An-Najah National University

Faculty of Graduate Studies

SURVIVAL RATE AND OUTCOMES AMONG CRITICALLY ILL COVID-19 PATIENTS REQUIRING INVASIVE MECHANICAL VENTILATION (IMV) IN PALESTINE

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Dedication

To those who left their homes and committed to hospitals, who gave all effort with their knowledge and skills to confront COVID-19 pandemic, the first line of defense, fellow medical staff.

To those who light the way of science and knowledge, who had the greatest role in education, guidance, follow-up and advice, my virtuous faculty.

To the one who taught me the love of science and the spirit of determination, my role model and first teacher, my dear father.

To the most generous, who has always been my best support and encouragement, my precious mother.

To my soul mate, who endured my busyness, my fatigue and my anxiety, my beloved wife.

To those who always stand by me, my dear brothers.

To the compassionate heart, my dear sisters.

To those who are happy with our success and sad by our failure, relatives in blood, heart and loyalty.

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Declaration

I, the undersigned, declare that I submitted the thesis entitled:

SURVIVAL RATE AND OUTCOMES AMONG CRITICALLY ILL COVID-19 PATIENTS REQUIRING INVASIVE MECHANICAL VENTILATION (IMV) IN PALESTINE

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

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Signature: _____

Date: _____

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SURVIVAL RATE AND OUTCOMES AMONG CRITICALLY ILL COVID-19 PATIENTS REQUIRING INVASIVE MECHANICAL VENTILATION (IMV) IN PALESTINE

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ABSTRACT

Introduction: COVID-19 is a respiratory infectious disease and can deteriorate to ARDS and respiratory failure, which necessitates the need of invasive mechanical ventilation. The varying treatment strategies and outcomes warrant the need to further explore patient characteristics and treatment plans, and their potential associations with morbidity and mortality.

Aim: To designate the survival rate and outcomes of COVID-19 patients who underwent IMV, as well as impact of their clinical characteristics and treatment strategies.

Method: A retrospective observational cohort design. All COVID-19 patients who were admitted to targeted hospitals between 1/8/2020 to 30/4/2021, older than 18 years and required IMV were enrolled. Data was gathered from the hospital information system and include Characteristics (demographic data, comorbidities, lab values), Treatment strategies (respiratory support, proning, intubation timing, mechanical ventilator settings and pharmacological treatments) and Outcomes (complications, length of stay on IMV, and mortality). Comparisons were then drawn between two subsets divided by mortality using the variables mentioned above using SPSS.

Results: 150 patients required IMV which represents 39.8% of COVID-19 patients and 13 (8.7%) of which survived to hospital discharge. The mean age was 64 years old and younger age was associated with lower mortality (OR 0.948, p=0.006). Cardiovascular Disease and peak creatinine were significantly higher in deceased patients (p=0.041, p=0.008) respectively. Patients who underwent pressure mode ventilation, with lower FiO2 and inspiratory pressure had a higher rate of survival (OR 4.416, 0.883, 0.478,

respectively, *p<0.05)*, as well as who were submitted to tracheostomy. Remedsivir had a significant correlation with survival (p-value=0.001). ICU median length of stay was 27 days for patients who survived and 11 for those who died (p-value <0.001), while IMV median LOS for survivors and deceased patients was 15 days vs. 6 days, respectively (p-value <0.001). Patients developed complications such as AKI (60.7%) and cardiovascular (45.3%) which are significantly correlation with deceased patients.

Conclusion: Survival rate among COVID-19 patients who underwent IMV was low (8.7%). Evidence based practice and multidisciplinary management are recommended in treatment of critically ill COVID-19 patients depending on research, to improve their outcomes.

Keywords: COVID-19, IMV, Mortality, Characteristics, Survival rate, Outcomes.

Chapter One

Introduction

1.1 Background

Atypical respiratory disease - pneumonia of unknown etiology - was first noted in December of 2019 in Wuhan, China, and it was later recognized that a novel coronavirus (2019-nCoV), named later SARS-CoV-2, was the virus which cause the disease which was subsequently termed COVID-19 (Guo et al., 2020).

COVID-19 spread rapidly worldwide and on March 11th, 2020, the World Health Organization (WHO) identified COVID-19 as a pandemic after 118,000 cases were diagnosed in 114 countries and 4291 individuals had died (World Health Organization, 2020). By June 10th, 2021, over 174 million had been infected and more than 3.7 million died over the world (Covid-19 map, 2021).

Not all patients who have been get COVID-19 present with symptoms. While asymptomatic patients have a positive COVID-19 nucleic acid test, they do not present with any clinical signs or symptoms, and mainly have unremarkable chest imaging. On the other hand, symptomatic patients may have different classifications according to the severity of these symptoms, with mild symptoms resembling those of acute upper respiratory tract infection (URTI), such as cough, fever, fatigue, myalgia, sneezing or rhinorrhea, or gastrointestinal symptoms, including, but not limited to, abdominal pain, nausea, vomiting, and diarrhea. Moderate symptoms include pneumonia, that is characterized by frequent cough and fever, accompanied with non-obvious hypoxemia, and lesions found in chest computed tomography (CT). Severe cases of COVID-19 are characterized by pneumonia with hypoxemia of oxygen saturation (SpO_2) < 92%, and critical cases are deteriorating cases due to a systemic inflammatory response (i.e., cytokine storm), which can result in acute respiratory distress syndrome (ARDS), shock (decreased tissue perfusion), myocardial injury, encephalopathy, coagulation dysfunction, heart failure, and acute kidney injury (AKI). (Yuki, Fujiogi, & Koutsogiannaki, 2020).

Patients who have been diagnosed with COVID-19 have undergone a variety of testing. COVID-19 testing can be done in two ways as per centers for disease control and prevention (CDC) guidelines: 1) a viral test that detects viral nucleic acid or antigen in a specimen collected from either the upper airway (polymerase chain reaction (PCR) via mouth or nasopharyngeal swab) or the lower airway of patients who have been tracheostomized patients or have already been invasively mechanically ventilated (tracheal or bronchial lavage) and 2) an antibody test, which detects antibodies generated to combat the virus. It is important to note that antibody tests cannot be used to diagnose an acute infection. (McFee, 2020).

Since the first cases of COVID-19 were discovered, and the increase of hospital admissions and their severity, numerous management approaches have been implemented, such as oxygen therapy by nasal canula or facial mask, symptomatic therapy, pharmacological therapy like antibacterial and antiviral depending on different clinical trials and supportive therapy for nutritional and psychological status .while severe cases should be observed for their hemodynamics and lab tests to assess any complications and vasopressors were given in case of shock, moreover prone positioning were performed and more advance devices needed for severe hypoxemia and ARDS such invasive mechanical ventilation (IMV) and extracorporeal membrane oxygenation (ECMO) . (Zhang et al., 2020)

Several studies have been conducted among COVID-19 patients to investigate the proportion of intensive care units (ICU) admissions and the prevalence of mechanical ventilation usage. A sample of epidemiological studies have been compared in a systematic review and found variety in the percentage of COVID-19 patients who required IMV. For example, Richardson et al. (2020) found that 20.2% of total hospitalized COVID-19 patients and 89.9% of ICU patients required IMV in a sample of 5,700 patients in New York City, and Grasselli, Pesenti, and Cecconi (2020) found a similar percentage of 88.5% of the ICU patients and 16.8% of the total hospitalized patients are on IMV in Italy, while Zhou et al. (2020) and Guan et al. (2020) found less percentage of 64.0% and 45.5% , respectively, of total ICU patients on IMV in China . These epidemiological varieties are linked to several factors, unrelated to the disease itself, such as clinical decision making and availability of resources.

A meta-analysis of 28 studies conducted in 7 countries by Chang, Elhusseiny, Yeh, and Sun (2021) explored the outcomes of Covid-19 patients who required IMV while admitted in the ICU, and found a pooled percentage of 21% were admitted to ICU and 69% required IMV, with a mean of 7.78 days' length of stay in ICU and 10.12 days on IMV, while the ICU mortality was 28.3% and IMV mortality was 43%. The most common risk factor that increased mortality among COVID-19 patients admitted into the ICU was IMV (16.46 times lower survival rates than non-IMV patients), followed by AKI (12.47 times lower survival rates than non-AKI patients) and ARDS (6.52 times lower survival rate than non-ARDS patients).

In Palestine, the first COVID-19 cases were discovered in Bethlehem on March 5th, 2020, infected by international tourists. The outbreak spread quickly, with 84 cases and one death within three weeks, despite the cases being quarantined and the city being locked down (Palestinian Authority, 2020). In spite of the barriers that resource limitations and the Israeli occupation pose on Palestine, the Palestinian outperformed many countries in confrontation to the pandemic in the early stages (M. AlKhaldi, et al. 2020). However, the increased mixing and transmission of Palestinian workers inside the Occupied Region of 1948, alongside several factors, have increased the number and burden of cases in the West Bank of Palestine exponentially. The current situation is more positive, as the percentage and availability of vaccinations increase, but is still inferior to the response of other countries because of barriers posed by the occupation, as well as sociopolitical and financial constraints, alongside the factors that affect people's hesitancy to receive the vaccine (Al-Jayyousi et al., 2021), even among health care workers (Maraqa et al., 2021).

COVID-19 reports are published on the Palestinian Authority Ministry of Health website and by an official speaker of the Palestinian Authority Government on TV, in which the report is published daily, and during some periods of the pandemic twice daily. This report includes the numbers of new and cumulative cases and deaths, the number of patients who recovered, and sometimes patients who admitted to ICU and received IMV. Demographically, cases were divided into three main regions according to geographical distribution: West Bank, Gaza Strip, and outside Palestine (i.e., diaspora). According to the Palestinian Ministry of Health, there have been 340,532 verified total cases and 3,807 deaths as of June 14th, 2021 (State of Palestine Ministry

of Health, 2021). COVID-19 numbers of all Palestinians living in the Occupied Region of 1948 are inaccurate since Israeli occupation authorities refuse to share information with the Palestinian Ministry of Health (M. AlKhaldi, Kaloti, et al. 2020).

For the general management of COVID-19 in Palestine, Hejaz (2020) stated that high flow nasal cannula (HFNC) or non-invasive mechanical ventilation (NIV) are preferred in situation where standard oxygenation using nasal cannula or simple face mask does not relieve respiratory symptoms for patients, with high flow nasal cannula being considered safer as it has a lower risk of transmission of infections. The IMV is then considered if the patient does not improve within one to two hours using the previous methods, as it avoids ventilator-induced injury, and enhances gas exchange using lung-protective ventilation. Due to a lack of medical resources, the WHO designated Palestine as a high-risk country for the COVID-19 pandemic, whereas the Palestinian health system lacks critical care units and mechanical ventilators (Palestinian Authority, 2020).

Despite the high proportion of Covid-19 patients who require IMV in ICUs in Palestine, their survival rates and outcomes remain unclear and poorly defined. Therefore, this study aims to describe the clinical characteristics and treatment strategies of COVID-19 patients in Palestine who are managed with invasive mechanical ventilation, as well as the impacts on survival rate and outcomes.

1.2 Problem Statement

In light of the rapid increase of acute respiratory failure cases in COVID-19 patients worldwide, governments and health systems fear the lack of mechanical ventilators, which prompted researchers to study how to decide if patients are indicated for intubation or they could be stable with oxygen supplies and when to start weaning for mechanically ventilated patients, without leading to disease progression or acute lung injury. In addition, experts have different opinions in intubation timing, early or delayed; while others consider that endotracheal intubation has fatal complications as decades of research. (Tobin, Laghi, & Jubran, 2020).

Researchers in Palestine studied several aspects of COVID-19, including the health system response to the pandemic and the policies implemented determinants and challenges in facing the COVID-19 pandemic, the epidemiology of incidence and risk

factors of deterioration, the impact of the pandemic and social distancing restrictions on people and recommendations for safe practice of different specialties. Nevertheless, the characteristics, comorbidities and treatment strategies of Covid-19 patients requiring IMV are poorly defined, and their effect on survival rate and outcome remains unclear.

1.3 Significance of the Study

This is the only study looking into the survival rates and outcomes of COVID-19 patients requiring IMV in Palestine, and it will provide researchers and the healthcare sector in Palestine with up-to-date information on COVID 19 patients' characteristics, treatment strategies, and the factors that affect the survival rates and outcomes. These findings will be utilized to develop guidelines for improving survival rates in COVID-19 intubated patients.

1.4 Aims of the Study

To determine the demographics, characteristics, and treatment strategies of COVID-19 patients in Palestine who are managed with invasive mechanical ventilation, as well as their impact on survival rate and outcome, and to predict the factors that contribute to IMV mortality, by achieving the following specific goals:

1. Investigate the prevalence of ICU admission among COVID-19 patients in Palestinian health care system comprised of 3 hospitals.

2. Investigate the prevalence of IMV in COVID-19 patients who were admitted to ICU’s in Palestine.

3. Investigate the survival rate of COVID-19 patients who were admitted to ICU in Palestine.

4. Investigate the survival rate of invasive mechanically ventilated COVID-19 patients in ICU settings in Palestine.

5. Explore patients’ demographics, comorbidities and characteristics associated with increased or decreased survival rate in critically ill COVID-19 patients who required IMV in multiple centers across Palestine.

6. Study treatment strategies used in COVID-19 patients requiring IMV and their correlation with mortality.

7. Investigate the risk factors associated with mortality in COVID-19 patients requiring IMV.

1.5 Questions of the Study

This study aims to explore the following questions:

1. What is the prevalence of ICU admission among COVID-19 patients in Palestine?

2. What is the prevalence of IMV for COVID-19 patients among ICU admissions and hospital admissions in Palestine?

3. What is the survival rate of COVID-19 patients who were admitted to ICU in Palestine?

4. What is the rate of survival in COVID-19 patients who were on IMV in ICU settings in Palestine?

5. What are the demographics, comorbidities, and characteristics of the COVID-19 patients and does a correlation exist with increased or decreased survival rates among COVID-19 patients who have been admitted to ICU and require IMV in Palestine?

6. What are the treatments strategies used in COVID-19 patients who require IMV?

7. What are the mortality risk factors of COVID-19 patients who need IMV?

1.6 Study Hypotheses

This study will aim to test the following hypotheses:

H_0: There is no significant difference in COVID-19 patients who require IMV in terms of survival rate according to their demographic data (age, gender, BMI … etc.) at a significance level of P-value = 0.05.

H_0: There is no significant difference in COVID-19 patients who require IMV in terms of survival rate according to their medical history and lab results (cardiac diseases, diabetes mellitus, renal diseases, and D-Dimer, Ferritin … etc.) at a significance level of P-value = 0.05.

H_0: There is no significant difference in COVID-19 patients who require IMV in terms of survival rate according to their COVID-19-related management (proning, NIV, HFNC, intubation timing and parameters of IMV… etc.) and pharmacological management (Remedsivir, hydroxychloroquine…etc.) at a significance level of P-value = 0.05.

H_0: There is no significant difference in COVID-19 patients who require IMV in terms of survival rate according to complications occurred in ICU (Acute Kidney Injury, ARDS …etc.) and length of stay in ICU and on IMV at a significance level of P-value = 0.05.

1.7 Conceptual framework

1.7.1 Conceptual definition

Coronavirus disease 2019 (COVID-19): “Is a contagious disease caused by the new corona virus type 2 severe acute respiratory syndrome (SARS-CoV-2)” (Rudrapal, Khairnar, Borse, & Jadhav, 2020).

ICU: “Is an organized system for providing care to critically ill patients that includes intensive and specialized medical and nursing care, increased monitoring capacity, and multiple modalities of physiologic organ support to sustain life during a period of life-threatening organ system insufficiency” (Marshall et al., 2017).

Mechanical ventilation “is a technique for moving gas toward and from the lungs using an external device that is directly attached to the patient” (Muñoz Bonet, 2003).

Age: “The length of a being's or thing's existence; the length of life or existence to the time pronounced." Or a span of human existence counted in years from birth and distinguished by a given stage or degree of mental or physical development, as well as legal responsibility and capacity.” (Dictionary.com, 2002).

Gender: "The state of being male or female (usually applied to social and cultural distinctions rather than biological differences)" (2020a, Oxford Dictionary of English)

1.7.2 Operational definition

COVID-19 Case: “A person who has a positive Nucleic Acid Amplification Test (NAAT) B or a positive SARS-CoV-2 Antigen-RDT AND meets either the probable case definition or the SARS-CoV-2 Antigen-RDT criteria. An asymptomatic person who is a contact of a probable or confirmed case and has a positive SARS-CoV-2 Antigen-RDT.”(World Health Organization, 2020).

COVID-19 Death: “A death will be classified as a COVID-19 death if COVID-19 was the primary cause or a substantial contributing cause of death, according to a trained medical practitioner.” (Oxford Dictionary of English, 2020b).

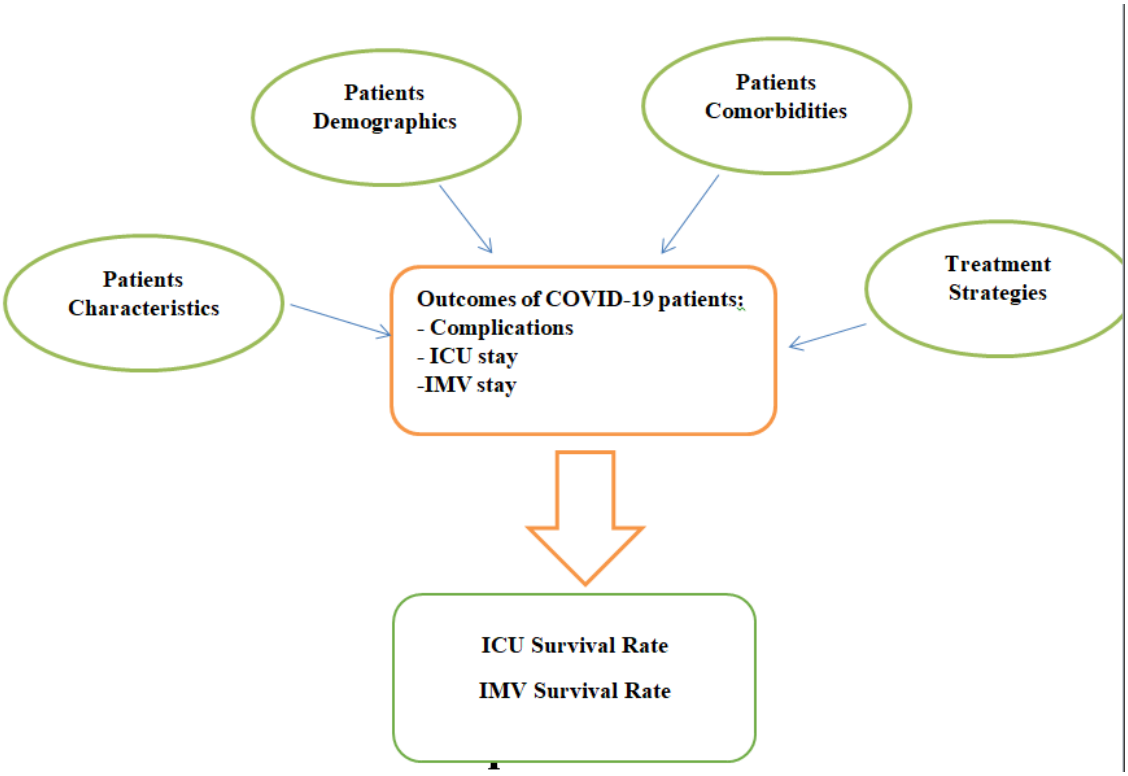
ICU: Patients who have been admitted to the intensive care unit (ICU) or died there.

MV: At least one mechanical ventilator episode was experienced by the patient.

Age: Adult patients are those that are over the age of 18.

Gender: In this study, both genders (male and female) were assessed.

1.7.3 Framework



Chapter Two

Literature Review

2.1 Introduction

The literature relating to the main concepts of this study is examined in this chapter. The literature review serves as a solid foundation for writing a research paper. It contributes to the study's basis and may elicit fresh research ideas. The report's early literature analysis gives readers a foundation for understanding current knowledge about the issues and emphasizes the significance of the new study. And it contains two parts: Background and Previous Studies.

2.2 Search strategy

A thorough literature search was carried out utilizing a variety of electronic databases, including Science Direct, Springer, Google Scholar, PubMed, and CINAHL. The study thoroughly examined crucial topics such as invasive mechanical ventilation, cytokine storms, and biomarkers, which were previously found in the study Covid-19.

