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ASSOCIATION OF COVID-19 CO-MORBIDITIES WITH MORTALITY RATE: AN ASSESSMENT-BASED SYSTEMATIC REVIEW

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Abstract

Background

The ongoing COVID-19 pandemic, caused by a novel coronavirus, has resulted in significant morbidity and mortality worldwide. Pre-existing health conditions, such as hypertension, cardiovascular diseases, obesity, asthma, immunodeficiency, chronic kidney disease, neurodegenerative disorders, and diabetes, have been shown to enhance the risk of infection and exacerbate prognostic outcomes. Countries that have observed this correlation between COVID-19 mortality and comorbidities include Italy, the United States, and the United Kingdom. Objective: So, the objective of the current study is to analyze how comorbidities affect clinical patterns and outcomes, emphasizing the importance of understanding their role in the severity of COVID-19.

Methodology

The methodology of the study involves conducting research in low- and middle-income countries while utilizing the Preferred Reporting Items for Systematic Reviews (PRISMA) guidelines for data extraction and screening.

Results

The results of this review analysis revealed that COVID-19 patients with comorbidities, specifically hypertension, diabetes, cardiovascular illnesses, respiratory disorders, and smoking, experienced higher mortality rates. It was observed that younger individuals had a greater infection rate, while

older individuals faced a higher risk of death due to complications. Notably, the age group between 18 to 59 years, representing the economically active population, exhibited the highest rate of COVID-19 infection. Conversely, individuals aged 60 years and above had a higher fatality rate attributed to disease-related complications.

Conclusion
Comorbidities such as cardiovascular diseases and diabetes were found to drastically increase the likelihood of severe outcomes among affected patients. So, the current systematic review findings confirm the close association between pre-existing health conditions and COVID-19-related fatalities.

Keywords: SARS-CoV-2, comorbidities, mortality.

Introduction

The Coronavirus Disease 2019 (COVID-19/), initiated by the Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2), emerged out of China in 2019 and rapidly escalated into a worldwide pandemic. As of May 30, 2020, a distressing total of 362,786 fatalities were recorded globally [1]. After some months, the World Health Organization announced this outbreak as a pandemic [2]. For every country and region, obtaining precise death toll statistics from this pandemic is critical in assessing its far-reaching impacts on public health. This accurate data serves not only to quantify the tragic loss of life, but also as an insightful tool for investigating contributing factors influencing discrepancies in fatality rates among diverse populations. It equally helps to forecast the potential course of future viral outbreaks. Notably, the clinical severity of COVID-19 patients spans a broad spectrum, with cases ranging from mild to severe, or even fatal. Increasingly, research suggests this variability in disease manifestation is partly attributed to underlying comorbidities in these patients [3]. Reflecting back, it is believed the initial case of COVID-19 displayed symptoms similar to pneumonia in Wuhan City, China, in December 2019, albeit from an unknown source. The subsequent proliferation of this novel single-strand RNA beta-coronavirus, or the COVID-19 pandemic, has led to substantial morbidity and mortality rates whose underlying causes continue to mystify scientists. While COVID-19 can affect healthy individuals, it is more prevalent among those with specific medical conditions and older age groups. SARS-CoV-2 affects multiple organs and primarily binds to angiotensin-converting enzyme 2 receptors[4]. Patients with underlying comorbidities, such as hypertension, cardiovascular diseases, obesity, asthma, immune deficiencies, chronic renal impairment, neurodegenerative diseases, and diabetes, face a higher risk of infection and poorer outcomes.

