abstracts of potentially includable studies and conducting a similar dual-review process. Discussion between two reviewers and consultation with a third reviewer was done to resolve any concerns regarding the study selections.

Data extraction and quality assessment

Two reviewers (B. M. F. and S. P. T.) independently extracted the data from the included studies. The lead supervisor was consulted to resolve any disagreement regarding data extraction. The extracted information included study participant demographic data, study setting, study methodology, details of NIV used, and outcome measures [Appendix 2 in the supplementary file].

The methodological quality of each study was assessed using the risk-of-bias tool in RevMan. This tool consists of the following six domains: Random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, and selective reporting. Each domain was graded "yes," "no," or "unclear" to reflect a high or low risk of bias and uncertain bias, respectively. One reviewer (B. M. F.) completed the risk of bias assessment which was checked by a second reviewer (A. M. T.).

Outcome measures

The primary outcomes of interest included the need for ETI and the mortality rate after applying BiPAP. The secondary outcomes of interest were length of intensive care unit (ICU) stay, length of hospital stay, complications from treatment, and blood gas following the start of NIV.

Statistical analysis

The descriptive analyses are reported, and meta-analysis was performed using RevMan; pooled risk ratios (RRs) and 95% confidence intervals (CIs) were computed and Chi-square test and I^2 statistics were used to assess the heterogeneity of the study results. The heterogeneity was defined as low, moderate, and high with I^2 values of >25%, >50%, and >75%, respectively. In the analysis of heterogeneity, a $P < 0.05$ was considered to be statistically significant.

Results

A total of 2485 records were identified through the database search after removing duplicates. Eighty-eight articles were identified for full-text assessment. Full-text reviews resulted in the exclusion of 82 studies for different

reasons, as shown in Figure 1. The detailed included studies' characteristics and the reasons for excluded studies are shown in Appendix 3 in the supplementary file.

Study characteristics

The characteristics of the included studies are summarized in Table 1. Six articles were included in the study, involving 320 participants.[14-19] These included four RCTs comparing BiPAP to CPAP[14-17] and two comparing BiPAP to oxygen (O_2) therapy.[18,19] All of the studies were RCTs using a parallel-group design. The six studies occurred in Italy,[15,18,19] the United States,[14] France,[16,17] Spain,[19] and Taiwan.[19] Four of the six articles were multicenter studies.[16-19] All reported on adult patients with AHRF due to ACPO[14-18] and malignancy.[19] The number of patients recruited in each study ranged from 27 to 100 with an average age of participants of 74.3 years; males and females accounted for 52% and 48% of the participants, respectively. Five studies reported intervention failure, demonstrated by the need for an ETI outcome, four studies compared intubation between BiPAP and CPAP[14-17] and one study compared intubation between BiPAP and O_2.[18] In-hospital mortality was reported in almost all the

Table 1: Characteristics of the included studies

Study	Disease	Participants (*n*)	Intervention (BiPAP)	Control	Outcomes
Mehta (1997)	ACPO	27	14	CPAP=13	ETI Mortality rate LOS: Hospital and ICU
Nava (2003)	ACPO	64	33	O_2=31	ETI Mortality rate LOS: Hospital
Bellone (2005)	ACPO	36	18	CPAP=18	ETI Mortality rate
Moritz (2007)	ACPO	57	29	CPAP=28	ETI Mortality rate LOS: Hospital
Rusterholtz (2008)	ACPO	36	17	CPAP=19	ETI Mortality rate LOS: ICU
Nava (2013)	ESSD	100	53	O_2=47	Mortality rate

ACPO=Acute cardiogenic pulmonary edema, BiPAP=Bi-level positive airway pressure, ETI=Endotracheal intubation, LOS=Length of stay, ICU=Intensive care unit, CPAP=Continuous positive airway pressure, ESSD=End-stage solid tumour, O_2=Oxygen