For literature that is likely to be relevant, checklists of selected articles were searched. The relevancy of the selected articles was established by drawing abstracts of the papers. This method has led to the discovery of a vast volume of literature. The papers were then organized into categories based on the study's keywords and subjects. Original research was identified in journals that were available in English in full text.

2.3 Background

2.3.1 COVID-19

COVID-19 disease is an infectious respiratory disease is caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). The disease, originally identified in Wuhan, China in 2019, has subsequently spread worldwide, resulting in the coronavirus pandemic of 2019-20(Hui et al., 2020). The novel virus was given the name SARS-CoV-2 virus by the International Committee on Virus Taxonomy (ICTV) due to the similarity of its genomic sequence to that of the severe acute respiratory syndrome coronavirus (SARS-CoV)(Gorbalenya et al., 2020). The coronavirus COVID-19 is an RNA virus that belongs to the coronavirus family. This outbreak has been labeled a major threat to international health by the World Health Organization (WHO)(Guan et

al., 2020). Despite the fact that the disease's clinic is consistent with the ARDS Berlin classification, Covid-19 is a distinct disease with distinct characteristics. Clinical evidence suggests that severe Covid-19 is most usually caused by viral pneumonia, in a way similar to ARDS (Acosta & Singer, 2020) .

The disease is characterized by a highly contagious clinical picture that advances in an ARDS-like clinic and includes many comorbidities with thrombotic consequences (Li & Ma, 2020). The main routes of transmission are respiratory droplets and contact, however new investigations have also confirmed the existence of a fecal-oral route of transmission (Guan et al., 2020).

2.3.2 COVID-19 Pathophysiology

Several specials can be infected by coronaviruses, which are enclosed, single-stranded RNA viruses. 229E, OC43, NL63, and HKU1 are the most prevalent coronaviruses found in clinical typing and they produce cold-like symptoms in individuals who are immune competent. In the last two decades, SARS-CoV2 has become the third coronavirus to cause significant sickness in humans around the world(Zhu et al., 2020).

SARS-CoV-2 has a diameter of 60 to 140 nanometers and pronounced spikes of 9 to 12 nanometers. The virus has the ability to adapt to new hosts through genetic recombination and increased diversity. SARS-CoV-2 is thought to be a natural reservoir in bats. It has been suggested that SARS-CoV-2 infects humans via an intermediary host, such as the pangolin, although the origins still remain unclear. The mode of transmission of SARS-CoV-2 is through respiratory droplets, particularly when close contact is made (Wiersinga, Rhodes, Cheng, Peacock, & Prescott, 2020).

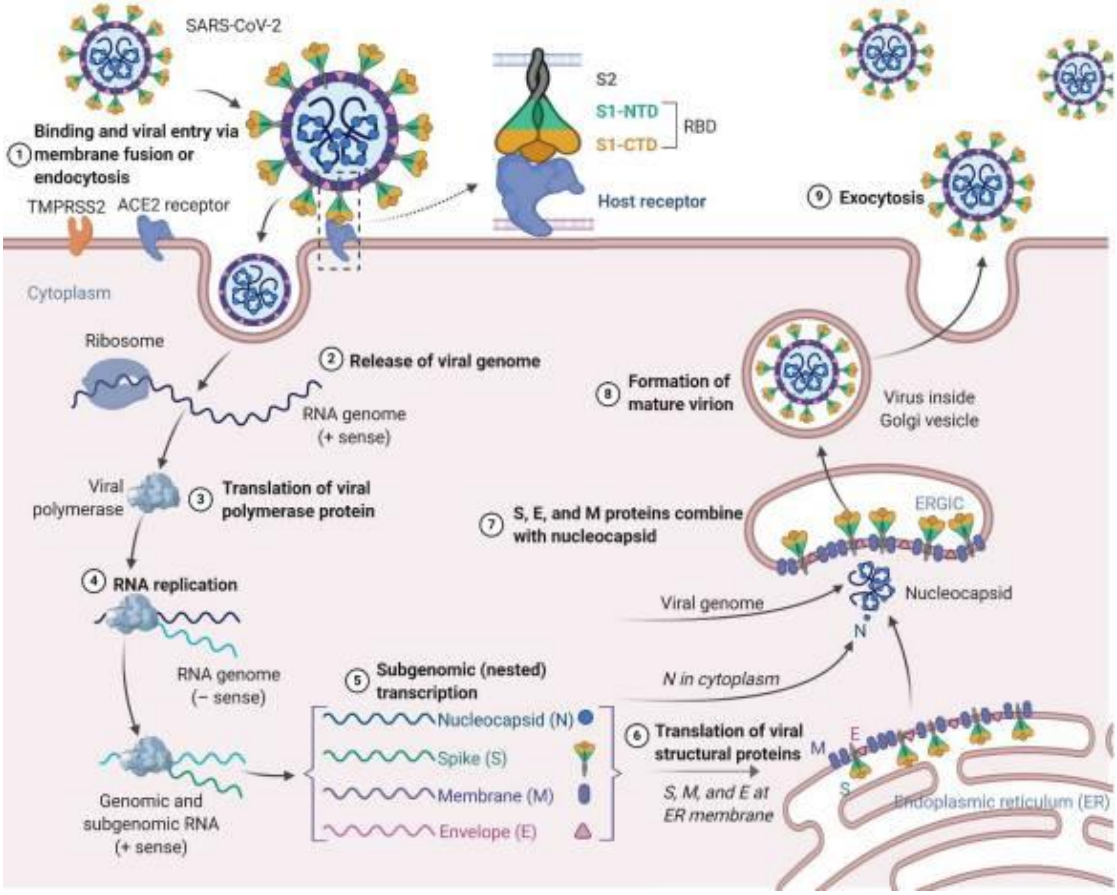
2.3.2.1 Viral Pathogenesis

SARS-CoV-2 accesses target cells such as host nasal and bronchial epithelial cells and pneumocytes via binding to angiotensin converting enzyme 2 (ACE2) via the surface spike (S) protein. The type 2 transmembrane serine protease (TMPRSS2) present in the host cell enhances viral uptake by cleaving ACE2 and activating the SARS-CoV-2 S protein, mediating the entry of coronavirus into host cells. Viral RNA is released and translated into viral protein polymerases after the virus enters the host cell. Sub-genomic negative sense RNAs are generated and used as a template to make messenger RNAs (mRNAs). In the cytoplasm, viral structural proteins such as S protein,

membrane (M) protein, envelope (E) protein, and endoplasmic reticulum (ER) protein are transcribed, followed by viral RNA and nucleocapsid (N) structural protein. In the ER-Golgi intermediate compartment (ERGIC), the structural proteins are integrated into the nucleocapsid and viral envelope to form a mature virion. Following that, the freshly produced virion is discharged from the host cell (X. Liu, Liu, Liu, Luo, & Xia, 2020). (Figure 2.1: Viral Replication and Spread)

Figure 2.1

Sars-Cov2 Viral Replication and Spread. (X. Liu et al., 2020)



2.3.2.2 Covid-19 Signs and Symptoms

The time it takes for symptoms to appear after coming into contact with Covid-19 is about 5 (2-7) days. Fever, dry cough, exhaustion, shortness of breath, sputum, myalgia, nausea-vomiting, diarrhea, and rhinorrhea are some of the symptoms that patients experience. In roughly 3% of those with Covid-19, anosmia may be the only symptom. Mild symptoms were observed in 81 % of the 44672 Covid-19 individuals studied in

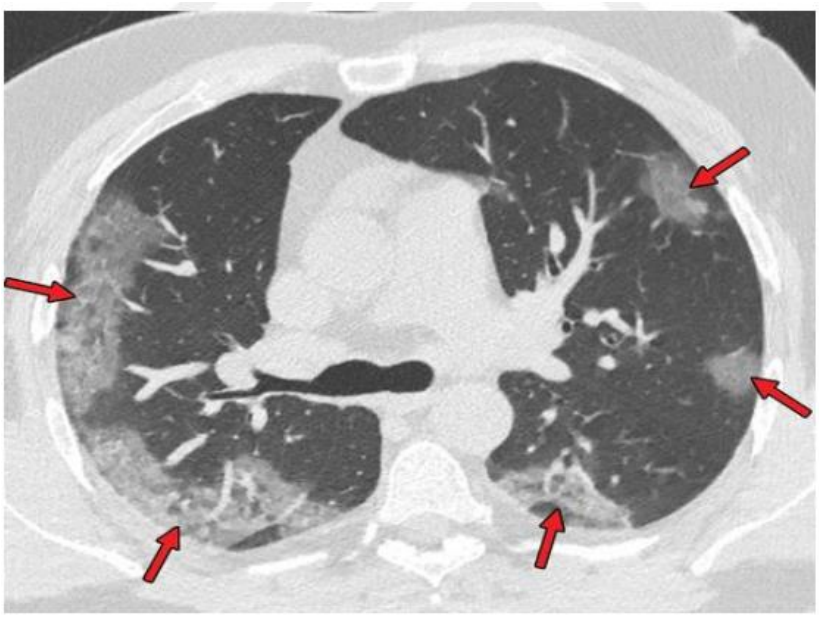
China, severe symptoms in 14 % , and critical symptoms in 5% (Alimohamadi, Sepandi, Taghdir, & Hosamirudsari, 2020).

2.3.2.3 Covid-19 Multisystem Effects

The epithelial-endothelial barrier becomes involved when the viral replication stage of the infection accelerates. SARS-CoV-2 binds to the endothelial cells of pulmonary capillaries and causes an inflammatory reaction. An influx of monocytes and neutrophils into the endothelium area is caused by virus involvement. Mononuclear cells and macrophages penetrating the air spaces create considerable thickening of the alveolar wall, in addition to the endothelialitis that result. Interstitial mononuclear inflammatory infiltrates and edema can be visualized on computed tomographic imaging, and are often described as “ground glass opacities” (Figure 2.2). Pulmonary edema, which causes hyaline membranes to fill the alveolar spaces, gives the appearance of ARDS. The disease's pulmonary involvement produces a decrease in oxygen diffusion capacity, in fact more than 75% of hospitalized patients diagnosed with Covid-19 require oxygen therapy. Additionally, approximately 35% of hypoxemic patients require intensive care (Wiersinga et al., 2020).

Figure 2.2

Covid-19 Pneumonia with Typical Imaging Features According to the North American Society of Radiology (RSNA) Chest CT Classification System (Kwee & Kwee, 2020)



In patients with COVID-19, acute liver injury (19%), acute kidney injury (9%), acute cerebrovascular disease and hepatic encephalitis characterized by elevations in aspartate aminotransaminase (AST), alanine aminotransaminase (ALT), and total bilirubin are the most frequent manifestations of this disease outside the respiratory system. In the COVID-19 intensive care unit patient subset (8%), bleeding and coagulation disorders (10%-25 %), and septic shock (6 %) are all seen (Wiersinga et al., 2020) (16). Additionally, high troponin levels, myocarditis, cardiomyopathy, ventricular arrhythmias, and hemodynamic abnormalities (7-17%) have all been noted as sequela of COVID-19.

In severe cases, COVID-19 can result in fulminant consumptive coagulopathy. According to research conducted in Wuhan, China, 71% of the 183 patients who died as a result of COVID-19 matched the criteria for disseminated intravascular coagulation (Levi, Thachil, Iba, & Levy, 2020). The formation of micro thrombi in infiltrating lung tissues, pulmonary endothelial cells, and the capillary vascular network causes deep vein thrombosis, pulmonary embolism, and thrombotic arterial consequences (acute ischemic stroke, myocardial infarction) (Wiersinga et al., 2020).

Cytokine storm and macrophage activation syndrome (MAS), a form of secondary hemophagocytic lymphohistiocytosis, is another uncommon complication among COVID-19 patients. Tumor necrosis factor (TNF), type I and II interferon's, interleukin-1 (IL-1), IL-6, IL-10, CCL2, and monocyte chemotactic protein-1 (MCP-1) are among the inflammatory cytokines and chemokine's implicated in the pathophysiology of this condition. Excessive immune cell activation results in the production of huge amounts of cytokines, which promotes systemic hyperinflammation. In the COVID-19 picture, MAS is viewed as the clinical picture that generates the ARDS picture (Wiersinga et al., 2020).

2.3.3 COVID-19 Pneumonia

COVID-19 pneumonia is a unique phenotype with its own set of symptoms. Patients with significant hypoxemia may have strong respiratory mechanics. The progression of hypoxemia varies widely amongst individuals. Patients having a median lung compliance of 50 ml/H2O were phenotyped based on lung dynamics and radiological imaging data and were divided based on relativity to this value. They are further divided into two subgroups: non-ARDS-like type 1 and ARDS-like type 2, each having its own distinct pathophysiology. CT scans can be employed to accurately differentiate between type 1 and type 2 patients who have been admitted into the hospital (Gattinoni et al., 2020).

Hypoxemia is caused by a decrease in hypoxic pulmonary vasoconstriction and impaired regulation of pulmonary blood flow in type 1 pneumonia patients who have a high gas volume and low lung recruit ability of ventilation areas. As a result, severe hypoxemia in type 1 is predominantly caused by a V/Q mismatch between ventilation and perfusion. High PEEP and prone positioning have no effect on areas that are not involved in recruitment for oxygenation. It may improve the V/Q relationship by shifting pulmonary perfusion as a method (Gattinoni et al., 2020).

Patients with type 2 pneumonia have severe hypoxia and low lung compliance (less than 40 ml/cmH2O), indicating severe ARDS (Maiolo et al., 2018). Prior to being sent to the intensive care unit, some patients with type 2 pneumonia receive non-invasive mechanical ventilation. Patients with very high respiratory impulses, significant inspiratory efforts, and negative intrathoracic pressures are admitted to the intensive

care unit. These patients may also have ventilator-induced lung damage in addition to viral pneumonia (Gattinoni et al., 2020).

2.3.4 COVID-19 and ARDS

When the lungs are directly or indirectly injured, ARDS develops. ARDS is a disorder that causes poor lung compliance and severe hypoxia and is linked to a variety of diseases. It is the result of a possible acute systemic inflammatory reaction. The breakdown of lung epithelial and endothelial cells causes diffuse alveolar injury(Force et al., 2012).

There exist variations between COVID-19-related ARDS and ARDS of varying etiologies, according to research. The ARDS Berlin criteria states “that a patient's onset of ARDS must occur within 1 week of a known clinical insult or new or worsening respiratory symptoms”; however, the typical time of onset in COVID-19-related ARDS was 8–12 days, implying that the ARDS Berlin criteria's 1-week onset limit does not apply to COVID-19-related ARDS (Li & Ma, 2020).

However, contrary to popular belief, lung compliance may be reasonably normal in some COVID-19-related ARDS patients that meet ARDS Berlin criteria. Furthermore, in several COVID-19-related ARDS patients, lung compliance was paradoxically high. These observations prove to be discordant with both the severity of hypoxemia and the definition of ARDS of non-COVID etiology. (Ferguson et al., 2012).

In the patients' lung tomography imaging, peripheral lung involvement and ground-glass pictures predominate. The photos do not exhibit a typical ARDS appearance, despite the consolidation and exudation(Maiolo et al., 2018).

According to the Berlin definition, “ARDS is classified into three phases based on the oxygenation index (PaO2/FiO2) on positive end-expiratory pressure (PEEP) ≥5 cmH2O: mild, moderate, and severe.” The disease severity and the treatment procedure are determined by the ARDS classification. According to a previous study, more than half of patients with moderate and severe ARDS who met the Berlin criteria did not have diffuse alveolar damage (Ferguson et al., 2012).

The clinical characteristics of ARDS linked to COVID-19 are largely unknown. There are no specific protocols for monitoring and application. For patients with PaO2/FiO2 < 150 mmHg, previous clinical data suggests a variety of treatments, including prone position, elective intubation, and heavy sedation with neuromuscular blockers. However, in the treatment of respiratory failure caused by COVID-19, the paO2/fiO2 ratio provides insufficient data to make an IMV choice. Clinical studies suggest that the Berlin classification is insufficient for accurately defining the degree of respiratory failure and guiding appropriate therapy (Li & Ma, 2020).

In ARDS patients, high-flow nasal oxygen (HFNO) lowers the requirement for endotracheal intubation compared to normal oxygen therapy (Ou, Hua, Liu, Gong, & Zhao, 2017). According to studies, HFNO is better for patients with mild ARDS (Li & Ma, 2020). HFNO, on the other hand, can be considered safe in patients with mild and mild-moderate COVID-related ARDS, as well as some moderate-severe patients, depending on clinical circumstances. This is in stark contrast to the tiered therapy options utilized to treat ARDS caused by other causes.

We can postpone the IMV choice if the patient can tolerate high-flow nasal oxygen or NIMV therapy, obtain appropriate oxygenation levels, and continue the process with minimal respiratory effort. Patients receiving HFNO should be continuously observed and provided cared for by skilled professionals who are capable of endotracheal intubation at any moment, because the state of severe COVID-19 patients can quickly deteriorate. COVID-19 most usually affects the respiratory system and some cases can quickly proceed to ARDS, necessitating the use of venous-venous extracorporeal membrane oxygenation (V-V ECMO) (Li & Ma, 2020).

Because of their ability to reduce inflammation and fibrosis, corticosteroids are being evaluated as a possible treatment for ARDS. Treatment with high-dose corticosteroids for an extended length of time has been shown to hasten the improvement of ARDS (G Umberto Meduri et al., 2016). Furthermore, in ARDS patients, methylprednisolone reduced the requirement for invasive mechanical ventilation and decreased mortality (Gianfranco Umberto Meduri, Siemieniuk, Ness, & Seyler, 2018).

2.3.5 COVID-19 and Cytokine storm

There is no such thing as a cytokine storm; it refers to “a hyperactive immune response marked by the production of interferon’s, interleukins, tumor necrosis factors, chemokine’s, and a variety of other mediators.” These mediators are part of a well-preserved innate immune response that is required for effective infection clearance. The term "cytokine storm" refers to a case, in which the number of cytokines released is detrimental to the host cells (Fajgenbaum & June, 2020).

In the pathophysiology of critical illness, however, distinguishing an appropriate inflammatory response from a dysregulated one has proven to be difficult. To add to the complexity, most mediators implicated in cytokine storm have pleotropic downstream effects and their biological activity is typically interdependent. These mediators' interactions, as well as the paths they inform, are not linear nor homogenous (Sinha, Matthay, & Calfee, 2020).

Several early case studies in COVID-19 reported plasma cytokine levels that were abnormally high (Qin et al., 2020). The term cytokine storm was created during the SARS pandemic caused by SARS-CoV-1, and it was associated with negative outcomes (K. J. Huang et al., 2005). SARS-CoV-2 may generate cytokine storms due to poor acquired immune responses and uncontrolled inflammatory innate responses (Hu, Huang, & Yin, 2021). A proinflammatory cytokine, interleukin-6, is implicated as a major mediator in the acute inflammatory response and the so-called cytokine storm. The cytokine storm in COVID19 is characterized by elevated IL-6 and TNF expression(Sinha et al., 2020). Hirano and Murakami have postulated that the angiotensin 2 (AngII) pathway mediates the cytokine storm that is observed in patients with COVID-19 (Hirano & Murakami, 2020).

When examining patients with severe COVID-19, , the median values of IL-6 in randomized clinical studies undertaken by the National Heart, Lung, and Blood Institute's ARDS Network are around 10- to 40-fold higher than patients with ARDS. Elevated proinflammatory cytokines, an increased incidence of shock, and poor clinical outcomes characterize the hyper inflammatory phenotype of ARDS. The features of this phenotype are the most similar to those associated with the cytokine storm. Those with the highly inflammatory phenotype of ARDS, on the other hand, have median IL-6

levels that are 10- to 200-fold higher than patients with severe COVID-19 (Calfee et al., 2014; Famous et al., 2017; Sinha et al., 2018).

As a result, the neutrophil-to-lymphocyte ratio (NLR) might be valuable in predicting the prognosis of COVID-19. Surprisingly, Ong et al (2020) discovered that most cytokines, except IL-1, increased after respiratory function nadir, implying that cytokine production may not be the main causal mechanism of COVID-19 patients' reduced respiratory function (Ong et al., 2020). Regardless, findings suggest that monitoring dynamic cytokine storms and NLR can be useful to clinicians in early detection of patients at risk of severe COVID-19 (Sinha et al., 2020).

In most patients with COVID-19, severe viral pneumonia causes primarily severe lung injury in the absence of the systemic responses previously reported in prior studies of the hyper inflammatory phenotype in ARDS (Calfee et al., 2014; Famous et al., 2017; Sinha et al., 2018). This may explain why clinical outcomes in COVID-19 are so poor in spite of relatively low circulating IL-6 levels (Sinha et al., 2018).