Although COVID-19 cases have been reported among cancer patients, there are limited treatment options available for this specific group. Apart from comorbidities advanced age and compromised immune systems, further impacted by cancer therapy, contribute to the severity and higher fatality rates observed in these cases. Moreover, older patients have more chronic diseases, such as hypertension, making them more susceptible to severe forms of COVID-19 based on some earlier reports [5,6]. Therefore, older people have higher mortality rates compared to younger patients (the mortality of people over 60 years old is 4.5% in comparison to 1.4% in people under 60) [7,8]. The case fatality rate (CFR) among cancer patients infected with SARS-CoV-2 ranges from 3.7% to 61.5% based on various studies conducted in different regions [9]. However, these reported cases exhibit heterogeneity in terms of clinical and biological mechanisms, disease progression, and treatment strategies, which limits their representativeness of the entire population with cancer [10]. Numerous countries, such as Italy, the United States, and the United Kingdom, indicate a correlation between COVID-19 death rates and the incidence of certain comorbidities [11]. Given that SARS-CoV-2 is still evolving and undergoing various mutations, the severity and clinical course of the virus are not fully understood to date. In this review, our objective is to investigate the high mortality rate among COVID-19 patients with comorbid conditions and explore risk factors that can

worsen COVID-19 symptoms. Moreover, by examining the correlation between SARS-CoV and the disability-adjusted life years associated with different comorbidities, we seek to shed light on the intriguing connection between COVID-19 mortality and pre-existing health conditions.

Methodology

Search Strategy

The literature research was carried out an extensive review of articles on COVID-19 spanning from 2019 to 2022. Our research aimed to understand the clinical relationship between pre-existing health conditions (comorbidities) and diseases that could be associated with COVID-19. To achieve this, we embarked on a comprehensive search on popular medical and academic databases including Google Scholar, PubMed, Science Direct, Medline, Psych Info, and CINAHL. In order to ensure the thoroughness of the search, a range of relevant search terms were utilized, including

COVID-19 associated comorbidities

The search term "COVID-19 associated comorbidities" was used to capture articles discussing the co-existing conditions or diseases alongside COVID-19. This search aimed to explore the relationship between COVID-19 and underlying health conditions.

COVID-19 associated comorbidities death rate

Expanding on the previous search, "COVID-19 associated comorbidities death rate" delved deeper into the topic by retrieving articles that specifically examined the interplay between COVID-19, accompanying comorbidities, and the resulting death rate. This search aimed to provide a more nuanced understanding of the impact of comorbidities on mortality in COVID-19 patients.

COVID-19 associated mortality rate

The search term "COVID-19 associated mortality rate" focused specifically on articles discussing the mortality rates associated with COVID-19. This search aimed to shed light on the severity and fatality of the disease.

SARS-CoV-2 associated comorbidities

Shifting the focus to SARS-CoV-2, the search term "SARS-CoV-2 associated comorbidities" targeted articles that explored the co-existing conditions or diseases with this particular type of coronavirus. This search aimed to identify specific comorbidities associated with SARS-CoV-2 infection.

SARS-CoV-2 associated death rate

Similarly, "SARS-CoV-2 associated death rate" aimed to retrieve articles that discussed the death rates specifically related to SARS-CoV-2. This search provided insights into the severity and fatality of SARS-CoV-2 infection.

COVID-19 or SARS-CoV-2 associated comorbidities

Expanding the scope, the search term "COVID-19 or SARS-CoV-2 associated comorbidities" widened the search to include articles that studied comorbidities associated with either COVID-19 or SARS-CoV-2. This approach aimed to broaden the understanding of the impact of comorbidities across different coronaviruses and identify common patterns.

COVID-19 or SARS-CoV-2 associated mortality rate

Likewise, "COVID-19 or SARS-CoV-2 associated mortality rate" retrieved documents that discussed the mortality rates associated with either COVID-19 or SARS-CoV-2. This search aimed to provide a comprehensive analysis of the fatality rates for both viruses.

COVID-19 or SARS-CoV-2 associated underlying disease

Lastly, the search term "COVID-19 or SARS-CoV-2 associated underlying disease" gathered results that explored underlying diseases in relation to either COVID-19 or SARS-CoV-2. This search aimed to provide a holistic view of the implications of these viral diseases on individuals with pre-existing health conditions.