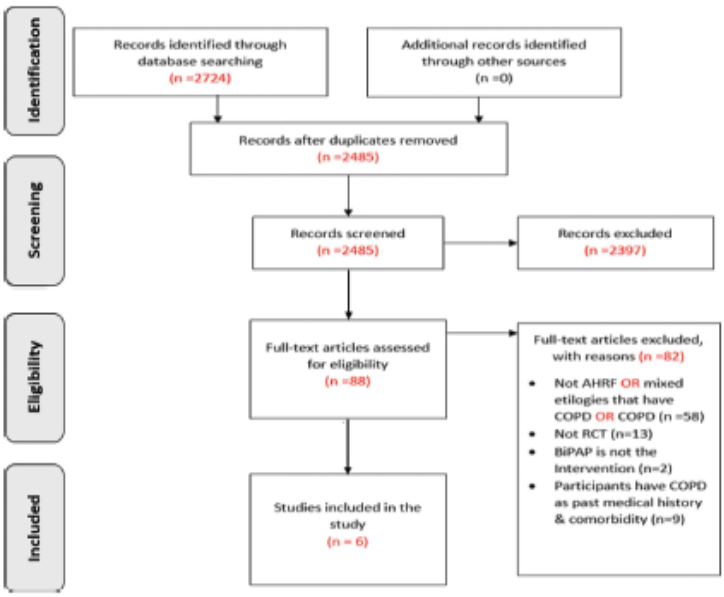

Figure 1: PRISMA diagram

studies; except for one study.[17] Three studies compared mortality between BiPAP and CPAP[14-16] and two studies between BiPAP and O_2.[18,19] Table 2 shows the different IPAP, EPAP, and O2 levels and the choice of patient-ventilator interface. The risk of bias summary for the individual studies is shown in Figure 2.

Endotracheal intubation

The results from four trials in ACPO (156 patients) were available for examining the effects of BiPAP vs CPAP on the incidence of ETI. A low level of heterogeneity was found among the identified comparisons ($I^2 = 0\%$; $P = 0.97$). Pooled analysis showed that the use of BiPAP was as effective as the control (CPAP) group with regard to the rate of intubation in hypercapnic respiratory failure patients, with no statistically significant difference between treatment groups (RR = 1.49; 95% CI: 0.62–3.62; $P = 0.37$) [Figure 3]. One study reported the effect of BiPAP vs O_2 with respect to ETI; this study showed that the percentage of patients with BiPAP needing intubation was significantly lower in a hypercapnic sub-group.[18]

In-hospital mortality

In-hospital mortality was reported in three trials (120 patients) examining the effects of BiPAP versus CPAP on the incidence of in-hospital mortality in ACPO. A low level of heterogeneity was found ($I^2 = 0\%$; $P = 0.75$). Pooled analysis showed that BiPAP had no superior effect over CPAP with regard to the rate of in-hospital mortality (RR = 0.71; 95% CI: 0.25–1.99; $P = 0.51$) [Figure 4]. In hypercapnic patients with end-stage tumor, patients with BiPAP had a better expected survival than patients receiving O_2 alone.[19]

Other outcomes

Two studies of BiPAP vs CPAP reported hospital length of stay as an outcome.[14-16] There were no significant differences in hospital length of stay observed between treatment groups in these studies. Bellone *et al.*[15] reported that there was a significant decrease in $PaCO_2$ for both groups; however, other studies reported that the BiPAP group had greater reductions and significantly greater improvement in $PaCO_2$ as compared to the control group.[14,18,19] Improvements in other physiological markers such as heart rate, blood pressure, pH, respiratory rate, and SpO_2 were similar in trials comparing BiPAP to CPAP[15-17] and more significant in the BiPAP group when compared to O_2 group.[18,19]

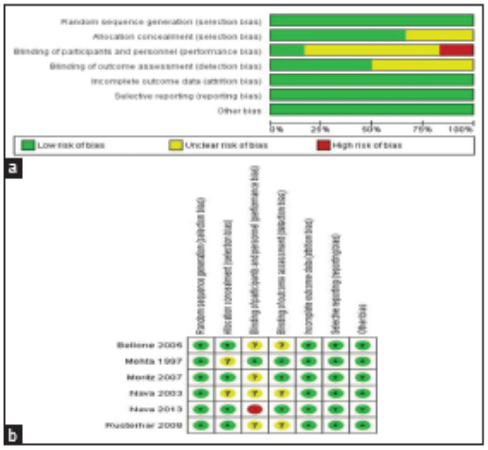

Figure 2: Summary of risk of bias in individual studies. (a) A graph with percentages for all included studies. (b) A summary of bias for each included study

