NEAR EAST UNIVERSITY

INSTITUTE OF GRADUATE STUDIES

DEPARTMENT OF NURSING

PREDICTORS AND ASSOCIATED FACTORS OF NON-INVASIVE VENTILATION FAILURE AMONG THE COVID-19 PATIENTS ADMITTED IN INTENSIVE CARE UNIT

M.Sc. THESIS

Hesam Aldin VARPAEI

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Approval

Approval

We certify that we have read the thesis submitted by **Hesamaldin Varpei** titled **"Predictors and associated factors of noninvasive ventilation failure among the COVID-19 patients admitted in intensive care unit"** and that in our combined opinion it is fully adequate, in scope and in quality, as a thesis for the degree of Master of Nursing (Surgical Nursing).

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Declaration

I thus certify that all material, documents, analyses, and results contained in this thesis were gathered and presented in accordance with the academic regulations and ethical principles of the Institute of Graduate Studies Near East University. I further declare that I have adequately cited and referenced information and data that are not unique to this work, as required by these rules of conduct.

HESAM ALDIN VARPAEI

15/06/2022

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This research would not have been possible without the support of almighty God. I would like to express my appreciation to my lovely family and supervisor (Dr. Nurhan Bayraktar) who showed a sincere interest in my success through unwavering patience, support and guidance.

In the memory and name of all the heroic and famous women, who tried with all their hardships and inequalities to promote science and knowledge.....

Dedication to all brave mothers and women.

My Mother,
Professor Maryam Mirzakhani, 1977 – ∞
Florence Nightingale, 1820 – ∞
Marie Curie, 1867 – ∞
Azar Andami, 1926 – ∞
Remziye Hisar, 1902 – ∞
Suzan Kahramaner, 1913 – ∞

And dedication to all nurses and doctors who bravely tried to save human lives in the Corona virus pandemic. Thanks heroes.

HESAM ALDIN VARPAEI

Özet

Yoğun bakım ünitesine kabul edilen COVID-19 hastalarında Non-invasive ventilation (NIV) yetersizliğinin göstergeleri ve ilişkili faktörler

Öğrencinin Adı: Hesam Aldin Varpaei

Danışman: Prof. Dr. Nurhan Bayraktar

Anabilim Dalı: Hemşirelik (Cerrahi Hemşireliği)

Amaç: Bu çalışmanın temel amacı, yoğun bakım ünitesine kabul edilen COVID-19 hastalarında NIV yetersizliğinin göstergelerini ve ilişkili faktörleri belirlemektir.

Gereç ve Yöntem:. Bu araştırma, İran Tahran'da Imam Khomeini Hospital Complex (IKHC) hastanesine kabul edilen COVID-19 hastalarının elektronik tıbbi verileriyle yürütülen kesitsel bir retrospektif çalışmadır. Bu çalışmaya toplam 150 hasta dahil edildi. Veriler, hastaların demografisi, geçmiş tıbbi geçmişi, laboratuvar testleri, arteriyel kan gazları, yaşamsal belirtiler, hemşirelik gözlemleri, Richmond ajitasyon skalası, APACHE II (Akut Fizyoloji ve Kronik Sağlık Değerlendirmesi) skoru, HACOR skoru, ROX indeksi ve GCS'yi içeren bir anket ile Mart 2021-Temmuz 2022 tarihleri arasında toplandı. Verilerin istatistiksel analizi SPSS sürüm 26 ile yapıldı.

Bulgular: Hastaların %55.3'ü erkek olup, yaş ortalaması 55.9±13.48'dir. Sırasıyla hipertansiyon (%34.7), diyabet (%28.7) ve iskemik kalp hastalığı (%16.7) en sık görülen eşlik eden hastalıklardı. Çalışmanın sonuçları %67,3 oranında NIV yetersizliğini gösterdi. Mortalite oranı %66.7 idi ve hastaların %3.3'ünde NIV yetersizliğine bağlı trakeostomiye ihtiyaç duyuldu. NIV yetersizliği olan hastaların yüzde 97'si kaybedildi. Ortalama ROX indeksinin zamana göre istatistiksel olarak önemli ölçüde farklılık gösterdiğini belirlendi. Ayrıca, ortalama HACOR puanı zamana göre istatistiksel olarak anlamlı farklılık gösterdi.

Sonuçlar: Yoğun bakım ünitesine kabul edilen COVID-19 hastalarının çoğunluğunun NIV yetersizliği olduğu sonucuna varılmıştır. NIV başladıktan 12 saat sonra artan HACOR skoru ve azalan ROX indeksi, NIV yetersizliğinin göstergeleriydi. İleri yaş NIV yetersiliği ile ilişkili bulundu.

Anahtar kelimeler: Non-invaziv ventilasyon, SARS-CoV-2, hemşirelik izlemi, entübasyon, kritik bakım, ventilasyon.

Abstract

Predictors of non-invasive ventilation (NIV) failure and associated factors among the COVID-19 patients admitted in intensive care unit (ICU)

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Advisor: Prof. Dr. Nurhan Bayraktar
Department: Nursing (Surgical Nursing)

Objective: The main aim of this study is to determine the predictors of NIV failure and associated factors in COVID-19 patients admitted to ICU.

Materials and Methods: This was a cross-sectional retrospective study conducted by electronic medical data of COVID-19 patients admitted at Imam Khomeini Hospital Complex (IKHC), Tehran, Iran. A total of 150 patients were included in this study. Data were collected by a questionnaire which include, patients' demographics, past medical history, lab tests, arterial blood gases, vital signs, nursing observations, Richmond agitation scale, APACHE II (Acute Physiology and Chronic Health Evaluation) score, HACOR score, ROX index, Glasgow Coma Scale from March 2021 until July 2022. Statistical analysis was performed by SPSS version 26.

Results: Of the patients, 55.3% were male and average age of population were 55.9±13.48. Concerning co-morbidities hypertension (34.7%), diabetes (28.7%), and ischemic heart disease (16.7%) were the most common co-morbidities respectively. Results of the study showed a 67.3% NIV failure rate. The mortality rate was 66.7%, and the 3.3% of patients need tracheostomy after NIV failure. A 97 percent of patient with NIV failure died and just 4.1 percent of non-NIV failure patients. Mean ROX index differed statistically significantly between time points. Also, mean HACOR score differed statistically significantly between time points.

Conclusions: It is concluded that rate of NIV failure accounts for the majority of the COVID-19 patients admitted to ICU. Increasing HACOR score after 12 hours and decreasing ROX index after NIV starting were the predictors of NIV failure. Higher age was associated with NIV failure.

Key words: Non-invasive ventilation, SARS-CoV-2, nursing monitoring, intubation, critical care, ventilation.

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List of Abbreviations

ABG: Arterial Blood gas

APACHE II: Acute Physiology and Chronic Health Evaluation II

ARDS: Acute respiratory distress

ARF: Acute respiratory failure

ASA: American Society of Anesthesiology

BP: Blood pressure

COPD: Chronic obstructive pulmonary disease

COVID-19: Coronavirus disease

CT scan: Computer tomography

CVD: Cardiovascular disease

CXR: Chest X-ray

DM: Diabetes mellitus

ECG: Electrocardiography

ED: Emergency department

GCS: Glasgow Coma Scale score

HACOR: Heart rate, acidosis, consciousness, oxygenation, respiratory rate

HR: Heart rate

ICU: Intensive Care Unit

IHD: Ischemic heart disease

NIV: Non-invasive ventilation

MR: Mortality

MV: Mechanical Ventilation

OSA: Obstructive sleep apnea

CHAPTER I

1. Introduction

1.1. Definition of the problem

Non-invasive ventilation (NIV) is the supply of oxygen (ventilation support) using a face mask, obviating the requirement for an endotracheal airway (Chilkoti, et al 2022). The intervention is recognized as an efficient treatment for chronic obstructive pulmonary disease, cardiogenic pulmonary edema, and other respiratory disorders without consequences such as respiratory muscle weakness, upper airway trauma, ventilator-associated pneumonia, or sinusitis (Pavone et al, 2012, Nava and Hill 2009). In some previous references, it has been suggested that, NIV can be considered as a standard treatment (approach) in acute hypercapnic respiratory failure (e.g., COPD exacerbation) (Comellini et al, 2019).

NIV works by generating positive airway pressure, which means that the pressure outside the lungs is larger than the pressure inside the lungs. This forces air into the lungs (down the pressure gradient), lowering the respiratory strain and labor of breathing. It also contributes to the expansion of the chest and lungs by raising the functional residual capacity (the amount of air left in the lungs after expiration) following a normal (tidal) expiration; this is the air accessible in the alveoli for gaseous exchange (Anon n.d.,2016). NIV is classified into two types: non-invasive positive-pressure (NIPPV) and negative-pressure ventilation (NPV). NIPPV describes the delivery of oxygen at either constant or variable pressures via a face mask, such as Bi-level Positive Airway Pressure (BiPAP) and Constant Positive Airway Pressure (CPAP). The most basic form of support is CPAP, which delivers continuous fixed positive pressure during inspiration and expiration, helping the airways to stay open and reducing the labor of breathing (Hooper, et al,2016, Nehyba 2006). This results in more inspired oxygen than other oxygen masks. High flow systems are utilized in hospitals to guarantee that the airflow rates are larger than those created by the disturbed patient. It can help cardiac function as well as respiratory function in individuals with poor cardiac output and pre-existing low blood pressure (Cao, et al 2016). It is also widely used to treat severe obstructive sleep apnea and type 1 respiratory failure, such as respiratory distress edema (by recruiting collapsed alveoli). It has been reported that in cardiac-dependent pulmonary edema, utilizing NIV can significantly improve oxygenation of patients, meanwhile did not show any effect on mortality (Gary et al, 2018). Accordingly, recent review suggested that CPAP or NIV should be consider for a primary approach in cardiac-dependent pulmonary edema patients (Bello, G., De Santis, P., & Antonelli, M,2018). A study from India (Arsude et al, 2019) also, suggested that in type 1 respiratory failure, using NIV and BIPAP enhance the oxygenation of patients and also may prevent need for invasive tracheal intubation. It has been claimed that NIV can be effective in critically ill patients with conditions such as COPD, cardiogenic pulmonary edema, OSA, and hypercapneic respiratory failure, but its utility in patients with pneumonia, acute respiratory distress syndrome (ARDS), and, in particular, COVID-19 is less clear. Evidence-based data from earlier viral pandemics such as SARS, MERS, and H1N1 may broaden our insight into acceptable usage during the COVID-19 pandemic (Sullivan et al, 2022). As a general rule, it can be said that the use of non-invasive ventilation in patients with COVID-19 ARDS can be beneficial as a primary treatment (as a trial period like 2 – 12 hours) (Menga et al, 2021, Alhazzani et al, 2021).

NIV outperforms traditional mechanical ventilation in terms of physiological advantages by lowering labor of breathing and enhancing gas exchange (Storre, et al 2014). According to research, noninvasive ventilation following early extubation appears to be beneficial in minimizing the overall number of days spent on invasive mechanical ventilation (Vaschetto et al. 2021). Weaning from invasive ventilation - A 2009 meta-analysis found that NIV, as a method of weaning critically ill adults from invasive ventilation, was significantly associated with lower mortality and ventilator-associated pneumonia (Burns,et al, 2009). The advantages of non-invasive ventilation are well meet if the oxygen delivery system of the mask is well fixed and there are no leaks (Silva et al, 2013).