Additional bibliography search

Subsequent to the application of the above Boolean operators, an exhaustive search of the bibliography of the initially retrieved articles was performed. This additional step ensures a thorough research that doesn't miss out on any pertinent articles indirectly related to the primary search terms. This overall approach enhances the chances to find all relevant articles, even those the initial search encompassed various Boolean operators to investigate the relationship between COVID-19, comorbidities, death rates, and mortality rates. To ensure comprehensive coverage, an additional search was conducted using the bibliography of the initially searched articles.

Inclusion and exclusion criteria

The inclusion and exclusion criteria were established to ensure that the study encompassed a broad representation of different socioeconomic contexts and comorbidities relevant to COVID-19 outcomes. In terms of inclusion criteria, research conducted in low- and middle-income nations was included based on the global bank's list of such nations. This approach aimed to provide a comprehensive understanding of the impact of COVID-19 in various socioeconomic settings. Additionally, studies that contained patient datasets with COVID-19 mortality data and major comorbidities, such as cardiovascular disease, hypertension, diabetes, kidney disease, malignancy, and other relevant conditions, were included to capture a wide range of factors that may influence COVID-19 outcomes. On the other hand, the exclusion criteria were established to maintain the reliability and validity of the findings and to focus on the general adult population. Studies that lacked sufficient or satisfactory data on COVID-19 mortality rates in relation to existing comorbidities were excluded to ensure the robustness of the results. Furthermore, studies specifically focused on maternal, pediatric, and geriatric cases were excluded to maintain consistency in the target population and concentrate on the general adult population. Additionally, systematic reviews, meta-analyses, discussions, commentaries, letters, editorials, and opinions were excluded to maintain a primary focus on original research studies. By applying these inclusion and exclusion criteria, the study aimed to gather reliable and relevant data to explore the clinical association between pre-existing comorbidities and associated diseases in the context of COVID-19.

Data extraction and screening

Data extraction and screening were conducted following the Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA) criteria, which provide a standardized approach for extracting and evaluating data [1]. The initial search strategy identified a total of 340 articles. After eliminating duplicate articles, 314 unique articles remained for review against the predefined inclusion and exclusion criteria. Among these, 243 articles were excluded as they did not meet the specified criteria, leaving 71 articles for further evaluation. Each of these articles underwent a thorough review of their full text, resulting in the selection of a final set of 27 articles to be included in the study.

Quality assessment

To assess the quality and ensure the validity of the data obtained from the selected articles, we employed the PRISMA criteria for systematic reviews and meta-analyses [1]. These criteria provide a comprehensive framework for evaluating the methodological rigor and reporting quality of studies, thereby enhancing the reliability and trustworthiness of the findings. Through the application of the PRISMA criteria, we aimed to maintain a high standard of data quality throughout the study.

