EFFECTS OF OBESITY ON THE RISK OF MECHANICAL VENTILATION, MORTALITY, SURVIVAL RATE AND POST COVID-19 SYMPTOMS AMONG HOSPITALIZED COVID-19 PATIENTS AT TERTIARY CARE HOSPITALS OF HYDERABAD AND KARACHI, PAKISTAN

ALI QURESHI

UNIVERSITI SAINS MALAYSIA

2024

EFFECTS OF OBESITY ON THE RISK OF MECHANICAL VENTILATION, MORTALITY, SURVIVAL RATE AND POST COVID-19 SYMPTOMS AMONG HOSPITALIZED COVID-19 PATIENTS AT TERTIARY CARE HOSPITALS OF HYDERABAD AND KARACHI, PAKISTAN

by

ALI QURESHI

Thesis submitted in fulfilment of the requirements
for the degree of
Doctor of Philosophy

July 2024

ACKNOWLEDGEMENT

I would like to express my gratitude to ALLAH SWT for giving me this opportunity and helping me endlessly in finishing my PhD work. Many blessings on our holy Prophet Muhammad Rasool Allah Salalaho Aleh Wa Sallam.

I would like to extend my thanks to my main supervisor Dr Nur Aizati Athirah binti Daud who mentored me to complete this project and guided me in the best possible manner. I must take this opportunity to especially thank my mentor and co-supervisor, Professor Dr Syed Azhar Syed Sulaiman who motivated me at each step in this journey and who helped in all possible ways.

A very special gratitude goes to my father Gul Hassan Qureshi who supported me in all possible ways under the shadow of his love and care. Parallel I would like to dedicate this successful work to my father Gul Hassan Qureshi and mother Azra Parveen Junejo (late).

I would like to thank my wives and kids (Um e Hani and Muhammad Ibrahim) for their cooperation and patients during the whole journey of my PhD research.

I am highly thankful to all those participants (patients) who provided me with their information. Equally, I extend my deepest condolences to the families of those who have lost their beloved ones during COVID-19 pandemic.

I am highly thankful to my religious teachers Sain Manzoor Hussain Sindhi, Sain Nathu Shah Bukhari, Sain Hafiz Abdul Ghani Sheikh, Sain Abdul Razaq Qureshi, for their utmost guidance.

I am thankful to my friend Narendar Kumar who have supported, motivated, and encouraged me in the whole process of my research unconditionally. I am highly thankful to Dr Shahid Junejo, Dr Shabana Junejo, Dr Mehran Abbassi, Dr Faisal Qureshi, Mr Zubair Ahmed Laghari and all those friends who have helped me in the data collection process.

Thanks to the Government of Sindh and the management of the concerned hospitals for their facilitations during the data collection process.

TABLE OF CONTENTS

LIST OF TABLES

Page

LIST OF FIGURES

Page

LIST OF ABBREVIATIONS

ALI	Acute Lung Injury
ARDS	Acute Respiratory Distress Syndrome
ASTH	Asthma
BMI	Body Mass Index
COPD	Chronic Obstructive Pulmonary Disease
CVDS	Cardiovascular diseases
DM	Diabetes Mellitus
HTN	Hypertension
PTSD	Post-traumatic shock disorder
TB	Tuberculosis

LIST OF APPENDICES

KESAN OBESITI TERHADAP RISIKO VENTILASI MEKANIKAL, KEMATIAN, KADAR KELANGSUNGAN HIDUP DAN SIMPTOM PASCA COVID-19 DALAM KALANGAN PESAKIT COVID-19 DI HOSPITAL PENJAGAAN TERTIARI HYDERABAD DAN KARACHI, PAKISTAN

ABSTRAK

Virus COVID-19 telah menjejaskan populasi yang besar di dunia, termasuk lebih daripada 3 juta kematian di seluruh dunia sehingga 2020. Kadar kematian kes setakat Disember 2020 ialah 2.29% di Pakistan. Seiring dengan COVID-19, satu lagi cabaran besar kepada komuniti kesihatan global ialah kelaziman obesiti. Obesiti adalah faktor risiko yang diketahui untuk jangkitan COVID-19 yang teruk. Dalam banyak kes, ia boleh membawa kepada kemasukan ke hospital, kemasukan rawatan rapi, pengudaraan mekanikal, dan akhirnya kematian. Ramai individu yang pulih daripada fasa akut jangkitan SARS-CoV-2 menghadapi simptom berpanjangan termasuk gangguan kognitif, masalah tidur, intoleransi senaman dan aduan autonomi. Keadaan ini dikenali sebagai sindrom pasca COVID-19. Matlamat kajian ini adalah untuk meneroka kesan obesiti terhadap risiko pengudaraan mekanikal, kematian, kadar kelangsungan hidup dan simptom selepas COVID-19 dalam kalangan pesakit COVID-19 yang dimasukkan ke hospital di hospital penjagaan tertiari di Hyderabad dan Karachi, Pakistan. Penyelidikan pelbagai ini dijalankan dalam 2 fasa, iaitu fasa retrospektif yang dijalankan dari Mac 2020 hingga Disember 2020 dan fasa prospektif dijalankan dari Januari 2021 hingga Julai 2021. Untuk menentukan perkaitan antara obesiti dan regresi logistik, analisis survival dan Cox-proportional regresi telah digunakan. Penemuan kami menunjukkan bahawa obesiti dikaitkan dengan peningkatan risiko pengudaraan mekanikal sebanyak 18 kali ganda dalam kalangan