Discussion

This systematic review and meta-analysis demonstrates the effectiveness of using BiPAP in non-COPD patients with AHRF. The difference between BiPAP and CPAP or O_2 was investigated, with regard to ETI and in-hospital mortality, and included studies generally showed little heterogeneity, perhaps due to our strict inclusion criteria. We were surprised to find that we were only able to meta-analyze studies of hypercapnic patients with ACPO, with a lack of RCTs for other hypercapnic non-COPD conditions. The number of studies using the treatment in ACPO was also lower than might be at first expected because many of the studies claiming to be treating a pulmonary edema population and included in prior systematic reviews,[20,21] in fact included high numbers of patients with coexistent COPD.[22-30]

The European Society of Cardiology and the American Heart Association have recommended the use of NIV in the treatment of acute heart failure,[31] so it would

Table 2: Inspiratory positive airway pressure, expiratory positive airway pressure, and oxygen levels and patient-ventilator interface

Study	IPAP (cm H_2O)	EPAP (cm H_2O)	CPAP (cm H_2O)	O_2	Interface
Bellone (2005)	15	5	10	-	Face mask
Mehta (1997)	14.35±1.73	5	10.08±1.24	-	Nasal mask
Moritz (2007)	12±3.2	4.9±0.9	7.7±2.1	-	Facemask
Rusterholtz (2008)	-	4	10	-	Face mask
Nava (2003)	14.5±21.1	6.1±3.2	-	Not stated	Face mask
Nava (2013)	10	5	-		Face mask

IPAP=Inspiratory positive airway pressure, EPAP=Expiratory positive airway pressure, CPAP=Continuous positive airway pressure, O_2=Oxygen

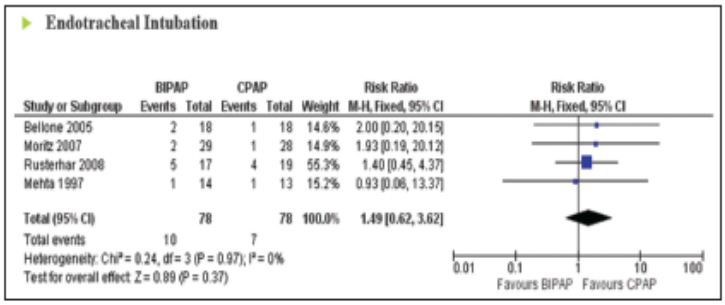

Figure 3: Forrest plot comparing endotracheal intubation rates in acute hypercapnic respiratory failure patients treated with bi-level positive airway pressure compared to continuous positive airway pressure

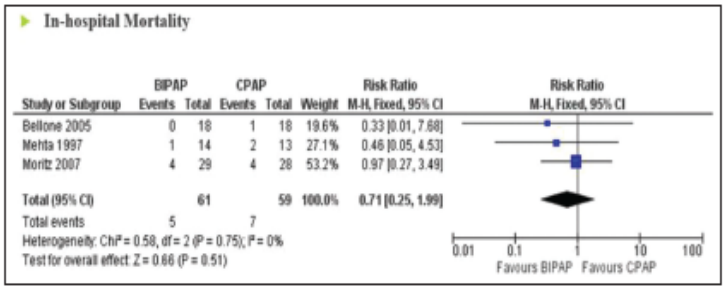

Figure 4: Forrest plot comparing in-hospital mortality rates in acute hypercapnic respiratory failure patients treated with bi-level positive airway pressure compared to continuous positive airway pressure

be beneficial to identify which of the ventilation modalities offers the optimal therapeutic benefit in patients with AHRF. Physiologically, BiPAP has a potential advantage over CPAP in reducing dyspnea and exhaustion by assisting the respiratory muscles in ACPO patients.[32] However, these physiological benefits did not translate into improved primary outcomes in our meta-analysis, which did not find any differences between BiPAP and CPAP with regard to ETI or in-hospital mortality. Nevertheless, hypercapnic patients, due to physiological reasons, were expected to benefit from BiPAP based on favorable results in some of the studies using BiPAP.[18,33] In hospitals where BiPAP is not available, however, CPAP would be a viable alternative based on the results.