As a result, the term "cytokine storm" in COVID-19-related ARDS may be misleading. The appropriate management of the diverse group of patients affected by COVID-19 Incorporating a poorly defined pathophysiological entity with no clear biological diagnosis may only add to the uncertainty about how to appropriately manage this diverse group of patients. Endothelial dysfunction and systemic inflammation are expected to occur as a result of enhanced circulating mediators in the supposed cytokine storm, resulting in fever, tachycardia, tachypnea, and hypotension(Famous et al., 2017).

In critically ill COVD19 patients, the cytokine storm has been implicated in negative clinical symptoms or even sudden fatality.. Therefore, it is reasonable to state that immunotherapies such as immunomodulators and cytokine antagonists are critical in the early management of COVID-19 patients to improve survival rates (Hu et al., 2021).

2.3.6 Covid-19 Diagnostic Tests

NAATs (Nucleic Acid Amplification Tests): Swabs are obtained from the upper respiratory tract, and sputum, endotracheal aspirate, or bronchoalveolar lavage is taken from the lower respiratory tract. Bronchoalveolar lavage specimens are exclusively collected in individuals who are on mechanical ventilation. The samples are kept at 4°C.

The reverse polymerase chain reaction (RT-PCR), which includes the production of a double-stranded DNA molecule from an RNA template, is used in the laboratory to amplify genetic material from spit or mucus samples. When there is enough genetic material, the conserved sections of the Sars-Cov2 genetic code are searched (Rajnik, Cascella, Cuomo, Dulebohn, & Di Napoli, 2021).

Serological Tests: In most people who have received Covid-19 asymptomatically or symptomatically, an antibody response (IgM, IgA, and IgG) develops after a period of time. As a result, serological tests cannot be utilized to diagnose the disease in its early stages. Despite the fact that the first antibody response (IgM) takes 5-7 days, most patients show antibody positive 10 days after the onset of symptoms. The quantities of IgG antibodies are directly related to the IgM response. Following an effective immune response, IgG positive appears within 3 weeks. It's unclear how long the IgG antibodies found offer immunity .NAAT tests are negative, however serological tests on serum samples taken in instances with a strong epidemiological link to Covid-19 can be done. Serological testing can also provide a retroactive assessment of the epidemic's attack rate and severity (Peeling et al., 2020).

2.3.7 Biomarkers Used in the Monitoring of COVID-19

Biomarkers are defined as laboratory parameters used to objectively measure and evaluate biological processes or the pharmacological response to a therapeutic intervention (Guan et al., 2020).

Biomarkers must be able to be measured accurately and reproducibly. They can be used for diagnosis, staging, prognosis of disease or abnormal conditions, and outcome of interventions. Due to the imprecise definitions of Covid-19, a definitive biomarker that can help diagnosis, prognosis and treatment methods has yet to be determined. In this study, C- reactive protein, leukocyte, lymphocyte, D-Dimer, platelet count, ferritin, troponin I, and creatinine biomarkers were examined.

2.3.7.1 C- Reactive Protein

Tillett and Francis discovered C-reactive protein (CRP) in 1930. CRP was first found as a compound in the serum of patients with acute inflammation in response to pneumococcal capsule's "C" carbohydrate antibody (Scherer, Neumaier, & von Gumppenberg, 2001).

The liver produces CRP, a pentameric protein, in response to inflammation. CRP is “an acute phase reactant protein that is largely generated by the action of IL-6 on the gene responsible for its transcription during the acute phase of an inflammatory/infectious process” (Brull et al., 2003).

Both pro-inflammatory and anti-inflammatory characteristics are found in CRP. Through attachment to phospholipids, histone, chromatin, fibronectin, and phosphocholine, CRP aids in the identification and clearance of invading infections and injured cells. It has the ability to activate the traditional complement system in addition to phagocytic cells via Fc receptors, resulting in the removal of cellular debris, injured or dead cells, and foreign pathogens in an efficient manner. CRP rises immediately with the initiation of the inflammatory stimulus and diminishes following infection control, contrary to the erythrocyte sedimentation rate, which is an indirect diagnostic for inflammation. Chronic infections and chronic inflammatory diseases, as well as inflammatory arthritis such as rheumatoid arthritis, can cause chronically increased CRP levels (Ahnach, Zbiri, Nejjari, Ousti, & Elkettani, 2020).

Interpretation of CRP levels: CRP levels must be less than 0.3 mg/dL to be considered normal (level seen in most healthy adults). Normal or modest height- 0.3 to 1.0 mg/dL (may be seen in obesity, pregnancy, depression, diabetes, common cold, gingivitis, periodontitis, sedentary lifestyle, smoking and genetic polymorphisms). 1.0 to 10.0 mg/dL- elevated to a moderate degree (systemic inflammation such as RA, SLE or other autoimmune diseases, malignancies, myocardial infarction, pancreatitis, bronchitis). Greater than 10.0 mg/dL- significant rise (acute bacterial infections, viral infections, systemic vasculitis, major trauma). Greater than 50.0 mg/dL- a severe elevation (acute bacterial infections). CRP values of 50 mg/dL or higher are linked to a 90 percent chance of bacterial infection. CRP has been utilized as a prognostic factor in a variety of investigations, including hepatitis C, dengue, and malaria (Vuong et al., 2020).

According to recent research, the measured CRP level upon admission can serve as a sensitive and early indication of COVID-19 severity (Chalmers, Khawaja, Wieruszewski, Gajic, & Odeyemi, 2019; W. Chen et al., 2020; Luo et al., 2020). Furthermore, CRP levels were found to be associated with lung lesions on tomographic images (G. Wang et al., 2020). It may be unreasonable to undertake a comprehensive panel of biomarkers on admission during emergent situations, but the routine screening of CRP holds predictive value in determining disease severity and can inform care of COVID-19 patients to varying degrees (Ahnach et al., 2020).

CRP normal limit levels in clinical applications are 0-5 mg/l. In healthy people, it is usually less than 5 mg/l. It reveals that when tissue injury occurs, CRP levels rise suddenly. Its level rises in conditions like heart illness, infections, malignant tumors, and rheumatoid arthritis. When inflammation occurs, the amount rises within the first 4-6 hours, then rises again after 36-50 hours, up to 100-1000 times. Following the end of the inflammation, the level returns to normal in 3-7 days. As a result, CRP is a critical measure for determining the severity of inflammation (Young, Gleeson, & Cripps, 1991).

2.3.7.2 Leukocyte

Neutrophils, monocytes, eosinophils, basophils, and lymphocytes make up this category of peripheral blood cells. Pathogens, dead or old cells, and foreign elements are removed from the body by them (Carrick & Begg, 2008).

When leukocytes mature in the bone marrow, 80-90% of them are kept here and rise quickly in the bloodstream when needed within hours. An increase in the leukocyte count can be caused by a variety of factors. Some of these include malignant causes including leukemia, lymphoma, and myeloproliferative disorders, as well as non-malignant reasons such infection, surgery, stress, burns, exercise, emotional stress, smoking, obesity, chronic inflammatory disease, and medications (Matsumoto et al., 2019).

One of the most crucial indicators of infection is leukocytosis. Although the predicted level in bacteremia is not as high as CRP and procalcitonin, leukocytosis is generally present (Riley & Rupert, 2015).

2.3.7.3 Lymphocyte

They account for around half of all leukocytes in circulation. The total lymphocyte count in healthy people is over 1500/mm3. T lymphocytes, B lymphocytes, and natural killer (NK) cells are the three types of lymphocytes found in the peripheral circulation (Rich & Chaplin, 2019). In studies of ICU patients, it was discovered that patients with low lymphocyte counts and percentages had higher mortality and susceptibility to nosocomial infections (Lee, Choi, Kim, Lee, & Shin, 2003). There are additional studies that demonstrate lymphopenia can indicate the severity of Covid-19 illness (Tan et al., 2020).

2.3.7.4 D-Dimer

It is a fibrin degradation product generated when the endogenous fibrinolytic system breaks down thrombus (Kearon et al., 2006). In patients with a low or moderate clinical probability of PTE, D-dimer negativity is frequently utilized to rule out the disease (Donzé et al., 2008). High D-Dimer values, on the other hand, have a low specific value. The presence of high D-dimer levels can be detected for a variety of reasons (trauma, sepsis, etc). In a study of 759 patients, it was discovered that 24% of those with high D-Dimer levels (>5000 g/l) showed an elevation related with sepsis (Schutte, Thijs, & Smulders, 2016).

The binding of virus envelope glycoprotein to ACE2 is one of the pathogenetic processes of SARS-CoV-2 infections(Zhang, Penninger, Li, Zhong, & Slutsky, 2020) . ACE2 has been found on cells from a variety of tissues, including alveolar epithelial, endothelial, intestinal epithelial, and other epithelial cells (Y. Zhang et al., 2020). The extreme pro-coagulative condition could be explained by an intrinsic preference for vascular endothelial cells and the harm they cause, as well as the intense activation of inflammatory responses and coagulation pathways (P. P. Liu, Blet, Smyth, & Li, 2020).

This predisposes to systemic microthrombotic changes and may explain why severe COVID-19 patients have a high rate of multi-organ failure, DIC, and, ARDS. The D-dimer is a non-specific indicator of active coagulation and thrombin production. It is released when plasmin, a fibrinolytic enzyme, cleaves fibrin to dissolve clots, and it is a reflection of endovascular thrombotic processes (Linkins & Takach Lapner, 2017). The changes in coagulation factors, particularly D-dimer, during SARS-CoV-2 infection are

severe, consistent, and linked with prognosis, sequelae, and chronic pneumonia rates, as shown in the clinical experiences described here. Tang et al. found that non-survivors' D-dimer levels were significantly higher than survivors', and WANG et al. found that non-survivors' D-dimer levels were significantly higher than survivors' (Tang, Li, Wang, & Sun, 2020; D. Wang et al., 2020). When compared to survivors, those levels continue to rise until death. Furthermore, according to a study by Zhang et al., D-dimer levels are considerably greater in severe patients compared to non-severe patients (J.-j. Zhang et al., 2020). Huang et al. found similar results when they categorised patients depending on whether or not they were admitted to the ICU (C. Huang et al., 2020). D-dimer levels were significantly higher in COVID-19 patients with ARDS compared to those without ARDS. Additionally, patients who had ARDS and did not survive had significantly higher D-dimer levels than ARDS patients who survived, according to Wu et al.. This implies that there exists a significant association between D-dimer elevation and the development of ARDS and the progression of ARDS to death (Wu et al., 2020). The probability of pulmonary thromboembolism should be evaluated in cases of abrupt or gradual oxygen level deterioration, ARDS-compatible symptoms, evidence of right ventricular progressive overload, or diffuse perfusion alterations of micro-thrombotic etiology (Danzi, Loffi, Galeazzi, & Gherbesi, 2020). This hypothesis is supported by recent pathology studies which have demonstrated the presence of pulmonary small artery micro-thrombotic aberrations in patients who died of COVID-19. (Q. Liu et al., 2020). These findings support the use of pulmonary angio-CT scans in patients with a marked elevation of D-dimer, decay of respiratory gas exchange, and progressive signs of right sided congestive heart failure to rapidly detect potential pulmonary embolic states and to guide subsequent pharmacologic interventions. (Hunt & Retter; Zuckier, Moadel, Haramati, & Freeman, 2020).

2.3.7.5 Platelet count

Bizzozero was the first to define platelets in the late 1800s, and they were revealed to play a role in thrombosis and hemostasis(Knaus et al., 1991). Megakaryocytes are the source of platelets. Bone marrow contains the greatest number of megakaryocytes. It is also found in the spleen and lungs. The nucleus of the megakaryocyte is destroyed by macrophages by phagocytosis after it converts into a thrombocyte. Platelets are generated in the bone marrow 90% of the time and in the lungs 10% of the time (Zimmerman, Kramer, McNair, & Malila, 2006). Platelets have a 10-day circulation life

after entering the peripheral blood. They are eliminated by the reticuloendothelial system in the liver and spleen at the end of this phase (Tavassoli, 1986).

Platelets help to achieve primary hemostasis by initiating coagulation and wound healing at the site of the damage (Lassila, 2016). They can also, like neutrophils and monocytes, exert direct antimicrobial activity and have a considerable impact on the acute inflammatory response (Lassila, 2016).

In many viral infections, platelets play a role in inflammation and thrombotic reactions (Hottz, Bozza, & Bozza, 2018). Because of massive platelet activation and thrombus formation, COVID-19 patients often have a low platelet count, which indicates increased consumption. It should be noted that activated platelets also express a functionally active tissue factor (TF) in this regard (Camera et al., 2015). Platelets not only aggregate in the hemostatic process to provide the negatively charged phospholipid bilayer for the assembly of coagulation factors, but they can also initiate the coagulation cascade. Finally, the cytokine storm associated with severe COVID-19 is characterized by increased plasma concentrations of several cytokines, including interleukin (IL)-6, which is thought to be a pathological underpinning for disease progression and multiorgan failure in these patients (Mehta et al., 2020). Anti–IL-6 receptor (IL-6R) inhibition with tocilizumab appears to be effective in preclinical investigations (Guaraldi et al., 2020; Toniati et al., 2020). However, in this clinical scenario, the effect of cytokine release on platelet and endothelial activation is almost completely unknown. As a result, while information about COVID-19-related coagulopathy and thrombosis risk is quickly becoming available, there is insufficient high-quality evidence to recommend antithrombotic therapy (Canzano et al., 2021).

2.3.7.6 Ferritin

Laufberger, a French chemist, discovered ferritin in 1937 after isolating it from horse spleen tissue (Laufberger, 1937). It's a protein found in all cells of the body, but it's most prevalent in bone marrow macrophages, the spleen, and the liver. It guarantees that iron is stored safely and conveniently in the cell. It protects cells from the toxicity of iron radicals and the interaction of iron with hydrogen peroxide (Cullis et al., 2018).

Various inflammatory and infectious events can cause an increase in serum ferritin levels. The stimulating action of IL-1a,b, IL6, IL18, tumor necrosis factor-a, interferons,

and macrophage-colony stimulating factors is suggested to be the cause of hyperferritinemia (Tripathy, Panda, & Das, 2015).

Ferritin, through direct immuno-suppressive and pro-inflammatory actions, is a significant modulator of immune dysregulation, especially in extreme hyperferritinemia, leading to a cytokine storm (Abbaspour, Hurrell, & Kelishadi, 2014). Associations have been observed between fatal COVID-19 cases and cytokine storm syndrome, implicating this syndrome as a moderating factor in illness severity (Vargas-Vargas & Cortés-Rojo, 2020). Many people with diabetes have high serum ferritin levels, and it is well established that they are more likely to develop severe COVID-19 symptoms (Association, 2020).

There exists variation in the levels of serum ferritin in individuals with severe and very severe COVID-19, with individuals classified as having "very severe COVID-19" demonstrating significantly higher serum ferritin levels than those classified as having "severe COVID-19" (Zhou, She, Wang, & Ma, 2020). Another study determined that "ferritin levels were high at admission to the hospital and during the hospital stay in individuals who died with COVID-19. After day 16 of hospitalization, the median serum ferritin levels in these patients exceeded the upper limit of detection, indicating that ferritin levels rose non-stop" (F. Zhou et al., 2020).

Chen et al. also looked at the clinical features of 99 individuals, finding that "63 of them had serum ferritin levels that were significantly higher than the normal range" (N. Chen et al., 2020). Autopsies of 12 individuals who died as a result of SARS-CoV-2 infection also revealed elevated ferritin levels(Fox et al., 2020). ferritin levels in the peripheral blood of 69 patients with severe COVID-19 were found to be higher than those classified as having less severe COVID-19. It is reasonable to conclude that serum ferritin levels are closely associated with the severity of COVID-19 (T. Liu et al., 2020).

Finally, laboratory results in COVID-19 patients demonstrated increased inflammatory markers, including ferritin, consistent with a cytokine storm, which has been associated with critical and life-threatening illness (Mehta et al., 2020).

Treatment with iron chelators could be a viable option for lowering ferritin levels. Deferoxamine, a non-toxic iron chelator that has been clinically authorized by the FDA and is beneficial for long-term iron chelation therapy in beta-thalassemia and other

illnesses involving iron overload(Mobarra et al., 2016), may be a good candidate. Manipulation of dietary iron levels should also be investigated because it has been proven to affect blood ferritin levels. As a result, they expected that this could prevent COVID-19 exacerbation, particularly in people with morbidities associated with increased ferritin levels, such as diabetes(Khalil et al., 2018).

2.3.7.7 Troponin I

Troponins are calcium-dependent structural proteins in skeletal and cardiac muscle that govern the interaction between actin and myosin. Troponins are divided into three subgroups: Troponin I (24 kDa), Troponin T (37 kDa), and Troponin C (18 kDa). Sensitive troponin T and I assays are based on specific antibodies against cardiac isoforms (Christenson et al., 1998).

In the early 1990s, biochemical examination of myocardial necrosis markers, especially cardiac troponins, became popular in the diagnosis and prognostication of patients with acute myocardial infarction. Troponin levels, in combination with clinical and electrocardiographic evidence, are now used to diagnose and treat acute coronary syndromes(Thygesen et al., 2010).

Troponin levels that indicate myocardial injury rise and fall often in patients with acute respiratory infections and are associated to illness severity. When using a high sensitivity cardiac troponin (hs-cTn) assay, abnormal troponin results are common in those who have COVID-19 infection. Detectable hs-cTnI was found in most patients with COVID-19, and hs-cTnI was significantly raised in more than half of the patients who died, according to a recent article detailing the clinical course of COVID-19 patients. Although the processes causing cardiac harm in persons infected with COVID-19 are unknown, direct ("noncoronary") myocardial damage is very certainly the most common cause, as it is in other severe respiratory infections. Given the widespread distribution of ACE2, the SARS-binding CoV-2's site, in cardiomyocytes, some have speculated that myocarditis could explain the spike in hs-cTn in some instances, especially because abrupt left ventricular failure has been reported in some case (Januzzi, 2020).

These studies support the hypothesis of measuring cardiac damage biomarkers both immediately after hospitalization for SARS-CoV-2 infection, as well as throughout the hospital stay, to identify a subgroup of patients who may have cardiac injury and predict the progression of COVID-19 (Lippi, Lavie, & Sanchis-Gomar, 2020).

Furthermore, as Varga et al (2020) have established, an elevation in troponin may be linked to clinical disorders other than heart disease, such as pulmonary embolism, renal failure, or a general involvement of endothelial cells (Varga et al., 2020).

2.3.7.8 Creatinine

The end products of nitrogen metabolism in humans are blood urea nitrogen (BUN) and creatinine (Cr). They are easily filtered from the nephrons since they are tiny molecules. BUN is usually reabsorbed in the range of 30% to 40% from tubules, whereas Cr is not efficiently reabsorbed(Matsue et al., 2017; Qian, Tang, & Yan, 2019). In patients with acute heart failure(AHF) , studies demonstrate that the damaged neurohormonal system is responsible for the reabsorption process (Matsue et al., 2017). Other studies have found that the BUN/Cr ratio is more useful than either BUN or Cr alone in predicting the course of AHF patients(Takaya et al., 2015; Tung, Chang, Chen, & Chu, 2015).

The novel coronavirus uses angiotensin-converting enzyme 2 (ACE2) as a receptor to enter cells (P. Zhou et al., 2020). ACE2 is expressed to a much greater degree (100 times) in the kidneys than in the lungs, according to recent human tissue RNA sequencing data (T. Wang et al., 2020). Coronavirus can alter kidney function by directly accessing renal cells in an ACE2-dependent manner30 and stimulating the renin-angiotensin-aldosterone system (RAAS) through the systemic effects it produces. The RAAS causes passive reabsorption of BUN by increasing water and sodium absorption in the kidney tubules (Murata et al., 2018; Takaya et al., 2015). Renal vasoconstriction is caused by these systemic effects, and as a result, glomerular filtration and BUN excretion are diminished (Murata et al., 2018). Regardless, as Cr is filtered through the glomeruli and not reabsorbed, the BUN/Cr ratio rises (Qian et al., 2019).

The BUN/Cr ratio and the NLR may be linked to illness severity, and routine use of these measures in disease evaluation may be useful (Ok, Erdogan, Durmus, Carkci, & Canik, 2021).

2.3.8 COVID-19 and Oxygenation

The respiratory assistance is firmly supplying patients, which is the most crucial of the basic health difficulties in the Covid-19 outbreak. Our knowledge and experience with ARDS guided the care of critically ill individuals during the outbreak. However, amid this situation, patients and clinicians are being pushed into unexplored regions. Our fundamental goal throughout this process, from service follow-up to critical care, has been to find a therapeutic technique that allows patients to adjust to the oxygen levels we want and give them.