pesakit COVID-19 (95% CI 12.62 – 25.67, P <0.001). Begitu juga pesakit diabetes adalah 12.26 kali lebih berkemungkinan memerlukan pengudaraan mekanikal (95% CI 8.89 – 16.89). Selain itu, pelbagai kelas obesiti mempunyai risiko besar kepada kematian akibat COVID-19. Berdasarkan analisis multivariate melalui model regresi logistik, didapati nisbah odds terlaras untuk pelbagai kelas obesiti juga sangat tinggi dengan kehadiran pelbagai faktor lain seperti komorbiditi, jantina, peningkatan umur dan ketagihan bahan. Selain itu, sebahagian besar kes discaj melaporkan gejala pasca COVID-19. Purata masa kelangsungan hidup pesakit adalah kurang ketara dalam kalangan pesakit obes berbanding pesakit bukan obes. Gejala yang paling dilaporkan adalah sakit otot (38.2%), batuk (30.9%),keletihan (21%), lemah (23.2%) dan kabus otak (21.9%). Oleh itu, boleh disimpulkanbahawa obesiti adalah penyumbang bebas kepada hasil buruk dalam COVID-19, terutamanya dengan kehadiran keadaan komorbid tertentu.

EFFECTS OF OBESITY ON THE RISK OF MECHANICAL VENTILATION, MORTALITY, SURVIVAL RATE AND POST COVID-19 SYMPTOMS AMONG HOSPITALIZED COVID-19 PATIENTS AT TERTIARY CARE HOSPITALS OF HYDERABAD AND KARACHI, PAKISTAN

ABSTRACT

The COVID-19 virus has affected a huge population of the world, including more than 3 million mortalities across the globe till 2020. The case fatality rate as of December 2020 was 2.29% in Pakistan. In parallel with COVID-19, another huge challenge to the global health community is the prevalence of obesity. Obesity is a known risk factor for severe COVID-19 infection. In many cases it can leads to hospitalization, intensive care admissions, mechanical ventilation, and eventually death. Many individuals who recovered from the acute phase of the SARS-CoV-2 infection face long lasting symptoms which includes cognitive impairment, sleep trouble, exercise intolerance, and autonomic complaints. This condition is known as post-COVID-19 syndrome. The aim of this study was to explore the effects of obesity on the risk of mechanical ventilation, mortality, survival rate and post COVID-19 symptoms among hospitalized COVID-19 patients at tertiary care hospitals of Hyderabad and Karachi, Pakistan. This multicentered research was conducted at two public sector hospitals of Sindh, Pakistan. The study was accomplished in two phases, which were the retrospective phase conducted from March to December 2020 and the prospective phase conducted from January to July 2021. Survival analysis including survival function curve and cox-proportional hazards regression was conducted to determine the impact of obesity on survival rate. Our findings showed that obesity was associated with an increased risk of mechanical ventilation by 18 times among

COVID-19 patients (95% CI 12.62 – 25.67, $P < 0.001$). Similarly, diabetic patients were 12.26 times more likely to require mechanical ventilation (95% CI 8.89 – 16.89). Moreover, various classes of obesity have a great risk to the mortality of COVID-19. Based on the multivariate analysis through logistic regression model, it was found that the adjusted odds ratio for various classes of obesity was also very high in the presence of various other factors such as comorbidities, male gender, increasing age and substance addiction. The mean survival time of patients was significantly less among the obese patients as compared to the non-obese patients. Additionally, the majority of discharged cases reported post-COVID-19 symptoms. The most reported symptoms were muscle pain (38.2%), cough (30.9%), fatigue (21%), weakness (23.2%) and brain fog (21.9%). Hence it can be concluded that obesity is an independent attributor to the poor outcomes of COVID-19, especially in the presence of certain comorbid conditions.

CHAPTER 1

INTRODUCTION

1.1 Background

Coronavirus disease 2019 (COVID-19) began in the form of a pneumonia outbreak, and the first case was detected in Wuhan, China, in January 2020 (Young et al., 2020). The virus has spread globally, with 4,806,299 active cases and 318,599 mortalities as of May 2020. In general, the death rate of COVID-19 was reported as 2.9%(Ciotti et al., 2020). The case fatality rate in Pakistan as of December 28, 2020, was 2.29% (Government of Pakistan, 2020).

The origin of the COVID-19 coronavirus has remained under debate since it was discovered. COVID-19 has distinctive characteristics that set it apart from other coronaviruses, according to a genome study and comparison with previously identified coronavirus genomes (Andersen et al., 2020).

Tyrell and Bynoe first described coronaviruses in 1966 after cultivating viruses from patients suffering from common colds. The coronaviruses were named based ontheir shape (Latin: corona = crown), which consisted of spherical viral particles with a core-shell and surface projections resembling a solar corona. The coronavirus is comprised of four subfamilies: alpha, beta, gamma, and delta. Gamma- and delta-viruses appear to have a different origin than alpha- and beta-coronaviruses, which are thought to have come from mammals, particularly bats (Velavan & Meyer, 2020).

Taxonomically, the COVID-19 virus belongs to the beta-coronavirus family. The coronavirus has a single-stranded, non-segmented RNA genome with positive polarity, and its virion comprises four primary structural proteins: nucleocapsid (N),

transmembrane (M), envelope (E), and spike (S) (Hasöksüz et al., 2020). The genetic sequencing of the COVID-19 virus is 79% similar to the previous severe acute respiratory syndrome coronavirus and 50% similar to the Middle East Respiratory Syndrome virus (Lee et al., 2020).

