CASE FATALITY RATE AMONG ELDERLY COVID-19 PATIENTS IN KELANTAN, MALAYSIA IN 2020 – 2022 AND ITS ASSOCIATED FACTORS

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by

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LIST OF ABBREVIATIONS

ACE2	Angiotensin-Converting Enzyme 2
ARDS	Acute Respiratory Distress Syndrome
BID	Brought-In-Dead
BMI	Body Mass Index
CFR	Case Fatality Rate
CI	Confidence Interval
COVID-19	Coronavirus Disease 2019
CRP	C-Reactive Protein
HFNO	High-Flow Nasal Oxygen
ICU	Intensive Care Unit
ILI	Influenza-Like Illness
IQR	Interquartile Range
MERS	Middle East Respiratory Syndrome
NAAT	Nucleic Acid Amplification Test
OR	Odds Ratio
PPE	Personal Protective Equipment
ROC	Receiver Operating Characteristic
RTK-Ag	Rapid Test Kit Antigen
RT-PCR	Reverse Transcription Polymerase Chain Reaction
SARI	Severe Acute Respiratory Illness
SARS	Severe Acute Respiratory Syndrome
SARS-CoV-2	Severe Acute Respiratory Syndrome Coronavirus 2
SpO2	Oxygen Saturation
SPSS	Statistical Package for The Social Science
USM	Universiti Sains Malaysia
VIF	Variance Inflation Factor
WHO	World Health Organization

LIST OF SYMBOLS

>	More than
<	Less than
≥	More than and equal to
≤	Less than and equal to
=	Equal to
α	Alpha
β	Beta
%	Percentage
°C	Degrees Celsius
®	Registered Trademark

ABSTRAK

KADAR KEMATIAN KES DI KALANGAN PESAKIT COVID-19 WARGA TUA DI KELANTAN, MALAYSIA PADA TAHUN 2020 – 2022 DAN FAKTOR-FAKTOR YANG BERKAITAN

Latar Belakang: Pandemik COVID-19 telah memberi kesan yang ketara terhadap kadar kematian di seluruh dunia, dengan populasi warga tua mengalami kesan yang lebih teruk. Berbanding individu yang lebih muda, individu warga tua lebih mudah mengalami gejala yang teruk, lebih cenderung dimasukkan ke hospital, dan kadar kematian kes yang lebih tinggi.

Objektif: Tujuan kajian dibuat adalah untuk menentukan kadar kematian kes dan mengenal pasti faktor yang menyumbang kepada kematian akibat COVID-19 di kalangan populasi warga tua di Kelantan, Malaysia, dari tahun 2020 hingga 2022.

Kaedah: Kajian ini dijalankan dengan menggunakan data sekunder dari pangkalan data kebangsaan COVID-19 untuk tempoh dari 1 April 2020 hingga 31 Mac 2022. Kajian ini melibatkan reka bentuk kajian keratan rentas dan kawalan kes. Persampelan secara rawak digunakan untuk memastikan set data yang mewakili populasi. Analisis data dilakukan dengan menggunakan kaedah regresi logistik mudah dan regresi logistik berganda.

Keputusan: Kajian ini merangkumi 28,295 pesakit warga tua (≥60 tahun). Pesakit-pesakit ini dibahagikan kepada kumpulan kes dan kawalan, dengan 780 pesakit dipilih secara rawak dari kumpulan kes dan 3,120 pesakit dari kumpulan kawalan. Kadar kematian kes untuk populasi warga tua dengan COVID-19 di Kelantan dalam tempoh ini ialah 3.6%. Daripada 28,295 pesakit warga tua, 27,204 pulih dari jangkitan, 1,024 meninggal dunia akibat COVID-19, dan 67 meninggal dunia dengan jangkitan COVID-19. Analisis regresi logistik berbilang menunjukkan faktor-faktor ketara yang menyumbang kepada kematian akibat COVID-19, termasuk umur ketika diagnosis dibuat (adjusted OR 1.09; 95% CI: 1.07, 1.10; p = <0.001), satu dos vaksin COVID-19 (adjusted OR 0.70; 95% CI: 0.51, 0.97; p = 0.034), dua dos vaksin COVID-19 (adjusted OR 0.13; 95% CI: 0.11, 0.16; p = <0.001), dan tiga dos vaksin COVID-19 (adjusted OR 0.004; 95% CI: 0.001, 0.030; p = <0.001).

Kesimpulan: Kadar kematian kes untuk populasi warga tua dengan COVID-19 di Kelantan masih tinggi. Penemuan dalam kajian ini memberikan pandangan bernilai mengenai faktor-faktor yang mempengaruhi kematian COVID-19 di kalangan kumpulan ini. Dengan mengiktiraf kepentingan umur dan dos penerimaan vaksin dalam menentukan hasil untuk pesakit warga tua, kumpulan penjagaan kesihatan dan pembuat dasar boleh merancang intervensi berfokus dan strategi kesihatan awam bertujuan mengurangkan risiko kematian dan meningkatkan hasil keseluruhan untuk populasi berisiko ini.

KATA KUNCI:

Kadar kematian kes, warga tua, COVID-19, faktor

ABSTRACT

CASE FATALITY RATE AMONG ELDERLY COVID-19 PATIENTS IN KELANTAN, MALAYSIA IN 2020 – 2022 AND ITS ASSOCIATED FACTORS

Background: The COVID-19 pandemic has significantly impacted global mortality rates, with the elderly population experiencing disproportionate effects. Compared to younger individuals, elderly individuals face a higher susceptibility to severe symptoms, hospitalization, and higher case fatality rates.