2.3.8.1 Conventional Oxygenation Therapy

Nasal cannulas with low oxygen flow, basic masks, and masks with reservoirs are among the equipment used in service follow-ups. The nasal cannula can deliver up to 6 liters of oxygen per minute. In facilities lacking HFNO, it is required to be utilized during oral nutrition in patients with critical oxygen levels.A basic face mask is a non-reservoir mask that gives 5-8 liters of oxygen per minute. Air-entraining techniques can increase the percentage of oxygen inhaled (high flow rate Venturi mask). With these technologies, a simple face mask may achieve a maximum oxygen concentration of 60%(Weekley MS, 2022).

The reservoir bag is a bag that is linked to non-rebreathing masks. Through a one-way valve, oxygen is sucked into the mask to fill it. On both sides, there are ports for exhalation, preventing the patient from inhaling again. Oxygen can be delivered to the patient at a rate of up to 10-15 liters per minute using reservoir masks. The oxygen concentration that reaches the patient might range from 60% to 95% (Weekley MS, 2022).

2.3.8.2 High Flow Nasal Oxygen Therapy

A high-flow nasal cannula is one that humidifies oxygen and delivers flow rates that are higher than the patient's inspiratory pressure. The HFNO technique allows the patient to eat and communicate while still getting enough oxygen (Wong et al., 2019). When low flow oxygen therapy approaches are ineffective in Covid-19 patients with acute hypoxemic respiratory failure, HFNO may be considered.

In comparison to other NIMV methods, HFNO can increase oxygenation and carbon dioxide clearance. It has a gas flow rate of up to 60 l/min with 100% FiO2. When compared to conventional ways, it has been demonstrated to reduce the need for IMV and NIMV. Because of the high current, it has a greater impact on aerosol and droplet generation than traditional approaches. In terms of infection dissemination, however, there is no credible study with COVID-19 (Agarwal et al., 2020). It's possible to use NIMV with this. Because of its high cost, we only utilized it for a small number of patients during the pandemic.

2.3.8.3 Non-Invasive Mechanical Ventilation Therapy

Methods that offer positive pressure oxygen assistance to the patient during inspiration are included in non-invasive mechanical ventilation. In the early stages of community-acquired pneumonia or ARDS, it is used on fully cooperative patients with no substantial organ failure. In hypoxemic respiratory failure, the ERS/ATS clinical practice recommendations propose using NIMV as a prophylactic measure to avoid intubation (Rochwerg et al., 2017).

Nasal masks, oro-nasal masks, mouthpiece masks, full-face masks, and helmet type equipment are examples of non-invasive ventilation application equipment. Clinicians have benefited from previous expertise in determining which patients should get NIMV in the event of COVID-19-induced acute respiratory failure. The patients were thought to have two distinct phenotypes. COVID-19 pneumonia with the Berlin ARDS criteria has "silent" hypoxemia (Type L) with normal lung compliance in more than half of the cases. Unless dyspnea is apparent, just oxygen therapy is suggested for this patient. HFNO and NIMV therapies can be employed if the patient has developed dyspnea. If, despite the HFNO and NIMV procedures, there is an increase in respiratory effort and worsening in oxygenation, a switch to the IMV method should be considered (Gattinoni et al., 2020).

Acute hypoxemic respiratory failure is defined by high respiratory frequencies and a PaO_2:FiO_2 ratio of less than 200mm/Hg in the absence of chronic respiratory distress and pulmonary edema in the patient (Girou et al., 2000). The HFNO and NIMV therapy modalities are used at this point. For NIMV, the optimal tidal volume is 6-8 mg/kg. Excessive tidal volumes are linked to increased respiratory effort and mortality rates

(Grieco et al., 2021). Positive end-expiratory pressure (PEEP) has been demonstrated to enhance arterial oxygenation in patients with acute hypoxemic respiratory failure caused by pulmonary edema, atelectasis, or pneumonia by boosting functional residual capacity (Navalesi P, 2013).

In Covid-19 patients, NIMV treatment with 5-10 cmH2O PEEP considerably reduces inspiratory respiratory effort when compared to normal oxygen therapies (Grieco et al., 2021).

The first step in deciding between NIMV approaches is to look at patient compliance and physician experience. According to some research, Helmet should be the first line of treatment for acute respiratory failure caused by Covid-19 pneumonia. The belief that wearing a helmet inhibits the dissemination of infection-related aerosol and so transmission is commonly shared(Ferioli et al., 2020; Radovanovic et al., 2020).

The management of NIMV is not without its disadvantages. Excessive swelling of normal alveolar gaps can increase physiological dead space and impair tissue perfusion, in addition to the danger of barotrauma. In patients with defective left ventricular movements, high peep values have a deleterious impact on cardiac output (Navalesi P, 2013).

The Helmet approach has a bigger internal volume than the full-face mask. CO2 rebreathing may be facilitated by this internal volume (Rodriguez, Papadakos, Carron, Cosentini, & Chiumello, 2013).

The volume of fresh gas going through the Helmet and the amount of CO2 produced by the patient are the two most important parameters in CO2 rebreathing. CO2 rebreathing is prevented at this stage because to the strong flow via the ventilator during CPAP application through helmet. Patients often tolerate a helmet better than a face mask(Patroniti et al., 2003).

It allows patients to be fed and watered orally without having to remove their mask for a few days, which promotes patient comfort, minimizes the risk of face decubitus, and allows them to be fed and hydrated orally during CPAP treatment(Chiumello et al., 2003).

The decision to provide NIMV should be based on peripheral oxygen saturation, respiratory rate, and the PaO2/FiO2 ratio (Guan et al., 2020). It's important to remember that dehydration, iatrogenic diarrhea, and metabolic alkalosis related to hypoalbuminemia can cause false peripheral oxygenation and low respiratory rates (Cunningham, Robbins, & Wolff, 2011). The hemoglobin-oxygen disassociation curve shifts to the left when blood gas pH levels rise, increasing oxygen affinity. It lowers the maximum amount of hypoxia that the tissues can tolerate (Easton, Slykerman, & Anthonisen, 1986). To protect patients against the necessity for a delayed IMV, a multidisciplinary approach is required.

If HFNO is missing or inefficient in Covid-19 patients with acute respiratory failure, the Surviving Sepsis Campaign (SSC) advocates the use of NIMV in its newest guideline (Poston, Patel, & Davis, 2020).

2.3.8.4 Invasive Mechanical Ventilation Therapy

During the SARS-CoV2 infection process, IMV techniques are employed in patients who do not respond to conventional and NIMV treatments. According to epidemiological studies, different areas make significantly varied mechanical ventilation decisions in patients undergoing intensive care treatment. In a study conducted in China, 29.1% of patients receiving critical care treatment received IMV treatment, whereas 89.9% received IMV treatment in a study conducted in the United States (Y. Wang et al., 2020). There are several issues that are not related to the infection. To begin with, it has been observed that clinics are unable to draw on their previous experience in managing the hypoxemia process caused by ARDS and are forced to make distinct clinical decisions and initiatives. Beyond the clinician's preferences, resource constraints can also influence their decisions. As a result, we do not expect clinicians to incorporate a set of widely accepted criteria in the IMV decision that COVID-19 patients would receive. It is a multidisciplinary approach that will keep clinicians from deciding on mechanical ventilation too early or too late.

According to Papoutsi et al. (2021), in their systemic review study to consider if there is effect of early intubation versus late on clinical outcomes of critically ill Covid-19 patients, early intubation was defined as the intubation during first 24 hours post ICU admission, while late intubation was defined as intubation at any time after 24 hours of ICU admission.

Studies have advocated for the use of mechanical ventilation early in the course of COVID-19 patients' disease to prevent them from advancing from moderate illness to more serious lung injury. These findings show that a high level of spontaneous inspiratory effort could result in P-SILI (patient self-induced lung damage) (Marini & Gattinoni, 2020). P-SILI is similar to ventilator-induced lung damage (VILI), according to previous experience and clinical research (Tobin, 2010). However, the data are insufficient to make an accurate conclusion about early intubation. Intubated patients have higher rates of immunosuppression (37.5% -6.7%) and lower PaO2/fiO2 (122 vs 177) than non-intubated patients, according to research (Carteaux et al., 2016).

At this stage, it is clear that the choice to intubate should be determined on a patient-by-patient basis. It has been demonstrated that individuals with acute respiratory failure who do not respond to NIMV therapy have larger tidal volumes than those who do (Carteaux et al., 2016). Close monitoring of the PaO_2:FiO_2 ratios, as well as rising tidal volume and respiratory rates, is a sign that intubation should be done as soon as possible. Increased P-SILI formation and VILI formation after ventilator attachment result from an unmet need for IMV and persistence in non-invasive methods.

Recommended Strategies in mechanical ventilation, for Covid-19 patients to protect lung and prevent VILI, include low tidal volume 4 – 8 ml\kg, sufficient PEEP to prevent lung collapse and keep it open, low airway pressure less than 30 cmH2O, respiratory rate up to 35 per minute to achieve normal PH 7.30-7.45, and can allow permissive hypercapnia but not to make more acidosis than 7.15, and titrate FiO_2 to achieve PaO_2 55-80 mmHg and SpO_2 88-95%. (Lentz et al., 2020)

Clinicians prefer IMV to NIMV because they believe NIMV induces aerosol spread and raises the danger of transmission to healthcare workers. Although early intubation is not beneficial to the patient, it does cause lots of new problems. Hypotension, ventilator-associated infection, balance abnormalities, and longer sedation durations are among

consequences of invasive mechanical ventilation (Arulkumaran, Brealey, Howell, & Singer, 2020). IMV techniques have been shown in trials to have no effect on mortality in Covid-19 patients (Grasselli et al., 2020).

2.3.8.5 Prone Position and Oxygenation

The prone position is one of the ways used to treat ARDS patients. It is utilized as an adjuvant therapy to increase ventilation. It can be used to treat patients with low tidal volumes (6-8 ml/kg) and to infuse neuromuscular blockers. The intermittent prone position enhances oxygenation and survival in ARDS patients (PIEHL & BROWN, 1976). Oxygenation and aeration in the dorsal lung regions increase in the prone posture. End-expiratory lung volume and elasticity of the chest wall increase. Tidal volume improves when alveolar shunt diminishes (Kallet, 2015).

It's critical to follow the right treatment regimen when it comes to patient selection and prone positioning. Prone posture procedures have been proven to reduce mortality in ARDS patients during the first 48 hours of hypoxemia (Mora-Arteaga, Bernal-Ramirez, & Rodriguez, 2015).

The prone posture, as well as favorable benefits on ARDS patients, should be considered. Patients with a ventilator in the prone posture, an inadvertent tracheal tube, the cradle or escape of the catheter and the chest tube, pressure sores, and an endotracheal tube in the mouth are at danger, according to (McCormick & Blackwood, 2001).

Before deciding on a position, the clinician should consider concerns such as pulmonary edema, alveolar collapse, high intraabdominal pressure, and impaired chest wall compliance. Because to the procedural complications, routine prone posture is not suggested in obese patients. For the improvement of oxygenation in Covid-19 patients, it is recommended to employ conventional, non-invasive, and invasive mechanical breathing therapy (Golestani-Eraghi & Mahmoodpoor, 2020).

2.3.8.6 Inhaled Vasodilators

Inhaled pulmonary vasodilators were used in the treatment of refractory hypoxemia, especially in severe ARDS patients with PaO2/FiO2 ratio less than 100, after failure of conventional management to treat it. Inhaled Nitric Oxide (iNO) can dilate alveolar capillaries by diffusion through endothelial walls, resulting in improved ventilation/perfusion ratio and PaO2. Despite localized effect and short half-life, iNO can cause methemoglobinemia and acute kidney injury. Moreover, iNO is expensive and need special delivery system which make inhaled Prostacyclines better because it is cheaper and can be delivered by ventilator nebulizer. Prostacyclines improves refractory hypoxemia especially which accompanied by pulmonary hypertension and right sided heart failure, however it has a rare adverse effect of platelets aggregation inhibition. (Cherian et al., 2018)

Despite of no mortality benefit proved, inhaled pulmonary vasodilators were suggested as a rescue treatment for refractory hypoxemia in Covid-19 patients while a rapid improvement of oxygenation should be monitored, and routine use of this therapy is not recommended. (Lentz et al., 2020). DeGrado et al., (2020) and Lubinsky et al., (2022) demonstrate that inhaled pulmonary vasodilators do not improve gas exchange in Covid-19 patients who complain of refractory hypoxemia.

2.4 Previous Studies

Krause, et al. (2020) conducted an observational cohort study that aimed to examine the relationship between mortality of COVID-19 patients who required invasive mechanical ventilation and their characteristics. Eighty-five COVID-19 patients on invasive mechanical ventilation in multicenter in United States were observed, retrospectively from date of admission and prospectively for 30 days, for their demographic data, chronic morbidities, disease progression and treatment interventions, and its association with 30-days mortality. They found the 30-days mortality of these patients was 23.5 % (n=20), and that the age, malignancy, insurance, and ethnicity were linked with increased mortality rate among these patients.

Auld et al. (2020) conducted a retrospective cohort study that aimed to determine the ICU and invasive mechanical ventilation mortality rates among critically ill COVID-19 patients who were admitted to ICUs of three hospitals in Georgia – United States. During the last month of the data collection day, 217 patients were observed retrospectively for their characteristics such as sociodemographic data, chronic diseases, initial findings in ICU and SOFA score, intensive treatments, some measurements like the initial ratio of PaO2:FiO2, and some lab tests such as D-Dimer and C-Reactive Protein and they tried to examine the association between these data and the ICU and IMV mortality rates. They concluded that ICU mortality was 28.6% and IMV mortality was 35.7%, and there is significant association between mortality and older age, lower body mass index, chronic renal disease, higher SOFA score, lower Pao2/Fio2 ratio, higher D-dimer and higher C-reactive protein, and they found that mortality rate increased in patients who required mechanical ventilation and renal replacement therapy, and who received vasopressors and vasodilators therapy.

Oliveira et al. (2021) conducted a retrospective cohort study that aimed to describe the clinical characteristics and outcomes for severe Covid-19 patients who were admitted to ICUs in multicenter in Florida-United states. They collected data from electronic health record, for all Covid-19 patients who were admitted to ICUs of targeted hospitals between March 11 to May 18 of 2020, which included demographic data, chronic diseases, triage vitals, baseline laboratory tests, pharmacological treatments, treatments interventions (IMV and CRRT), IMV settings and their outcomes such as length of stay and mortality. They found that 83.2% of 131 patients required IMV and 6.9% received ECMO, and IMV length of stay was 14 days for survivors and 8.5 days for non-survivors, while ICU length of stay was 14 for survivor and 9.5 for non-survivors, and 21 for survivors and 10 for non-survivors was the length of stay in hospital. Regarding mortality, ICU mortality rate was 21.6% and IMV mortality rate was 26.5%.

King C.S. et al. (2020) conducted a study that aimed to investigate the clinical characteristics and outcomes of COVID-19 patients treated with invasive mechanical ventilation. They gathered data for all COVID-19 positive patients who were put on IMV for acute respiratory failure at the Inova Health System in Northern Virginia between March 5, 2020 and April 26, 2020, by reviewing their electronic health records, which include demographic data (race, ethnicity, age, gender), comorbidities, the

laboratory data (initial and highest values of WBC, ferritin, CRP and D-Dimer), respiratory therapies (muscle relaxant, prone positioning, inhaled pulmonary vasodilators, and ECMO), COVID-19 pharmacological therapies (use of toculizumab, hydroxychloroquine, remdesivir, convalescent plasma), ventilator settings (highest PEEP, highest FiO_2 required and lowest PO_2:FiO_2 ratio), and patients outcomes (complications such as secondary infections and acute kidney injury and if they needed CRRT, length of stay in hospital, survived or died, and cause of death). They found that from 1023 COVID-19 patients who were admitted to target hospitals, 164 (16%) patients needed IMV and 94 (57.3%) of them survived, and by comparing survived patients with died, they found that died patients were older age, had higher initial D-Dimer and peak Ferritin and had lower PO_2:FiO_2 ratio. On the other hand, "there was no significant difference in peak d-dimer, initial ferritin, or initial or peak CRP and WBC, also in intubation timing." The mean length of stay in hospital was 24.5 days for survivors and 11 days for died patients, and on mechanical ventilator was 14.6 days for survivors and 9.3 days for died patients. The most common cause for death was hypoxemic respiratory failure.

Estenssoro E. et al., (2021) conducted a prospective multicenter cohort study in Argentina to illustrate clinical features, ventilator parameters and treatments for COVID-19 patients who underwent invasive mechanical ventilation and find out the outcomes and intra hospital mortality. They developed electronic forms and paper forms for entering data by the investigators who collect data for COVID-19 patients who required IMV in different ICU's and followed them until discharge of hospital or death. Collected Data included several variables such as patient's demographics and characteristics (date of admission, age, sex, BMI, APACHE II score, SOFA score, smoking status, alcohol consumption, need for vasopressors, laboratory results) at admission, also signs and symptoms at the onset of disease, number of days from onset to hospital admission, use of respiratory support (NIV, HFNC) and number of days from hospital admission to intubation. Additionally, mechanical ventilator parameters were recorded at day 1, 3 and 7 of ICU admission such as PaO_2:FiO_2 ratio, tidal volume in ml/kg, FiO_2, respiratory rate, PEEP, compliance, driving pressure and arterial blood gases (ABG's). Moreover, complications were observed such as ARDS, acute kidney injury, septic shock, maximum fever value, bacteremia, ventilator associated pneumonia (VAP) and venous thromboembolism (VTE). Cause of death was selected from nine

causes previously determined include refractory hypoxemia, septic shock, multiorgan dysfunction syndrome, acute myocardial infarction, stroke, pulmonary embolism, acute heart failure, do-not-resuscitate order and other. Hospital and ICU length of stay and IMV duration were recorded by investigators.

They found that from 63 ICU's, 1909 patients required IMV, and their median age was 62 years. Most of them were male (67.8%), and 91.7 % had comorbidities such as hypertension (46.9%), obesity (44.4%) and diabetes (29%), vasopressors were used in 49.2 %, the most lab values variations were elevated WBC, LDH, D-Dimer, ferritin, and lactate. IMV median duration was 13 days and mechanical ventilator parameters were as followed (median tidal volume was 6.1 ml/kg, median PEEP was 10 cmH2O, PaO_2:FiO_2 median ratio was 160, compliance 36 ml/cmH_2O, plateau pressure was 23 cmH_2O, FiO_2 was 60%). Intra-hospital mortality for COVID-19 patients who required IMV was 57.7%. Non-survivors were significantly older in age, higher Charlson score, APACHE II and SOFA scores, had comorbidities such as (cardiovascular disease, chronic renal disease, immunosuppression, smoking, hypertension, diabetes, ischaemic heart disease, heart failure and malignancy), and use vasopressors more than survivors. However, survivors had higher PH, and ratio of PaO_2:FiO_2, and had lower $PaCO_2$ and lactate concentration. PEEP and Tidal volume were same in both survivors and non-survivors but the increase in tidal volume from day1 to day 7 was less in non-survivors. Additionally, both groups complained about frequent complications such as ARDS (87.6%), septic shock, AKI, and VTE (8.9%). Treatment strategies observed as followed, prone positioning used in 61.6% and more frequent in non-survivors, ECMO used just for one patient and survived and 25% of patients underwent tracheostomy which more frequent in survivors. Hospital and ICU length of stay and IMV duration were shorter in non-survivors.

Murthy et al., (2021) conducted an observational cohort study in Canada to describe the characteristics of COVID-19 patients who admitted to 32 hospitals, to investigate factors affect the outcomes and to compare with international outcome. They gathered data for all COVID-19 patients who admitted to selected hospitals between January 24th and July 7th of 2020, data were gathered and filled in tools and forms from admission and followed to discharge from hospital or death, which include demographic data, comorbidities, treatment strategies and the outcomes such as in-hospital mortality and

length of stay in ICU and hospital. They found that 328 patients admitted to ICU from 811 admissions in selected duration, 61% of all patients were male, median age was 64 years, the most common symptoms on admission were fever (73.7%), SOB (67.1%), cough (48.6%), malaise (43.3%) and diarrhea less common 26.1%. Patients had comorbidities as followed HTN (44.5%), diabetes (25%), cardiac disease (21%) and CKD (12.6%), and different pharmacological treatments were given such as antibiotics to 78.9% of patients, oxygen (74.2%), antiviral medications (21.2%) and 18.6% of patients who were not admitted to the ICU received systemic corticosteroid while 28.9% of ICU patients received it. Intra-hospital mortality was 20.5%, ICU mortality was 26.1% and 31.2% who underwent invasive mechanical ventilation had died, 69.2% of patients who treated with ECMO and 46.9% of patients who treated with CRRT also had died. There was a significant relationship between mortality and older age and present of comorbidities especially chronic pulmonary disease and chronic renal disease.