The studies revealed that age, gender, and the existence of co-morbid conditions such as hypertension, diabetes, pulmonary diseases, and malignancies are contributing factors towards COVD-19-related mortalities (Parohan et al., 2021; Surendra et al., 2021), and case fatalities are higher as compared to the normal population (Yang et al., 2020). Moreover, various clinical manifestations, including fever, cough, diarrhoea, lethargy, muscle ache, headache, skin problems, hemoptysis, and sore throat have been reported among COVID-19 patients (Jayroe et al., 2023). If the condition is left untreated, it can lead to COVID-19-associated pneumonia (Lee et al., 2020) and eventually death (Parohan et al., 2020). Many COVID-19-infected patients die due to respiratory distress (Qi et al., 2021). It has been shown that age, gender, and the existence of co-morbid conditions such as cardiovascular complications (Mehra et al., 2020), hypertension, diabetes, lung-related problems, and malignancies are contributing factors towards COVD-19-related mortalities (Alkodaymi et al., 2022; Parohan et al., 2021; Surendra et al., 2021), and among those cases, the fatality rate is higher than the normal population (Yang et al., 2020). Based on gender, there is no difference in the occurrence rate of COVID-19 among men and women.

However, the survival rate of males is lower as compared to females(Deng et al., 2020).

1.1.1 Prevalence and common symptoms of COVID-19

As of March 2020, around 571,678 cases of COVID-19 had been identified, and over 26 thousand deaths had been reported globally (CDC, 2022). Since the outbreak, there have been 770,437,327 confirmed cases of COVID-19, with 6,956,900 deaths reported to WHO as of September 6, 2023 (World Health Organization, 2023). Particularly in Pakistan, as of January 2021, over 483,362 cases were reported, out of which 35,130 were active, 10,258 were death cases, and 438,974 were recovered (Government of Pakistan, 2020). Most of the cases show symptoms such as fever, flu, cough, fatigue, gastric disturbance, sore throat, headache, rashes, loss of taste, loss of smell, and conjunctivitis. However, COVID-19 could be asymptomatic (Organization, 2021).

1.1.2 COVID-19 and Obesity

Obesity is a known risk factor for severe COVID-19, which may be due to chronic inflammation that affects immunological responses to pathogens as well as reduced lung function caused by excess weight. Obesity is a widespread metabolic condition that affects the majority of people in the United States, and it is a risk factor for other chronic diseases such as diabetes, heart disease, several malignancies, hospitalization, intensive care unit ICU or step-down unit admission, Invasive Mechanical Ventilation (IMV), and death. Subsequently, the risk of COVID-19-related hospital admissions is noticed least among patients with a normal body mass index as compared to those with a high body mass index (Kompaniyets et al., 2021).

Physiologically, obesity is related to chronic inflammatory pathways caused by the overaccumulation of adipose tissue. Obesity causes hypoxia, cell stress, and apoptosis due to the existence and hypertrophy of adipocytes (Demeulemeester et al.,

2021). Pragmatically obese patients are more vulnerable to spreading contagious viral infections. The virus sustains itself longer inside the body of obese patients, and this facilitates the virus' ability to bring more mutations that are potentially harmful (Michalakis et al., 2021).

Naturally, angiotensin-converting enzyme-I (ACE-I) prompts the constriction of blood vessels, and angiotensin-converting enzyme-II (ACE-II) works against the renin-angiotensin system (RAS). The angiotensin-converting enzyme-II receptors are present in adipose tissue, which links ACE-II with various systems of the body, such as the urinary tract, reproductive system, respiratory system, and central nervous system. Adipose tissue facilitates the connectivity of ACE-II. The COVID-19 virus also binds with ACE-II, and this is how it can penetrate various other organs of the body. This mechanism also precipitates the chance of acute respiratory distress syndrome (ARDS) among COVID-19-infected patients (Demeulemeester et al., 2021). According to a genome study and comparison with previously identified coronavirus genomes; the S1 or S2 spike junction has a cleavage site with a maximum affinity for the angiotensin-converting enzyme (ACE-II) receptors, which influences efficacy (Andersen et al., 2020).

Following the recommendation by the Centers for Disease Control and Prevention (CDC), a body mass index above 40 must be considered a risk factor for severe COVID-19 disease, and hospitals should devise an effective plan to serve those patients. Doctors must encourage patients to do physical activity to enhance their immunity (Long et al., 2020).

1.2 Prevalence of Obesity

Over 650 million individuals around the globe have been suffering from obesity since 2016 and mortality is more prevalent among obese people as compared to underweight people. The global burden of obesity has risen three times from 1975 to 2016 (Organization, 2022). In recent decades not only the Western world but also countries from the Middle East, American and Asian regions have been facing a huge burden of obese population, which is closely associated with various diseases (James, 2004; Seidell, 2005). Moreover, it has been estimated that if the prevalence of obesity continues to rise at the present speed, then 2.7 billion individuals will be overweight and 177 million will be obese by the next few years (Federation, 2022).

As per the World Obesity Foundation report, Pakistan stands among the top 200 countries across the globe about the prevalence of obesity (Lobstein & Brinsden, 2019). It is also estimated that by the year 2030, more than five million school-going children are expected to be obese (Federation, 2019). Therefore, obesity is also one of the challenges that Pakistan is facing (Tanveer et al., 2022). It has been estimated that in Pakistan more than 40 % of mortalities occur due to non- communicable diseases and most of them have an association with obesity (Maira Siddiqui et al., 2018). Globally, the presence of obesity depends on ethnicity and various other attributing factors including age, gender, dietary habits and living pattern(Chooi et al., 2019). Moreover, in Pakistan obesity is mainly associated with high fat food, and lack of physical work (Butt et al., 2019; Hunter & Reddy, 2013).