Objectives: The aim of this study is to determine the case fatality rate and identify factors contributing to death due to COVID-19 among the elderly population in Kelantan, Malaysia, from 2020 to 2022.

Methodology: The study was conducted utilizing secondary data from the national COVID-19 database for the period of 1st April 2020 to 31st March 2022. This study involved cross-sectional and case-control study designs. Simple random sampling was employed to ensure a representative dataset. Data analysis was carried out using simple and multiple logistic regression methods.

Results: The study included 28,295 elderly patients (≥60 years old). These patients were divided into case and control groups, with 780 patients randomly selected from the case group and 3,120 patients from the control group. The case fatality rate for the elderly population with COVID-19 in Kelantan during this period was 3.6%. Out of 28,295 elderly patients, 27,204 survived the infection, 1,024 died due to COVID-19, and 67 died with COVID-19. Multiple logistic regression analysis revealed significant factors associated with death due to COVID-19, including age at diagnosis (adjusted OR 1.09; 95% CI: 1.07, 1.10; p = <0.001), one dose of the COVID-19 vaccine (adjusted OR 0.70; 95% CI: 0.51, 0.97; p = 0.034), two doses of the COVID-19 vaccine (adjusted OR 0.13; 95% CI: 0.11, 0.16; p = <0.001), and three doses of the COVID-19 vaccine (adjusted OR 0.004; 95% CI: 0.001, 0.030; p = <0.001).

Conclusions: The case fatality rate for the elderly population with COVID-19 in Kelantan remains high. The findings in this study offer valuable insights into factors influencing COVID-19 mortality among this vulnerable group. By recognizing the importance of age at diagnosis and vaccination status in determining outcomes for elderly patients, healthcare professionals and policymakers can devise targeted interventions and public health strategies aimed at reducing mortality risk and improving the overall prognosis for this at-risk population.

KEYWORDS:

Case fatality rate, elderly, COVID-19, factors

CHAPTER 1

INTRODUCTION

1.1 Epidemiology of COVID-19

SARS-CoV-2 (Severe Acute Respiratory Syndrome Coronavirus-2) was discovered in Wuhan in December 2019 and was declared a worldwide pandemic by the World Health Organization (WHO) on 11th March 2020 (Albitar *et al.,* 2020). Malaysia announced its first case of COVID-19 on 25th January 2020, originated from three Chinese citizens who contracted the virus during their visit to Singapore. Following this, the first Malaysian person infected with COVID-19 was detected on 4th February 2020. Concerns have been raised about the virus's potential effect on vulnerable groups, particularly the elderly, who are more sensitive owing to physiological alterations associated with age and comorbidities (Arvinder-Singh, 2022).

Because of their vulnerability to severe illness and higher mortality rates, research on COVID-19 in the elderly is essential. When compared to younger individuals, the elderly are more prone to have severe COVID-19 complications such as death and hospitalization (Dadras *et al.*, 2022; Lu *et al.*, 2022). Age is not the only risk factor for severe COVID-19 among the elderly. Being vaccinated, sex, and comorbidities all have an influence on the severity and course of the illness (Zheng *et al.*, 2022; Sharifi *et al.*, 2023). COVID-19 has a significant influence on systems of healthcare and elderly care. An increase in elderly admissions and admissions to intensive care units has put an added burden on healthcare resources (Suah *et al.*, 2021).

1.2 COVID-19 mortality

At a specific point in time, the case fatality rate (CFR) calculates the proportion of confirmed deaths among individuals diagnosed with a specific disease, making it an essential epidemiological measurement. It is different from the mortality rate, which is a measurement of the number of fatalities that occur within a population over the course of a particular time period. In assessing the severity of a disease and estimating the risk of mortality, the CFR serves as a valuable tool. This provides critical information that can be used by healthcare providers and policymakers when formulating policies to manage and minimise the impact of an epidemic of a disease. Within the scope of the research topic centered on COVID-19 among the elderly population, the CFR is utilized to determine the percentage of COVID-19-related deaths among the confirmed cases of elderly COVID-19 patients. It enables us to determine not only the increased susceptibility of those in this population to severe outcomes, but also the potential factors that contribute to the elevated CFR. Some of these potential factors include age-related physiological changes, comorbidities, and disparities in access to healthcare resources (Passarelli-Araujo *et al.*, 2022).

With a significant impact on public health globally, the COVID-19 pandemic has led to varying outcomes among demographic groups, particularly the elderly population, who have experienced notably worse consequences. Repeatedly, it has been discovered that the elderly infected with COVID-19 consistently exhibit a significantly higher mortality rate compared to younger individuals. This heightened mortality rate among the older population is a reason to be concerned and highlights the necessity of targeted public health measures to safeguard and support this vulnerable group of people (Akhavizadegan *et al.*, 2021).