Since the analysis was mainly based on an ACPO cohort, information on myocardial infarction (MI), which is an important cause of ACPO, was an important element to assess in our review. Overall, the incidence of MI was similar between the BiPAP and CPAP treatment groups in these studies. Although Mehta *et al.*'s study presented a higher rate of MI with BiPAP, Moritz *et al.*'s study also showed no significant differences in the incidence of MI when comparing BiPAP to CPAP. Moritz *et al.*'s findings were consistent with the other RCTs, as there were no differences between either technique on the incidence of MI.[22,27,34] This suggests that irrespective of the etiology of ACPO, whether it is due to MI or not, CPAP is equally effective as BiPAP and is safe to use.

The studies included in the review generally used IPAP, EPAP, and CPAP pressures that are not different from previous reviews on different hypercapnic conditions or the same condition but with different inclusion criteria. In addition, with regard to the NIV interfaces, most of the included studies used face mask interfaces which are consistent with the previous systematic reviews that reports the positive outcomes on hypercapnic respiratory failure patients.[20,35-37]

This meta-analysis is strengthened by its robust exclusion of coexistent COPD patients, such that we can be confident of the results with respect to conditions other than COPD. It also used a broad search strategy and multiple data sources, with no language restrictions, hence all available evidence was considered. However, it also has limitations. First, the sample size of the trials included in the meta-analysis was small, which could have underpowered our analysis of BiPAP compared to CPAP with regard to ETI and mortality. Second, a publication bias test was not performed due to the low number of included trials, and so these results should be viewed with caution.

Conclusion

Based on our systematic review and meta-analysis, we conclude that NIV reduces the incidence of intubation rate and mortality in hypercapnic patients with ACPO and that BiPAP appears equally effective as CPAP. This implies that patients with AHRF due to ACPO can be safely managed with CPAP, which is available in more non-ICU settings than BiPAP in most countries. For example, in the UK, CPAP is often available in coronary care units and acute medical units, whereas BiPAP is only available in specialized respiratory wards. This may aid patient flow through the hospital by opening up more locations in which such patients can be safely managed with taking in consideration healthcare providers' experience and confidence with the management of the ARF. Further research is needed in this area which includes various other conditions which can cause AHRF, in particular obesity-hypoventilation. No RCTs of NIV in obesity-hypoventilation-related AHRF were seen, yet cohort studies suggest a beneficial effect[38] and sufficiently good in-hospital mortality[39] such that management in a ward-based setting may be preferable to the more costly and resource intensive ICU setting.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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Appendix 8

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Research Article

Ward-Based Noninvasive Ventilation for Acute Hypercapnic Respiratory Failure Unrelated to Chronic Obstructive Pulmonary Disease

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Background. The use of ward-based noninvasive ventilation (NIV) for acute hypercapnic respiratory failure (AHRF) unrelated to chronic obstructive pulmonary disease (COPD) remains controversial. This study evaluated the outcomes and failure rates associated with NIV application in the ward-based setting for patients with AHRF unrelated to COPD. *Methods.* A multicentre, retrospective cohort study of patients with AHRF unrelated to COPD was conducted. COPD was not the main reason for hospital admission, treated with ward-based NIV between February 2004 and December 2018. All AHRF patients were eligible; exclusion criteria comprised COPD patients, age < 18 years, pre-NIV pH < 7.35, or a lack of pre-NIV blood gas. In-hospital mortality was the primary outcome; univariable and multivariable models were constructed. The obesity-related AHRF group included patients with AHRF due to obesity hypoventilation syndrome (OHS), and the non-obesity-related AHRF group included patients with AHRF due to pneumonia, bronchiectasis, neuromuscular disease, or fluid overload. *Results.* In total, 479 patients were included in the analysis; 80.2% of patients survived to hospital discharge. Obesity-related AHRF was the indication for NIV in 39.2% of all episodes and was the aetiology with the highest rate of survival to hospital discharge (93.1%). In the multivariable analysis, factors associated with a higher risk of in-hospital mortality were increased age (odds ratio, 95% CI: 1.034, 1.017–1.051, $P < 0.001$) and pneumonia on admission (5.313, 2.326–12.131, $P < 0.001$). In the obesity-related AHRF group, pre-NIV pH < 7.15 was associated with significantly increased in-hospital mortality (7.800, 1.843–33.013, $P = 0.005$); however, a pre-NIV pH 7.15–7.25 was not associated with increased in-hospital mortality (2.035, 0.523–7.915, $P = 0.305$). *Conclusion.* Pre-NIV pH and age have been identified as important predictors of surviving ward-based NIV treatment. Moreover, these data support the use of NIV in ward-based settings for obesity-related AHRF patients with pre-NIV pH thresholds down to 7.15. However, future controlled trials are required to confirm the effectiveness of NIV use outside critical care settings for obesity-related AHRF.