NIV failure is considered as a significant problem. NIV failure is described as "The requirement for endotracheal intubation (ETI) or death has been characterized as NIV failure (Moretti et al. n.d., 2020) ". Its prevalence ranges from 5 to 60%, depending on a variety of circumstances, including the origin of acute respiratory failure (ARF) (Confalonieri et al. 2005). Unsuccessful NIV was demonstrated to be an independent predictor of mortality, particularly in individuals with de novo ARF (Demoule Emmanuelle Girou Jean-Christophe Richard Solenne Taille Laurent Brochard et al. 2006). Nicolini et al (Nicolini et al. 2014) reported NIV failure in 20% of community acquired pneumonia (CAP). Also, Menzella et al (Menzella et al. n.d.) address the NIV failure rate of 51.9% (41 out of 79). However, Mukhtar et al. (Mukhtar et al. 2021) reported the NIV failure rate was 26% (13 out of 49 patients) in their study. Since, COVID-19 pandemic account thousands of deaths around the world (due to respiratory failure). It seems that NIV failure is more common in COVID-19 patients than in COPD, CAP, and ARF. NIV failure is reported to be associated with increased mortality for respiratory distress patients (Demoule et al, 2006). Also, NIV failure is correlated with more hospital stay that can be costly for both patients and health systems (like health insurances). In addition, NIV failure may put patients at the risk of other complications like acute kidney injury, acute liver failure, sepsis, and heart complications. Other dire consequence of NIV failure maybe face scare (ulcer) in results of NIV interfaces (Maruccia et al, 2015).

Understanding the predictors of NIV failure enables ICU nurses and physicians to keep high-risk patients under close monitoring and provide the necessary treatments as soon as possible to avoid NIV failure (intubation) and hospital death. Ideally, it is recommended that Polysomnography monitoring should be utilized for patients under NIV (Georges et al. 2020). However, it is highly costly and unavailable everywhere. Primary findings of Patout et al (Patout et al. n.d.) revealed that combination of Polysomnography or limited respiratory monitoring with nurse-led titration protocol to safely can develop good monitoring for patients who need to treated by NIV. It was reported that vital signs, arterial blood gases (ABG), and oximetry are the most important elements of monitoring for patients under NIV (Georges et al. 2020).A study in Turkey used arterial blood gas, vital signs, and mask compliance as monitoring tools for nurses who deliver care to patients under NIV in ICU (Yaman et al. 2021, Nava et al (Nava and Hill 2009) suggested that in addition to vital signs and blood gas, other parameters such as patients comfort and mask tolerance should be consider as monitoring of NIV every 30 minutes for the first six-to-twelve hours of treatment. GCS and level of consciousness can be used as an evaluation for NIV failure according to Scala et al (Scala et al. 2005). Andrey et al (Avdeev et al. 2021) reported that higher ages, respiratory rate, PaCO2, D-dimer levels before NIV, and higher minute ventilation and ventilatory ratio on the first day of NIV were all linked with NIV failure. Outside of the intensive care unit, NIV is viable in patients with COVID-19 and acute hypoxemic respiratory failure, and it can be regarded a beneficial alternative for the therapy of acute hypoxemic respiratory failure in these patients.

ROX index was reported to be an appropriate tool to predicts NIV failure in both COVID-19 and non-COVID-19 patients (Ferrer et al. 2021, Roca et al. 2016). HACOR score is another scale (tool) that reported to have high capability to predict NIV failure in COPD (Duan et al. n.d.) patients and also non-COPD patients (Ding et al. 2021).

Nurses are one of the most important healthcare providers in critical care settings. Oxygen therapy and delivering appropriate care is one of the crucial nurse's duties in ICU. To our knowledge patients who admitted to intensive care unit due to respiratory diseases (such as COPD exacerbation, COVID-19, and FLU) need oxygen supplementation. In ICUs, nurses keep patients under their close monitoring and they are responsible for reporting any serious changes that could threaten the patient's life. Summer and Yadegarfar's (Sumner and Yadegafar 2011) study, which sought to investigate the practice of delivering non-invasive ventilation (NIV) in non-designated areas within a large university teaching hospital by critical care outreach nurses, discovered that inappropriate use of NIV in non-designated areas is associated with a high mortality. Critical care outreach nurses can have a significant impact on patient selection for NIV. Contou et al (Contou et al. 2013) revealed that nurse-driven NIV protocol can significantly influence the NIV failure and prevent intubation by 15% and mortality rate by 5%. Stoltzfus suggested that Congestive heart failure who receiving NIV should be under close monitoring of critical care nurse. Cabrini et al (Cabrini et al. n.d., 2016) indicated that nurses are motivated to learn more training on NIV to be an active member of healthcare provider who engaged with patients' treatment. It seems that the knowledge of nurses about NIV is insufficient and this can greatly affect care approaches.

Nurses are responsible to delivering care to the patients who requiring NIV and nurses should pay attention to their psychological and physiological needs. As a holistic approach of nursing process, nurses should consider both environment and individuals in the time of NIV treatment. Nurses should pay attention to the physiological and psychological needs of patients, reduce environmental barriers, and try to optimize ventilation and oxygenation of patients under NIV (Venkatesaperumal et al. 2013). About the importance of nursing practice and knowledge regarding NIV, it is stated that (Sorensen et al. 2013) each nurse may monitor the patient's health and respond to NIV. The conceptualization of complexities in nurses' reasoning and actions revealed their proclivity to divide challenging circumstances into three interconnected components: (1) achieving noninvasive adaptation, (2) ensuring effective ventilation, and (3) responding closely to patients' perceptions of non-invasive ventilation. Each item is made up of a collection of nursing reasoning and actions used by experienced nurses to ensure therapeutic effectiveness.

Monitoring during oxygen therapy and particularly when patient is under NIV is one of the most important nursing responsibilities. Nurses must check patients' respiration rate, level of awareness, chest wall movement, accessory muscle usage, and comfort every 15 minutes after NIV begins, and this can be lowered if the patient's condition improves. For the first 12 hours of NIV, pulse oximetry and ECG monitoring should be continuous (Yaman, Aygun, and Erten 2021). In addition, lack of knowledge (Cabrini et al. n.d.) or insufficient knowledge about NIV can also cause ignoring patients who are under NIV.

Usually, nurses are responsible of delivering care to more than one patient in ICUs. It can be challenging particularly in the time of crisis just like COVID-19 pandemic. Therefore, due to high level of workload, they may have not enough time to screen their patients under close monitoring for any supposed (potential hazard) like cardiac arrest, NIV failure, and disease exacerbation. Knowing the factor/s that may predict NIV failure enables nurses to take appropriate action before it is too late. Also, they will be enabling to mark the patients as "high risk for NIV failure" and assigned the most experienced nurse to deliver care. Because of COVID-19 pandemic, it is highly important to understand more about pathology and dire consequence of this disease. Cost of ICU care is highly expensive and long stay of patients can put pressure on health economy systems. Also, there is not a well-designed original study about NIV failure and associated factors. Therefore, this research can be the first paper in the world about NIV failure and associated factors and broaden our horizons to nursing care of COVID-19 patients.

1.8. Aim of the Study

The main aim of this study is to determine the predictors of NIV failure and associated factors in COVID-19 patients admitted to ICU.

Study questions are as followings:

- What are the predictors of NIV failure among the COVID-19 patients admitted to ICU?
- What are the associated factors for NIV failure in COVID-19 patients?

CHAPTER II

2. Background, Physiology of ventilation

The flow of air via the conducting channels between the atmosphere and the lungs is referred to as ventilation or breathing. The air travels through the channels due to pressure gradients created by diaphragm and thoracic muscle activity. Inspiration (inhalation) is the process of taking air into the lungs (active action). Expiration (exhalation) is the process of letting air out of the lungs during the breathing cycle (passive action). The most important role of ventilation is to remove carbon dioxide (CO_2) from blood stream. For monitoring ventilation, capnography is the best tool. Ventilation is generally a mechanical process and follows the laws of pressure (physics).

The molecular absorption of oxygen is referred to as oxygenation. Air enters the lungs, and oxygen is taken up by hemoglobin in red blood cells, where it is transported and distributed to the body's tissues. Oxygenation (delivery of O_2 to the body cells) happens in all parts of the body. Disruption of oxygenation can lead to cell death (necrosis) by this time. Specifically, oxygenation of vital human organs (brain and heart) is essential and less than 5 minutes of lack of oxygenation can result in death. For monitoring ventilation, pulse oximetry is the best tool. Oxygenation is a biochemical process that follows the rules of biochemical laws of emission and osmosis of gases (chemistry).

Respiration is a broad term that refers to the act of breathing by combining ventilation and oxygenation. It is the biological process of absorbing oxygen and expending carbon dioxide.

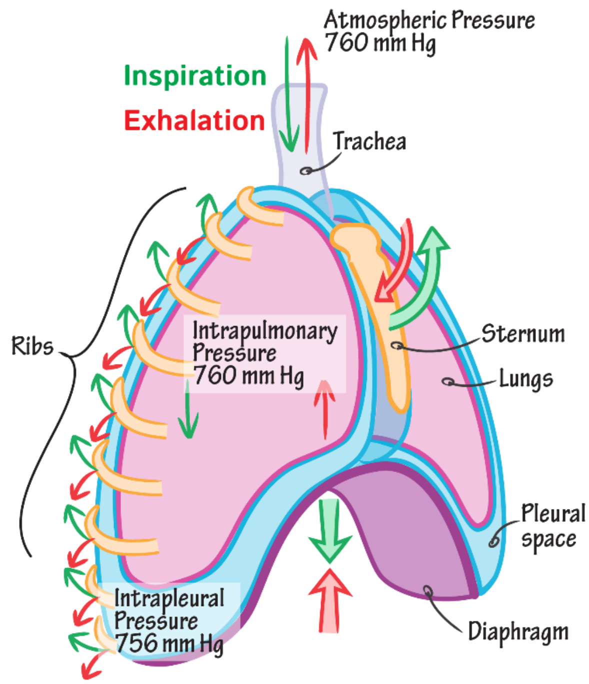

Figure 1 - Anatomy of respiratory system (reference link)

There two types of muscles involved in breathing. Muscles that aid in the expansion of the thoracic cavity are known as inspiratory muscles because they aid in inhaling. Expiratory muscles are those that compress the thoracic cavity and cause exhalation (figure 1 & 2).