1.3 Problem statement

The global morbidity and mortality rates have been significantly impacted by the COVID-19 pandemic, with a disproportionate impact on the elderly population. In comparison to younger individuals, this group exhibits a higher likelihood of experiencing severe symptoms, requiring hospitalization and intensive care, and demonstrating a higher case fatality rate (Hwang *et al.*, 2020; Yanez *et al.*, 2020; Victora *et al.*, 2021). In Malaysia, multiple studies have revealed that the elderly, especially those with comorbidities, face a higher risk of adverse outcomes and elevated mortality rates. Despite the implementation of prevention and control measures, such as vaccination programmes, the elderly mortality rate remains high (Mat Din *et al.*, 2021; Abdul Taib *et al.*, 2022; Gani *et al.*, 2022). The objectives of this study are to explore the case fatality rate and examine the factors linked to death due to COVID-19 within the elderly population of Kelantan, Malaysia.

1.4 Rationale of study

Motivated by the necessity to gain a deeper understanding of the challenges faced by the elderly population amidst the COVID-19 pandemic, this research aims to investigate the factors contributing to heightened morbidity and mortality among older individuals. Specifically, it will examine elements such as comorbidities, age-related physiological changes, and healthcare accessibility. The insights derived from this study will be instrumental in shaping public health policies and clinical practices. Furthermore, it will serve as a foundational study for future research endeavours focused on devising targeted interventions to enhance the health outcomes and overall well-being of the elderly population, both during and after the COVID-19 pandemic.

The findings of this study may provide those working in health care with new information that may be used to enhance preventative efforts and to reduce death rates, particularly among the older population.

1.5 Research questions

1. What is the case fatality rate among elderly COVID-19 patients in Kelantan, Malaysia in 2020 – 2022?
2. What are the factors associated with death due to COVID-19 among elderly COVID-19 patients in Kelantan, Malaysia?

1.6 Objectives of study

1.6.1 General objective

To study the case fatality rate in 2020 – 2022 and the factors associated with death due to COVID-19 among elderly COVID-19 patients in Kelantan, Malaysia.

1.6.2 Specific objectives

1. To determine the case fatality rate among elderly COVID-19 patients in Kelantan, Malaysia in 2020 – 2022.
2. To determine the factors associated with death due to COVID-19 among elderly COVID-19 patients in Kelantan, Malaysia.

1.7 Hypothesis

1.7.1 Null hypothesis

There is no association between factors (sociodemographic factors, cluster-related status, source of infection and vaccination status) and death due to COVID-19 among elderly with COVID-19 in Kelantan, Malaysia.

CHAPTER 2

LITERATURE REVIEW

To investigate the case fatality rate of COVID-19 and its predictive factors among the elderly population, a thorough literature review was conducted. The search incorporated databases including PubMed, Scopus, and Google Scholar, employing various search strategies that involved combining terms utilizing Boolean operators (AND, OR, NOT). The review included any relevant studies that were published between 2020 and 2023. The terms COVID-19, case fatality rate, mortality rate, elderly, and older persons and the predictors of death were all determined to be keywords.

2.1 SARS-CoV-2

Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) is responsible for the infectious disease known as COVID-19, which has had a profound global impact. SARS-CoV-2 belongs to the Coronaviridae family and is characterized as a single-stranded RNA virus. Within the Coronaviridae family, various viruses are recognized for causing a spectrum of illnesses, containing mild respiratory ailments such as the common cold to more severe respiratory diseases (Rashedi *et al.*, 2020). SARS-CoV-2 is classified under the Betacoronavirus subfamily, alongside the viruses accountable for and Middle East Respiratory Syndrome (MERS) and Severe Acute Respiratory Syndrome (SARS) (Memish *et al.*, 2013; Wartecki and Rzymski, 2020).

2.1.1 Structure of SARS-CoV-2

Within the SARS-CoV-2 genome, there are genes for non-structural proteins encoded by open reading frame 1a (ORF1a) and ORF1b, alongside genes for structural proteins including spike (S), envelope (E), membrane (M), and nucleocapsid (N) (Wu *et al.*, 2020b).

With a 96.2% sequence homology to the bat coronavirus RaTG13 strain and 79.5% to SARS-CoV, the genome of the virus indicates a likely bat origin, accompanied by mutations in the S and N genes that facilitate human infection (Benvenuto *et al.*, 2020; Zhou *et al.*, 2020b). Exhibiting a stronger affinity compared to SARS-CoV, SARS-CoV-2 utilizes its S protein to bind to the angiotensin-converting enzyme 2 (ACE2) receptor on host cells (Wrapp *et al.*, 2020). High expression of angiotensin-converting enzyme 2 (ACE2) receptors is observed in various cell types, including lung cells and oral mucosa epithelial cells. Consequently, these cells are susceptible to binding by SARS-CoV-2, and the oral mucosa cells can potentially serve as a site for viral replication and transmission (Xu *et al.*, 2020).

The virus presents varying clinical manifestations in those infected. In 80% of instances, individuals are either asymptomatic or experience mild upper respiratory tract symptoms. In some cases, approximately 20% of patients experience pneumonia accompanied by symptoms like fever, cough, shortness of breath, and fatigue. This condition can potentially advance to respiratory and multi-organ failure. Factors such as underlying health conditions and age have an impact on the severity and outcome of symptomatic cases (Huang *et al.*, 2020). Both genetic and acquired factors influence an individual's susceptibility and the severity of the disease. Risk factors do not directly cause the disease, but they show correlation, indicating an increased likelihood of disease development. By identifying, assessing, and managing relevant factors, early diagnosis and treatment can reduce disease complications, ultimately increasing the number of individuals recovering from COVID-19 (Rashedi *et al.*, 2020).