Chapter Three

Methodology

3.1 Study Design

The study used a retrospective observational cohort design to follow up on data from medical records that were related to the survival rates of COVID-19 patients in ICU who were connected to IMV.

This design has several advantages, including the fact that cohort studies in general allow the researcher to study multiple exposures and outcomes at the same time, whereas the benefits of retrospective design include time and cost savings, as the researcher conducts the desired investigation using an already existing database (Euser, Zoccali, Jager, & Dekker, 2009).

3.2 Site and Setting

The research was carried out in three medical centers in Palestine: Palestine Medical Complex - Ramallah, Hugo Chavez (Venezuelan Palestinian Hospital), and St. Joseph Hospital - Jerusalem. These hospitals reflect two important dimensions: they have the highest number of COVID-19 admissions in the targeted area, and they have both governmental and non-governmental health settings. Communication and data collecting are also easier at these institutions; nevertheless, each hospital has its own computerized health system, this necessitated specialized training for data collectors.

3.3 Sample Population and Sampling

The participants in this study include all COVID-19 positive patients that were admitted to ICU departments, intubated, and started on IMV in the hospitals that were included. Furthermore, the sample was targeted, consisting of all patients admitted between August 1st, 2020, and April 30th, 2021.

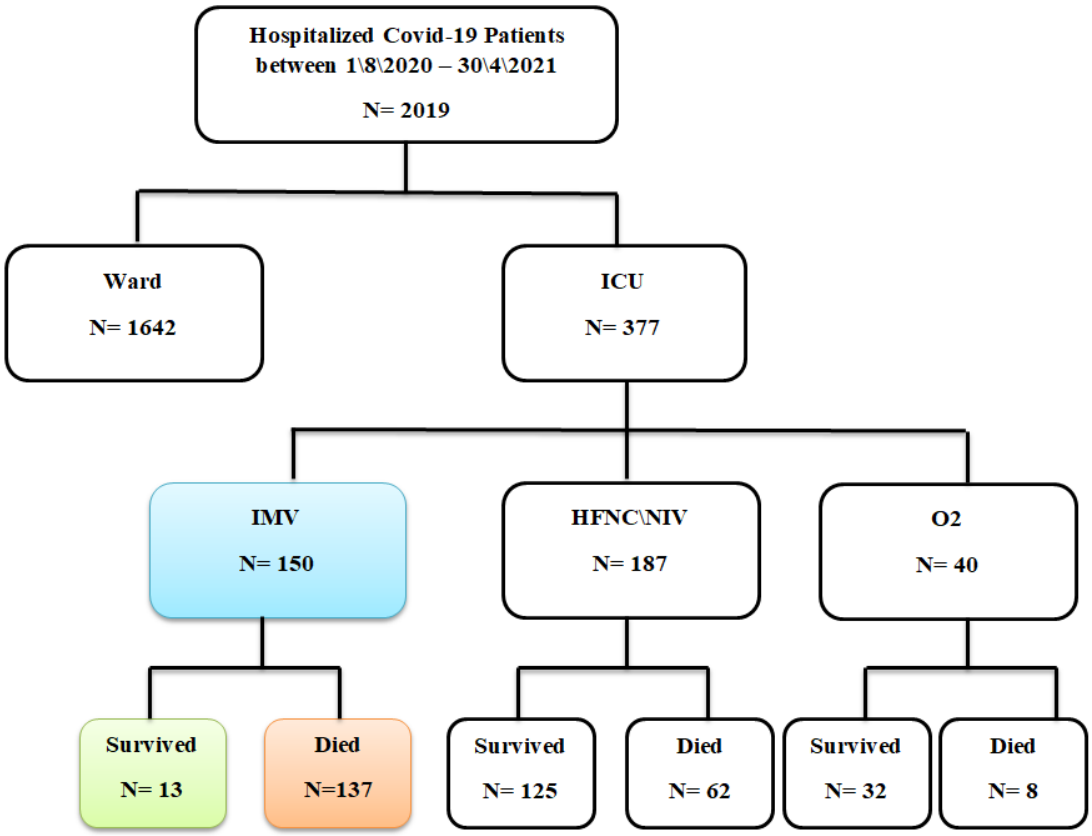
3.4 Inclusion and Exclusion Criteria

Patients with positive COVID-19 (proven by PCR test) were included in the study if they were over the age of 18, regardless of gender or educational level. They were also admitted to the ICU departments of the targeted hospitals, intubated, and started on IMV after non-invasive or standard oxygenation methods failed.

On the other hand, patients under the age of 18, or who were outside of the ICU department, not intubated, or outside of the targeted hospitals were excluded. Figure (3.1) clarify study flow diagram.

Figure 3.1

study flow diagram of Covid-19 patients who admitted to ICU and underwent IMV.



3.5 Period of the Study

From September 2021 to March 2022, data were extracted for all COVID-19 patients who were intubated to IMV and admitted to three COVID-19 designated ICU's at three hospitals between August 1st, 2020 and April 30th, 2021, which represents the highest percentage of the second wave of COVID-19 in Palestine, which was also associated with the highest number of complicated cases admitted to ICU. It is also a good time frame for gathering a sufficient number of patients to meet the quantitative sample size criterion.

3.6 Data Collection Tool and process

After reviewing related literature (Krause, Douin, Kim, Fernandez-Bustamante, & Bartels, 2020; Auld et al., 2020; Oliveira et al., 2021) the researcher developed a data sheet (Appendix 1), which was divided into four sections. The first section of the sheet contains 4 questions about basic demographic information such as gender (Male, Female), age, weight, and height, while the second section focuses on the patients' clinical characteristics, such as specific co-morbidities (HTN, DM, COPD, etc.), initial and peak readings of selected blood tests (WBC, CRP, D-Dimer, ABG's, and so on). The third section is concerned with the respiratory and pharmacological treatment approaches used for patients, with the respiratory dimension involving specific treatment options (prone position, ECMO, etc.), intubation timing (early or late), minimum and maximum ventilation parameters used during IMV, The pharmaceutical dimension deals with the use of certain drugs (remdesivir, corticosteroids, and so on). The fourth section is concerned with the patients' outcomes, including whether there were any complications (ARDS, AKI, septic shock, etc.), length of stay in the hospital, ICU, and on IMV, and whether they survived or not, as well as the cause of death, which was determined through chart review. The data sheets then divided into two major groups based on the patients' survival or mortality status, and then data filled in tables consist of four columns: variable, all sample, survived and deceased.

Data was obtained from patients' computerized records, with the researcher retrieving data from patients' records in each institution using an authorized account after receiving approval. Data retrieval was similar between different Health Information Systems (HIS) of hospitals based on the researcher's clinical expertise and previous training, whereas the researcher did it all by himself for all hospitals. Missing data from the patient's records is left blank on the data sheet and is treated as a missing value by statistical analysis software, that statistical measures were done according to “all sample” value.

3.7 Validity and Reliability

The data sheet was developed by the researchers and then reviewed by critical care experts, including an intensivist doctor who is a member of the national scientific committee and has supervised the treatment of critically ill Covid-19 patients in ICUs, and an academic doctor who specializes in critical care nursing. Their comments were

considered when developing the data collection tool to its final form in order to collect data in the most appropriate way for obtaining the best possible data and for the data analysis process.

3.8 Statistical Analysis

The data acquired from the medical records analyzed using The Statistical Package for Social Sciences (SPSS) software on Windows operating system, using the descriptive and analytical (inferential) functions. The descriptive results included generating frequencies, percentages, mean and standard deviation for the variables related to patients' demographic data, comorbidities, clinical presentation, initial and peak laboratory tests, pharmacological and non-pharmacological treatment approaches, complications, and length of stay, with the differences between survived and deceased patients. Moreover, analytical results included the differentiation between survived and deceased patients in their data, including all of the mentioned variables, using chi-square test for the differentiation according to categorical variables and independent sample t-test for the differentiation according to scale variables. Also, for the purpose if predictability testing, binary logistic regression was used to investigate the predictors of the significantly correlated variables with the survival state of patients. The binary logistic regression was used because survival is a dichotomous categorical variable (i.e., has two valid options: survived and deceased). In the binary logistic regression, the beta value (B) was addressed to investigate for the direction of the prediction, in which positive value indicates higher survival rate among higher incidence of the predictor, and vice versa. Moreover, p-value was addressed to investigate the significance of the prediction, while Exp(B) was addressed as the odds ratio (OR) for the power of prediction likelihood, with 95% confidence interval (CI) for the OR.

3.9 Ethical Considerations

The research presented in this thesis was carried out in compliance with the Helsinki Declaration. The approval to begin data collecting was acquired from the Institutional Review Board (IRB) (Appendix 2) of the Faculty of Medicine and Health Sciences at An-Najah National University. After that, a facilitating paper was obtained from the Palestinian Ministry of Health in order to collect data from governmental hospitals, while facilitation papers were obtained from each non-governmental hospital for its own purposes. Furthermore, the data was kept anonymous; participant information and the

results obtained were retained in a secure location where no one could access them; and the data was collected only for research purposes.

Chapter Four

Findings of the Study

4.1 COVID-19 Patients Survival Rate and Respiratory Support Prevalence

A total of two thousand and nineteen COVID-19 patients were admitted to the target Palestinian hospitals in the second wave of pandemic from August 1st of 2020 to April 30th of 2021. The prevalence of ICU admission was 18.7% (n=377) of total admissions and 170 (45.1%) COVID-19 patients of them survived to hospital discharge. While 150 patients required invasive mechanical ventilation which represents 39.8% of COVID-19 patients who were admitted to ICU and 13 (8.7%) patients of them survived to hospital discharge. The ICU mortality and IMV mortality were 54.9% and 91.3%, respectively. Table 4.1 described the frequency and percentage of survived and deceased Covid-19 patients who admitted to ICU and their usage of respiratory support.

Table 4.1

Covid-19 patients who admitted to ICU and respiratory support strategies.

Respiratory Support Strategy	Total ICU 377 (18.7%)	Survived ICU 170 (45.1%)	Died ICU 207 (54.9%)
IMV	150 (39.8%)	13 (8.7%)	137 (91.3%)
HFNC/NIV	187 (49.6%)	125 (66.8%)	62 (33.2%)
O2	40 (10.6%)	32 (80%)	8 (20%)

4.2 Demographic Data and Clinical Characteristics

Table (4.2) distributed the frequencies and percentages of the demographic data and clinical characteristics related to the study sample, and differentiate between them according to the survival status of the patients. The table shows that the mean age of all patients was 64.06 years old, with a significantly younger age between survived (53.76 years old) and deceased (65.04 years old) patients (p-value = 0.004). Also, the table shows that the most common comorbidities found in the COVID-19 patients who were admitted to the ICU were hypertension (58.7%), followed by diabetes mellitus type 2 (54.7%), with more than fifth of them having coronary artery diseases (CAD, 22.7%), followed by chronic kidney disease (CKD) which was found in 16% of the patients. There were significantly lower observations of morbid obesity (p-value < 0.001) and higher observations of CAD (p-value = 0.041) in deceased patients compared to survived ones. On the other hand, there we no significant differences in the rest of

comorbidities between survived and deceased patients (p-value > 0.05). Finally, the table show that majority of patients (83.3%) were admitted to ICU with severe forms of clinical presentations of COVID-19, with no significant difference in the COVID-19 clinical presentation between deceased and survived patients (p-value = 0.414). The following figures illustrate the description of patients' demographic data and clinical presentation, and their differences between survived and deceased patients.

Table 4.2

Distribution of patients' demographic data and clinical characteristics (all sample and between who survived or deceased, presented in frequency (%), unless stated otherwise)

Variable	Values	All sample N = 150	Survived N = 13	Deceased N = 137	p-value
Age	Mean (SD)	64.06 (13.43)	53.76 (16.380	65.04 (12.76)	0.004
Gender	Male	89 (59.3%)	8 (61.5%)	81 (59.1%)	0.866
	Female	61 (40.7%)	5 (38.5%)	56 (40.9%)	
Co-morbidities	Hypertension	88 (58.7%)	9 (69.2%)	79 (57.7%)	0.418
	Diabetes mellitus II	82 (54.7%)	6 (46.2%)	76 (55.5%)	0.519
	COPD	11 (7.3%)	1 (7.7%)	10 (7.3%)	0.959
	Morbid obesity	12 (8.0%)	5 (38.5%)	7 (5.1%)	< 0.001
	CAD	34 (22.7%)	0 (0.0%)	34 (24.8%)	0.041
	CHF	16 (10.7%)	1 (7.7%)	15 (10.9%)	0.716
	Malignancy	8 (5.3%)	1 (7.7%)	7 (5.1%)	0.692
	CKD	24 (16.0%)	0 (0.0%	24 (17.5%)	0.100
	Liver disease	3 (2.0%)	0 (0.0%)	3 (2.2%)	0.590
	Immunosuppressed	4 (2.7%)	0 (0.0%)	4 (2.9%)	0.532
	Other diseases	27 (18.0%)	4 (30.8%)	23 (16.8%)	0.210
Severity of COVID-19 clinical presentation	Asymptomatic	0 (0.0%)	0 (0.0%)	0 (0.0%)	0.414
	Mild	1 (0.7%)	0 (0.0%)	1 (0.7%)	
	Moderate	23 (15.3%)	0 (0.0%)	23 (15.3%)	
	Severe	101 (83.3%)	7 (53.8%)	94 (68.6%)	

Figure 4.1

Distribution of Patients' Mean Age (All and Survived vs Deceased)

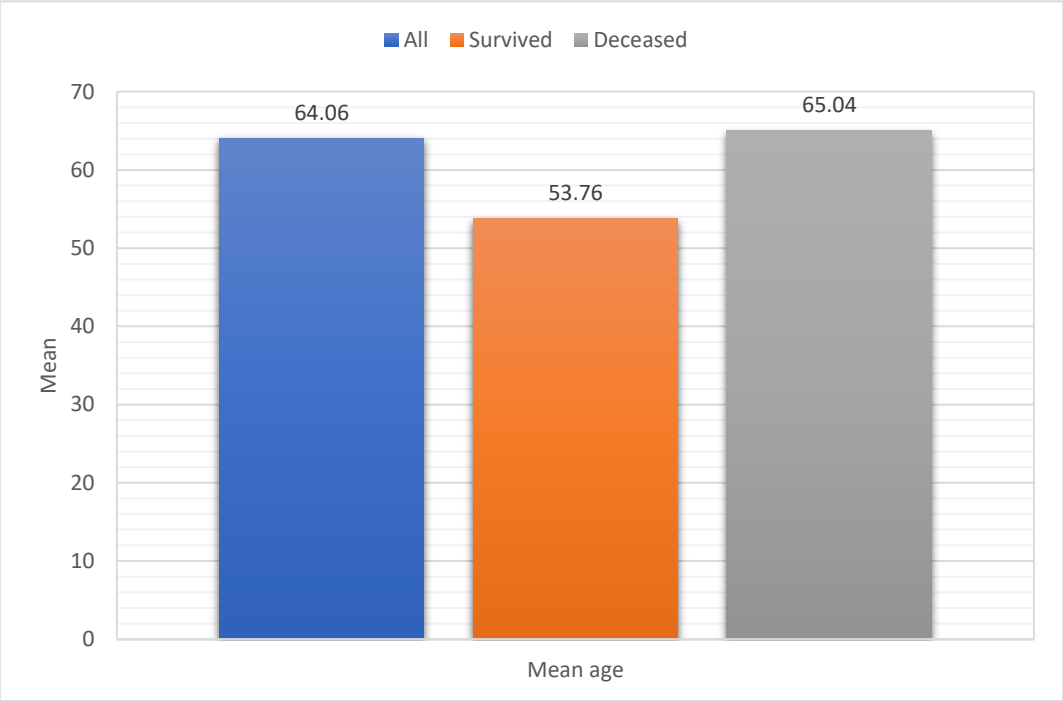
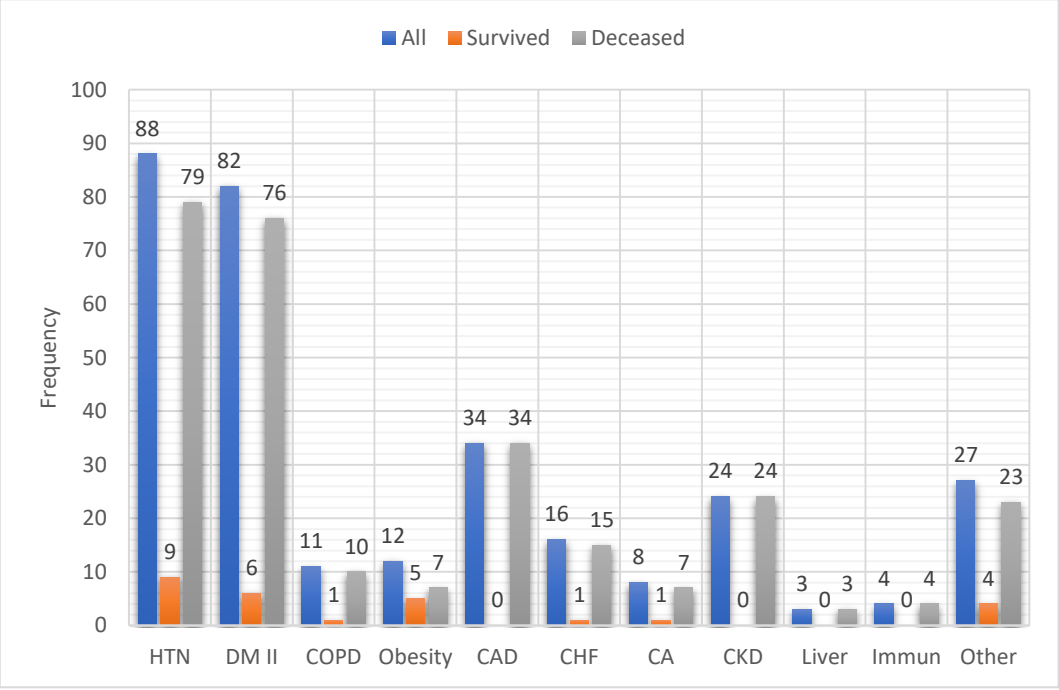


Figure 4.2

Distribution of Patients' Comorbidities (All and Survived vs Deceased)



4.3 Laboratory Tests

Table (4.3) describes the mean values of the lab tests of the patients and the differences in their initial and peak readings, as well as the differences between survived and deceased patients in both initial and peak readings (taking in consideration that the comparison in pO2 and pO2:FiO2 was between their initial and lowest readings). In general, the initial readings were worse in deceased patients compared to survived patients when first admitted to the ICU, except for the platelets (almost the same) and glucose readings. On the other hand, no significant difference was found between deceased and survived patients in both initial and peak readings, except for the peak creatinine readings, which was significantly higher in deceased patients (1.40 vs 0.99, p-value = 0.008), and initial pCO2 reading, which was significantly higher in survived patients (45.17 vs 36.59, p-value = 0.024). The following figures illustrate the differences in mean initial and peak readings between the deceased and survived patients.

Table 4.3

Descriptive statistics of the blood tests (all sample and between survived and deceased, presented in mean (SD).