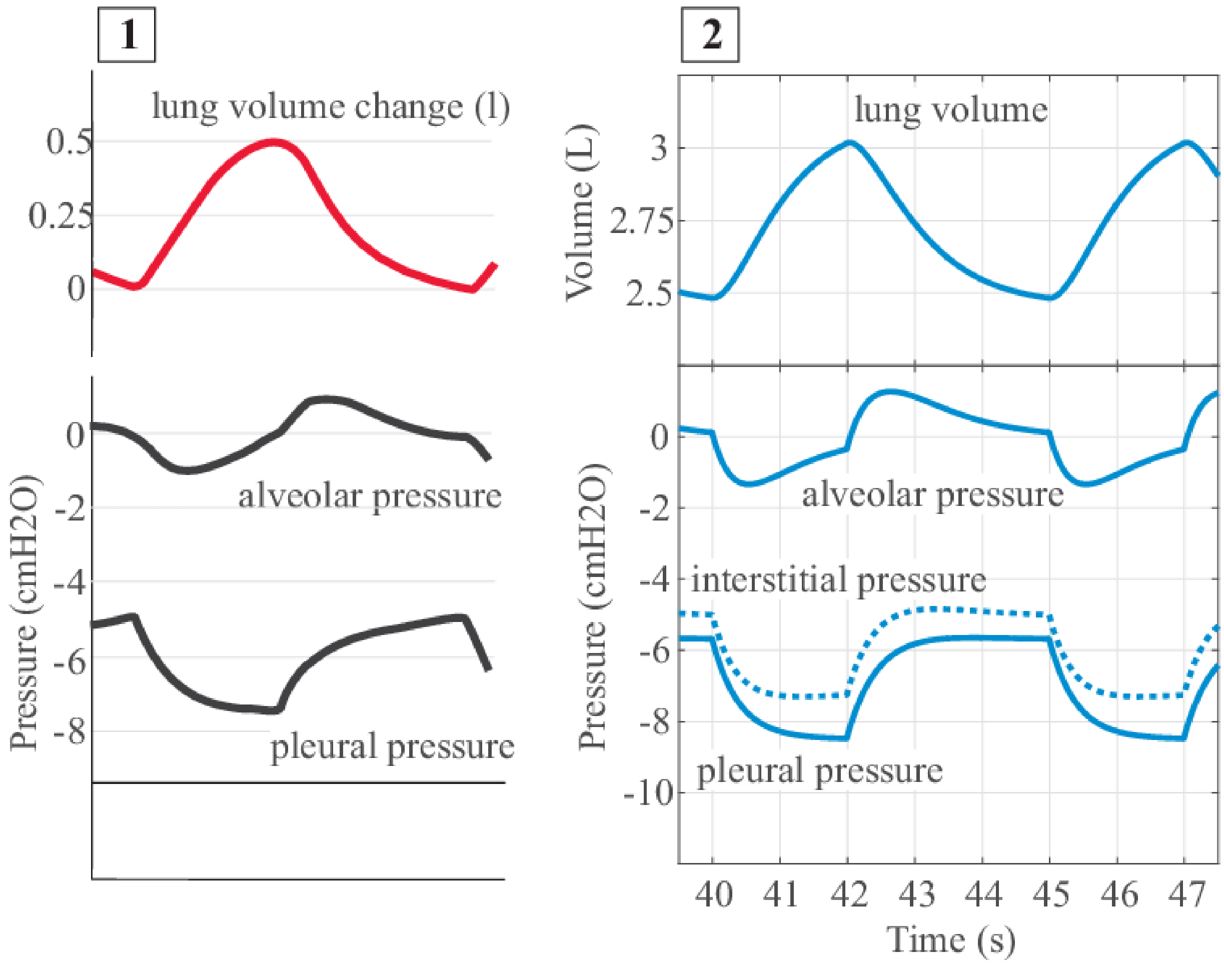

Figure 2 – ventilation pressures

https://en.wikipedia.org/wiki/Dual-control_modes_of_ventilation

As it is evident in these charts, two chest pressures and volume mostly trigger respiration. Respiration starts with decreasing pleural pressure (also called alveolar pressure) along with increasing the lung volume. This active action is called "inspiration". When the lung reaches its max volume capacity, the "expiration" starts (passive).

2.1. NIV application

NIV can be defined as an approach of oxygen therapy through special masks (figure3). These masks may cover whole of patients' head, nose, nose and mouth, and face (BaHammam et al, 2018).

Figure 3 – NIV interfaces

A: nasal mask, B: oronasal mask, C: nasal pillows, D: oral mask, E: total face mask, and F: helmet photograph. https://rc.rcjournal.com/content/63/2/227

In ARF, NIV efficacy is more crucial than patient tranquility; nonetheless, proper mask fitting and care are required to maximize patient tolerance and, as a result, NIV outcome (Brill, A. K, 2014). Because there is no generally perfect NIV interface, selecting one necessitates a detailed assessment of patient characteristics, ventilatory modes, and respiratory failure type (Davidson et al, 2016. Nava et al, 2009). The form of the patient's face anatomy, mouth, and nose; breathing pattern; preference; and the medical staff's expertise all impact the choice of correct interface.

2.2. Indications and Contradictions of NIV

The following are absolute contraindications to NIV:

- Unstable cardiorespiratory state or respiratory arrest

- Patients that are uncooperative
- failure to protect the airway (impaired swallowing and cough)
- Face-related trauma or burns
- Surgery on the face, esophagus, or stomach
- Apnea (poor respiratory drive)
- Consciousness has been reduced. Or loss of Consciousness
- Syndrome of air leakage

The following are the relative contraindications for NIV:

- Anxiety to the extreme
- Obesity with morbidity
- Extensive secretions
- The requirement for constant or practically continuous ventilatory support
- Inadequate respiratory drive
- Diseases characterized by air trapping (for example, asthma) - Periodic monitoring is essential in a kid on CPAP; if the clinical state and arterial blood gases worsen despite CPAP assistance, intubation should be considered.

2.3. NIV and nursing

Nurses have various duties when providing non-invasive ventilation to patients. Checking and recording patients' vital signs is one of the most important responsibilities of nurses in the care of patients under non-invasive ventilation. The administration of the prescribed medicines according to the doctor's order and taking blood samples from the patients according to the doctor's order are also duties of nurses. Patients under mechanical ventilation have a lot of anxiety, and they may not be able to speak as the NIV interface may not be proper. Therefore, nurses should try to use non-verbal methods to communicate with patients (such as nodding to answer the nurse's questions or pressing the nurse's hand in response to a question). Patients under non-invasive ventilation should not be neglected under any circumstances. Due to the variability of patients' conditions within a few seconds, they should be closely monitored by nurses, because nurses can quickly notice the failure of non-invasive ventilation and inform the doctor based on the changes in patients' conditions and work experience. In a study, nearly two-thirds of nurses reported that (Cabrini et al., 2009) they did not get involved in decision-making processes for starting NIV for patients. Meanwhile, they stated that they have insufficient knowledge regarding NIV and they demand a training program to understand it better. This will help them to understand the NIV application that makes for more proficient conversation between nurses and physicians for their patients.

It is reported (Baxter et al, 2013) that some of healthcare staffs (including nurses) are not sure about the necessity or need for application of NIV for patients. However, they thought that use of NIV for patients experiencing end-of-life care can be advantageous. In another study (Dieperink et al, 2009) nurses (91%) had positive attitudes toward successfulness use of NIV.

2.4. NIV monitoring

Some studies (Ergan et al, 2018) reported various variables to consider as monitoring option for patients under NIV. They considered clinical parameters such as NIV face mask tolerance, pain (face), APACHE score (calculate at the time of ICU admission), physiological parameter (SpO2, PH, PaCO2, PaO2), cardiological parameters (ECG, BP, HR), as well as radiological parameter (not for a routine basis) (CXR, CT scan, Ultrasonography).

ICS as well as BTS (Davidson et al, 2016) recommended that for patients under NIV continuous monitoring of SpO2, arterial PCO2, and PH should be utilized. It is generally and clinically accepted that ABG is the most available monitoring element for patients receiving oxygen therapy like NIV. It is suggested that (Confalonieri et al, 2005) evaluation of ABG should be applied at baseline, 1 and 2 hours after NIV started (This is the case for COPD patients particularly). An improvement and proper response to NIV can be consider if (Ram, et al, 2003):

- A reduction in terms of PCO2, 3 mmHg (0.40 kPa), and
- An increment of arterial PH, 0.03

It is recommended that ABG monitoring (Moretti et al, 2000) should be continued until the patient's status changed to normal (non-hypoxic). Also, there is a susception of recurrence, clinicians can repeat ABG.

2.5. COVID and NIV

Several guidelines (WHO, 2020, CCCGWG, 2020, NCCET, 2020, Indian CDC, 2020, NHS (NIV), 2020) stated that patients with worsening respiratory status, hemodynamic instability, multiorgan failure, or abnormal mental status should not receive NIV instead of other options such as invasive ventilation or early endotracheal intubation. These guidelines were consistent with those previously issued by the American Thoracic Society and the European Society of Intensive Care Medicine (Fan et al., 2017) or the Chinese National Health Commission (NHC & SATCM, 2020). These organizations advised that severe patients be closely followed after receiving NIV. If their health does not improve, or worsens, within 1-2 hours, they should have invasive ventilation and endotracheal intubation. NHS (critical care) decided there was lack of evidence from UK experience to offer any recommendation for using NIV in patients with post-extubation (NHS (critical care), 2020). ICSI (ICSI, 2020) recommended, however, that NIV may be kept in patients as long as there was no weariness. If airborne PPE is employed, Thomas et al. (2020) underline the need of using stringent airborne PPE. To far, there has been limited consensus on the use of NIV in post-extubation clients.

Previous research has concluded that it provides no advantage and may even be harmful due to the delay in intubation (Keenan et al., 2002). (Esteban et al., 2004). However, one research found that it might reduce the length of hospital stay and death rate while avoiding reintubation (Ferrer et al., 2003). Given the unknown consequences mentioned above, it is thought especially important to thoroughly monitor the use of NIV, with almost half of the guidelines offering clinical recommendations on the subject. Although some recommendations did not specify a time frame, most suggested that patients' conditions be assessed within 2 hours or even 1 hour of utilizing NIV. Only NHS (critical care) proposed extending the duration to 1-4 hours (NHS (critical care), 2020). To conclude, the recommendations advised vigilant monitoring and timely review of each patient's status to avoid the use of NIV causing a delay in intubation.

It has been proposed that using NIV increases the likelihood of aerosol production. As a result, the recommendations recommended that NIV be used in a single room, a negative-pressure ward, or a hospital devoted to treating confirmed patients (NHS (management), 2020).

2.6. NIV failure

There are different definitions for NIV failure, however the most common explanation is " need for orotracheal intubation" or "cardio-pulmonary arrest" or "patients' death during NIV" (Ozyilmaz et al, 2014, Moretti et al, 2000, and Farhadi et al, 2022).

Previous research has found that various characteristics, including as disease severity, pulse rate, respiratory rate, level of consciousness, and arterial blood pH, might predict NIV failure in COPD patients (Ko et al,2015, Fiorino et al, 2015, Nicolini et al,2014, Kida et al,2015, van Gemert et al, 2015). However, no one factor can accurately predict NIV failure. Several factors together may improve forecasting accuracy. Confalonieri et al. (Confalonieri et al, 2005) used an APACHE II score, GCS, respiratory rate, and pH chart to predict NIV failure at the start and after 2 hours of NIV in COPD patients. This graphic predicted NIV failure with excellent accuracy. The APACHE II score, on the other hand, has a significant number of questions and cannot be utilized to measure results during an NIV intervention. Furthermore, serum creatinine and white blood cell counts are not always available within 1-2 hours after NIV for every patient. Furthermore, there was no external validation done on that chart, therefore it is uncertain whether it can be extended to other centers (Duan et al, 2019).

CHAPTER III

3. Materials and Methods

3.1. Study Design

The study was designated as a descriptive, cross-sectional and retrospective study.