2.1.2 Transmission

Human involvement in nature and ingestion of wild animals contributed to the spread of coronaviruses from animals to people. Initially found in bats, the virus was transmitted to an intermediate host, underwent slight changes in transmission capacity, and eventually infected humans. Subsequently, the virus rapidly spread among the population in China before extending its reach to over two hundred countries worldwide (Li *et al.*, 2020b; Lu *et al.*, 2020). Factors like the source of the pathogen, the number of infected individuals, the ease and speed of transmission, and the clinical severity of the disease play a crucial role in the dissemination of zoonotic viruses. In terms of transmissibility, SARS-CoV-2 surpasses both SARS-CoV and MERS-CoV, with a reproduction number of 3.28 (Liu and Rocklöv, 2021). Transmission of the virus can occur from animals to humans, between humans, and from humans to animals (Li *et al.*, 2020b; Zhou *et al.*, 2020b).

Droplets produced during coughing and sneezing are the primary means of virus transmission. Infectious particles are spread through the mouth during close contact with others (Wu *et al.*, 2020a). Transmission is also possible during the recovery and incubation periods (Rashedi *et al.*, 2020). Because the virus can persist in aerosols for a prolonged period, poorly ventilated interior environments pose a risk of transmission (Van Doremalen *et al.*, 2020). In the mouth and lower respiratory tract's epithelial cells, the virus undergoes proliferation and shedding for an extended period. Shedding intensifies during the prodromal phase and reaches its peak on days 3-5 of the disease. In some patients, this shedding can persist for up to 37 days (Zhou *et al.*, 2020a). Unbeknownst to their infection and lacking monitoring, asymptomatic individuals make a significant contribution to the transmission process. Moreover, they outnumber symptomatic individuals within society (Lai *et al.*, 2020).

The virus can survive on surfaces like aluminium, plastic, and steel for extended periods, enabling transmission through contact (Van Doremalen *et al.*, 2020). Social gatherings are a critical factor in spreading the disease (Wang *et al.*, 2020b). Elderly care centers, homeless shelters, prisons, schools, universities, and stadiums are consequently at higher risk for transmission. To break the chain of transmission in these settings, increased control and monitoring are necessary (Rashedi *et al.*, 2020).

2.1.3 Risk factors

The COVID-19 pandemic has disproportionately affected the elderly population, highlighting the importance of understanding and addressing the various risk factors associated with the disease. Risk factors can be categorized into host, environmental, and viral factors, each playing a significant role in the susceptibility and severity of the infection (Rashedi *et al.*, 2020).

2.1.3(a) Host risk factors

Risk factors for COVID-19 in hosts include advanced age, male sex, and comorbidities such as diabetes, hypertension, cardiovascular disease, cancer, chronic obstructive pulmonary disease, chronic renal disease, malnutrition, immunodeficiency, specific genotypes, asthma, autoimmune diseases, cerebrovascular disease, and chronic liver disease (Rashedi *et al.*, 2020). Older individuals are more susceptible due to age-related decline in lung function and immune response (Opal *et al.*, 2005). Men are at higher risk possibly due to higher exposure, behavioral differences, and hormonal factors (Rizzo *et al.*, 2020). Diabetes impairs innate immunity and causes pulmonary complications, while hypertension may affect lung function and oxygen delivery (Pitocco *et al.*, 2012; Rashedi *et al.*, 2020).

Cardiovascular disease increases sensitivity due to ACE2 expression in heart tissue, and cancer patients are more susceptible due to weakened immune systems (Gallagher *et al.*, 2008). Other factors compromise various bodily systems, increasing vulnerability to infection (Wang *et al.*, 2020a).

2.1.3(b) Environmental risk factors

Risk factors for COVID-19 transmission in the environment include overcrowding, a lack of knowledge, occupational hazards, inadequate ventilation, animal contact, poor hygiene, jails, nursing homes, dorms, bad living circumstances, unemployment, a high body mass index (BMI), stress, and public transportation (Rashedi *et al.*, 2020). Crowded spaces and gatherings increase the risk of contamination, while inadequate education can result in improper prevention measures (Van Doremalen *et al.*, 2020; Wang *et al.*, 2020b). Greater exposure to the virus is faced by healthcare workers and individuals in other high-risk occupations (Rashedi *et al.*, 2020). Poor ventilation in public spaces can facilitate transmission, and contact with infected animals poses risks (Lai *et al.*, 2020). COVID-19 spread and severity are influenced by a variety of environmental variables (Rashedi *et al.*, 2020).

2.1.3(c) Viral risk factors

Transmissibility, viral evolution, and viral load are among the viral risk factors associated with COVID-19 (Rashedi *et al.*, 2020). SARS-CoV-2 has a high transmission rate and can survive on various surfaces, increasing its spread (Liu and Rocklöv, 2021). The virus changes via mutations, which may challenge vaccine development by influencing replication, transmission, immunological responses, virulence, treatment resistance, and host adaptability (Pachetti *et al.*, 2020; Rashedi *et al.*, 2020).

The transmission of the virus is influenced by the viral load present in both asymptomatic and symptomatic patients, and a high viral load can pose a risk to patients' lives by triggering severe inflammation and cytokine storms (Lai *et al.*, 2020; Rizzo *et al.*, 2020). Identifying these factors helps in developing targeted strategies for rapid diagnosis and treatment.