1.2.1 Risks of severe illness and mortality due to obesity

According to one report, obesity has been associated with a wide range of catastrophic effects on the body such as hypertensive crisis, diabetes mellitus, various

cardiovascular complications, liver disease, stroke, myalgia, and various types of mental illness (CDC, 2022).

Obesity can reduce the residual volume of the lungs, and this is the reason obese people have difficulty breathing. Studies have shown that the risk of severe illnesses, ventilation and mortality could be enhanced among COVID-19 patients due to increased body mass index and obesity (Allotey et al., 2020; Kompaniyets et al., 2021). Physiologically the extra adipose tissues within the body play an important role in the synthesis of inflammatory modulators such as interleukin-6 (IL-6), therefore pharmacologically cessation of such mechanisms could be beneficial (Xu et al., 2020).

1.2.2 Post-COVID-19 sequelae

Many individuals who recovered from the acute phase of the COVID-19 infection have lasting symptoms. This includes mental fogginess, sleep problems, exercise intolerance, and autonomic complaints. Some people may report prolonged low-grade fevers and lymphadenopathy. The condition is known as “long-haul COVID” (Nath, 2020) and “post-COVID-19 syndrome” (Greenhalgh et al., 2020). Post-COVID-19 syndrome appears to be a multisystem disease that can emerge even after a modest acute sickness (Nath, 2020). Post- COVID-19 affects both adults and children and presents them with a variety of symptoms. Fatigue, shortness of breath, cognitive difficulties, a persistent cough, speech difficulties, muscle aches, loss of smell or taste, and fever are among the symptoms that are frequently experienced.

One of its most challenging aspects is the unpredictable duration, with symptoms persisting for weeks to months (Organization, 2020). According to reports, the condition can last three months, though some people have said it can last up to six

months or even nine months(Organization, 2021). The prevalence of post-COVID-19 consequences among positive cases of SARS-CoV-2 infection has been estimated at up to 35% cases (Greenhalgh et al., 2020). It has been reported that patients younger than 40 were more likely to develop post-COVID-19 complications. Most cases had fever, cough, insomnia, headache, malaise, and respiratory complications (Mahmud et al., 2021). The increasing number of cases of long-haul COVID indicates an alarming situation ahead (Mahmud et al., 2021).

Around 10% of SARS-CoV-2 virus-positive patients stay ill for more than three weeks, and a lesser proportion for months (Pavli et al., 2021). It is possible for individuals with mild to moderate illnesses to experience post-COVID-19 symptoms as well as those with severe disease. 30% of patients with COVID-19 experience symptoms that last longer than the 2 weeks needed for convalescence, and 10% of patients experience symptoms that last longer than 12 weeks (Barinov A.N., 2021). Patients with post-COVID-19 symptoms could face acute to life-threatening complications such as shortage of oxygen, lung complications, cardiovascular crisis, and severe inflammatory issues (Nabavi, 2020), but more often patients with post-COVID-19 sequelae mostly have fatigue, shortness of breath, brain fog, insomnia, headache, post-traumatic stress disorder (PTSD), myalgia, and loss of concentration (Crook et al., 2021).

1.2.3 Mechanical Ventilation in COVID-19 Patients

Severe respiratory failure and pneumonia are common in COVID-19 patients, and many of them may require respiratory assistance through mechanical ventilation. The SARS-COV2 virus causes inflammation and permeation of the inner lining of the lungs, thus leading to visceral oedema and subsequently progressing to the

malfunctioning of the lungs (Möhlenkamp & Thiele, 2020). In addition, patients with severe COVID-19 may suffer from an acute lung injury, which is identified by the perfusion ratio, elastance, right-to- left shunt, lung weight, and lung recruit ability (Cronin et al., 2022). This often leads to severe respiratory distress, necessitating artificial or mechanical ventilation to ensure proper gaseous exchange (Elsayed et al., 2021; Fan et al., 2020). There are various factors related to the ventilation need among COVID- 19 patients, including the inability to breathe on their own and the need for protection from viral transmission by hospital staff (Domecq et al., 2021; Möhlenkamp & Thiele, 2020).

The risk of mechanical ventilation among COVID-19 patients can vary from 29% up to approximately 90% (Wunsch, 2020). Particularly, patients with poor health outcomes and age over 50 years have more risk of mechanical ventilation (Carson et al., 2012; Damuth et al., 2015). Patients who have pre- existing respiratory issues, low PaO2/FiO2 ratio and high PCO2 levels often require mechanical ventilation (Melamed et al., 2022). Moreover, patients at the state of receiving mechanical ventilation are always at a high risk of death. In the UK 65% of patients who were receiving mechanical ventilation have died, likewise in the US, more than 80% of patients have died (Richardson S, 2020).

1.3 Problem Statement

With its global impact and high mortality rates, the COVID-19 pandemic poses a serious threat to the world's healthcare systems. Like many other nations, Pakistan has experienced a significant number of COVID-19 cases and associated fatalities. The population worldwide is experiencing a substantial impact from the fatal outcomes of obesity at an extensive scale. Being overweight or obese can have a serious impact on

health (Organization, 2022). Obese people are more susceptible to severe COVID-19 infection, which is one of the notable trends seen during the pandemic. Obesity has emerged as a recognized risk factor that puts people at higher risk for developing more serious conditions, which can lead to hospitalization, admission to intensive care units, mechanical ventilation, and even death. The presence of diseases such as respiratory complications, cardiovascular crises, diabetes mellitus, and hypertension, along with certain malignant conditions, significantly exacerbates the detrimental effects of COVID-19, elevating them to catastrophic levels (Krams et al.) impacting the quality of life for survivors.