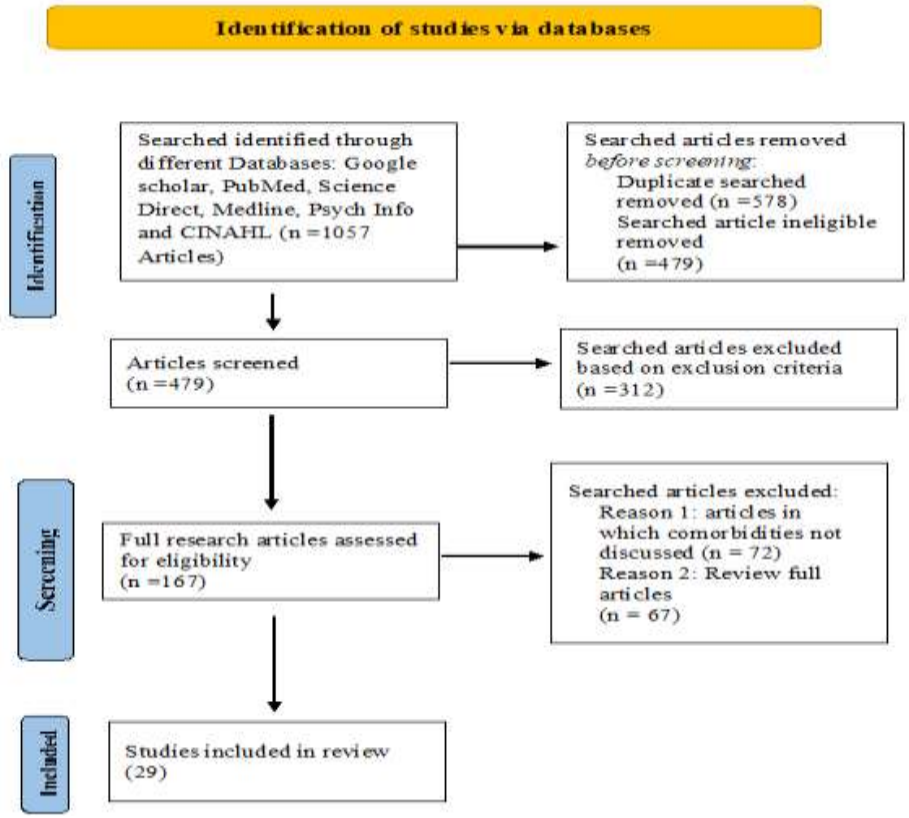

Figure 1: PRISMA flowchart for identifying studies for this systematic review.

Result:

Study characteristics and results of individual studies

The table one comprises an overview of 29 eligible studies, covering a broad sample sizes and diverse comorbidities, such as hypertension, diabetes, anemia, cancer, and other diseases or factors. Among these studies, one was a randomized controlled trial (RCT). These included cross-sectional studies, retrospective and prospective cohort studies, and institutional databases. Moreover, Table one provides a detailed summary of evidence concerning higher mortality rates in COVID-19 patients in connection with various comorbidities.

Table 1: Study Characteristics and Results of Individual Studies.

Author, year & country	Sample size	Study design	Death rate	Results	Conclusion
Ana Teixeira-Vazy (2022) Portugal	The study consisted of a total of 178 patients. Out of these, 17 patients had a history of CVD, while the remaining 161 patients did not have a history of CVD.	The study followed a prospective cohort design.	Within the study's timeframe, a total of 59 patients death rate was recorded.	The research found that, out of 178 patients, 17 (or 9.6%) had a history of cardiovascular disease (CVD). The majority of CVD cases were ischemic strokes (47.1%), followed by transient ischemic attacks (23.5%), silent strokes (17.6%), and hemorrhagic strokes (11.8%). Patients with a history of CVD were more likely to have ischemic heart disease and dyslipidemia. During the study, the Intensive Care Unit (ICU) experienced a 33% death rate (n = 59). At 30 days, the ICU mortality rate was 64.4% (n = 38), which increased to 84.7% (n = 50) by 90 days.	This research emphasizes the importance of prioritizing vaccinations for critically ill COVID-19 patients, enhancing surveillance efforts, and incorporating cardiovascular disease factors into prognostic models.
Yichun Cheng (2020) China	In this study, a total of 701 patients were analyzed, each exhibiting varying baseline serum creatinine levels. Among these patients, 600 displayed normal	The study followed a prospective cohort design.	The study recorded a total of 113 in-hospital deaths.	During their hospitalization, 5.1% of patients developed Acute Kidney Injury (AKI). Notably, patients with heightened baseline blood creatinine levels experienced a considerably higher incidence of AKI at 11.9%, compared to the 4.0% incidence among patients with normal baseline levels. Furthermore, patients with elevated baseline serum	In Wuhan, China, the presence of kidney disease during hospital admission and the development of AKI while hospitalized correlated with an increased risk of in-

Author, year & country	Sample size	Study design	Death rate	Results	Conclusion
	baseline serum creatinine levels, while 101 had elevated levels.			creatinine faced a substantial 33.7% in-hospital death rate, which was markedly higher than the 13.2% rate observed among patients with normal baseline serum creatinine levels.	hospital death. These findings emphasize the crucial need for early detection and intervention to reduce COVID-19-related mortality.