1. Introduction

NIV has been widely used in intensive care units (ICUs) for many years to treat conditions such as acute exacerbations of COPD (AECOPD) and is regarded as effective for avoidance of endotracheal intubation [1] and decreasing mortality in patients with AHRF. In 2000, findings from a randomised controlled trial supported the use of ward-based NIV for patients with acute exacerbation of COPD outside ICUs (in general medical wards) as it improved the mortality rate and reduced the need for invasive mechanical ventilation [2]. Currently, managing patients who require NIV in an ICU

Table 1: Participant baseline characteristics.

Characteristics	Median (IQR) OR *n* (%)			*P*
	Total *n* = 479	Obesity-related AHRF* *n* = 188	Non-obesity-related AHRF *n* = 291	
Age (years)	73 [62–81]	69 [60–75]	76 [65.75–84]	<0.001
Male	192 (40.1)	66 (35.1)	126 (43.3)	<0.001
Female	287 (59.9)	122 (64.9)	165 (56.7)	0.011
Survival to discharge	384 (80.2)	175 (93.1)	209 (71.8)	0.083
In-hospital mortality	95 (19.8)	13 (6.9)	82 (28.2)	<0.001
Pre-NIV pH	7.27 [7.21–7.31]	7.27 [7.23–7.31]	7.26 [7.20–7.31]	0.042
Pre-NIV pH thresholds				
pH > 7.15	61 (12.7)	16 (8.5)	45 (15.5)	<0.001
pH 7.15–7.25	138 (28.8)	50 (26.6)	88 (30.2)	0.001
pH < 7.25	280 (58.5)	122 (64.9)	158 (54.3)	0.031
NIV failure	101 (21.1)	15 (8.0)	86 (29.6)	<0.001
Subgroup (BHH)				
Duration of NIV (days)	5 [3–9]	6 [4–10]	4 [2–9]	0.015
RF to NIV (minutes)	123 [63.5–302.5]	123 [63.5–302.5]	122 [60.0–316.0]	0.692
Domiciliary NIV	44 (23.4)	27 (14.4)	17 (5.8)	0.132

*Obesity-related AHRF patients due to obesity hypoventilation syndrome; IQR, interquartile range; BHH, Birmingham Heartlands Hospital; NIV, noninvasive ventilation; RF, respiratory failure; AHRF: acute hypercapnic respiratory failure.

Table 2: Prevalence of conditions causing AHRF.

Diagnosis	*n* (%)		
	Total	Survived to discharge	In-hospital mortality
Pneumonia	53 (11.1)	36 (67.9)	17 (32.1)
Bronchiectasis	40 (8.4)	30 (75)	10 (25)
Obesity-related AHRF	188 (39.2)	175 (93.1)	13 (6.9)
Neuromuscular disease	85 (17.7)	63 (74.1)	22 (25.9)
Fluid overload	48 (10)	35 (72.9)	13 (27.1)
Other	65 (13.6)	45 (69.2)	20 (30.8)
Total	479 (100)	384 (80.2)	95 (19.8)

AHRF: acute hypercapnic respiratory failure.

In the univariable analysis for the two subgroups (obesity- and non-obesity-related AHRF), the patients who died in-hospital were older than those who survived to discharge. There were statistically significant differences in survival between the three hospitals ($P = 0.017$), as well as significant differences between survivors and those who died with regards to the underlying diagnosis. Pre-NIV pH was higher in the survived to discharge group compared to the in-hospital mortality group. More than two-thirds of the in-hospital mortality group had NIV failure. In one of the included hospitals (BHH, $n = 237$), more data were available, which enabled additional analyses in this subgroup. There were significant differences between the groups (survived vs. died) in the number of days using NIV and the proportion of patients who were treated with domiciliary NIV. No significant differences were noted between the two groups in the time from diagnosis to NIV application (Supplementary Tables 1 and 2).