This study addresses the critical matter of the influence of obesity on COVID-19 outcomes, including the likelihood of requiring mechanical ventilation, mortality rates, survival rates, and the prevalence of post-COVID-19 symptoms among COVID-19 patients hospitalized in tertiary care hospitals in Hyderabad and Karachi, Pakistan. It is crucial to thoroughly investigate the relationship between obesity and COVID-19 outcomes, particularly in the context of Pakistan's healthcare system, given the potential implications for healthcare management and public health policy.

In 2020, a French study was conducted to observe the prevalence of patients who were admitted in critical condition and were on mechanical ventilation. The findings of the study revealed that obese and severely obese patients were more likely to receive mechanical ventilation. Notably, it's important to emphasize that this study solely focused on the use of mechanical ventilation and did not delve into the effect of obesity on the severity of COVID- 19 symptoms (Simonnet et al., 2020).

In China, obesity was mainly responsible for the progression of disease severity especially in the male gender in contrast to those having normal body mass index.

However, as per this study, body mass index was found to have no impact on the progression of symptoms. Also, significant differences were found in terms of the duration of disease progression between the different BMI groups. People with higher BMIs experienced a faster progression of the disease compared to those with lower BMIs. The connection between female gender and obesity was less clear because of the lower prevalence of obese women in the study (Yu et al., 2021).

These complex factors highlight the need for a thorough investigation of the complex interactions between obesity, COVID-19 results, and the resulting gender differences in disease progression. This emphasizes the necessity for a comprehensive examination of the intricate relationships and interplay between obesity, COVID-19 outcomes, and gender disparities in disease progression (Naaraayan et al., 2021). For instance, obesity can exacerbate the severity of COVID-19 symptoms (Nezhadmoghadam et al., 2024), leading to distinct outcomes in male and female patients due to physiological, immunological, and hormonal differences (Nezhadmoghadam et al., 2024). Furthermore, societal, and behavioral factors may also contribute to the observed gender disparities in disease progression (Kharroubi & Diab-El-Harake, 2022). Therefore, a thorough investigation of these complex interactions is crucial to understand the nuanced mechanisms underlying the differential impact of obesity on COVID-19 outcomes across genders.

Since COVID-19 has come to its end (Sarker et al., 2023), but obesity is still a huge global concern (Sharafetdinov & Plotnikova, 2020), and based on the findings of this study, more focus would be given to the individuals with certain medical conditions including obesity, and will be helpful on preparing vigilant plans including targeted vaccination, enhanced clinical guidelines, public health campaigns and preventive measures, long term management of surviving patients, in case of future

viral outbreaks. This will provide a comprehensive framework to enhance future health outcomes.

1.4 Research Objectives

i. To describe the characteristics of COVID-19 hospitalised patients based on their socio-demographic and co-morbidity profiles.

ii. To determine the effect of obesity on the risk of mechanical ventilation among COVID-19 patients.

iii. To determine the association between different levels of obesity and the risk of mortality among COVID-19 patients.

iv. To determine the effects of obesity, various classes of obesity on hazard ratio and survival rate among hospitalised COVID-19 patients.

v. To determine the effect of obesity on the risk of developing post-COVID-19 symptoms among the recovered patients.

1.5 Significance of Study

This research study carries immense significance as it explores the complex relationship between obesity and COVID-19 outcomes in the context of the Pakistani population. The findings have real-world applications that could change clinical procedures and public health regulations. Recognizing obesity as a significant risk factor for a severe COVID-19 infection, this study provides a crucial tool for healthcare providers to identify and prioritize high-risk patients, particularly in areas where obesity is common, by revealing a strong association between obesity and severe COVID-19 outcomes, such as the need for mechanical ventilation and

mortality. This information makes it possible to create interventions and treatment plans that are specifically tailored for obese patients, potentially reducing the adverse impacts of obesity on COVID-19 outcomes. and putting vaccination campaigns as the top priority.

Secondly, hospitals and healthcare facilities can use the knowledge gained from this research to effectively allocate crucial resources during the pandemic's peak times, thereby improving care. Additionally, public health initiatives can be improved to address obesity as a modifiable risk factor, with policies and educational campaigns aimed at reducing the population's obesity rates. The study also highlights the value of long-term health monitoring and rehabilitation for COVID-19 survivors, particularly those who are obese, to improve their quality of life. In conclusion, the significance of this study may pave the way for informed clinical decision-making and the development of more successful public health strategies, not only in Pakistan but possibly in a variety of global contexts grappling with the complex interplay between obesity, COVID-19 outcomes, and associated risk factors.

CHAPTER 2

LITERATURE REVIEW

2.1 Sociodemographic features of COVID-19 cases

Previously, it was reported that sociodemographic factors such as age and gender are critical in determining the prevalence of COVID-19-related hospitalizations. For instance, as reported by centers for disease control and prevention (CDC) in the United States the risk of hospitalisation was higher for individuals aged over 65 years compared to younger age groups (CDC, 2023). Similarly, in the United Kingdom, hospitalizations were predominantly observed among the individuals over 75 years old, with a significant proportion of male cases. These findings highlight the importance of considering sociodemographic factors in understanding the impact of COVID-19 on different populations (Edouard Mathieu, 2020).

Based on a study conducted in China, hospitalisations due to COVID-19 weremore prevalent among individuals aged 50 years or older (T. Chen et al., 2020). An Italian study revealed that COVID-19 hospitalisations were higher among individuals 65 years and above (Grasselli, 2020). In Spain and the United Kingdom, COVID-19 hospitalisations were more prevalent among men, while those aged below 60 years were less likely to be hospitalised as compared to those who were over 60 (De la Rica, 2020; Docherty, 2020). A similar French study elucidated that the ratio of COVID-19- affected patients over 70 years was more at risk (Girard, 2020). In Iran, the male gender was mostly affected, but the study revealed that people over 50 years were more prone towards COVID-19-related complications. This fact showed that even middle-aged adults, who are above 50 years old, can also be affected by COVID-19 (Kiani, 2021).