3.2. Study Setting

This research was conducted as a retrospective study, using electronic medical data of Imam Khomeini Hospital complex (IKHC), Tehran, Iran. This is one of the biggest governmental hospitals in Tehran and contain nearly 1000 bed, 18 wards, 6 operation rooms, and 5 ICUs.

There is not a united protocol to use NIV for COVID-19 patients in ICU, and utilization of NIV was according to clinical judgment of physicians. Continues heart rate, respiratory rate, pulse oximeter, non-invasive blood pressure, and ABG each 2 hours was used as a standard monitoring of COVID-19 patients under NIV.

3.3. Sample

In this study, all data was collected from electronic record of ICU patients from March 2021 until July 2022 retrospectively. Annually, it is estimated that 500 COVID-19 patients need NIV at IKHC. All convenient patients meeting the inclusion criteria were included in this study. Final sample size for the study was 150 patients.

The accessible population of this study was consisting of critically-ill COVID-19 patients who requiring non-invasive ventilation (NIV), both male and female (adults) in ICUs. All patients should had confirmed real-time PCR of SARS-Cov-2 or rapid antigen test of SARS-Cov-2 or significant signs and symptoms of disease that are approved by a physician for COVID-19.

Inclusion criteria are

- Age between 18 and 80 years.
- No history of blood dyscrasias and lung fibrosis

Exclusion criteria are

- Pregnant patients
- Recent extubated patients
- End stage cancer patients

3.4.Study Tools

Data were collected by researcher-designed questionnaire which include, patients' demographics, past medical history, lab test at the time of ICU admission, oxygen saturation (SpO2), arterial blood gases (PaO2, PCO2, at admission, 6h and 12h after NIV initiation), vital signs, nursing observation regarding the presence of facial ulcer, Richmond agitation scale, APACHE II (Acute Physiology And Chronic Health Evaluation) score (Phua, et al, 2005), HACOR (heart rate, acidosis, consciousness, oxygenation, and respiratory rate) score (Ding, et al, 2021), ROX index (ratio of oxygen saturation) (Ferrer, at al, 2021), GCS, and final outcome (discharged/expired) (Appendix III & IV). All of these tools are standardized scales (anonymous) and previously have been proved for reliability. We have used standard English version (main version) and did not translate it to other language. Therefore, no need for permission and reliability checking (figure 4).

The Glasgow Coma Score is computed by adding the total points specified for each component (eye, verbal, and motor) below, for example, "15 points" (Appendix V). This score was developed by Dr. Bryan Jennett & Dr. Graham Teasdale in early 2000. This score has 3 main components as eye (min 0, max 4), verbal (min 0, max 5), and motor response (min 0, max 6). GCS less than 10 is loss of consciousness, less than 7 is comma, and less than 3 is deep coma. Patients with scores ranging from 3 to 8 are deemed to be in a coma. In general, brain damage is characterized as severe (GCS 8-9), moderate (GCS 8 or 9-12 (debatable), or minor (GCS 13).

APACHE score was developed by Dr. William Knaus in 1970 as a predictor tool for ICU mortality (This includes 15 parameters). The APACHE-II Score estimates ICU mortality depend on a set of laboratory data and patient symptoms, taking into consideration both acute and chronic illness. The data utilized should be from the first 24 hours in the ICU, with the worse value (far away from baseline/normal) being used. APACHE-II is categorized as a Likert scale. So, APACHE-II 0-4 predicts 4% of ICU mortality, 5-9 predicts 8%, 10-14 predicts 15% of ICU mortality, 15-19 predicts 25%, and 20-24 predicts 40% of mortality. APACHE-II: more than 24 is correlated with more than 50% of mortality (for nonoperative patients).

Richmond Agitation-Sedation Scale (RASS) was developed by Dr. Curtis Sessler (2000) a professor at Virginia Commonwealth University (VCU) Health System. Oriol Roca, MD PhD, is a critical care specialist at the Vall d'Hebron University Hospital in Barcelona, Spain. Dr. Roca's primary research is focused on clinical predictors and respiratory support success in acute respiratory distress syndrome. The inter-rater reliability of RASS was proven in two phases in a single-center ICU population: before and after RASS adoption. The scale was shown to have strong inter-rater reliability (k=0.80) among qualified nurses in the second phase of the study. The inter-rater reliability of RASS in a medical ICU population was examined prospectively in this single-center study. Nurses once again revealed high inter-rater reliability (k=0.91) (Ely et al, 2003).

RASS definition and scoring are as follows:

Criteria	**Definition**	**Points**
Combative	Overtly combative, violent, immediate danger to staff	+4
Very agitated	Pulls or removes tube(s) or catheter(s); aggressive	+3
Agitated	Frequent non-purposeful movement, fights ventilator	+2
Restless	Anxious but movements not aggressive vigorous	+1
Alert and calm		0
Drowsy	Not fully alert, but has sustained awakening (eye-opening/eye contact) to voice (>10 seconds)	-1
Light sedation	Briefly awakens with eye contact to voice (<10 seconds)	-2
Moderate sedation	Movement or eye opening to voice (but no eye contact)	-3
Deep sedation	No response to voice, but movement or eye opening to physical stimulation	-4
Unarousable	No response to voice or physical stimulation	-5

He developed ROX index (1999). This index is calculated as follows:

$$ROX\ index = \frac{SpO2/_{FiO2}}{Respiratory\ Rate\ (RR)}$$

HACOR scale (heart rate, acidosis, consciousness, oxygenation, respiratory rate) was developed by Duan, J et al in 2017. HACOR scale induces 5 parameters include Heart rate, respiratory rate, GCS, PF ratio, and arterial PH. According to this tool, each component will be allocated a score for final calculation (see the appendix V).

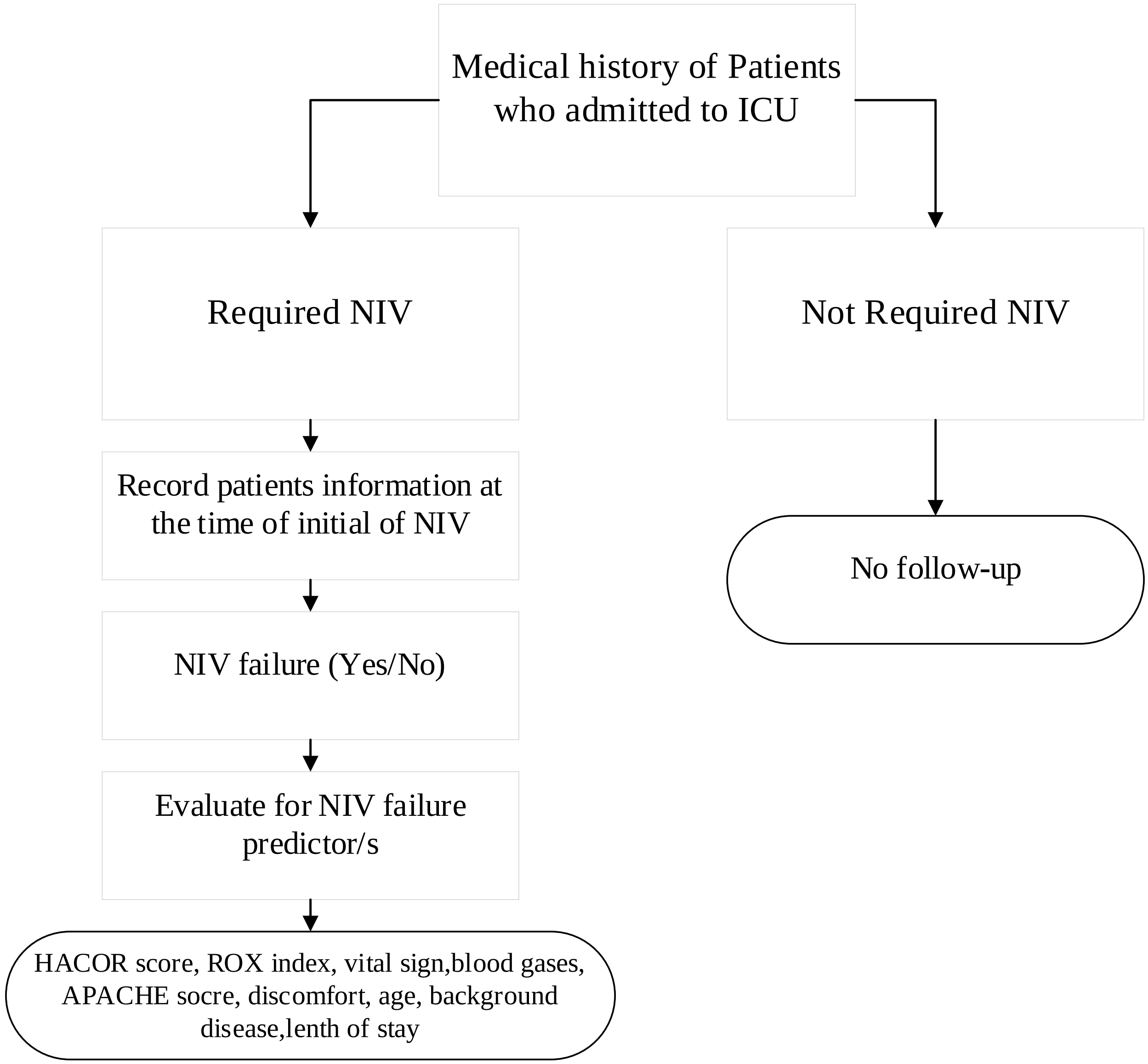

Figure 4 – flow chart of the study

3.5. Data Collection

Data was collected from electronic record of ICU patients from March 2021 until July 2022 (Retrospectively). If they meet the inclusion criteria, they were included in this study, and the researcher was collected the necessary information. Electronical medical record of COVID-19 patients who admitted to ICU will be assessed. Vital signs, lab tests, and blood gas were extracted from medical record.

Patients' demographic data and vital sign were recorded as the time of NIV starting. Oxygenation index include ROX index, HACOR score, PCO2 and SPO2 were collected at three times (Start of NIV, 6h after NIV initiation, and 12h after NIV initiation).

If a patient needs oxygen supplementation via NIV, it is eligible to enter the study (if meet inclusion criteria). Patients' vital signs, lab tests, and blood gas from medical record were collected. Occurrence of NIV failure (according to the definition), length of ICU stays, final outcome, and face ulcer (according to nursing reports of face ulcer) were collected from patients' medical records too. After collecting data from electronic medical record, patients who represented NIV failure and patients who did not, will be compare according to all variables.

Step by step:

1 – assess patients' electronic data for eligibility to include this study

2 – Record patients laboratory and oxygenation (ROX, HACOR, PCO2, SPO2) data at time of initiation of NIV in ICU.

3 – Record oxygenation (ROX, HACOR, PCO2, SPO2) data at 6 hours after NIV initiation.

4 – Record oxygenation (ROX, HACOR, PCO2, SPO2) data at 12 hours after NIV initiation.

5 – Follow-up patients until the end of ICU stay for primary (NIV failure) and final outcome (discharge/expire).

Criteria for NIV failure is followed:

Patients' agitation so that cannot tolerate the NIV mask and need an invasive airway. Or

Need for intubation after utilizing NIV trial. Or

Cardiac/ Respiratory arrest when patients is under NIV. Or

Lack of improvement in terms of oxygenation despite oxygen therapy via NIV.