Blood test	All sample		Survived		Deceased		p-value	
	Initial	Peak	Initial	Peak	Initial	Peak	Initial	Peak
WBC	9.94 (4.850	24.06 (9.440	9.16 (4.44)	21.21 (6.35)	10.02 (4.89)	24.33 (9.65)	0.546	0.255
CRP	118.54 (104.36)	207.74 (125.71)	118.25 (119.97)	173.07 (110.99)	118.56 (103.23)	211.16 (126.93)	0.992	0.299
D-Dimer	16.17 (147.7)	48.69 (303.22)	1.02 (0.97)	12.12 (11.06)	17.63 (154.62)	52.49 (318.46)	0.700	0.649
Ferritin	961.07 (860.210	2662.55 (3619.47)	762.98 (464.61)	2128.69 (2023.80)	981.66 (890.01)	2722.38 (3757.43)	0.385	0.577
Creatinine	1.37 (1.24)	3.01 (2.18)	0.99 (0.48)	1.50 (0.68)	1.40 (1.28)	3.15 (2.21)	0.265	0.008
Platelets (initial v lowest)	223.09 (101.76)	141.62 (80.39)	223.31 (136.163)	137.07 (98.78)	223.06 (98.53)	142.08 (78.76)	0.994	0.831 (lowest)
Glucose	194.45 (118.12)	288.05 (124.83)	207.55 (187.26)	347.50 (157.18)	191.35 (98.55)	273.18 (113.51)	0.716	0.134
Troponin	0.48 (2.71)	3.20 (6.64)	0.089 (0.078)	1.313 (3.653)	0.516 (2.824)	3.374 (6.835)	0.618	0.327
pO2 (initial vs lowest)	66.93 (24.65)	48.61 (12.12)	65.0 (24.3)	47.25 (17.29)	67.16 (24.80)	48.79 (11.38)	0.776	0.682 (lowest)
pCO2	37.51 (12.49)	67.14 (20.84)	45.17 (13.91)	75.25 (20.75)	36.59 (12.05)	66.06 (20.72)	0.024	0.152
pO2:FiO2 (initial vs lowest)	113.32 (66.41)	67.85 (36.77)	136.133 (81.73)	80.64 (26.02)	110.31 (64.06)	66.21 (37.73)	0.207	0.222 (lowest)

Figure 4.3

Differences in Initial and Peak D-Dimer Readings between Survived and Deceased patients

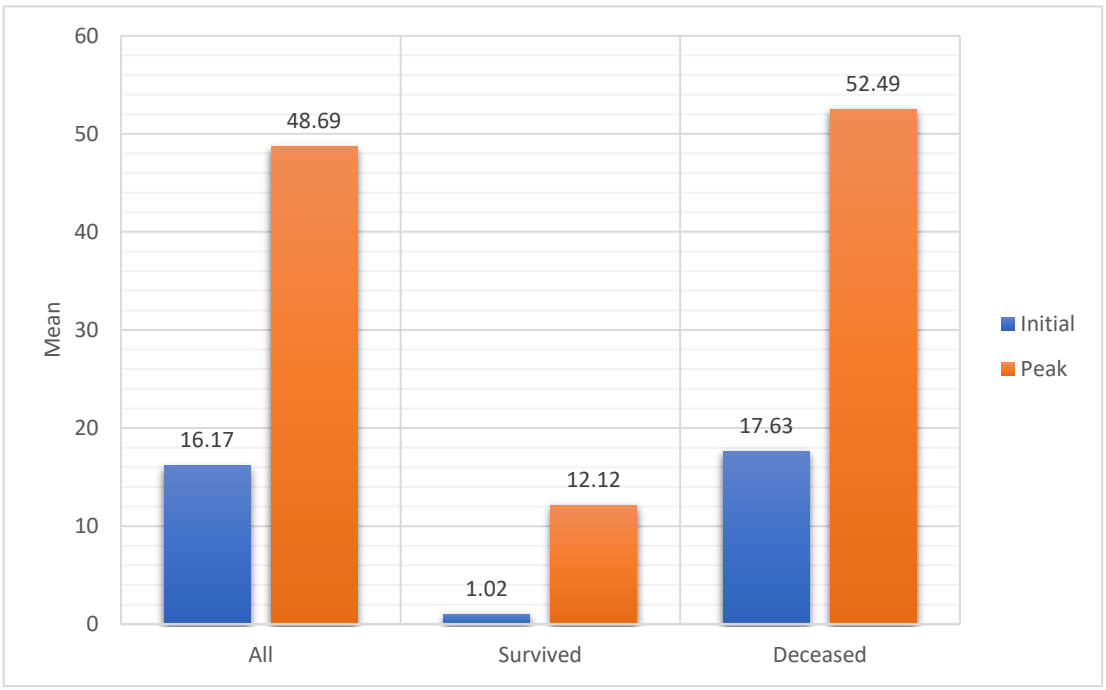


Figure 4.4

Differences in Initial and Peak Creatinine Readings Between Survived and Deceased Patients

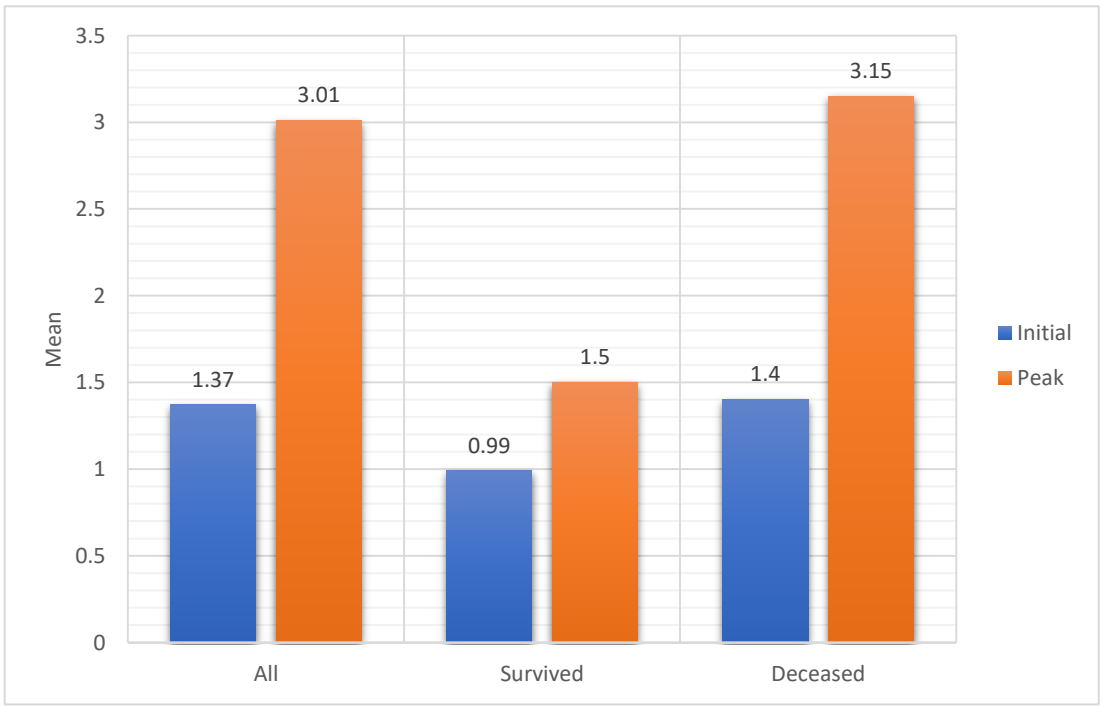


Figure 4.5

Differences in Initial and Peak Troponin-I Readings Between Survived and Deceased Patients

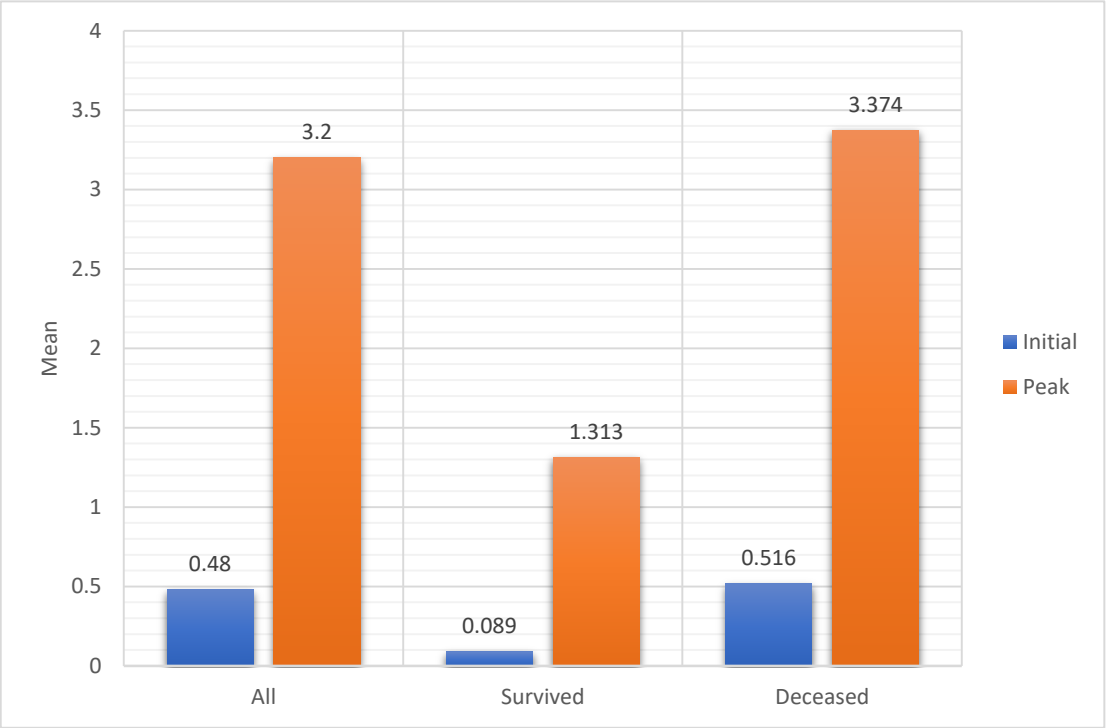
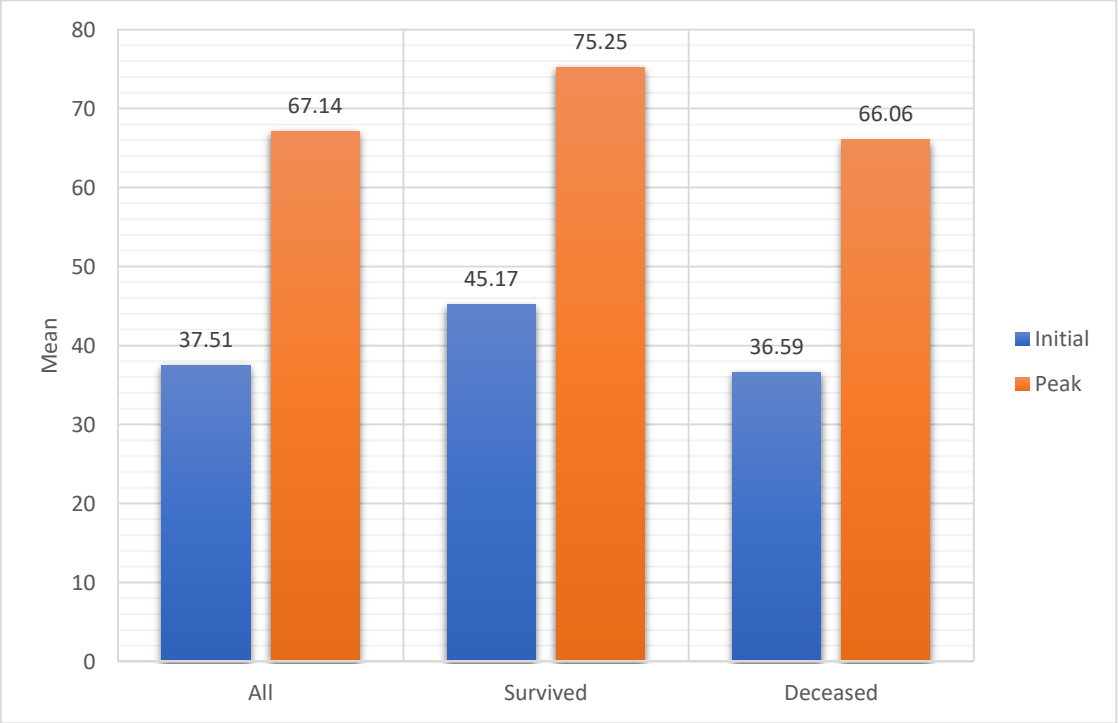


Figure 4.6

Differences in Initial and Peak pCO2 Readings between Survived and Deceased Patients



4.4 Treatment Approaches

This part explains the pharmacological and non-pharmacological treatment approaches that were used with COVID-19 patients who were admitted to ICU, and the differences in them between survived and deceased patients. Table (4.4) shows that most of non-pharmacological treatment approaches were used in patients, with prone positioning being the most common (40.7%), followed by the need for tracheostomy insertion (12.7%). In less than tenth of the patients (9.3%), hemodialysis or CRRT was used. Also, there was a significantly higher use of tracheostomy in survived (61.5%) compared to deceased patients (8.0%, p-value < 0.001), while the use of the rest of the non-pharmacological treatment approaches had no significant differences between survived and deceased patients.

The table also shows details related to respiratory management and support used in the ICU patients. Most of the patients were supported by oxygen supplementation (nasal cannula, face mask, … etc.) in 82% of the cases, while non-invasive ventilation (NIV) and high-flow nasal cannula (HFNC) were used in 81.3% of the patients, before intubation, with no significant differences between alive and deceased patients in both pre-intubation respiratory support. regarding intubation, most of the cases (66.7%) had late intubation process (after 24 hours of ICU admission), with no significant difference in intubation timing between survived and deceased patients (p-value = 0.627). Lastly, around two thirds of the intubation patients were put on volume-control mode of mechanical ventilation (64.7%). Also, there was a significantly higher use of volume-control mode in deceased (67.2%) more than survived (38.5%) patients, while there was a significantly higher use of pressure-control mode in survived (46.2%) compared to deceased (18.2%) patients (p-value = 0.050).

Moreover, according to Table (4.4), the most common pharmacological agents that were used for COVID-19 patients who were admitted to ICU were corticosteroids (98.7%), followed by low-molecular weight heparin (LMWH, 94.7%), muscle relaxants (52.7%) and vitamin-D with Zinc supplements (50.0%). In around fifth to fourth of the patients, colchicine was used in 26.7% of the cases, while blood products were infused in 25.3%, followed by remdesivir (20.0%), with a significantly higher use of remdesivir in survived patients (53.8%) compared to deceased patients (16.8%, p-value = 0.001),

while the rest of the pharmacological approaches had no significant differences in their use between survived and deceased patients (p-value > 0.05).

Table 4.4

Distribution of respiratory and pharmacological treatment approaches for the patients (all sample and between survived and deceased, presented frequency (percentage))

Variable	Values	All sample N = 150	Survived N = 13	Deceased N = 137	p-value
Non-pharmacological respiratory treatment approaches	Prone position	61 (40.7%)	5 (38.5%)	56 (40.9%)	0.866
	Inhaled vasodilators	5 (3.3%)	1 (7.7%)	4 (2.9%)	0.360
	ECMO	0 (0.0%)	0 (0.0%)	0 (0.0%)	---
	Dialysis / CRRT	14 (9.3%)	0 (0.0%)	14 (10.2%)	0.226
	Tracheostomy	19 (12.7%)	8 (61.5%)	11 (8.0%)	< 0.001
	Bronchoscopy	8 (5.3%)	2 (15.4%)	6 (4.4%)	0.091
Respiratory support when admitted to ICU	Oxygen supplements	123 (82.0%)	9 (69.2%)	114 (83.2%)	0.210
	NIV / HFNC	122 (81.3%)	13 (100%)	109 (79.6%)	0.071
Intubation timing	Early intubation	48 (32.0%)	5 (38.5%)	43 (31.4%)	0.627
	Late intubation	100 (66.7%)	8 (61.5%)	92 (67.2%)	
Mechanical ventilator mode	Volume control	97 (64.7%)	5 (38.5%)	92 (67.2%)	0.050
	Pressure control	31 (20.7%)	6 (46.2%)	25 (18.2%)	
	Both modes	21 (14.0%)	2 (15.4%)	19 (13.9%)	
Pharmacological treatments	Blood products	38 (25.3%)	3 (23.1%)	35 (25.5%)	0.845
	Muscle relaxants	79 (52.7%)	6 (46.2%)	73 (53.3%)	0.623
	Remdesivir	30 (20.0%)	7 (53.8%)	23 (16.8%)	0.001
	Immunomodulators	14 (9.3%)	2 (15.4%)	12 (8.8%)	0.433
	Antiparasitic agents	5 (3.3%)	1 (7.7%)	4 (2.9%)	0.360
	IV bronchodilators	5 (3.3%)	1 (7.7%)	4 (2.9%)	0.360
	Corticosteroids	148 (98.7%)	13 (100.0%)	135 (98.5%)	0.661
	Hydroxychloroquine	1 (0.7%)	0 (0.0%)	1 (0.7%)	0.757
	LMWH	142 (94.7%)	12 (92.3%)	130 (94.9%)	0.692
	Co-zinc, vitamin-D	75 (50.0%)	9 (69.2%)	66 (48.2%)	0.147
	Colchicine	40 (26.7%)	4 (30.8%)	36 (26.3%)	0.762

4.5 Mechanical Ventilator Parameters

Regarding mechanical ventilator parameters, Table (4.5) shows that there was a significantly higher mean initial pO2 in deceased patients (62.31%) compared to survived patients (38.54%, p-value < 0.001), with a significantly higher mean initial pressure control in deceased patients (19.54 mmHg) compared to survived patients (9.86 mmHg, p-value = 0.001). On the other hand, there were insignificant differences in minimum and maximum mechanical ventilator parameters between survived and deceased patients (p-value >0.05). The following figures illustrate the differences in mechanical ventilator parameters used in survived and deceased ICU COVID-19.

Table 4.5

Descriptive statistics of the mechanical ventilator parameters during IMV (all sample and between survived and deceased, presented in mean (SD)

Parameter	All sample		Survived		Deceased		p-value	
	Min	Max	Min	Max	Min	Max	Min	Max
FiO2 (%)	59.58 (20.08)	94.16 (12.340	38.54 (6.67)	89.23 (13.05)	62.31 (19.63)	94.63 (12.21)	< 0.001	0.132
PEEP	8.72 (2.62)	12.85 (7.16)	8.08 (2.56)	13.85 (3.18)	8.81 (2.63)	12.76 (7.44)	0.348	0.602
Tidal volume	388.68 (64.96)	441.35 (62.95)	396.67 (76.59)	460.0 (48.65)	388.0 (64.46)	440.14 (63.76)	0.756	0.421
Respiratory rate	18.66 (3.96)	22.77 (5.26)	17.46 (3.89)	23.0 (4.85)	18.81 (3.96)	22.75 (5.31)	0.249	0.871
Pressure	17.93 (7.28)	23.00 (6.94)	9.86 (2.73)	20.50 (3.66)	19.54 (6.82)	23.47 (7.32)	0.001	0.271