The impact of COVID-19 has been adversely associated with the body's immune system and elderly individuals have compromised immune functioning. This is also one of the reasons why older age patients were highly affected by the COVID-19 pandemic (Promislow, 2020). Patients of older age have mostly abnormal cascade of inflammatory response known as cytokine storm, which augments the shortness of breath and insufficient oxygen to the various parts of the body. In parallel, cytokine storm also prompts severe inflammatory responses in various organs of the body such heart, kidney, liver, lungs, and brain. This condition often leads to life-threatening consequences such as organ damage and eventually death (Weaver & Behrens, 2017). The major reason behind this cytokine-storm activation among COVID-19 geriatric patients is not completely known (Mueller et al., 2020).

Males were found to be more likely to be admitted to hospitals than females, based on studies in various countries (Edouard Mathieu, 2020, Chen, 2020, Grasselli, 2020, Girard, 2020). Studies conducted in the US and the UK found that over 50% of individuals hospitalised with COVID-19 were male (Apea VJ, 2021; McCarthy CP, 2020; Williamson et al., 2020). A multicentered study conducted in California in 2020 found that COVID-19 disproportionately affected elderly men (Richardson S, 2020), while another study conducted in Brazil reported higher COVID-19 hospitalisation rate among males aged 60 years or older (Fonseca, 2021). In Spain and the United Kingdom COVID-19 hospitalisations were more prevalent among men, while those aged below 60 years were less likely to be hospitalised as compared to those who were over 60 (De la Rica, 2020; Docherty, 2020)

One of the factors contributing to COVID-19's greater impact on men is the probable abundance of interleukins. This makes males more vulnerable towards the severity and mortality of COVID-19 (Latifi-Pupovci H, 2022). A study conducted in

2020 revealed that males have a greater number of angiotensin- converting enzyme-II (ACE-II) receptors, and it is considered a key receptor for binding COVID-19 virus. This receptor is present in various body parts including the lungs. Thus, it can be a key contributor to COVID-19 hospitalisations, especially in males (Beyerstedt et al., 2021).

A study also reported that hypertension (56%), obesity (42%), diabetes (34%), and cardiovascular disease (28%) were the most prevalent comorbidities observed among patients. These results emphasize the need to consider common comorbidities as risk factors for severe COVID-19 outcomes and further highlight the importance of understanding the demographic characteristics of those affected by the disease (McCarthy CP, 2020). The study also showed that hospitalisations for COVID-19 were more likely among individuals with concomitant diseases such as hypertension, diabetes, and chronic pulmonary disease (Vaughan, 2021). In New York, the mean age of the participants was 63 years, and over 60% of the population was male. Hypertension was found to be the most common condition, affecting more than 56%of individuals, followed by obesity, affecting approximately 42% of individuals. The study also revealed that over 12% of the population required mechanical ventilation, and the overall mortality rate was 21% (Richardson S, 2020).

According to a study done in India, COVID-19 hospitalisation rates are higher for men who are older than sixty and have long-term respiratory illnesses like chronic lung disease (Malik, 2021).

Another study also revealed that diabetic patients were more at risk of death due to COVID-19 (Apea VJ, 2021; Williamson et al., 2020). According to a study conducted in Brazil, individuals who were hospitalised due to COVID-19 were more

likely to have pre-existing medical conditions such as hypertension, diabetes, and chronic kidney disease (Fonseca, 2021).

Based on a study conducted in China, hospitalizations due to COVID-19 were more prevalent among those with pre-existing medical conditions such as hypertension, diabetes, and cardiovascular disease (T. Chen et al., 2020). An Italian study revealed that COVID-19 hospitalizations were higher among males, individuals 65 years and above, and those with pre-existing medical conditions such as hypertension, diabetes, and chronic obstructive pulmonary disease (Grasselli, 2020). In Spain and the United Kingdom COVID-19 hospitalizations were more prevalent among individuals with pre-existing medical conditions such as hypertension, diabetes, cardiovascular disease, and chronic kidney disease were more prone to the severity due to COVID-19 (De la Rica, 2020; Docherty, 2020). A French study elucidated that hypertensive, diabetic and renal problem patients were highly affected by COVID-19 (Girard, 2020). In Iran, in line with other studies, hypertensive, diabetic and cardiovascular patients were at high risk of being affected by COVID-19 (Kiani, 2021).

A growing amount of evidence suggests that social and behavioral variables might have a substantial impact on difficulties connected to COVID-19 (World Health Organization, 2023). According to research, public health behaviors have a significant impact on the virus's transmission rates, pointing to a relationship between behavioral tendencies and the severity of the outbreak. Understanding how social and behavioral factors contribute to COVID-19-related complications could therefore be crucial for developing effective public health interventions (Centres for Disease Control and Prevention, 2023). In 2021, a study was conducted to analyse data from various countries regarding COVID-19-related risk factors. This states that men are more

likely to be exposed to the virus because they work in vital industries and occupations that require them to interact with others. As a result, they frequently engage in activities like drinking and smoking without masks, increasing their risk of being infected with COVID-19. This study suggested that social and behavioral factors can be the key attributors to COVID-19-related complications (Kharroubi & Diab-El-Harake, 2022).