3.6.Ethical Consideration

Ethical approval was obtained from Institutional Reviews Board (IRB) of Near East University before conducting the study (Appendix1). Also, confirmation by IKHC and head of ICU was issued. (Appendix2)

3.7. Data Analysis

Statistical analysis was performed by SPSS version 26. Graphs and charts were drawn by GraphPad software version 8.2. Alpha level to reject the null hypothesis below 5 percent considered significant. All numerical data primary analyzed for parametric assumptions (Kolmogorov Smirnov). Data that met parametric assumptions was analyzed by independent t test, and ANOVA test (also Tukey for post hoc test). In case that parametric assumptions did not meet, Mann-Withey U test, and Kruskal Wallis H test were used.

To predicting NIV failure, binary logistic test was used. Also, to address diagnosis accuracy of data ROC curve analysis was used. Evaluation of the HACOR, ROX, APACHE, Richmond scales were used by their standard questionnaire.

There is no threshold for these variables to detect NIV failure of COVID-19 patients yet.

CHAPTER IV

4. Results

Table 4.1 – Descriptive characteristics of the patients (N:150)

Descriptive characteristics		N	%
Gender	Male	83	55.3
	Female	67	44.7
Diabetes Mellitus	No	107	71.3
	Yes	43	28.7
Cardiovascular Diseases	No	132	88.0
	Yes	18	12.0
Hypertension	No	98	65.3
	Yes	52	34.7
Hypothyroidism	No	138	92.0
	Yes	12	8.0
Chronic Kidney Disease	No	140	93.3
	Yes	10	6.7
Asthma	No	144	96.0
	Yes	6	4.0
COPD	No	149	99.3
	Yes	1	0.7
Ischemic Heart Disease	No	125	83.3
	Yes	25	16.7
Cancer	No	135	90.0
	Yes	15	10.0
		Mean	**SD**
Age		55.90	13.48

A total of 150 patients were included in this study. 55.3% were male and average age of population were 55.9±13.48. Concerning co-morbidities hypertension (34.7%), diabetes (28.7%), and ischemic heart disease (16.7%) were the most common co-morbidities respectively (table 4.1.).

Table 4.2 – Predictors and associated factors of NIV (N:150)

Variables	Baseline		6 hours		12 hours	
	Mean	SD	Mean	SD	Mean	SD
BMI (kg/m^2)	26.13	5.16				
APACHE score	21.34	3.12				
ROX	4.01	1.22	4.00	1.15	3.97	1.20
HACOR	8.68	2.28	7.81	1.63	8.81	2.47
SPO2 (%)	86.62	6.44	88.17	6.02	89.00	6.09
PCO2 (mmHg)	43.21	10.10	43.11	8.20	42.44	9.03
Pulse Rate (pulse/min)	94.52	20.61				
Respiratory Rate (per min)	28.91	7.46				
Systolic Blood Pressure (mmHg)	122.38	17.63				
GSC	14.35	1.01				
RASS	-0.96	1.36				
VAS	1.81	1.86				
CRP (mg/dl)	91.31	60.56				
LDH (IU /lit)	959.36	345.41				
ESR (mm/h)	58.12	28.60				
SF ratio	108.21	8.92				
Length of ICU stay (days)	10.00	7.21				

Results showed that, average mean of body mass index of the patients was 26.13±5.16. The overall trend of the ROX index was downwards, and the HACOR scale had a downwards trend within 6 hours of NIV initiation, and then (6 hours to 12 hours after starting NIV), the trend became upwards (table 4.2.). Although SPO2 increased over the time period ($p<0.001$), PCO2 decreased over the period ($p<0.001$). In terms of inflammatory parameters (LDH, CRP, ESR), the mean of these parameters was higher than the normal threshold, which means that the majority of patients experienced degrees of inflammation. The length of the ICU stay was 10±7 days.

Table 4.3 NIV failure status and outcome of the treatment

Variables		N	%
NIV failure	No	49	32.7

	Yes	101	67.3
Outcome of the treatment	Discharged	50	33.3
	Death	100	66.7
Tracheostomy	No	145	96.7
	Yes	5	3.3
Ulcer on face	No	133	88.7
	Yes	17	11.3

Results of the study showed a 67.3% NIV failure rate. The mortality rate was 66.7%, and the 3.3% of patients need tracheostomy after NIV failure. According to nursing report, 11.3% of patient had face ulcer in result of NIV interface (Table 4.3).

Table 4.4 – NIV failure based on descriptive characteristics and treatment outcomes (N:150)

Descriptive characteristics and treatment outcomes		**NIV failure**				**Test statistics**	**P value**
		No		**Yes**			
		N	**%**	**N**	**%**		
Gender	Male	31	63.3	52	51.5	χ^2=1.85	0.17
	Female	18	36.7	49	48.5		
Diabetes Miletus	No	36	73.5	71	70.3	χ^2=0.162	0.68
	Yes	13	26.5	30	29.7		
Cardiovascular Diseases	No	46	93.9	86	85.1	χ^2=2.381	0.12
	Yes	3	6.1	15	14.9		
Hypertension	No	35	71.4	63	62.4	χ^2=1.194	0.27
	Yes	14	28.6	38	37.6		
Hypothyroidism	No	44	89.8	94	93.1	χ^2=0.480	0.52
	Yes	5	10.2	7	6.9		
Chronic Kidney Disease	No	46	93.9	94	93.1	χ^2=0.035	0.99
	Yes	3	6.1	7	6.9		
Asthma	No	47	95.9	97	96.0	χ^2=0.001	0.99
	Yes	2	4.1	4	4.0		
COPD	No	49	100.0	100	99.0	χ^2=0.488	0.99
	Yes	0	0.0	1	1.0		
Ischemic Heart Disease	No	39	79.6	86	85.1	χ^2=0.733	0.39
	Yes	10	20.4	15	14.9		

Cancer	No	45	91.8	90	89.1	χ^2=0.273	0.60
	Yes	4	8.2	11	10.9		
Tracheostomy	No	49	100.0	96	95.0	χ^2=2.509	0.17
	Yes	0	0.0	5	5.0		
Outcome	Discharged	47	95.9	3	3.0	χ^2=128.26	<0.001
	Death	2	4.1	98	97.0		
		Mean	**SD**	**Mean**	**SD**		
Age		52.10	13.96	57.74	12.91	*U*=1865.5*	0.015
BMI		25.83	3.97	26.28	5.66	*U=2389.5*	0.733

*** Mann-Whitney U test.**

According to the chi-square test results (table 4.4.), NIV failure has a significant relationship with patient mortality. Patients with NIV failure was more likely to expire (p<0.001). It means that, 97 percent of patient with NIV failure died and just 4.1 percent of non-NIV failure patients. However, patients' comorbidities (such as DM, HTN, etc.) did not show association with NIV failure. The mean age of patients who failed NIV trials was significantly higher than that of non-failed patients (57 vs 52) (p=0.015). However, BMI did not associated with increased risk of NIV failure.

Table 4.5 – Comparison of predictors and associated factors with NIV failure status (N:150)

Predictors and associated factors of NIV	**NIV failure**				**Test statistics**	**P Value**
	No		**Yes**			
	Mean	**SD**	**Mean**	**SD**		
APACHE II	18.61	1.96	23.5	2.60	*U*=755.5*	<0.001
BMI	25.83	3.97	26.28	5.66	*U=2389.5*	0.733
ROX baseline	4.71	1.19	3.67	1.09	*U=1236.5*	<0.001
ROX after 6 hours	5.11	1.10	3.46	.70	*U=479.5*	<0.001
ROX after 12 hours	5.28	1.04	3.33	.62	*U=158.5*	<0.001
HACOR baseline	7.33	1.53	9.34	2.30	*U=1117.0*	<0.001
HACOR after 6 hours	6.53	1.00	8.43	1.51	*U=751.5*	<0.001
HACOR after 12 hours	6.37	1.03	10.00	2.06	*U=242.5*	<0.001
Pulse Rate	87.57	15.31	97.89	22.04	*U=1843.5*	0.011
Respiratory Rate	24.94	6.67	30.84	7.08	*U=1326.0*	<0.001
Systolic Blood Pressure	120.14	14.02	123.47	19.11	*U=2159.0*	0.206
GSC	14.76	.52	14.15	1.13	*U=1696.0*	<0.001
RASS	-1.33	1.26	-0.78	1.38	*U=1872.5*	0.008

VAS	1.06	1.83	2.18	1.77	*U=1552.5*	<0.001
SPO2	88.69	5.09	85.61	6.80	*U=1787.0*	0.006
SPO2_2	91.90	3.37	86.37	6.20	*U=992.0*	<0.001
SPO2_3	93.59	3.18	86.77	5.92	*U=642.5*	<0.001
PCO2	39.68	9.08	44.92	10.17	*U=1712.0*	0.002
PCO2_2	39.78	7.65	44.73	8.01	*U=1599.5*	<0.001
PCO2_3	35.58	5.77	45.77	8.43	*U=657.0*	<0.001
CRP	77.67	52.83	97.52	63.03	*U=1901.0*	0.078
LDH	818.13	306.18	1023.56	344.67	*U=1054.5*	<0.001
ESR	63.90	32.72	55.73	26.54	*U=1711.0*	0.278
SF ratio	110.78	6.23	106.96	9.75	*U=1859.0*	0.013
ICU stay	9.76	5.38	10.12	7.97	*U=2279.0*	0.489

*Mann Whitney U test.

NIV failure patients had a higher APACHE II score at the time of ICU admission (p<0.001) (Table 4.5.).

In terms of vital signs, pulse and respiratory rate, there were statically significant difference in the two groups of patients, so that NIV failure patients had higher pulse (97 vs 87, p=0.011) and respiratory rate (30 vs 24, p<0.001). Systolic blood pressure was not statically different across the two groups of patients (p=0.20). On average, both groups of patients had a GCS of more than 14, but as the GCS increment is by 1 scale, it is tough to say that there is a significant difference between NIV failure patients.

Regarding the inflammatory factors of patients, just LDH was higher in patients with NIV failure (p<0.001). ESR and CRP did not show any statically difference between two groups of patients.

SF ratio was slightly higher in non-NIV failure patients in comparison to NIV failure group (110 vs 106, p=0.013). Length of ICU stay did not show a statically differences between two groups of patients (p=0.48).

A repeated measures ANOVA with a Greenhouse-Geisser correction determined that mean ROX index differed statistically significantly between time points ($F(1.216, 180.021) = 42.158$, $\eta 2=0.22$, $\lambda=0.75$, $P < 0.0001$) (**figure5**).