Figure 4.7

Differences in Minimum and Maximum FiO2 between Survived and Deceased Patients

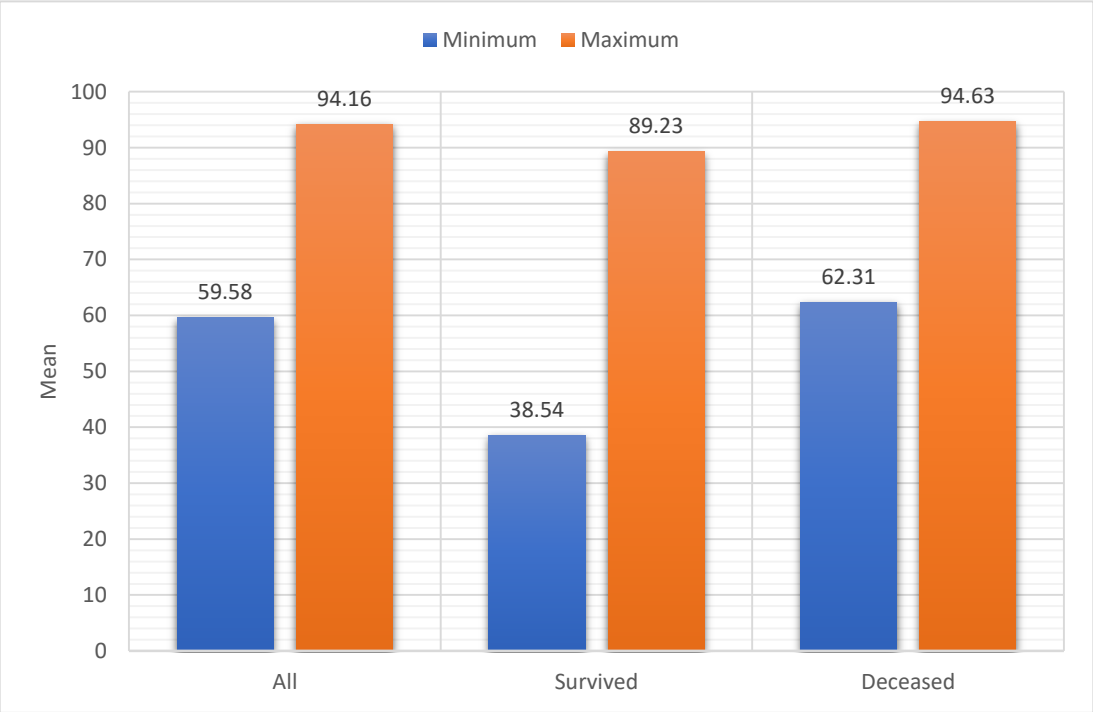
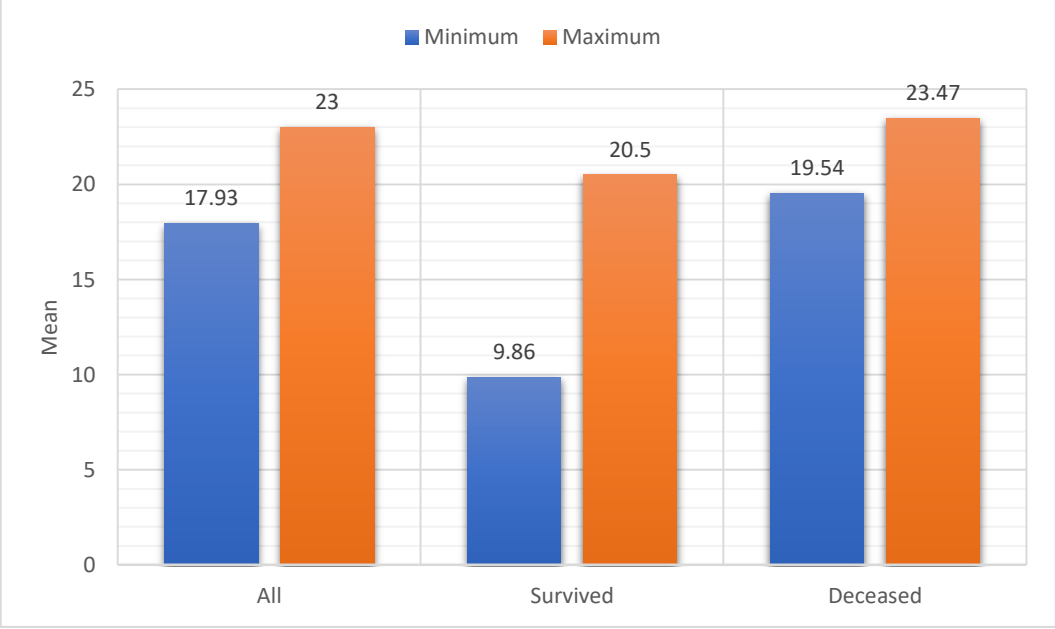


Figure 4.8

Differences in Minimum and Maximum Inspiratory Pressure Between Survived and Deceased Patients



4.6 Patients Outcomes

Table (4.6) distributes the medical and surgical complications that both survived and deceased patients suffered from in their stay inside the ICU. It shows that the most common complication was acute kidney injury (AKI, 60.7%), followed by secondary infection (54.7%), and septic shock (50.0%), then cardiovascular events (45.3%), including dysrhythmias and infarction, while bleeding disorders occurred in 30% of the cases, followed by ARDS in 26% of them. The table also shows that there were significantly higher incidences of AKI and cardiovascular events in deceased than survived patients (p-value = 0.021 and 0.023, respectively) while there were significantly higher incidences on secondary infections and pneumothorax among survived patients compared to deceased patients (p-value = 0.004 and 0.050, respectively).

In terms of length of stay (LOS), the mean hospital LOS was 17.33 days, while the mean ICU LOS was 13.86 days, with a mean of 8.26 days of LOS on IMV. Also, higher median LOS was found in survived than decease patients in terms of hospital LOS (36 days vs 14 days, respectively, p-value < 0.001), ICU LOS (27 days vs 11 days, respectively, p-value < 0.001) and LOS on IMV (15 days vs 6 days, respectively, p-value < 0.001).

In general, 91.3% of the patients did not survive, with cardiopulmonary arrest being the lead cause of death (71.3%), followed by bradycardia (10.7%) and hypotension (8.7%) events.

Table 4.6

Distribution of patients' outcomes (all sample and between who Survived or Deceased, presented frequency (percentage))

Variable	Values	All sample N = 150	Survived N = 13	Deceased N = 137	p-value
Complications during ICU stay	ARDS	39 (26.0%)	3 (23.1%)	36 (26.3%)	0.801
	PE	4 (2.7%)	0 (0.0%)	4 (2.9%)	0.532
	AKI	91 (60.7%)	4 (30.8%)	87 (63.5%)	0.021
	Cardiovascular	68 (45.3%)	2 (15.4%)	66 (48.2%)	0.023
	Septic shock	75 (50.0%)	5 (38.5%)	70 (51.1%)	0.384
	Secondary infection	82 (54.7%)	12 (92.3%)	70 (51.1%)	0.004
	Pneumothorax	13 (8.7%)	3 (23.1%)	10 (7.3%)	0.050
	Surgical emphysema	21 (14.0%)	1 (7.7%)	20 (14.6%)	0.493
	Bleeding disorder	45 (30.0%)	4 (30.8%)	41 (29.9%)	0.950
	DIC	6 (4.0%)	1 (7.7%)	5 (3.6%)	0.477
	CVA	1 (0.7%)	0 (0.0%)	1 (0.7%)	0.757
Hospital LOS	Mean (SD)	17.33 (11.79)	40.31 (18.85)	15.15 (8.11)	< 0.001
	Median	15	36	14	
ICU LOS	Mean (SD)	13.86 (10.02)	31.23 (15.02)	12.21 (7.66)	< 0.001
	Median	11.5	27	11	
IMV LOS	Mean (SD)	8.26 (7.25)	17.85 (11.10)	7.36 (6.10)	< 0.001
	Median	7	15	6	
Did the patient survive?	Yes	13 (8.7%)			
	No	137 (91.3%)			
Cause of death	Cardiopulmonary arrest	107 (71.3%)			
	Hypotension	13 (8.7%)			
	Bradycardia	16 (10.7%)			
	Multiorgan failure	1 (0.7%)			

4.7 Predictability testing

In this part, binary logistic regression test was used to investigate the predictability of the significantly correlated variables with survival among COVID-19 patients who were admitted to the ICU. Each variable was tested individually to test its significance level in regression to survival, and, if significant, the odds of surviving.

Table (4.7) explains the results of the binary logistic regression that was conducted to individually investigate the predictability of the significantly correlated independent variables with the survival of COVID-19 patients admitted to ICU. Age is a negative predictor for survival (B = - 0.054, *p*= 0.006), and each one-year patient is older, probability of survival decreases by 5.2%. Regarding comorbidities, the morbid obesity is a significant predictor of survival (p-value < 0.001), and patients who have morbid obesity have the odd of surviving by 11.607 times compared to non-obese patients. On the other hand, having CAD is not a significant predictor of survival (p-value = 0.998).

The table also shows that the significantly correlated laboratory test are significant predictors of survival. The peak creatinine level is a negative predictor (B = - 0.845) of survival (p-value = 0.010), and each 1 mg/dL increase decreases the survival by 57.4% (1 – 0.426), while the initial pCO2 reading is a positive predictor of survival (B = 0.044, p-value = 0.032), and each 1 mmHg increase in pCO2 increased the survival by 4.5%, taking in consideration that most of the patients had a normal pCO2 range, and thus the increase is to be in the normal range. Moreover, tracheostomy insertion had the positive prediction (B = 2.908) of survival (p-value < 0.001), and the patients who had tracheostomy had 18.237 times the odd of survival.

When comparing to volume-control mechanical ventilation mode, the pressure-control ventilation mode had a positive prediction (B = 1.485) of survival (p-value = 0.022), and patients who were put on pressure-control mode had 4.416 times the survival rate compared to volume-control patients, while patients who were put on both modes alternatively had no significant prediction with survival (p-value = 0.449). On the other hand, remdesivir use was the only pharmacological treatment that was significantly related with survival and is also a significant predictor of survival (p-value = 0.004), and patients who used remdesivir had 5.783 times more survival rate than patients who did not start on remdesivir.

Patients who had pneumothorax as a complication when admitted to ICU were not significantly predicted to survive or not (p-value = 0.069), while patients who were complicated with AKI are predicted to less survive (B = - 1.365, p-value = 0.029), with patients who developed AKI had 74.5% less odd of survival (1 – 0.255). Also, patients who developed cardiovascular complications were also predicted to less survive (B = - 1.632, p-value = 0.038), and patients who developed cardiovascular complications had 88.4% less odd of survival compared to patients who didn't develop cardiovascular complications (1 – 0.196), while patients who developed secondary infection was significantly predicted to survive (p-value = 0.021), in which patients who developed secondary infections have the odd to survive by 11.486 times compared to patients who didn't develop secondary infections.

Lastly, when investigating for the length of stay predictors to survival, the prolonged hospital LOS significantly predicts more survival (p-value < 0.001), in which each day increased in hospital LOS increases the odd of survival by 20.2%, while each day increased in ICU LOS increased the survival by 18.5%, and each increase in IMV by one day is predicted to increase survival by 16.2%.

Table 4.7

Binary logistic regression of significantly correlated variables with survival rate (CI: Confidence interval, OR = Odds ratio)

Predictor	B	Wald	p-value	OR	95% CI
Demographics					
Age	-0.054	7.513	0.006	0.948	
Comorbidities					
Morbid obesity	2.452	12.639	< 0.001	11.607	3.004 – 44.845
CAD	-19.133	0.000	0.998	< 0.001	0.000 - .
Laboratory tests					
Peak creatinine level	-0.854	6.675	0.010	0.426	0.223 – 0.814
Initial pCO2 level	0.044	4.577	0.032	1.045	1.004 – 1.088
Nonpharmacological treatment					
Had tracheostomy	2.908	19.957	< 0.001	18.237	65.654
Mechanical ventilator mode compared to volume-control mode					
Pressure-control mode	1.485	5.283	0.022	4.416	1.245 – 15.669
Both modes	0.661	0.571	0.449	1.937	0.349 – 10.736
Mechanical ventilator parameters					
Minimum FiO2	-0.125	11.862	0.001	0.883	0.822 – 0.948
Minimum pressure	-0.738	6.623	0.010	0.478	0.272 – 0.839
Pharmacological treatment					
Remdesivir	1.755	8.512	0.004	5.783	1.779 – 18.798
Complications					
AKI complication	-1.365	4.745	0.029	0.255	0.075 – 0.872
Cardiovascular comps.	-1.632	4.293	0.038	0.196	0.042 – 0.916
Secondary infection	2.441	5.365	0.021	11.486	1.453 – 90.778
Pneumothorax	1.338	3.306	0.069	3.810	0.901 – 16.111
Lengths of stay					
In hospital	0.184	18.196	< 0.001	1.202	1.104 – 1.307
In ICU	0.170	17.505	< 0.001	1.185	1.094 – 1.283
On IMV	0.150	14.421	< 0.001	1.162	1.075 – 1.256

Chapter Five

Discussions and Conclusions

This chapter reviews the discussion of the present study's findings by comparing them to those of earlier studies and provides a critical overview from the researchers' perspective.

5.1 Discussion of survival rate

The primary finding of the study is that mortality rate is high in COVID-19 patients who required invasive mechanical ventilation, especially in those who are older and have coronary artery disease (CAD) as comorbidity. Pooled ICU mortality rate among IMV patients was of 91.3%. The number of COVID-19 patients on mechanical ventilation mortality is larger than previously reported in Northern Virginia 42.7% (King et al., 2020), New York 24.5% (Richardson et al., 2020), Atlanta 35.7% (Auld et al., 2020), 71–75% from Seattle (Arentz et al., 2020; Bhatraju et al., 2020), United States 23.5% (Krause et al., 2021) Washington State 67% (Arentz et al., 2020), China 49% (Wu & McGoogan, 2020) , Italy 53% (Grasselli et al., 2020), and Germany 55% (Karagiannidis et al., 2020), but it should be noted that most studies followed patients for a narrow duration which mean some patients were still receiving treatment and didn’t reach endpoint (died or survived) and that decreases mortality rate comparing with this study where we followed each patient to the end . On the other hand, mortality rate was in line with Wuhan's IMV mortality rate of 86–97% (Zhou et al., 2020).

The findings of the investigation could be explained in a variety of ways. Because patients were more critically ill, as 83.3% had severe symptoms on admission to hospital during the pandemic, in addition to that patients underwent to IMV after all respiratory support failed as most of them (66.7%) were intubated late and they were extremely sick as their initial PaO_2:FiO_2 ratio was 113.32. Greater mortality could be accounted in part by higher average patient age or disease severity.

Other relevant factors that, in the researcher opinion, may have influenced the study outcomes were that healthcare delivery system was overwhelmed due to improper facility infrastructure, insufficient equipment, a lack of beds, and lower quality of care due to the high and sustained burden on health-care personnel. There is evidence that

increased ICU strain has an effect on health-care employees. The researcher believes that the increase in mortality over time reflects the pandemic's severe impact on the health system.

5.2 Discussion of the descriptive characteristics of COVID-19 patients who were mechanically ventilated in the ICU.

Patients over the age of 65 account for the vast majority of deaths in our cohort. At the time the data was censored, 137 patients aged 65.04 or older were dead (p=0.004). Initial reports from China and Italy, similar to study findings, identified age as a risk factor for increased mortality (Wu, Chen & Cai, 2019; Grasselli et al., 2020). Patients in Northern Virginia and Florida (King et al., 2020; Oliveira et al., 2021) were approximately 6 years older than those in our study (71.5 years), while patients from Italy and Argentina were roughly the same age (65 years) (Grasselli et al., 2020; Estenssoro et al., 2021). Study findings support the hypothesis that an increase in old death rates is due to the "accumulation of damage" that occurs in many biological structures and systems, as well as a decrease in the rate of damage repair (Ledberg, 2020).

In terms of comorbidities, cardiovascular diseases (CVD) were significantly associated with ICU mortality (p=0.041), which is consistent with Wang et al. (2020), who discovered that CVD, in addition to HTM and DM, correlated with COVID-19 severity and mortality. According to Grasselli et al (2020), the most common comorbidity was hypertension, followed by cardiovascular disorders, hypercholesterolemia, and diabetes.

In general, other researches indicate that COVID-19 patients who required mechanical ventilation, have at least one comorbidity (Grasselli et al., 2020; Ñamendys-Silva et al., 2020; Doidge et al., 2021; Ranzani et al., 2021).

Obesity was few observed in deceased patients (5.1 %), however, it is statistically significant higher in survived patients (38.5%, p-value = <0.001) which contradict with Popkin et al. (2020) who demonstrated that obesity increase morbidity and mortality among COVID-19 patients, as well with Plourde et al., (2021) who found that obesity significantly associated with COVID-19 mortality. Researcher explain that result due to inaccurate measurement for this variable because weight and height were not recorded

and therefore BMI could not be calculated, so we depended on subjective physician assessment.

In different studies such as Auld et al. (2020) found that chronic kidney disease/end-stage renal disease was considerably greater (p= 0.022, 38.7%) in persons who died, while Oliveira et al. (2021) found that non-survivors had evidence of heart failure, chronic kidney disease (CKD), and dementia. Furthermore, Estenssoro et al. (2021) discovered that comorbidities such as arterial hypertension, diabetes, chronic kidney failure, cardiovascular disease, and immunosuppression were more common in non-survivors, as well as a review that associated these same comorbidities to disease severity and ICU admissions (Liu et al., 2020; Chang et al., 2021).

5.3 Discussion of the results of blood tests performed on COVID-19 patients who were mechanically ventilated in the ICU.

The only laboratory differences between survivor and deceased groups in this cohort study were initial and peak D-Dimer [(1.02, 12.12) vs (17.63, 52.49)] and peak Troponin (1.313 vs. 3.374) , but no significant difference was found between survived and deceased patients in both initial and peak readings of D-Dimer and peak Troponin [p-value= (0.7, 0.649), (0.327)] ,respectively, but almost there was no difference between the two groups among initial and lowest pO_2:FiO_2 ratio and initial and peak C-reactive protein, however, initial PCO_2 reading was significantly higher in survived patients (45.17 vs 36.59, p-value = 0.024). Previous laboratory findings contradict the findings of Auld et al. (2020), who found that mortality was significantly associated with lower PaO_2:FiO_2 ratio, higher d-dimer, and higher C-reactive protein, counter to Oliveira et al. (2021), who found no significant differences in laboratory and inflammatory markers between survivors and non-survivors. Deceased patients exhibited greater initial d-dimer (2.22 vs. 1.31, p = 0.005) and peak ferritin levels (2998 vs. 2077, p = 0.016) than survivors, according to King et al (2020).

Peak Creatinine readings were significantly higher in deceased patients (1.50 vs 3.15, p-value = 0.008), consistent with Estenssoro et al (2021) study, that blood urea nitrogen and serum creatinine concentrations were already significantly different on admission between survivors and non-survivors. In contrast, Chang et al (2021) found that WBC, AST, D-dimer PT, CRP, lactate, LDH, and total bilirubin, as well as lower PaO_2:FiO_2,

lymphocyte count, and albumin, were significantly associated with ICU mortality in their systematic review.

According to initial and lowest PaO_2:FiO_2 readings, there was no significant difference found between deceased and survived patients (p=0.207 vs p=0.222), which is consistent with King et al (2020). While inconsistent with Oliveira et al (2021), average PaO_2:FiO_2 during hospitalization was lower in non-survivors versus survivors (p <0.001), Auld et al. (2020) confirmed that mortality was significantly associated with lower PaO_2:FiO_2 ratio, and studies done in Italy, France, Spain, and the Netherlands confirmed reduction in PaO_2:FiO_2 ratio of COVID-19 patients (Grasselli et al., 2020; Botta et al.,2021; Ferrando et al., 2021)

5.4 Discussion of the ICU mechanically ventilated COVID-19 patients' treatment approaches.

Patients within study cohort were offered to adjunct interventions, where Prone position was performed to 61 patients (40.7%) but there is no significant difference between survived and deceased (p-value =0.866), which is consistent with King et al (2020), as well as CRRT or dialysis (9.3%) hasn't a significant difference (p-value=0.226), which contradict with Auld et al (2020) who found that CRRT or HD were used significantly more in died patients (p-value<0.001) as King et al (2020) p-value = 0.011. However, tracheostomy was done significantly more in survived patients (61.5%) than deceased (8% , p-value < 0.001), which is consistent with Oliveira et al (2021) who found a significant difference in using tracheostomy between survived and deceased patients (p-value =0.044), and renal replacement therapy was used significantly more in deceased (57.7%) than in survived (8.65%, p-value = 0.001) which contradict to study findings in using CRRT, also they found that ECMO was used in 6.9% of patients with no significant difference (p-value=1) as in Auld et al (2020) p-value = 0.257 ,but contradict with King et al (2020) who found ECMO was used significantly more in survived patients (p-value=0.042). In this study, CRRT or dialysis was performed to only 9.3% while 16% had CKD and 60.7% developed AKI, so no significant effect can be attributed to low prevalence, and ECMO wasn't used at all, and we explain this by asserting that study hospitals do not have enough devices and health care providers do not have extensive experience with high-volume ECMO programs.

On the other hand, the most common pharmacological agents used in this study were corticosteroids (98.7%) then low molecular weight heparin (Clexane) 94.7 %, but this findings do not suggest a significant effect of such treatment between survived and deceased patients (p-value > 0.05), which consistent with Oliveira et al (2021) research, which found corticosteroids were used in 58.8% of patients and anticoagulant were used in 36.6% of patients with no significant difference between survived and deceased patients (p-value > 0.05). Toclizumab (Actemra) was given to 14 patients (9.3%) and no significant difference was observed between the two groups (p-value = 0.433), which consistent with Oliveira et al (2021) (p-value =0.831), but contradict with King et al (2020) who found Toclizumab was given significantly more to survived patients (38.3%) than died patients (18.6%, p-value= 0.006), while just one patient received Hydroxychloroquine and had died but also no significant difference (p-value= 0.757) which is consistent with Auld et al (2020), King et al (2020) and Oliveira et al (2021) (p-value > 0.05). Muscle relaxants (paralysis) were given to 79 (52.7%) patients with no significant relationship with survive or dead (p-value = 0.623), as found in King et al (2020) study (p-value= 0.74). Whereas inhaled pulmonary vasodilators also hadn't significant relationship (p-value= 0.360), King et al (2020) found a significant relationship with surviving (p-value = 0.008), counter to Auld et al (2021) who found a significant relationship with deceased patients (p-value= 0.004), and we attribute that to confounding factors affected Auld finding, because its known that inhaled pulmonary vasodilators improve oxygenation and had minimal adverse effects, and the neutral result finding because the low use of inhaled vasodilators (3.3%) due to lack of expensive gases and its special devices which make benefit cannot be observed.