2.1.4 Case definition

Classification of COVID-19 cases is crucial for effective pandemic management and control. These classifications facilitate healthcare professionals in making informed decisions regarding testing, treatment, and isolation procedures. Cases are categorised into three categories: suspected, probable, or confirmed. Each category is subdivided further into different options based on a combination of clinical, epidemiological, and diagnostic criteria (Ministry of Health, Malaysia, 2020).

Suspected cases of SARS-CoV-2 infection can be categorized into three options based on specific criteria. The first option applies to individuals who meet both clinical and epidemiological criteria. Clinical criteria include the presence of an acute fever and cough or at least two of the following symptoms: fever, cough, fatigue, headache, myalgia, sore throat, coryza, dyspnea, anorexia/nausea/vomiting, diarrhea, or altered mental status. Epidemiological criteria require being in a high-risk setting, residing in or traveling to an area with community transmission, or working in a health setting within 14 days prior to symptom onset. The second option is applicable to patients with severe acute respiratory illness (SARI), characterized by respiratory infection with fever ($\geq 38°C$), cough, onset within the last 10 days, and requiring hospitalization. Lastly, the third option involves asymptomatic individuals who do not meet epidemiologic criteria but have a positive SARS-CoV-2 rapid test kit antigen (RTK-Ag) (Ministry of Health, Malaysia, 2020).

There are four categorized options for a probable case of SARS-CoV-2 infection. The first option applies to a patient who meets the previously mentioned clinical criteria and is either a contact of a probable or confirmed case or linked to a COVID-19 cluster. The second option includes a suspected case with chest imaging revealing findings suggestive of COVID-19 disease. The third option refers to an individual experiencing a recent onset of anosmia or ageusia without any other identifiable cause. Lastly, the fourth option relates to an unexplained death in an adult who exhibited respiratory distress prior to death and was either a contact of a probable or confirmed case or linked to a COVID-19 cluster (Ministry of Health, Malaysia, 2020).

There are three options for classifying a confirmed case of SARS-CoV-2 infection. The first option applies to a person with a positive Nucleic Acid Amplification Test (NAAT), including RT-PCR, Rapid Molecular, and Gene X-pert tests. The second option includes a person with a positive SARS-CoV-2 RTK-Ag who also meets either the probable case definition or suspected criteria. Lastly, the third option refers to an asymptomatic person with a positive SARS-CoV-2 RTK-Ag who is a contact of a probable or confirmed case (Ministry of Health, Malaysia, 2020).

2.1.5 Case detection

Detecting COVID-19 cases is essential for the efficient management and prevention of the virus. This can be accomplished by implementing multiple surveillance systems, targeted screenings, pre-admission screening, and monitoring at entry points. These methods facilitate early case identification, allowing healthcare providers to provide prompt and appropriate care to infected individuals and prevent the spread of the virus among vulnerable populations.

Surveillance systems, such as COVID-19 sentinel surveillance, SARI surveillance, and pre-operative screening, are essential resources for case detection. Case definitions for individuals with symptoms of acute respiratory infection, such as fever, cough, and onset within the last ten days, are used in clinical or laboratory-based Influenza-Like Illness (ILI) monitoring. Typical ILI surveillance samples consist of nasopharyngeal and oropharyngeal swabs. Similarly, laboratory-based SARI surveillance involves the collection of nasopharyngeal, oropharyngeal, sputum, and aspirate samples from hospitalized patients with acute respiratory infection symptoms. Pre-admission screening for COVID-19 is an additional crucial aspect of case detection, as it helps to prevent nosocomial transmission of the virus.

Entry points, including airports, seaports, and land borders, serve as vital for case detection. Screening and testing travellers upon entry can aid in identifying and isolating infected individuals, thereby reducing the transmission of the virus both within the country and internationally. Targeted screening is a valuable measure for case detection because it focuses on populations or locations with a higher infection risk. Passive case detection from healthcare facilities involves identifying COVID-19 cases among patients seeking medical care for unrelated conditions. By aiding in the identification of potential transmission chains, this method can provide valuable information on the prevalence of the virus within a community. Screening for BID cases is an essential aspect of case detection because it provides information about the overall mortality associated with COVID-19. Screening for BID can help identify factors contributing to severe outcomes and inform interventions aimed at reducing fatalities, particularly in vulnerable groups like the elderly.

2.1.6 Screening

Effective COVID-19 screening is essential for mitigating the pandemic's effects on the population. By establishing appropriate screening protocols in healthcare facilities, it is possible to detect suspected cases early, effectively manage them, and prevent their spread.

Patients arriving at healthcare facilities should be screened for suspected COVID-19 at triage. Establishing a designated location for the evaluation and management of suspected cases will allow patients direct access while minimizing the risk of exposure to others. To further reduce the risk of transmission, suspected cases should be managed by qualified personnel whenever feasible. When a patient presents at the triage counter with any of the following criteria, suspicion of COVID-19 should arise: attendance at an event or area associated with a known COVID-19 cluster or red zone; travel to or residence in a foreign country within 14 days before the onset of illness; or close contact with a confirmed case of COVID-19 within 14 days before illness onset.

Healthcare providers are obligated to implement infection prevention and control measures to reduce the risk of transmission when a patient fulfills the criteria for suspected COVID-19. These measures include separating patients by at least one meter and designating an isolation area or room within clinics and emergency rooms. Both medical professionals and suspected patients should practice meticulous hand hygiene. In addition, surgical masks should be provided to patients, unless contraindicated, and healthcare workers must always utilize the recommended personal protective equipment (PPE). After each encounter, it is necessary to dispose of used PPE and decontaminate the isolation area and any used apparatus.