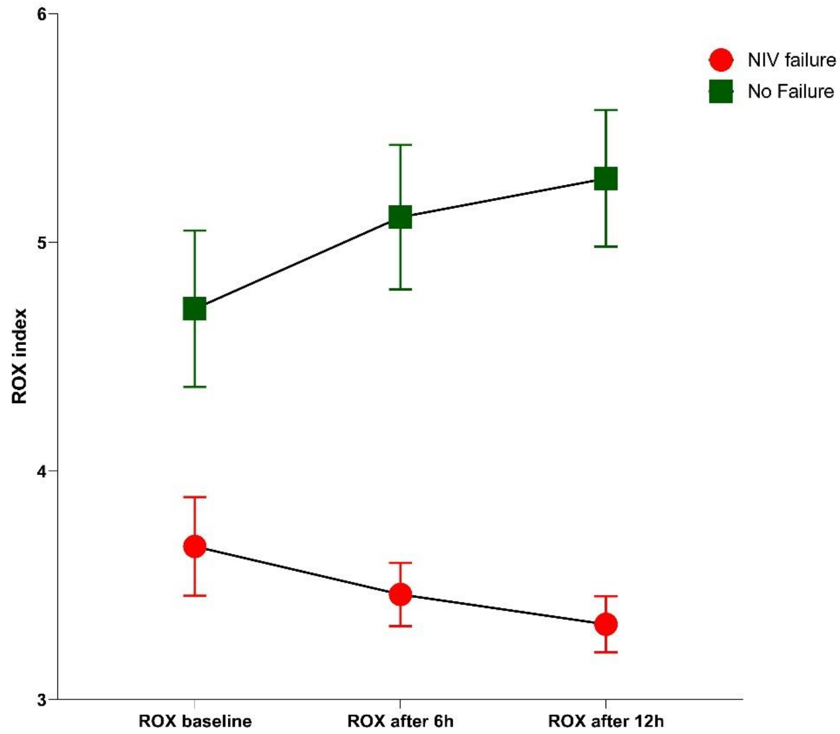

Figure 5 – comparison ROX index between two groups of patients across the time

With the passage of time from the start of non-invasive ventilation, ROX index in NIV failure patients decreased significantly, while in patients without NIV failure it increased steadily. On the other hand, after NIV initiation, ROX would increase in patients who successfully complete NIV and decrease in patients who develop NIV failure. Therefore, after starting the NIV treatment, if the ROX index continuously decreases during the next 6 to 12 hours, it can be a predictor of failure.

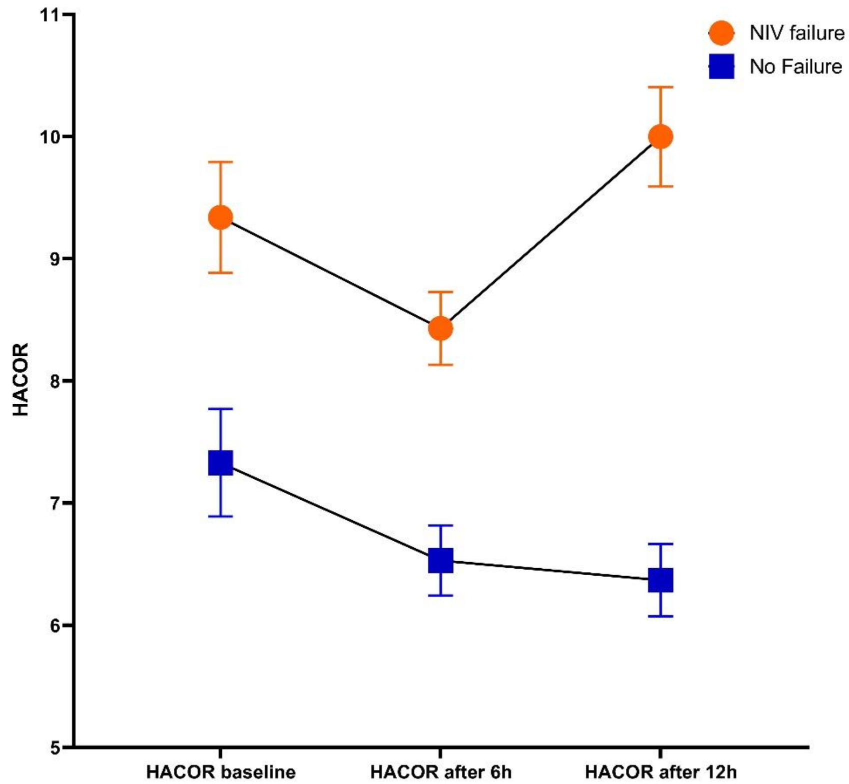

Figure 6 – comparison HACOR between two groups of patients across the time

Also, repeated measures ANOVA results (Greenhouse-Geisser correction) showed that mean HACOR score differed statistically significantly between time points F (1.910, 282.627) = 30.803, $\eta 2$=0.17, λ=0.65, P < 0.0001) (**figure6**). After the start of non-invasive ventilation in all patients, HACOR score gradually decreased until 6 hours later. After 6 hours, the HACOR score of patients with ventilatory failure increased significantly, while it gradually decreased in patients without ventilatory failure. Therefore, a continuous decrease in the HACOR favors the success of the treatment, and an increase in the HACOR after 6 hours can favor the failure of the treatment (NIV failure).

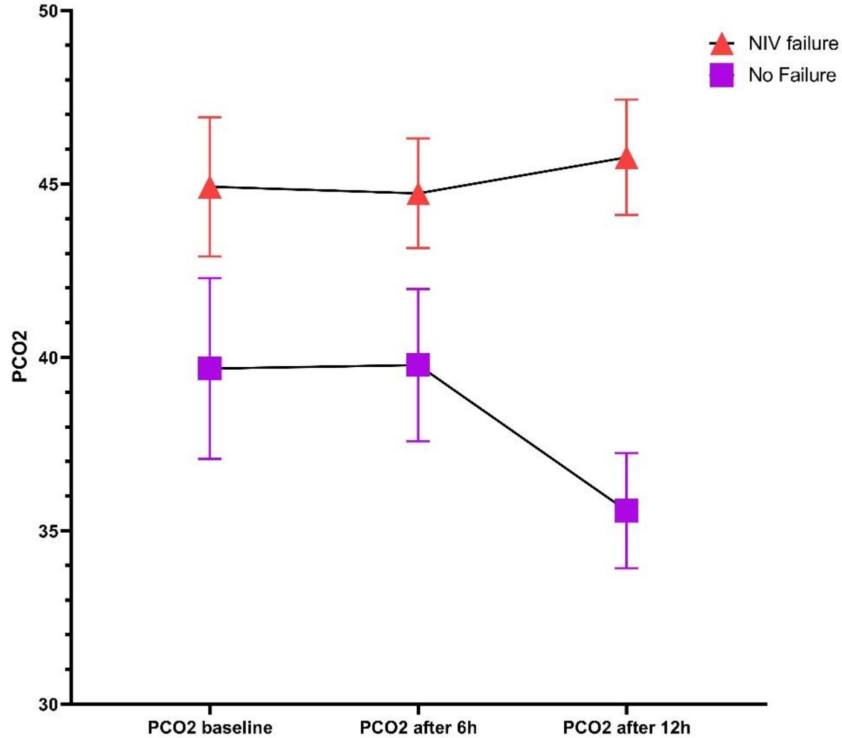

Figure 7 – comparison PCO_2 between two groups of patients across the time

Finally, mean PCO2 differed statistically significantly between time points (F (1.66, 245.693) = 7.962, $\eta 2=0.04$, $\lambda=0.86$, P = 0.001) (*figure7*). Although no significant difference was shown in terms of PCO2 in two groups of patients from the time of non-invasive ventilation to 6 hours later, from 6 hours to 12 hours after the start of non-invasive ventilation, PCO2 was significantly different in patients without NIV failure. On the other hand, PCO2 after 6 hours steadily decreased steadily until 12 hours in no NIV failure patients. However, in NIV failure patients from 6 to 12 hours later this trend was slightly upward. Although there was no significant difference in the average blood carbon dioxide pressure of the patients from the start of the treatment to 6 hours later, the decrease in the blood carbon dioxide flux after 6 hours is in favor of the success of the treatment and its increase or stability can be a predictor of failure.

CHAPTER V

5. Discussion

The present study aimed to determine predictors and associated factors of NIV failure among the COVID-19 patients admitted to the ICU. Primarily, we found that age was the only demographic factor that can be associated with NIV failure. So that, older patients more than 57 years old are more likely to develop NIV failure. This was aligned with all of previous study that confirmed higher age is a risk factor for NIV failure and consequently morality (Duan et al, 2019) (Corrêa et al., 2015), (Mohammadi et al,2022) (Imam et al, 2020). BMI did not seem to be associated with NIV failure. In our study, the mean NIV of the study population was 26±5 that is in a range of normal to overweight. So, the majority of patients were normal or overweight, and a small number of patients were obese (grade 1 and 2). Therefore, the population of study in terms of BMI is not large enough to make a strong conclusion. Previous research has linked obesity (mostly comorbid obesity: BMI > 35) to NIV failure and poor ICU outcomes (Nicolini et al., 2017) (Duarte et al., 2007). In both of the previous studies, researchers focused on comorbidly obese patients. However, in our study we did not have any comorbidly obese cases.

NIV was indicated in some diseases with the support of a strong level of evidence, like COPD, asthma, acute respiratory failure, and cardiogenic pulmonary edema (Keenan, S. P., & Mehta, S. 2009). All of the NIV-failed patients in this study were intubated after a trial of NIV. This means that all NIV failures were defined as a need for intubation in COVID-19 in the ICU. This was consistent with previous research (Moretti et al., 2000; Ozyilmaz et al., 2014; Thale et al., 2013). The rate of NIV failure was reported at 67.3% in our study. In a previous study, it was reported that NIV failure accounts for 50.2% for COPD patients (Duan et al, 2019), 20.6% in different patients (Corrêa et al., 2015), 50% in hypoxic patients and 25% for hypercapnic (Hess D. R., 2013), 46% in ARDS patients (Antonelli et al, 2007), 61 % in ARDS and 35% in non-ARDS patients (Thille et al,2013), 66% in CAP patients (Jolliet et al., 2002), and 15.5% in children with ARF (Mayordomo et al, 2009). This means that the NIV failure rate varies, ranging from 15.5 to 67.3 percent in non-COVID-19 patients. Recently, it was reported that rate of NIV failure in COVID-19 patients accounts for 66.7% (Mohammadi et al,2022). It is highly aligned with our findings. Therefore, it seems that NIV failure is highly correlated with primary respiratory disease

(CAP, COVID, ARF,) and COVID-19 patients in critical care setting are more likely to develop NIV failure.

It was found that co-morbidities were not associated with NIV failure. It means no background diseases were associated with a higher (or lesser) rate of NIV failure Previously, a study reported that (Meireles et al., 2018) the age-adjusted Charlson Comorbidity Index did not relate to NIV failure. This means that NIV failure is not associated with comorbidity that is aligned with our findings. This is due to the fact that some patients with any comorbidity may be hospitalized in EDs or other wards and may die before ICU admission. In our study, we just focused on patients admitted to the ICU. In a cohort study in Michigan, USA, it is reported that higher age and a greater number of comorbidities are independent predictors of NIV failure in COVID-19 patients (Imam et al., 2020). This difference is because of the same issue; Imam et al. focused on all hospitalized COVID-19 patients, which is different than our study population. In addition, they had a large scale of patients (1305 COVID-19 patients). However, to confirmed that, more studies are needed.