In multivariable logistic regression, in total non-COPD AHRF group, significant predictors of in-hospital mortality were pre-NIV pH < 7.25, age, and underlying cause of AHRF, whereby the aetiology with the best prognosis was obesity-related AHRF (Table 3). This condition was taken as the reference value, and hazard ratios for death relative to this were calculated in the regression models. However, in the obesity-related AHRF subgroup, pre-NIV pH of below 7.15 was associated with a significant increase in mortality (7.800, $P = 0.005$) but not between 7.15 and 7.25 (2.035, $P = 0.305$). Moreover, age was not associated with a significant increase in mortality (1.030, $P = 0.231$) when compared to the age in the non-obesity-related AHRF subgroup. In the BHH subgroup, where additional data were available, we were also able to assess the contribution of domiciliary NIV to the model; receipt of this appeared to be protective. A Kaplan–Meier curve was constructed comparing in-hospital mortality in groups split by aetiology of AHRF (obesity-related AHRF vs. non-obesity-related AHRF) (Figure 1).

4. Discussion

Our study has shown that patients with obesity-related AHRF have a high rate of survival to hospital discharge (93.6%) when managed in ward-based settings. We have also shown that obesity-related AHRF patients with a pre-NIV pH between 7.15 and 7.25 exhibit similar prognosis to patients with a higher pre-NIV pH, unlike in other conditions causing AHRF. This suggests that obesity-

prognosis is equal or better than those already routinely managed in this setting. Whilst rates of in-hospital mortality in recent studies appear higher than the landmark randomised controlled trial in COPD [2], this may be related to the selection of patients who were not expected to survive, either due to their condition and its severity or due to comorbid disease [21].

The in-hospital mortality rate of 6.9% for patients with obesity-related AHRF was significantly lower than for other conditions which strongly suggests that NIV should be considered for use in obesity-related AHRF in ward-based settings, given that their risk of a poor outcome is lower. This finding is consistent with the results of a study of patients managed in a critical care setting, in which mortality was found to be lower in obesity-related respiratory failure patients compared to COPD patients managed with NIV [17]. Moreover, this is consistent with a recent study that reported a 15% mortality rate for the obesity-related respiratory failure group which was lower compared to the other diagnostic groups [20].

Patients with pneumonia had the highest rate of in-hospital mortality (32.1%), with a high odds ratio of mortality when compared to obesity-related AHRF patients (5.313, $P < 0.0001$) and other diagnostic groups. This finding is in line with the National Confidential Enquiry into Patient Outcome and Death (NCEPOD) data, which indicated that patients with pneumonia experienced higher in-hospital mortality [21]. Moreover, the British Thoracic Society/Intensive Care Society guidelines for the ventilatory management of acute hypercapnic respiratory failure in adults already recommend against the use of ward-based NIV in patients with pneumonia [22]. The higher in-hospital mortality rate noticed in patients with pneumonia highlights and emphasises the importance of the NCEPOD recommendation that "Early senior review and escalation planning is essential to ensure these patients receive appropriate treatment in the correct location." [21].

This study showed that a significantly higher proportion of the in-hospital mortality group had NIV failure compared to the discharged group (83.2% vs. 5.7%, $P < 0.0001$). One possible explanation for this is that most of them may have received NIV as a ceiling treatment, which is not fully reported in the database; this might explain why they were being treated in ward-based setting, instead of critical care settings with advanced treatment.