By adhering to these best practices and protocols, healthcare providers can effectively screen the population for COVID-19, thereby reducing the risk of transmission and enhancing the health outcomes of the vulnerable groups. The adoption of these screening approaches, along with supporting viral containment and community protection, helps with the general oversight of the COVID-19 pandemic.

2.2 Case fatality rate of COVID-19

When studying infectious diseases like COVID-19, the case fatality rate (CFR) holds great importance as it quantifies the proportion of confirmed cases resulting in death, thus providing an estimate of the disease's severity. Numerous studies have reported a wide range of CFR, varying across different geographies and demographic groups (Li *et al.*, 2020a; Onder *et al.*, 2020; Sim *et al.*, 2020; Wu and McGoogan, 2020; Ioannou *et al.*, 2022; Passarelli-Araujo *et al.*, 2022). The aim of this literature review is to critically investigate the CFR in relation to the COVID-19 pandemic.

Li *et al.* (2020a) performed a research at Wuhan University's Renmin Hospital, which indicated a CFR of 37.3% among 204 elderly individuals (≥60 years old) diagnosed with COVID-19, with 76 people passing away from the condition. The study further underscored age and underlying health conditions as the primary risk factors contributing to fatality. Conversely, Onder *et al.* (2020) reported a significantly lower overall CFR of 7.2% in Italy, with 1,625 deaths out of 22,512 confirmed cases up to 17th March 2020. This difference may potentially highlight regional variations in response to the disease or differences in the demographic composition of the populations studied.

Sim *et al.* (2020) performed an extensive study in Malaysia, analyzing the clinical records of all RT-PCR confirmed COVID-19 individuals over the age of 12. Individuals admitted to 18 selected hospitals between 1st February and 30th May 2020 were included in the research. The study recorded 73 in-hospital deaths out of 5,889 cases, resulting in a CFR of 1.2%. In China, Wu and McGoogan (2020) reported an overall CFR of 2.3%, based on a study of 72,314 COVID-19 cases. Supporting the findings of Li *et al.* (2020a) on age being a critical risk factor, the CFR escalated to 8.0% among individuals aged 70 to 79 years and further rose to 14.8% in those aged 80 years and older.

Ioannou *et al.* (2022) conducted a retrospective cohort analysis on patients over the age of 65 admitted to the COVID-19 Department of the University Hospital of Heraklion. The research showed a 13.4% CFR among 224 individuals, with fatalities occurring mostly in older male patients. Lastly, a study conducted by Passarelli-Araujo *et al.* (2022) in Brazil reported a CFR of 2.8% among a total of 59,853 confirmed cases. Table 2.1 presents a summary of the comparisons in case fatality rates among COVID-19 patients across various studies.

Table 2.1: Summary of comparison in case fatality rate among COVID-19 patients

References	Study location	Time period	Case fatality rate (%)
Li *et al.* (2020a)	China	31st January – 20th February 2020	37.3 (≥60 years old)
Onder *et al.* (2020)	Italy	Data up to 17th March 2020	7.2 (overall patients)
Sim *et al.* (2020)	Malaysia	1st February – 30th May 2020	1.2 (overall patients)
Wu and McGoogan (2020)	China	December 2019 – February 2020	2.3 (overall patients), 14.8 (≥80 years old), 8.0 (70-79 years old)
Ioannou *et al.* (2022)	Greece	Data up to August 2021	13.4 (>65 years old)
Passarelli-Araujo *et al.* (2022)	Brazil	1st January – 20th October 2021	2.8 (overall patients), 6.1 (fully vaccinated), 2.6 (unvaccinated)

2.3 Factors associated with death due to COVID-19 among elderly patients

Compared to younger age groups, the elderly population has experienced higher mortality rates as a result of the significant impact of the COVID-19 pandemic (Dadras *et al.*, 2022). To facilitate specific interventions and improve patient outcomes, a thorough knowledge of the variables associated with mortality in elderly COVID-19 patients is required. In the context of a disease or infection, predictor factors are variables that, when present or at certain levels, enhance the likelihood of a particular outcome, such as death (Puchongmart *et al.*, 2023). Identifying these factors can assist healthcare providers, policymakers, and researchers in developing strategies to reduce the pandemic's impact on this vulnerable population (Damayanthi *et al.*, 2021).

In this review of the literature, several predictor factors were investigated. Through examination of existing research, a thorough comprehension of the variables contributing to the heightened risk of death in the elderly population with COVID-19 can be established. This process also enables the identification of potential knowledge gaps that require further investigation. Ultimately, this review can serve as a basis for devising evidence-based interventions and policies to better support the health and well-being of the elderly throughout the ongoing pandemic and beyond.

2.3.1 Age

Consistently, age has been found to be a risk factor for increasing disease severity and death in COVID-19 patients. Akhavizadegan *et al.* (2021) have demonstrated that advancing age is associated with various physiological changes that can negatively impact an individual's response to the virus. One of the primary factors contributing to this increased vulnerability is the decline in immune system function that often accompanies aging. This inadequate response to pathogens may result in a diminished ability to effectively combat the virus, subsequently leading to more severe cases of COVID-19. Furthermore, organ failure is more likely in the elderly, enhancing the risk of morbidity and death associated with COVID-19. This decline in organ function, coupled with the immune system's reduced efficacy, can lead to accelerated inflammation. This heightened inflammatory response may result in multiple organ failure and, ultimately, death, particularly in the context of intensive care unit treatment.