2.2 Risk of mechanical ventilation in COVID-19 cases

A study was conducted at the University of California, Los Angeles on 112 COVID-19 patients to outline the progression of respiratory failure in COVID-19 and investigate risk factors for IMV. They found that the risk of ventilation is higher in the case of obese and smokers. For patients who required mechanical ventilation, 18% (5 out of 28) did not survive. People who were obese were 5.82 times more likely to need mechanical ventilation than those who were not, after considering their age, sex, and other health conditions. Patients who used to smoke in the past were 8.06 times while current smokers were 10.33 times more likely to need mechanical ventilation. Moreover, increased inflammatory biomolecules can also precipitate the condition in COVID-19 patients. However, several limitations were identified in this study, which was a single-centre study with a small sample size, which precluded a more robust evaluation of risk factors associated with mortality (Monteiro et al., 2020). The entire cohort included 1042 patients at Mass General Brigham hospitals (median age, 64 years; 56.8% male). Based on the findings of another study, four factors were independently predictive of mechanical ventilation requirement, which are diabetes mellitus, SpO2:FiO2 ratio, C-reactive protein, and lactate dehydrogenase (Nicholson et al., 2021).

Another study was conducted in Brazil to describe the clinical characteristics and predictors of mechanical ventilation of adult inpatients with COVID-19 in a single centre. A retrospective cohort study was performed and included adult inpatients hospitalised from March 17th to May 3rd, 2020, who were diagnosed with SARS-CoV-2 infection. Overall, 88 consecutive patients were included in this study. The median age of the patients was 63 years, males were 67%, 33% of patients were admitted to the intensive care unit, 20% of patients needed mechanical ventilation, and 10.2% died during hospitalisation. The research outlines that in the initial group of patients who were admitted to hospitals with COVID-19, the greatest risk factor for respiratory failure and the requirement for mechanical ventilation in their population was age (Bastos et al., 2020).

Another study was conducted to identify early indicators among the patients under IMV. This retrospective study was conducted from September 2020 to 8 August 2021. The total subjects were 1,613 confirmed COVID-19 patients, and 22.6% of patients needed IMV. Factors associated with mechanical ventilation included older age than 65 years, smoking, critical disease at admission, and chronic kidney disease (Kabbaha et al., 2022).

Between March 12 and June 1, 2020, a multicenter, prospective study was conducted involving mechanically ventilated patients with ARDS, as per the Berlin criteria, and confirmed COVID-19 cases (evidenced by positive SARS- CoV-2 nasal or pharyngeal swab results). The study included individuals admitted to a network of 36 Spanish and Andorran ICUs. In total, 742 patients with complete 28-day outcome data were analyzed, revealing that 17.1% had mild ARDS, 44.6% had moderate ARDS, and 38.1% had severe ARDS (Ferrando et al., 2020).

Older age, higher body mass index, and certain comorbidities were associated with an increased risk of death in mechanically ventilated patients. In a comprehensive study focusing on mechanically ventilated COVID-19 patients in New York City, crucial insights emerged from an analysis of 5700 hospitalised individuals. Among this cohort, 1999 patients required mechanical ventilation, revealing a strikingly high mortality rate of 88.1% among those who received this intervention. However, it is important to note that while the study provided valuable information regarding these risk factors, it did not furnish details regarding the timing of mechanical ventilation, its duration, or the specific ventilator settings employed (Grasselli, 2020).

Based on the facts of the study on the respiratory mechanism in COVID- 19 conducted on twelve mechanical ventilation COVID-19 patients in Italy, that mostly patients with severe COVID-19 have compromised pulmonary functioning due to poor compliance and subsequently they required mechanical ventilation. However, the study had a very small sample size and did not include a control group of non-COVID-19 patients with similar respiratory failure (Bellani et al., 2016).

Overall, these studies suggest that mechanical ventilation is a common intervention for patients with severe COVID-19 but is associated with high mortality rates. Key factors associated with poor outcomes include older age, higher body mass index, and certain comorbidities. However, more research is needed to better understand the optimal timing, settings, and duration of mechanical ventilation in COVID-19 patients, as well as the underlying pathophysiology of COVID-19-associated respiratory failure.

2.3 Risk of ventilation due to obesity

Obesity was one of the main factors that increased the risk of mechanical ventilation needs among COVID-19 patients. A retrospective observational cohort study was carried out within the time frame of March 12, 2020, to April 16, 2020. This work consists of 112 COVID-19 patients who were admitted consecutively to the Los Angeles hospital. The primary objective of the study was to provide a comprehensive description of the various features, treatment options, and path of respiratory distress and mortality within the specific cohort. Additionally, it was sought to investigate the potential factors that may be associated with the requirement for IMV. It was observed that obese patients were 5.82 times more likely to require mechanical ventilation. However, there were a few limitations of this study, primarily, it was a single-centered study which increases the bias for results. Secondly, the sample size was too small to evaluate better risk analysis, and lastly, the follow-up time was only one month (Monteiro et al., 2020).

Other potential factors affecting the risk of mechanical ventilation among COVID-19 patients include age and ethnicity. A study was conducted in the UK to meticulously examine and scrutinize the intricate relationship between obesity and the outcomes of coronavirus disease 2019 (COVID-19), with a particular emphasis on the diverse ethnic groups that comprise the study population. This study encompassed those individuals who were admitted to healthcare facilities in the United Kingdom due to the novel coronavirus disease (COVID-19) during the specified time frame of February 6 to October 12, 2020. The study cohort included a total of 54,254 subjects, with a mean age of 76 years with various ethnicities. It was observed that patients above 70 years are at high risk of MV. The deleterious consequences of obesity have been found to be significantly correlated with various health outcomes across diverse

ethnic groups, with a particularly pronounced effect observed among individuals of black ethnicities. However, this study did not mention anything about Asian ethnicity which can be considered one of the lacking in this study (Yates et al., 2021).