Table 1: *Continue*

Author, year & country	Sample size	Study design	Death rate	Results	Conclusion
Joel Dave et al (2021) South Africa	A total 64,476 patients diagnosed with COVID-19. Among these patients, 9,305 were identified as People Living with Diabetes (PLWD), whereas the remaining 55,171 patients did not have diabetes.	The study followed a prospective cohort design.	Within the study's timeframe, a total of 2993 patients death rate was recorded.	In the group of PLWD, hospitalization was required for 44.9%, intensive care was needed for 4.0%, mechanical ventilation was utilized for 0.6%, and sadly, 15.4% succumbed to the disease. In contrast, for the cohort without diabetes, the corresponding values were notably lower: 12.2% required hospitalization, 1.0% needed intensive care, 0.1% required mechanical ventilation, and 4.6% unfortunately passed away. The odds of hospitalization and death were significantly higher for PLWD, as confirmed by the Odds Ratio (OR: 3.01, 95% Confidence Interval CI: 2.76-3.28).	These findings necessitate further education, monitoring, and implementation of interventions to reduce the high-risk burden in this population. Numerous population-based studies have corroborated these results, demonstrating that individuals with diabetes are more likely to experience severe COVID-19.
Hernández-Galdamez et al., (2020) Mexico	A total of 211,003 individuals were examined. Of these, 20,006 were ambulatory patients with hypertension, and 22,447 were hospitalized patients also suffering from hypertension.	The study followed a cross-sectional design.	The study recorded 7,135 deaths.	The presence of comorbidities was identified in 47.40% of the cases. The most frequently reported Non-Communicable Diseases (NCDs) were diabetes and hypertension, with incidences of 16.44% and 20.12% respectively (as per Table 2). Furthermore, obesity and smoking - both modifiable risk factors - were reported in 19.59% and 7.79% of the cases respectively.	The impact of the COVID-19 pandemic in Mexico underscores the pressing need for prioritized management of chronic illnesses. Furthermore, this study puts a spotlight on the importance of prevention and control strategies for non-communicable diseases, especially during the prevalence of an infectious disease such as COVID-19.

Table 1: *Continue*

Author, year & country	Sample size	Study design	Death rate	Results	Conclusion
Jorge Escobedo-de la Pena (2021) Mexico	A total of 64,957 individuals. Among them, 13,948 were outpatient females with hypertension, 12,995 were outpatient males with hypertension, 22,019 were in-patient females with hypertension, and 26,850 were in-patient males with hypertension.	This institutional database-based study.	The study recorded a death rate of 2,080.	The case fatality rate was found to increase in the presence of diabetes, hypertension, and/or obesity. Additionally, age, sex, pneumonia, diabetes, hypertension, obesity, immunosuppression, and end-stage kidney disease emerged as substantial independent risk factors for mortality. Notably, the population-attributable proportion of obesity in outpatients was calculated to be 16.8%.	The findings of this study indicate that patients infected with COVID-19 who have significant cardiovascular risk factors or other comorbidities are at a heightened risk of death. Identifying populations with high mortality rates in Mexico due to COVID-19 delivers much-needed insight for health services on how to effectively address and tackle this pandemic.
Harbuwono et al., (2022) Indonesia	A total of 20,481 patients were included. Among them, 705 were diagnosed with Diabetes Mellitus (DM), while 19,776 did not have DM.	The study followed a retrospective cohort study design.	The study regretfully reported a considerable death rate of 21.28%.	The results show that the presence of DM in COVID-19 patients was significantly associated with an elevated mortality rate. More specifically, DM patients were nearly twice as likely to succumb to COVID-19 compared to non-DM patients.	The findings from this study also suggest that DM increases the severity of COVID-19 symptoms and enhances the risk of mortality due to the disease. These outcomes could prove instrumental in shaping future policies and strategies to prevent and manage COVID-19, particularly among the population of diabetes patients in Indonesia.