Albitar *et al.* (2020) identified advanced age as a risk factor for COVID-19 mortality. Compared to younger patients, older individuals with COVID-19 often exhibit higher peak viral loads. Although the median viral load difference between severe and mild cases of the disease is not significant, a high initial viral load has been linked to increased mortality in patients infected with SARS-CoV, a virus closely related to SARS-CoV-2, the causative agent of COVID-19. The heightened susceptibility of elderly patients to severe outcomes and mortality from COVID-19 may be attributed to a weakened immune response associated with advanced age. This compromised immune function renders older individuals more prone to developing acute respiratory distress syndrome (ARDS), which is a common complication in severe cases of COVID-19 and has been strongly associated with higher mortality rates, particularly among the elderly population.

The observed patterns of case fatalities in relation to age differ somewhat between countries. For instance, in Italy, the majority of COVID-19-related fatalities have been reported among individuals aged 60 and above, whereas in China, more than 50% of fatalities have occurred in individuals aged 50 and older (Asaduzzaman *et al.*, 2022). These findings highlight the increased vulnerability of older adults to severe outcomes and death due to COVID-19, regardless of geographical location. Among hospitalized individuals with COVID-19, research specifically targeting patients aged 60 years and above has uncovered that frailty, characterized by age-related declines in physiological reserve and function leading to increased vulnerability, is linked to a greater risk of death and heightened disease severity (Azevedo *et al.*, 2022). These findings suggest that frailty, along with advanced age, may significantly influence COVID-19 outcomes in the elderly.

According to Azwar *et al.* (2020), elderly individuals account for 38.6% of COVID-19 fatalities in Indonesia. A further examination of the data indicates a greater number of non-survivors aged 70 and older than survivors, with a ratio of 40% to 30%. Notably, the mortality rate among hospitalized older persons with COVID-19 in this research was 23% higher than the COVID-19 case fatality rate among Indonesia's elderly population, with a difference of 14.9% versus 23%. This data highlights elderly people's increased sensitivity to severe COVID-19 outcomes, especially among those who need hospitalization.

Numerous studies have repeatedly shown a relationship between age and COVID-19 risk, demonstrating that being older is closely associated with a higher possibility of severe consequences and fatality. For example, Williamson *et al.* (2020) reported that people aged 80 and beyond experienced a higher risk compared to those aged 50-59 years. This finding is supported by Dadras *et al.* (2022), who noted that old age is a significant predictor of poor prognosis, suggesting that aging-related mechanisms may play a crucial role in disease severity.

Demirci Üçsular *et al.* (2022) discovered a steady increase in the probability of mortality with increasing age. The researchers suggested 56 as an appropriate cut-off point for calculating mortality risk. Djaharuddin *et al.* (2021) emphasized the link between COVID-19's elevated mortality rate and the degree of severity of the illness, as well as the prevalence of underlying disorders. They observed that the age group of 60 years and over had the greatest death rate (51.47%), followed by the 45-59 year age group (48.53%), and the less than 45 year age group (12%). This highlights the significant impact of age on COVID-19 mortality.

In a similar vein, Liu *et al.* (2020) discovered that COVID-19 patients aged ≥60 years had a greater likelihood of failure of the respiratory system and required longer treatment durations than patients under 60. When compared to the younger age group, their results showed that older COVID-19 patients had a much more severe illness and a less favourable response to therapy. These studies highlight the relevance of age as a critical element in the care of COVID-19 patients, as well as the need to modify treatment programs to fit the unique needs and risk profiles of elderly individuals. Yanez *et al.* (2020) demonstrated that persons aged ≥65 years exhibited considerably higher COVID-19 death rates than younger individuals in their research involving 16 nations. Furthermore, males were shown to be at a greater risk of COVID-19 mortality than women. These data show the importance of age and sex in understanding the effect of the COVID-19 pandemic on various demographic groups.

In their study, Zhang *et al.* (2022) underscored the increased risk faced by older individuals in developing severe illness and experiencing a poor prognosis upon infection with SARS-CoV-2, which subsequently heightens the likelihood of mortality. Consequently, it is vital for older individuals to adopt enhanced protective measures to minimize exposure to the virus. The study further indicated that once older individuals contract SARS-CoV-2, the virus replicates and spreads at an accelerated rate within their bodies, leading to a higher probability of symptomatic manifestation and accelerated disease progression. Surendra *et al.* (2021) reported that among the studied patients, the median age was 46 years, with 5% being children and 52% being men. They found that deceased patients were generally older, more likely to be men, and presented with a higher frequency of symptoms such fever and shortness of breath. The study also revealed that age-specific mortalities varied across age groups. The study showed a clear increase in mortality with advancing age.

2.3.2 Frailty

Kumar *et al.* (2022) described frailty as a state of diminished physiological reserve and capacity, which can occur at any age, although it is often considered a geriatric condition. Aging naturally leads to a gradual decline in physiological functions; however, frailty represents an accelerated deterioration in these functions, resulting in impaired homeostatic capacity. Salini *et al.* (2022) emphasized that multiple studies consistently indicate a higher mortality risk among older COVID-19 patients with frailty compared to non-frail individuals. Even when other clinical and demographic characteristics are taken into account, the link between frailty and an increased risk of death remains strong. As a result, detecting and treating frailty as a strong factor in poor outcomes in elderly COVID-19 patients is critical. It is critical to put in place adequate measures to reduce the effect of frailty on this vulnerable group.