One of the most important definitions and concepts of this study was to differentiate between associated factors and predictors. In this study, it is revealed that standard scores such as HACOR and ROX index are defined as predictors. Moreover, the demographic factor (just age) is considered as an associated factor. It can be explained by the fact that associated factors are major and irreversible (unchangeable), like gender, comorbidities (such as DM, HTN, etc.), and age. However, predictors are defined as physiological parameters that can be changed according to body physiology, like the ROX index, which is calculated by SpO2 and respiratory rate. In a recent published study (Ding et al., 2021), it was proved that the HACOR scale can be a highly potent tool for prediction of NIV failure in non-COPD patients who receive NIV. Also, it is reported that (Duan et al., 2022) the HACOR scale can come in handy to predict NIV failure in hypoxic patients with respiratory failure. One of the advantages of the HACOR scale is that it is simple to calculate at patients' bedsides and its reliability has been proved already (Duan et al., 2017). It should be said that most of the mentioned studies related to non-COVID-19 patients in different wards, including ICUs, should be excluded. Interestingly, all of them were aligned with our findings, suggesting that in terms of respiratory failure pathophysiology, COVID-19 NIV failure may be similar to ARF, COPD, and hypoxic patients. According to a new study (Guia et al.,2021) the HACOR scale is reliable tool for predicting NIV failure in COVID-19 patients. In addition, we have found that ROX index (decreasing) can be another predictor of NIV failure in COVID-19 patients. According to (Valencia et al.,2021), the HACOR and ROX index are effective tools for predicting COVID-19 NIV failure. They claimed that, in terms of accuracy and predictive value, they had no advantages over each other. It is also claimed (Ferrer et al.,2021) that ROX index within 24 hours can be a good predictor for HFNC and NIV success (and failure). The result of a meta-analysis revealed that (Prakash et al.,2021) ROX index can be a good tool to predict NIV failure among COVID-19 patients admitted ICU. In non-COVID-19 patients the efficacy and reliability of ROX index to determine the NIV failure had been proved (Zhou et al.,2022). On the other hand, ROX index is a good predictive tool for NIV failure in both COVID-19 and non-COVID-19 patients.

Our study showed that utilization of NIV in COVID-19 patients can improve the oxygen saturation in all patients. This means that this treatment is beneficial for all COVID-19 patients with severe respiratory failure due to COVID-19. It should be noted that this treatment should just be used for a trial period (ranging from 1 to 24 hours) according to the physicians' judgments. This is due to the fact that there is no international agreement on the use of NIV in COVID-19 patients (Hussain Khan et al.,2022, Winck, J. C., & Ambrosino, N. ,2020). Although utilization of NIV is so common in COVID-19 patients, this treatment is not associated with lower complications and mortality (Radovanovic et al., 2021). It seems more research is needed to prove the efficacy of NIV and the trial period in COVID-19 patients.

Nursing care in ICU is highly correlated with nurse-patients' interactions (Kwame, A., Petrucka, P.M., 2021). Nurses are responsible for providing care to patients who use NIV, and they must pay attention to their patients' psychological and physiological requirements. Nurses should consider both the environment and persons during NIV therapy as part of a holistic approach to the nursing practice (Dougherty et al, 2015). They should pay attention to patients' physiological and psychological demands, remove environmental obstacles, and strive to optimize ventilation and oxygenation of NIV patients (Venkatesaperumal et al. 2013). Concerning the significance of NIV nursing practice and knowledge, Srensen et al. (Srensen et al. 2013) noted that each nurse can monitor the patient's health and respond to NIV. The conceptualization of complexities in nurses' reasoning and actions revealed their proclivity to divide difficult situations into three interconnected components: (1) achieving noninvasive adaptation, (2) ensuring effective ventilation, and (3) closely responding to patients' perceptions of noninvasive ventilation. Each item is comprised of a set of nursing reasoning and actions employed by experienced nurses to ensure therapeutic efficacy.

One of the most critical nursing roles (care of patients under NIV) is monitoring during oxygen therapy. Nurses must monitor the patient's respiratory rate, degree of consciousness, chest wall movement, accessory muscle usage, and comfort every 15 minutes after NIV starts, and this can be reduced if the patient's status improves. Pulse oximetry and ECG monitoring should be continuous during the first 12 hours of NIV (Yaman, Aygun, and Erten 2021). Furthermore, a lack of information (Cabrini et al. n.d.) or insufficient knowledge about NIV may result in patients receiving NIV being neglected. Therefore, it is highly important for nurses to know the mechanism of NIV, nursing care during delivery, and monitoring. Nurses should be aware of changes in NIV failure predictors and call physicians as soon as possible.

CHAPTER VI

6. Conclusion

Increasing HACOR score after 12 hours and decreasing ROX index after NIV starting were the main predictors of NIV failure. Higher age (more than 57) was associated with NIV failure. Co-morbidities, BMI, and gender were not associated with NIV failure.

In addition, PCO2 was another predictor of NIV failure. Although, PCO 2 did not changed in the first 6 hours of NIV in both groups of patients, after 6 hours increasing PCO2 can be an independent predictor of NIV failure in COVID-19 patients in ICU.

Finally, the HACOR scale and ROX index aligned with PCO2 can be good predictors of NIV failure and can be used in patients' bedsides. Nurses should understand the importance of vital sign changes as predictors of NIV failure. They should monitor the symptoms and signs of the NIV.

Nurses should know about the ROX index and HACOR scale, which are good predictors of NIV failure. It is recommended that these standard scores should be calculated regularly and any significant change (increasing HACOR scale and decreasing ROX index) should be reported.

It is suggested that future studies be designed on a larger scale to improve external validity and generalizability. Also, it is recommended that interaction of organ failure/s and NIV failure that we did not consider in our study.

CHAPTER VII

7. Findings and Recommendations

7.1. Findings

The standardized scores (ROX index, HACOR) and PCO2 are the predictors of NIV failure in COVID-19 patients. Among demographic data only age was associated with NIV failure, so that patients with higher ages are more likely to develop NIV failure.

7.2. Recommendations

Patients under NIV should be under close monitoring by their nurses and physicians. Patients should be under continuous monitoring of ECG rhythm, pulse oximeter, pulse and respiratory rate. Also, according to the clinical decision of the physician, patients should be evaluated in terms of arterial blood gas after NIV starts.

Nurses should understand the importance of vital sign changes as predictors of NIV failure. They should monitor the symptoms and signs of the NIV.

Nurses should know about the ROX index and HACOR scale, which are good predictors of NIV failure. It is recommended that these standard scores should be calculated regularly and any significant change (increasing HACOR scale and decreasing ROX index) should be reported.

It is suggested that future studies be designed on a larger scale to improve external validity and generalizability. Also, it is recommended that interaction of organ failure/s and NIV failure that we did not consider in our study.

Predictors of NIV failure (HACOR, ROX index, PCO2) should be monitored according to physicians' orders and nurses should know the importance of these predictors to be able to report any vital changes as soon as possible.

The associated factor for NIV failure was detected to be age. Therefore, older patients should be monitored closely for any changes in vital signs. In addition, older patients should be controlled for any co-morbidity/s to prevent dire consequences, including NIV failure.

7.3. Limitations

This study had some limitations. First, the present study was a retrospective cohort study that increase the risk of selection bias. Secondly, the sample size was in a medium scale and it is hard to make a strong conclusion association. Thirdly, this study was a single center research. Fourth, we did not assess patients for organ failure as a consequence of NIV failure and mechanical ventilation. Finally, we did not consider the timing of NIV failure (for example early vs late failure).

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APPENDICES

Appendix 1

YAKIN DOĞU ÜNİVERSİTESİ
BİLİMSEL ARAŞTIRMALAR ETİK KURULU

ARAŞTIRMA PROJESİ DEĞERLENDİRME RAPORU

Toplantı Tarihi :30.06.2022
Toplantı No :2022/104
Proje No :1577

Yakın Doğu Üniversitesi Hemşirelik Fakültesi öğretim üyelerinden Prof. Dr. Nurhan Bayraktar'ın sorumlu araştırmacısı olduğu, YDU/2022/104-1577 proje numaralı ve **"Predictors of non-invasive ventilation failure and associated factors among the COVID-19 patients admitted in ICU"** başlıklı proje önerisi kurulumuzca değerlendirilmiş olup, etik olarak uygun bulunmuştur.

Prof. Dr. Şanda Çalı
Yakın Doğu Üniversitesi
Bilimsel Araştırmalar Etik Kurulu Başkanı

Kurul Üyesi	**Toplantıya Katılım** *Katıldı(✓)/ Katılmadı(X)*	**Karar** *Onay(✓)/ Ret(X)*
Prof. Dr. Tamer Yılmaz	✓	✓
Prof. Dr. Şahan Saygı	✓	✓
Prof. Dr. Nurhan Bayraktar	✓	✓
Prof. Dr. Mehmet Özmenoğlu	✓	✓
Prof. Dr. İlker Etikan	✓	✓
Doç. Dr. Mehtap Tınazlı	X	X
Doç. Dr. Nilüfer Galip Çelik	✓	✓
Doç. Dr. Emil Mammadov	✓	✓
Doç. Dr. Ali Cenk Özay	✓	✓

https://etikkurul.neu.edu.tr/

Appendix II

دانشگاه علوم پزشکی تهران
Tehran University of Medical Sciences

Imam Khomein Hospital Complex
مجتمع بیمارستانی امام خمینی(ره)

General Intensive Care Unit (ICU) - Imam Khomeini Hospital Complex

Tehran University of Medical Sciences

Approval Date: 30 /06/2022

I hereby certify that the project was found to be in accordance with the ethical principles and the national norms and standards for conducting medical research in Iran.

Thesis Title: ***Predictors of non-invasive ventilation failure and associated factors among the COVID-19 patients admitted in the ICU.***

It is hereby certified that **Mr. Hesam Aldin Varpaei** has permission to access the data of patients with COVID-19 hospitalized in the general intensive care unit of IKHC for use in the thesis entitled "Predictors of non-invasive ventilation failure and associated factors among the COVID-19 patients admitted in ICU".

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فوق تخصص مراقبت های ویژه
۴۳۳۳۱

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Appendix III

Patients No:			**Date :**
Gender: M/F	**Age:**	**BMI:**	**Smoker: Yes/No**
Chronic disease : ………….			
Medication : ………..			
COVID-19 Patients who need oxygen supplementation via NIV at the time of starting NIV			
1st. Beginning	2nd. 6 hours after beginning	3rd. 12 hours after beginning	
1. Vital signs (BP: PR: RR: T:)			
2. Richmond agitation scale =			
3. APACHE2=			
4. P/F ratio =			
5. S/F ratio =			
6. SpO2=	2nd =	3rd =	
7. HACOR score =	2nd =	3rd =	
8. ROX index =	2nd =	3rd =	
9. PH =			
10. PCO2 =	2nd =	3rd =	
11. CRP, LDH, ESR, D-dimer =			
12. Quality of NIV mask Fixation =			
13. Pain/ discomfort =			
Day/s in ICU=	Hour/s on mechanical ventilation=	Face ulcer =	
NIV failure = Yes / No			
NIV failure due:			
• Cardiac/Respiratory Arrest			
• Patients' agitation/ intolerance of NIV and need for endotracheal tube			
• Lack of oxygenation improvement after NIV trials			
Final Outcome: Discharge / Expire			

Appendix IV
HACOR score

Parameter Range	Score
Heart rate	
≤120	0
≥121	1
pH	
≥7.35	0
7.30–7.34	2
7.25–7.29	3
<7.25	4
GCS	
15	0
13–14	2
11–12	5
≤10	10
P_{aO_2}/F_{IO_2}	
≥201	0
176–200	2
151–175	3
126–150	4
101–125	5
≤100	6
Breathing frequency	
≤30	0
31–35	1
36–40	2
41–45	3
≥46	4

In patients receiving noninvasive ventilation for hypoxemic respiratory failure, a HACOR score >5 at 1 h of noninvasive ventilation predicted failure.