In a retrospective study conducted at a single hospital in France from February27 to April 5, 2020, the primary outcome measure was the need for mechanical ventilation. Mechanical ventilation was confirmed when the oxygen required was more than 10 litre/minute, with respiration over 25 breaths per minute and with acute respiratory distress in the presence of supplementary oxygen. As per the findings of the study, patients with COVID-19 illness were seven times more at risk of mechanical ventilation due to the presence of obesity, especially among the severe obesity cases with body mass index above 35 kg/m2. The drawback of this study was that it was conducted in one centre only (Simonnet et al., 2020).

2.4 Risk of mortality in COVID-19 cases

As of September 6, 2023, there have been 770,437,327 confirmed cases of COVID-19 worldwide, resulting in 6,956,900 fatalities. In Pakistan specifically, there have been 1,580,631 confirmed cases of COVID-19, with 30,656 reported deaths, according to information reported to the World Health Organization (WHO) (World Health Organization, 2023). Various studies have been conducted since the outbreak of COVID-19, showing different factors that contribute to the mortality of COVID-19. As per one study on morbidity and mortality among diabetic COVID-19 patients, it was shown that diabetes was highly associated with the risk of morbidity and mortality in COVID-19 hospitalized patients. More mortalities were noticed among patients with elevated glycemic levels (Gupta et al., 2020).

A similar pattern study was conducted on the risk factors for mortality among diabetic patients with COVID-19 in New York. It was revealed that the overall mortality rate was above 30% with most individuals being either old age or with concomitant health problems such as obesity and diabetes. Additionally, the mortalities due to obesity were more prevalent among the male gender as compared to the female. In line with other factors, such as CVDs, kidney problems, and COPD were significantly associated with mortality. However, hypertension was not addressed in this study (Agarwal et al., 2020).

A thorough study and meta-analysis was conducted on fatalities in COVID-19 patients having ARDS and usage of corticosteroid. It was found that COVID-19 patients with ARDS used corticosteroids was linked to a lower risk of death. However, the best dose and the length of corticosteroid treatment were not clear in this study (Ye et al., 2020).

In New York, another research was conducted on the risk factors for mortality in patients with COVID-19. This study revealed that different factors such as older age, male gender, and concomitant illnesses (i.e. hypertension, cardiac complications, diabetes), and obesity are contributing to a huge risk of mortalities (Richardson S, 2020).

In Italy, a study assessed 1,500 active COVID-19 patients and found that the same factors continued to be associated with high mortality rates, particularly among those who required admission to intensive care and mechanical ventilation (Richardson S, 2020). A meta-analysis comprising 31 studies conducted across diverse regions has yielded the conclusion that among various comorbid conditions, hypertension, diabetes, and cardiovascular issues exhibited a strong association with a

significant number of COVID-19-related deaths. Biological markers such as D-dimmer and laboratory parameters can also be used as predictors associated with mortality in COVID-19 (Wynants et al., 2020).

2.5 Obesity as a factor for mortality in COVID-19 cases

In a study conducted in 2020, researchers investigated the association between body mass index (BMI) and risk of adverse health outcomes. Specifically, they aimed to determine if individuals with a BMI over 35 were at a higher risk compared to those with lower BMI values. The findings of this study shed light on the potential health implications of elevated BMI levels. The study employed a retrospective cohort design, utilizing a sample size of 383 (Cai et al., 2020).

Similar research on the mortality associated with obese COVID-19 patients was conducted which highlighted a high mortality rate, especially among young patients (Tartof et al., 2020).

Another investigation was conducted to explore the potential relationship between obesity and the severity of COVID-19 in individuals diagnosed with fatty liver disease. This research aimed to determine how obesity affects the health of COVID-19 individuals with fatty liver disease. It was postulated that obesity-related adipose tissue may exacerbate the severity and mortality of COVID-19 by compromising immunological response, causing ongoing inflammatory conditions, and increasing insulin resistance. However, the knowledge of the processes via which fat enhances COVID-19 severity and mortality is lacking (Kassir, 2020).

A study was conducted to investigate the association between obesity and diabetes in patients and their susceptibility to severe COVID-19 outcomes, including

mortality. It was found that individuals with both obesity and diabetes exhibit an elevated risk of experiencing severe COVID-19 manifestations and increased mortality rates. Furthermore, it was analysed that the risk could be amplified among individuals with high body mass index and diabetes (Hussain et al., 2020).

2.6 Post-COVID-19 symptoms and effect of obesity

Long COVID-19, characterized by the persistent presence of symptoms following a COVID-19 infection, is a topic of growing concern and extensive research. It is crucial to understand the prevalence, symptoms, and factors associated with this condition to better address its impact on affected individuals. Research was carried out at Washington Hospital in United States, with 177 subjects involved in this work. The majority of subjects were women. The main purpose of this research was to observe the post- COVID-19 sequelae after six months. Of the total participants of this study, 30% of individuals have reported the presence of post-COVID-19 symptoms that lasted for more than 6 months. However, this study was conducted in a single centre and with limited sample size (Logue et al., 2021).

In the Kingdom of Saudi Arabia (KSA), a meta-analysis of 63 earlier studies on the causes and severity of post-COVID-19 symptoms was conducted. It was revealed that patients with old age, female gender, and patients with a history of critical or severe illness of SARS-COV2 had a significant association with the development of post-COVID-19 symptoms. However, there are several limitations associated with the research included in this analysis and the overall study design. Previously published systematic reviews have shown that the research studies included in this one were lack of consistent symptom terminology, standardized methods for recording symptoms, and categorization of multiple symptoms under overarching terms