Djaharuddin *et al.* (2021) concentrated on the effect of immunosenescence, a reduction in immune function associated with age, on the vulnerability of elderly individuals to respiratory tract infections in their research. Immune system failure associated with immunosenescence has been related to increased susceptibility and severity of clinical symptoms in older persons infected with COVID-19. As a result, frailty, which is commonly linked with immunosenescence in the elderly, might serve as a predictor of poor outcomes in COVID-19 patients. When analyzing the likelihood and severity of COVID-19 infections in the elderly, the role of frailty and its influence on the immune system must be considered.

Gani *et al.* (2022) highlighted the impact of immune senescence, a decline in immune function, and reduced cell-mediated immunity in the elderly population, which significantly contribute to their heightened susceptibility to severe illness. This susceptibility is worsened by a rising number of comorbidities among the elderly, which raises the risk of severe illness on its own. In addition, Hadinejad *et al.* (2021) highlighted those factors such as immunosuppression, diminished organ function, and inadequate health management contribute to the increased vulnerability of the elderly to viral exposure. Immune dysregulation and increased inflammation not only enhance the pathophysiology of COVID-19 but also increase susceptibility, pathogenicity, and viral infection in older persons. As a consequence, the disease's severity and fatality rates rise in this group.

2.3.3 Sex

Azwar *et al.* (2020) discovered among the elderly COVID-19 patients that not only were confirmed cases primarily male, but 90% of non-survivors were also male. This observation reveals a correlation between male sex and COVID-19 mortality, signifying a heightened risk for males compared to females. Similarly, Williamson *et al.* (2020) identified sex as an acknowledged factor in devastating COVID-19 outcomes. According to their findings, more than 90% of COVID-19 mortality in the UK occurred in people over the age of 60, with men accounting for 60% of these fatalities. These results highlight the need to address both age and sex when examining the risk variables associated with catastrophic outcomes in COVID-19 cases amid elderly people.

Across all age groups, Barreto Parra *et al.* (2022) discovered that men exhibit higher COVID-19 mortality rates than women. One potential explanation for this discrepancy is that men, when considering age, tend to have a greater prevalence of comorbidities compared to women. Comorbidities such as obesity and kidney disease are recognized as being linked with an elevated risk of COVID-19 mortality. Among elderly individuals with COVID-19 infection, Damayanthi *et al.* (2021) pinpointed several factors, including advanced age, male sex, dyspnea, and dementia, that were linked to an elevated risk of death. These findings underscore the significance of considering the interplay between age, comorbidities, and sex when assessing the risk of severe outcomes in older COVID-19 patients.

2.3.4 Nationality

Lim *et al.* (2022) reported that between March and November 2021, one in five COVID-19 mortality in Malaysia were classified as BID cases which were more frequently found among non-Malaysian citizens. Non-Malaysian individuals can be further divided into legal and illegal workers or migrants. Legal workers, such as students, typically have medical insurance and can travel within the country without the fear of being arrested or detained. In contrast, illegal workers may lack financial coverage for medical care and may avoid seeking treatment at medical facilities due to the fear of being apprehended or detained. The findings revealed that foreign nationals in Malaysia had a 4.32 times higher risk of dying as BID cases from COVID-19 compared to Malaysian citizens. This suggests that the likelihood of foreigners in Malaysia dying outside hospitals due to COVID-19 was greater than that of Malaysians. The studies concluded that nationality played a crucial role in determining whether a COVID-19 patient died as BID or within a hospital setting (Arvinder-Singh, 2022).

2.3.5 Comorbidities

The comorbid conditions of individuals with pre-existing chronic illnesses have been linked to their increased susceptibility to contracting the virus and experiencing severe symptoms. Studies have shown an elevated mortality rate among COVID-19 patients, which can be attributed to their underlying conditions (Djaharuddin *et al.*, 2021).

Possibly due to prevalent comorbidities such as hypertension, diabetes, and cardiovascular diseases, elderly COVID-19 patients are particularly susceptible to severe illness (Bongiovanni *et al.*, 2021). Older individuals tend to have higher rates of comorbidities and may experience stronger inflammatory responses, putting them at an increased risk of death (Dadras *et al.*, 2022). Additionally, individuals who are elderly and immunocompromised and who have comorbidities such as hypertension, diabetes and cardiovascular diseases are more severely impacted by COVID-19 and demonstrate a higher case mortality rate (Dhama *et al.*, 2020).

In patients aged 65 years and older, Demirci Üçsular *et al.* (2022) observed a significantly higher prevalence of comorbidities such as malignancy (17%), diabetes mellitus (24%), cardiovascular disease (24%), chronic obstructive pulmonary disease (25.7%), and hypertension (47%). Similarly, Mat Din *et al.* (2021) discovered that a large proportion of COVID-19 mortality among elderly individuals was among people with at least one underlying medical illness, especially those aged ≥70 years old. Diabetes and hypertension were the most often detected illnesses in this cohort, and they were acknowledged as the most important risk factors for COVID-19 mortality in the elderly, along with age.