In this cohort study there is significantly higher use of Remdesivir in survived patients (53.8%) compared to deceased patients (16.8%, p-value=0.001), in Auld et al. (2020) over half of the patients received at least one dosage of hydroxychloroquine and nearly a quarter received at least one dose of a study drug as part of the ACTT trial (remdesivir vs placebo), but there was no difference in survival between the two groups. Remdesivir was used in 10.7% of the total population in Oliveira et al (2021) research, but there was no significant correlation between survival and mortality rate.

According to Intubation timing, the majority of cases (66.7 %) had intubation lately after 24 hours of ICU admission in this cohort analysis, and there was no significant difference in the time between intubation for deceased patients and survivors (p=0.627), which is consistent with King et al (2020) there was no significant difference in the mean time to intubation between the deceased patients and survivors (p= 0.54), and with Papoutsi et al (2021) who found in their systemic review study that from 3981 deaths 45.4% were intubated early and 39.1% were intubated lately, and there was no significant correlation between intubation timing and mortality (p-value=0.08) , guidelines emphasized early intubation and standard lung protective ventilation strategies.

5.5 Discussion of the mechanical ventilator settings of ICU mechanically ventilated COVID-19 patients.

In study cohort, volume control mode was used in majority of patients (64.7%), and pressure control mode used in 20.7%, while 14% underwent to both modes. Despite that volume control mode is recommended in guidelines, pressure control mode was significantly associated with increase survival rate (p-value= 0.022, OR=4.416) in this study.

Regarding mechanical ventilator settings, there were no significant differences between survived and deceased groups (p-value > 0.05), even PEEP (p-value for minimum =0.348, p-value for maximum = 0.602), which is consistent with king et al (2020) (p-value = 0.26) but contradict with Oliveira et al (2021) who found PEEP was higher in deceased patients (10) than survived patients (9.2, p-value = 0.004). Except minimum FiO_2 was substantially higher in deceased patients (62.31%) than survived patients (38.54 %, p-value <0.001), as well as minimum inspiratory pressure was higher in deceased patients (19.54 mmHg) than survived patients (9.86 mmHg, p-value = 0.001).

Boscolo et al., (2021) studied the association between mechanical ventilator settings and measurements and ICU mortality among COVID-19 patients, and found that Respiratory Rate, FiO_2 and Tidal Volume / kg of IBW were not associated with ICU mortality, which contradict to this study regarding FiO_2, in the other hand, they found a linear relationship between ICU mortality and PEEP and Plateau Pressure, and a significant correlation between static Compliance and Driving pressure with ICU

mortality, which disagree with Auld et al (2020) who found no difference in compliance between survived and deceased patients (p-value = 0.759), also disagree with Oliveira et al (2021) who found no difference in driving pressure between the two groups (p-value=0.627), and for this study, this measurements were not included because it wasn't recorded.

The variations of study findings than previous studies can contributed to lack of adherence to guidelines. We could not locate any data on ventilator parameters and their impact on mortality rates in mechanically ventilated ICU patients in the literature to compare with study findings.

5.6 Discussion of patient outcomes in COVID-19 patients who were mechanically ventilated in the ICU.

According to complications during ICU Stay, the most prevalent complication was acute kidney injury (AKI) (60.7%), AKI and cardiovascular events were considerably more likely in deceased patients than in survivors (p-value=0.021 and 0.023, respectively). This finding is consistent with Chang et al (2021), who found three correlates with ICU mortality, one of which is AKI. Additionally, Cheng et al (2020) and Chaibi et al (2020) show that Renal dysfunction in COVID-19 develops in patients on invasive mechanical ventilation and is associated with a worse prognosis. This, combined with study findings, raises the possibility that AKI is underestimated in critically ill COVID-19 patients. In contrast, some researchers even concluded that COVID-19 does not cause AKI (Wang et al., 2020).

Secondary infections and pneumothorax were substantially more common in survived patients than in deceased patients (p-values = 0.004 and 0.050, respectively). According to Oliveira et al (2021), in contrast, ICU Complications such as pneumothorax, self-extubation and decubitus ulcer happened to deceased more than survivors except DVT happened to survivors more, and all had no significant differences between survived and deceased patients (p-value > 0.05). Although the presence of complications such as secondary infection and pneumothorax will deteriorate and increase hospital LOS.

A number of factors could have influenced the results. First, the COVID-19 pandemic arrived and peaked sooner in Palestine than in many of the regions previously reported. Establishing organizational structures, acquiring equipment, preparing employees,

developing consensus-driven clinical protocols, and aligning resources across a major healthcare system may not be possible at that time, which leads to lack of adherence to protocol in giving antibiotics and adjust mechanical ventilator parameters. In addition to that secondary infection was defined to any infection developed after ICU admission including MDRO's, which mean it can be mild infections, and we think that another factors contribute to increase survival rate in these patients like age , that maybe these patients were younger or healthier.

It was discovered that a mean LoS in ICU of 13.86 days, which was higher than the results of a review reporting a median LoS of 7.8 days (Chang et al., 2021) and also higher than a review reporting a median LoS of 8 days for patients from China and 7 days for patients from outside China (Rees et al., 2020). In addition, the ICU LoS in survivors vs. non-survivors (31 vs. 12) of study cohort was greater than Oliveira et al. (2021) ICU LoS (14 vs. 9.5, $p<0.001$).

For deceased patients, the ventilator and hospital LoS were 7.36 (± 6.10SD) and 15.15 (±8.11 SD) days, respectively. According to IMV LoS, the average duration of ventilator support for survivors was 17 days (±11 SD), which was greater than the 14.6 days recorded by King et al (2020), Chang et al. (2021) reported an average IMV duration of 8 days, Almeshari et al. (2021) reports 10–17 days from Wuhan and Seattle. Study finding in line with Oliveira et al (2021) survivors had a longer MV length of stay (17.85 vs 7.36, $p <0.001$) than non-survivors.

Previous researchers have expressed concern about the possibly detrimental abuse of IMV, because IMV has hazards that can influence survival (Slutsky & Ranieri, 2014). In addition, poor intubation timing (too early or too late), undertrained or overwhelmed staff, as well as wrong ventilation settings and IMV-associated pneumonia, might all significantly increase mortality; all of these factors should be investigated further in COVID-19 cases.

Cardiopulmonary arrest was the leading cause of mortality in the majority of patients (n = 107, 71.3 %), whereas King et al (2020) showed that hypoxemic respiratory failure was the leading cause of death (n = 56, 80%). And we contribute this finding to that cause of death was recorded as physician declaration in their notes, and we think that's

inaccurate because most of patients developed several complications can lead to cardiopulmonary arrest which is the end result, not the cause.

Finally, study findings show that COVID-19 ICU and IMV rates and outcomes differ significantly between regions. Regional variances in local health systems and resources, as well as genetic differences among people and likely virus evolution over time, can all account for such differences and should be studied as the pandemic progresses. Regional differences also suggest the necessity for flexible region-specific treatment procedures especially in resource-limited situations (Dondorp et al., 2020) instead of the aim to develop universal international protocols for treatment.

5.7 Conclusion

The mortality rate of COVID-19 patients requiring invasive mechanical ventilation in Palestinian health facilities is extremely high, with particularly high mortality seen in patients over the age of 65 with coronary artery disease as comorbidity. Clinical management was upon physicians' decision not on specific criteria. Moreover, adjunctive treatments (ECMO, HD or CRRT) and pharmacological treatments (Remedisvir, Actemra or Kineret, Ivermectin, Hydroxychloroquine, Colchicine and inhaled vasodilators) were used rarely. These findings indicate that our facilities have inadequate infrastructure, insufficient equipment, and a lack of beds, and that COVID-19 arrived in Palestine earlier than in many other regions, leaving limited time to establish adequate organizational structures, acquire equipment, train personnel, develop consensus-driven clinical protocols, and align resources across a large healthcare system.

5.8 Limitations

1. This study was limited to three hospitals in the West Bank of Palestine, limiting generalizability to all Palestinian health systems.

2. Despite a multivariate regression study, significant confounders may go undetected when looking at several factors linked to survival.

3. There was no follow-up after discharge, thus the researcher would not know whether a patient was re-admitted to another hospital.

4. Doctors did not follow any specific or formal guidelines when treating COVID-19 patients.

5. Due to the fact that this is a retrospective study, there are missing data such as ABGs and body weight.

6. There are numerous challenges in gathering data, such as the lack of a standard method for recording data, which forces researchers to interpret doctors' notes in order to extract the information they require; also, there are patients for whom doctors do not write for three days.

7. There could have been differences in admission policies and patient management between the centers in our study.

8. The health facility did not classify patients admitted to ICU or with IMV, which would need researchers to actually spend time and physical effort to identify patients.

5.9 Recommendations

1. More research is needed to better understand the effects of individual patient risk factors, clinical interventions and therapies, and health-care system determinants on mortality in the context of this worldwide epidemic.

2. Increase the sample size by including more medical centers from different locations.

3. Our recommendation to health-care facilities is to create a health-information system that includes all records and encourages documentation.

4. Create protocols and guidelines and follow up medical team compliance.

5. Develop HIS for research goals, to facilitate sorting patients and extracting data.

List of Abbreviations

Abbreviation	Meaning
ACS	Acute Coronary Syndrome
ARDS	Acute Respiratory Distress Syndrome
AKI	Acute Kidney Injury
CAD	Coronary Artery Disease
CHF	Congestive Heart Failure
CRF	Chronic Renal Failure
CRP	C-Reactive Protein
CRRT	Continuous Renal Replacement Therapy
CDC	Centers for Disease Control and Prevention
CRYO	Cryoprecipitate
CXR	Chest X-Ray
COPD	Chronic Obstructive Pulmonary Disease
CVA	Cerebrovascular Accident
DM	Diabetes Mellitus
DIC	Disseminated Intravascular Coagulation
ECMO	Extra Corporeal Membrane Oxygenation
FiO2	Fraction Of Inspired Oxygen
FFP	Fresh Frozen Plasma
HTN	Hypertension
HFNC	High Flow Nasal Canula
I.V.	Intra Venus
IMV	Invasive Mechanical Ventilation
NIV	Non-Invasive Ventilation
PEEP	Positive End Expiratory Pressure
PRBC's	Packed Red Blood Cells
PLT	Platelets
PCR	Polymerase Chain Reaction
SOB	Shortness Of Breath
S.C.	Sub-Cutaneous
SARS-CoV	Severe Acute Respiratory Syndrome Corona Virus
WBC	White Blood Cells

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Appendices

Appendix (A)

Data Sheet

Basic Information's

Date of admission to hospital
Date of admission to ICU
Date of intubation
Date of extubation or Death
Date of discharge from ICU or Death
Date of discharge from hospital or Death

Part One: Demographic Data

Variables	**Options**
Age (in complete years)	
Gender	Male
	Female
Weight (in kilograms)	
Height (in centimeters)	
BMI (kg\m^2)	

Part Two: Clinical Characteristics

Variable	**Options**	
Does the patient have any of the following co-morbidities?	Hypertension (HTN)	
	Diabetes mellitus (DM)	
	Chronic obstructive pulmonary disease (COPD)	
	Morbid obesity (BMI > 40)	
	Coronary artery disease (CAD)	
	Congestive heart failure (CHF)	
Does the patient have any of the following co-morbidities?	Malignancy	
	Chronic kidney disease (CKD)	
	Liver disease	
	Immunosuppressed disease	
	Others	
Clinical Presentation / Covid-19 Severity	Asymptomatic	
	Mild	fever, cough, sore throat, malaise, headache, muscle pain, nausea, vomiting, diarrhea, loss of taste and smell
	Moderate	SOB, Dyspnea, Abnormal CXR (while SPO2 ≥94%)
	Severe	SPO2<94%, PaO2/FiO2 <300, RR>30, Lung Infiltration > 50%
Blood test	**Initial reading**	**Peak reading**
White blood cells (WBC, k/uL)		
C-Reactive protein (CRP, mg/dL)		

D-Dimer (mg/L)		
Ferritin (ng/ml)		
Creatinine (mg/dL)		
Platelets (k/uL)		
Serum glucose level (mg/dL)		
Troponin (ng/ml)		
PaO2 (mmHg)	Initial:	Lowest:
PaCO2 (mmHg)	Initial:	Highest:
PaO2\FiO2 ratio	Initial:	Lowest

Part Three: Treatment approaches

Respiratory treatment			
What of the following was used in respiratory treatment?	Prone position		
	Inhaled vasodilators		
	ECMO		
	CRRT \ dialysis		
	Tracheostomy		
	Bronchoscopy and bronchial suction		
	Use of muscle relaxant (Paralyze)		
Respiratory Support when admitted to ICU	Oxygen supplement (nasal canula , face mask, …)		
	Noninvasive ventilation (NIV) or HFNC		
Intubation timing	Early intubation (within 24 hours from ICU admission)		
	Late intubation (more than 24 hours)		
Mechanical Ventilator Mode	Volume Control		
	Pressure Control		
	Both		
Ventilation parameters during IMV		**Minimum**	**Maximum**
	FiO_2 (%)		
	PEEP (cmH_2O)		
	Tidal volume (ml)		
	Respiratory rate (breath/min)		
	Pressure		
Pharmacological treatment			
Did the patient receive any of the following treatments?	Blood products (PRBC's, FFP , PLT, CRYO)		
	Muscle relaxant drugs		
	Inhaled vasodilators (nitric oxide)		
	Remdesivir , Favipiravir		
	Immunomodulators (Actemra (Toclezumab), Anakinra (kineret))		
Did the patient receive any of the following treatments?	Antiparasitic drug (Ivermectin)		
	I.V. Bronchodilator (Aminophylline, Magnesium sulfate)		
	Corticosteroids		
	Hydroxychloroquine (antimalaria and immunosuppressant)		
	Low-molecular weight heparin (Clexane)		
	Co-Zinc , Vitamin-D		
	Colchicine		

Part Four: Patient's outcomes

Variables	Options
Complications occurred during ICU stay	ARDS
	Pulmonary Embolism (PE)
	AKI
	Cardiovascular (dysrhythmia, ACS)
	Septic shock
	Secondary infection
	Pneumothorax
	Surgical (S.C.) Emphysema
	Bleeding (Upper GI , hematuria, Epistaxis, melena)
	DIC
	CVA (Stroke)
Length of stay in hospital (days)	
Length of stay in ICU (days)	
Length of IMV (days)	
Did the patient survive?	Yes
	No
Cause of death	

Appendix (B)

IRB Approval

An-Najah
National University
Health Faculty of medicine&
Sciences
IRB

جامعة النجاح
الوطنية
كلية الطب وعلوم الصحة
لجنة اخلاقيات البحث العلمي

Ref: Mas August *2021/15*

IRB Approval Letter

Study Title:

Survival rate and outcomes among critically ill Covid-19 patients requiring Invasive Mechanical Ventilation

Submitted by:
Fadi Saliba Jeries Assi

Supervisor:
Aidah Alkaissi, Wael Sadaqa

Date Approved:
25th August 2021

Your Study Title "**Survival rate and outcomes among critically ill Covid-19 patients requiring Invasive Mechanical Ventilation**" reviewed by An-Najah National University IRB committee and was approved on 25th August 2021

Hasan Fitian, MD

IRB

IRB Committee Chairman
An-Najah National University

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جـامعـــة النجاح الوطنية

كليـــة الدراســـات العليـــا

معدل البقاء على قيد الحياة والنتائج للحالات الحرجة من المرضى المصابين بفايروس كورونا المستجد والذين خضعوا لأجهزة التنفس الاصطناعي في فلسطين

إعداد

فادي صليبا جريس عاصي

إشراف

د. عايدة القيسي

د. وائل صدقة

قدمت هذه الرسالة استكمالا لمتطلبات الحصول علي درجه الماجستير في تمريض العناية المكثفة، من كلية الدراسات العليا، في جامعة النجاح الوطنية، نابلس– فلسطين.

2022

معدل البقاء على قيد الحياة والنتائج للحالات الحرجة من المرضى المصابين بفايروس كورونا المستجد والذين خضعوا لأجهزة التنفس الاصطناعي في فلسطين

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د. وائل صدقة

الملخص

خلفية الرسالة: كوفيد-19 هو مرض شديد العدوى يصيب الجهاز التنفسي ويمكن ان يؤدي الى متلازمة الضائقة التنفسية الحادة وفشل الجهاز التنفسي مما يستلزم الحاجة إلى الخضوع لأجهزة التنفس الاصطناعي. استدعى الاختلاف في استراتيجيات العلاج والنتائج الى استكشاف الخصائص الديموغرافية والسريرية للمريض، وخطط العلاج المحددة، وارتباطاتها المحتملة بالمراضة والوفيات.

أهداف الرسالة: لتحديد معدل البقاء على قيد الحياة والنتائج لمرضى كوفيد-19 الذين خضعوا لأجهزة التنفس الاصطناعي وتأثير الخصائص السريرية واستراتيجيات العلاج عليها.

منهجية الرسالة: تم استخدام تصميم دراسة التعرض المبني على المراقبة بأثر رجعي, تم تسجيل جميع مرضى كوفيد-19 الذين تم إدخالهم إلى المستشفيات المستهدفة في الفترة ما بين 2020/8/1 إلى 2021/4/30، والذين تزيد أعمارهم عن 18 عامًا والذين خضعوا الى أجهزة التنفس الاصطناعي. تم جمع البيانات من نظام معلومات المستشفى، وتشمل الخصائص مثل البيانات الديموغرافية، والأمراض المصاحبة، ونتائج الفحوصات المخبرية، واستراتيجيات العلاج مثل الدعم التنفسي، ووضعية المريض، وتوقيت التنبيب، وإعدادات جهاز التنفس الصناعي والعلاجات الدوائية. ومن النتائج مثل المضاعفات ومدة الخضوع لجهاز التنفس الاصطناعي والوفيات. ثم تم إجراء مقارنات بين مجموعتين فرعيتين تنقسم الى الناجين من الوباء و المتوفيين بناءا على المواصفات المذكورة أعلاه باستخدام SPSS كبرنامج إحصائي.

نتائج الدراسة: احتاج 150 مريضًا إلى جهاز التنفس الاصطناعي والتي تمثل 39.8٪ من مرضى كوفيد-19 ,حيث نجا منهم 13 (8.7٪) مريضا. كان متوسط العمر عند الدخول الى المستشفى 64 عامًا وكان العمر الأصغر مرتبطًا بانخفاض معدل الوفيات (0.948 OR، 0.006 = P). كان مرض شرايين القلب وذروة قيمة الكرياتينين مرتبطين بشكل ملحوظ في المرضى المتوفين (p = 0.041) (p = 0.008) بالترتيب. المرضى الذين خضعوا لأجهزة التنفس الاصطناعي على وضع التحكم في الضغط، مع انخفاض نسبة الاكسجين المكمل وضغط الشهيق كان لديهم معدل بقاء أعلى (4.416، 0.883، 0.478، على التوالي، p <0.05)، وكذلك الذين تم إخضاعهم لفغر القصبة الهوائية. وكان العلاج الدوائي الوحيد الذي له علاقة كبيرة بالبقاء على قيد الحياة هو ريميدسفير (P = 0.001). كان متوسط مدة الإقامة في وحدة العناية المركزة 27 يومًا للمرضى الناجين و11 يومًا لأولئك الذين ماتوا (القيمة الاحتمالية <0.001)، بينما كان متوسط الخضوع لجهاز التنفس الاصطناعي للناجين والمرضى المتوفين 15 يومًا مقابل 6 أيام على التوالي (P <0.001>)). أصيب المرضى بمضاعفات مثل القصور الكلوي الحاد (60.7٪) وأمراض القلب والأوعية الدموية (45.3٪) والتي ترتبط ارتباطًا وثيقًا بالمرضى المتوفين.

الاستنتاجات: كان معدل البقاء على قيد الحياة بين مرضى كوفيد-19 الذين خضعوا لأجهزة التنفس الاصطناعي منخفضًا (8.7٪)، يوصى بالممارسة القائمة على الأدلة والإدارة متعددة التخصصات في علاج الحالات الحرجة من مرضى كوفيد- 19 اعتمادًا على البحث العلمي، لتحسين نتائجهم.

الكلمات المفتاحية: كوفيد-19، معدل الوفاة، جهاز التنفس الاصطناعي، الخصائص، النتائج.