Appendix V
GCS

Component	Response	Points
Eye	Eyes open spontaneously	+4
	Eye opening to verbal command	+3
	Eye opening to pain	+2
	No eye opening	+1
	Not testable*	NT
Verbal	Oriented	+5
	Confused	+4
	Inappropriate words	+3
	Incomprehensible sounds	+2
	No verbal response	+1
	Not testable/intubated*	NT
Motor	Obeys commands	+6
	Localizes pain	+5
	Withdrawal from pain	+4
	Flexion to pain	+3
	Extension to pain	+2
	No motor response	+1
	Not testable*	NT

*Individual components may be not testable due to any of the following (note this is not a comprehensive list):

- **Eye:** local injury and/or edema.
- **Verbal:** intubation.
- **All (eye, verbal, motor):** sedation, paralysis, and ventilation eliminating all responses.

Appendix VI
Turnitin Similarity Report

PREDICTORS AND ASSOCIATED FACTORS OF NIV FAILURE AMONG THE COVID-19 PATIENTS ADMITTED IN ICU

ORIGINALITY REPORT

20%	16%	12%	%
SIMILARITY INDEX	INTERNET SOURCES	PUBLICATIONS	STUDENT PAPERS

PRIMARY SOURCES

1	docs.neu.edu.tr Internet Source	3%
2	www.mdcalc.com Internet Source	2%
3	www.physio-pedia.com Internet Source	1%
4	covid19dataportal.es Internet Source	1%
5	Www.Physio-Pedia.Com Internet Source	1%
6	Sørensen, Dorthe, Kirsten Frederiksen, Thorbjoern Grøfte, and Kirsten Lomborg. "Practical wisdom: A qualitative study of the care and management of non-invasive ventilation patients by experienced intensive care nurses", Intensive and Critical Care Nursing, 2012. Publication	1%

Appendix VII

Results of statistical analysis for diagnostic accuracy

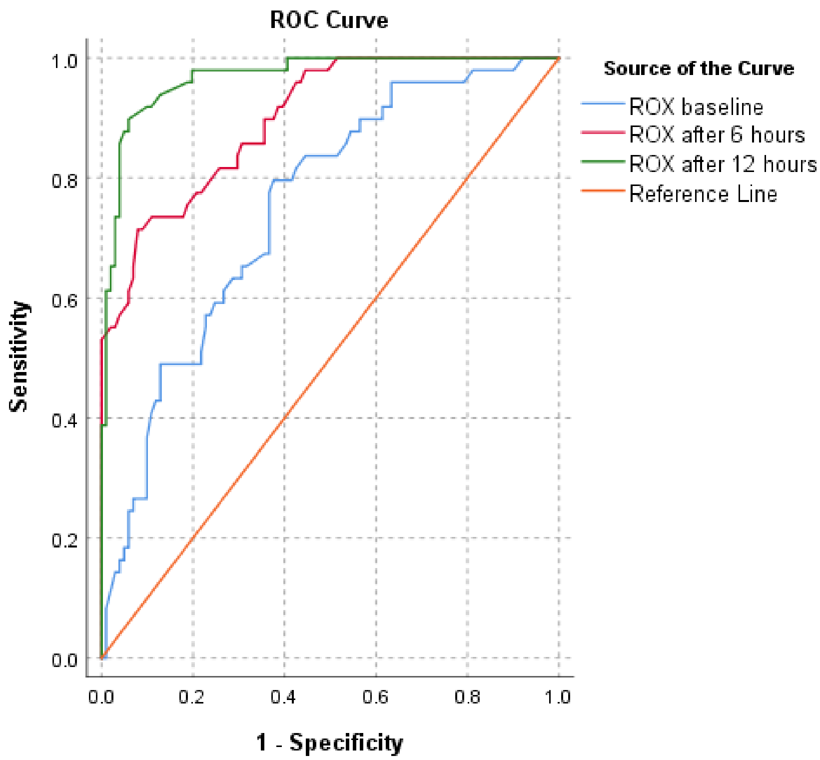

Figure 8 – ROC curve of ROX index for diagnostic accuracy of NIV failure

Table 4.5 – ROC curve analysis to diagnostic accuracy of NIV failure according to ROX index

Test Result Variable(s)	AUC (95% CI)	Cut-off	Sensitivity	Specificity	P value
ROX baseline	.750 [0.67-0.83]	3.65	79	39	<0.001
ROX after 6 hours	.899 [0.85-0.94]	3.47	98	48	<0.001
ROX after 12 hours	.968 [0.94-0.99]	3.36	100	42	<0.001

Receiver operator characteristic (ROC) analysis showed that, ROX index after 12 hours (AUC=96%, Sensitivity=78%, Specificity=39%), after 6 hours (AUC=89%, Sensitivity=98%, Specificity=48%), and at baseline (AUC=75%, Sensitivity=100%, Specificity=42) had well diagnostic accuracy to predict NIV failure in patients. This means that, by passing time after NIV initiation, the accuracy of ROX index for predicting NIV failure would be increased. On the other hand, sensitivity of it would be increased.

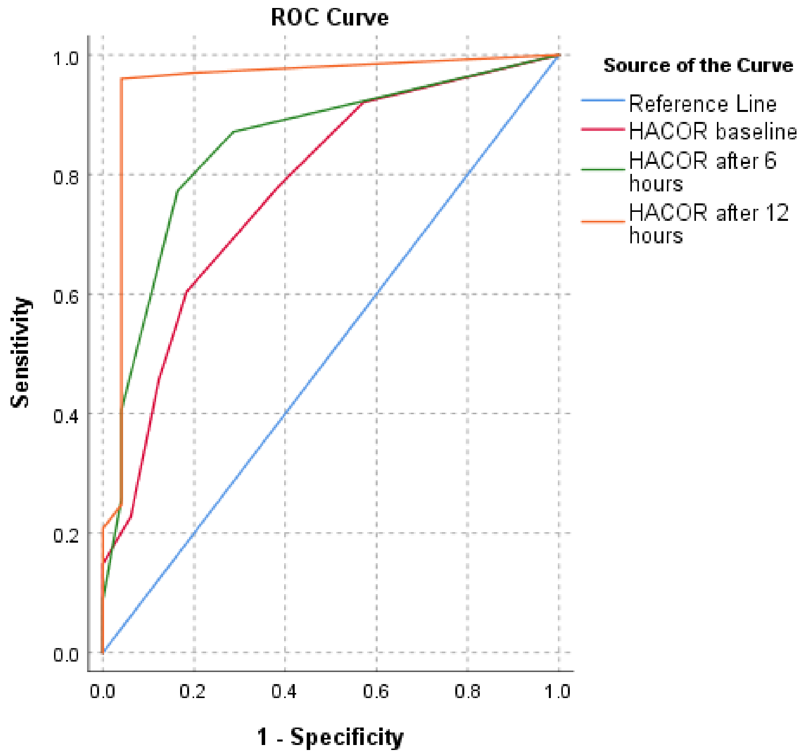

Figure 9 – ROC curve of HACOR scale for diagnostic accuracy of NIV failure

Table 4.6 – ROC curve analysis to diagnostic accuracy of NIV failure according to HACOR scale (N:150)

Test Result Variable(s)	AUC (95% CI)	Cut-off	Sensitivity	Specificity	P value
HACOR baseline	.774 [0.69-0.85]	9	60	18	<0.001
HACOR after 6 hours	.848 [0.78-0.91]	8	77	16	<0.001
HACOR after 12 hours	.951 [0.90-0.99]	10	63	4	<0.001

ROC analysis showed that, HACOR scale after 12 hours (AUC=95%, Sensitivity=60%, Specificity=18%), after 6 hours (AUC=84%, Sensitivity=77%, Specificity=16%), and at baseline (AUC=95%, Sensitivity=63%, Specificity=4%) had a good diagnostic accuracy to predict NIV failure in patients. It should be noted that HACOR after 6 hours had the highest Sensitivity of NIV failure.

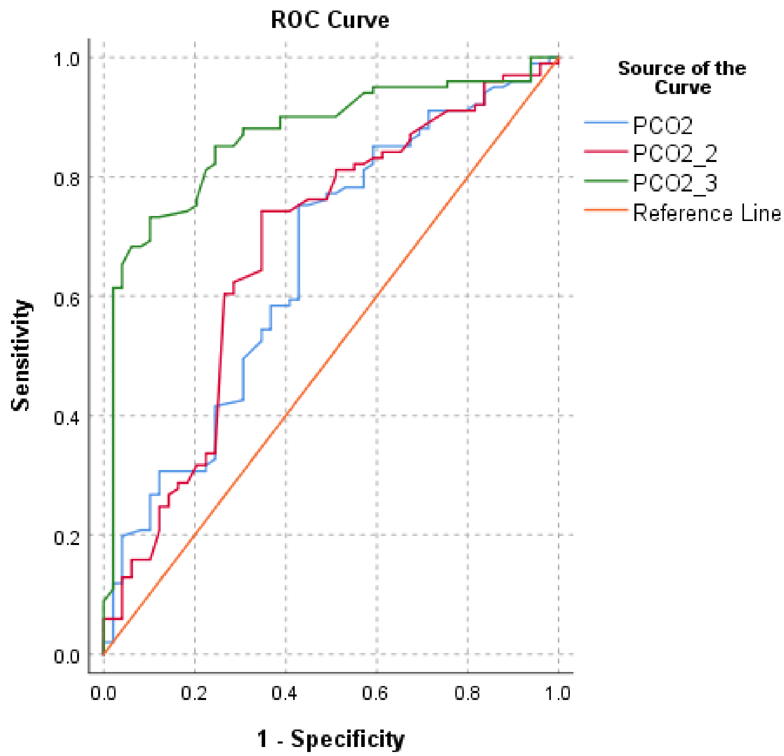

Figure 10 – ROC curve of PCO_2 for diagnostic accuracy of NIV failure

Table 4.7 – ROC curve analysis to diagnostic accuracy of NIV failure according to PCO2

Test Result Variable(s)	AUC (95% CI)	Cut-off	Sensitivity	Specificity	P value
PCO_2 baseline	.654 [0.55-0.74]	44.85	42	30	<0.001
PCO_2 after 6 hours	.677 [0.58-0.77]	44.65	60	28	<0.001
PCO_2 after 12 hours	.867 [0.80-0.92]	45.5	39	2	<0.001

ROC analysis showed that, PCO_2 after 12 hours (AUC=86%, Sensitivity=39%, Specificity=2%), after 6 hours (AUC=67%, Sensitivity=60%, Specificity=28%), and at baseline (AUC=65%, Sensitivity=42%, Specificity=30%) had a good diagnostic accuracy to predict NIV failure in patients. It should be stated that PCO_2 after 6 hours had the highest Sensitivity of NIV failure.

CURRICULUM VITAE

1. Personal Information

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2. Education

Year	Grade	University	Field
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3. Academic & Professional Experience

PERIOD	TITLE	DEPARTMENT	UNIVERSITY
March, 2020 – August, 2021	Researcher	ICU	Tehran University of medical sciences

4. Computer Knowledge

Microsoft Office	Very good
SPSS	Good
GraphPad PRISM	Good