4.2. Predictors of In-Hospital Mortality. Pre-NIV pH was a significant predictor of in-hospital mortality when it was analysed as a continuous variable and when it was grouped by thresholds. The importance of pre-NIV pH seen in our study was consistent with the findings of the UK national audit of COPD patients treated with NIV [19] where pre-NIV pH < 7.15 and 7.15–7.25 were associated with a higher risk of mortality (2.223, $P = 0.021$, and 1.865, $P = 0.023$, respectively). However, in contrast to the findings seen in COPD patients in the national audit, we were able to show that there was no difference in the rate of in-hospital mortality between obesity-related AHRF patients with pre-NIV pH 7.15–7.25 and those with pre-NIV pH < 7.25 and that this effect was driven by low death rates in the obesity subgroup at lower pH levels. This suggests that a pre-NIV pH threshold of 7.15–7.25 could be chosen for managing obesity-related AHRF patients in lower intensity settings (outside the ICU). We have previously shown this in COPD patients also [14], but the message appeared stronger in the obesity-related AHRF subgroup here than in our prior data.

Age was also an important predictor of in-hospital mortality in non-COPD AHRF patients treated with NIV. This is consistent with studies done on AHRF due to COPD [14, 23] and AHRF unrelated to COPD [20]. It was expected that an association between age and mortality would be found since age is not necessarily a limitation to the treatment and, in general, older age is associated with worse prognosis.

The time from AHRF to NIV application was no different in the in-hospital mortality group. The British Thoracic Society 'Quality Standards for Acute NIV in Adults' notes that "Patients who meet evidence-based criteria for acute NIV should start NIV within 60 minutes of the blood gas result associated with the clinical decision to provide NIV and within 120 minutes of hospital arrival for patients who present acutely" [24]. This is because delays in treatment have been associated with reduced survival; however, it is also notable that some patients with COPD deteriorate late, and these also represent a poor prognostic group [23]. A longer wait for NIV application could result in high numbers of emergency hospital admissions, poor NIV capacity, or inadequate clarity within the hospital's NIV pathway. Notably, the time from diagnosis to NIV application was generally at or close to the national standard of 120 mins (120 vs. 140 minutes, survived vs. died) in our group which may have reduced power to detect differences based on this factor.

4.3. Strengths and Limitations. The key strengths of this study include the multiple centres with a large cohort size, which is larger than other recent cohort studies targeting the same population [20], and the detailed data available particularly at BHH, which allowed assessment of the impact of timing of acute NIV treatment as well as the impact of previous domiciliary NIV. The study's findings, however, were limited by the uncontrolled, retrospective cohort design.

5. Conclusion

In summary, based on our difficulty in ascertaining from the database which patients had NIV as ceiling of treatment and what were the comorbidities, from April 2019, we have upgraded our database to capture that information in real time. We have built upon previous work within COPD patients, in which pre-NIV pH has been identified as an important predictor of surviving ward-based NIV treatment. Our findings support the use of NIV in ward-based settings for obesity-related AHRF patients with pre-NIV pH thresholds from 7.15 upwards. Based on the promising outcomes for the obesity-related AHRF group in this study

and in other recent studies, future controlled trials are required to prove the effectiveness of using NIV outside critical care settings for obesity-related AHRF.

Abbreviations

NIV: Noninvasive ventilation
ICU: Intensive care unit
COPD: Chronic obstructive pulmonary disease
AECOPD: Acute exacerbations of COPD
AHRF: Acute hypercapnic respiratory failure
IQR: Interquartile range
NCEPOD: National Confidential Enquiry into Patient Outcomes and Deaths.

Data Availability

The data that support the findings of this study are available from the corresponding author, BMF, upon reasonable request.

Conflicts of Interest

Prof. Turner reports grants from ResMed and Philips outside the submitted work. Dr. Mukherjee reports personal fees and nonfinancial support from Pfizer, personal fees from Boehringer Ingelheim, and personal fees from ResMed, outside the submitted work. Otherwise, the authors declare that there are no conflicts of interest regarding the publication of this article.

Authors' Contributions

B. M. F. was responsible for idea conceptualization, study methodology, data curation, formal data analysis, and manuscript writing (original draft). D. P. and A. M. T. contributed to study supervision, idea conceptualization, data curation, and manuscript writing (review and editing). S. P. T. and J. M. performed data curation and manuscript writing (review and editing). R. M. took part in study supervision and manuscript writing (review and editing).

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Supplementary Materials

Supplementary Tables 1 and 2 are tables that describe the baseline characteristics of obesity-related AHRF and non-obesity-related AHRF based on survival to discharge and in-hospital mortality rates. (*Supplementary Materials*)

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