Table 1: *Continue*

Author, year & country	Sample size	Study design	Death rate	Results	Conclusion
Orioli et al., (2021) Belgium	A total of 77 patients were included.	The study followed a retrospective design.	The study recorded 11 deaths.	The cohort under consideration predominantly consisted of diabetic in-patients with COVID-19 from a single institution in Belgium. Most of these patients were diagnosed with Type 2 Diabetes, and commonly exhibited vascular issues attributed to hyperglycemia. Additionally, they suffered from comorbidities such as hypertension.	Notably, this patient population did not show any statistically significant differences in the Case Fatality Rates (CFR) when juxtaposed with patients who did not have diabetes.
Karasneh et al., (2022) Jordan	This cohort study focused on a population of 1,613 patients. Obesity was found in 699 patients, hypertension in 963, and diabetes in 802 patients.	The study followed a cohort design.	The study, unfortunately reported a death count of 609.	It was observed that patients with heart failure, Cardiovascular Accidents (CVAs), immunocompromising conditions, or cancer represented a larger portion of those who died in comparison to those who survived.	Several factors - including clinical and laboratory risk factors as well as demographic information - were identified in this study. The severity status on admission was one particularly significant indicator. However, there is a need to carry out additional studies to identify early predictors that can enhance the management and control of the impacts of this disease.

Table 1: *Continue*

Author, year & country	Sample size	Study design	Death rate	Results	Conclusion
Martinez et al., (2021) Brazil	The study evaluated a total of 287,836 patients.	The main analytical methods used were the Kaplan-Meier curves and the Cox regression model.	The study recorded 81 deaths.	The presence of comorbidities in COVID-19 patients showed a robust correlation with mortality. According to the findings, individuals aged 30-59 years with comorbidities had a greater risk of death, highlighting the need to consider them as a vulnerable demographic.	In conclusion, patients with specific comorbidities generally middle-aged individuals with various health conditions were found to be susceptible. They should also be considered as a high-risk group.
Gustani-Buss et al., (2022) Brazil	A total of 423488 patients were included in this study.	The study followed a cross-sectional design.	The study reported a staggering number of 7,234 deaths.	The largest proportion of increased mortality rates in ICU patients, falling under three severity categories, was chiefly associated with neurological disorders, neoplastic diseases, and kidney diseases. In addition to these, heart disease, diabetes, and Chronic Obstructive Pulmonary Disease (COPD) also had a significant correlation with higher mortality rates.	The study emphasized the immense value of predicting assessments for formulating public healthcare policies to ameliorate the effects of COVID-19. The findings further demonstrated the influential role non-pharmaceutical interventions could play in controlling the spread of the virus in the population.
Jassat. Et al., (2022) South Africa	A total of 219,265 patients included. Of these, 27,555 individuals (65.8% of the study population) were reported to have comorbidities such as hypertension (36.8%), diabetes (29.6%), obesity (19.7%), and HIV (8.7%).	The study followed a cohort design.	Regrettably, 51,037 (23.3%) of the 219,265 patients diagnosed with SARS-Cov-2 succumbed to the illness.	Among the available data, HIV, diabetes, and hypertension were the three most commonly observed comorbidities; the report also noted that 3.6% of these patients had Tuberculosis (TB).	The study underscored that advancing age and the existence of chronic health conditions - such as hypertension and diabetes - are significant factors associated with COVID-19-related mortality in middle-income African countries.

Table 1: *Continue*

Author, year & country	Sample size	Study design	Death rate	Results	Conclusion
Cordero-Franco et al., (2021) Mexico	The study examined a total of 56,715 patients. Among them, 14% suffered from pneumonia, 20.7% required hospitalization, 2.9% required intubation.	The data was obtained from an open-access database of the General Directorate of Epidemiology from the Ministry of Health.	The study reported a staggering number of 2860 deaths.	Certain health conditions invariably increased the likelihood of complications such as pneumonia, intubation, and death, with diabetes being the exception. On the other hand, risk factors for pneumonia and death - including immunosuppression and chronic kidney disease - or protective factors against COVID-19 infection did not evidently correlate with the aforementioned complications. Surprisingly, conditions traditionally deemed risky like Chronic	Important risk factors for COVID-19 infection and subsequent complications were identified as older age, hypertension, and obesity.

				Obstructive Pulmonary Disease (COPD), asthma, and cardiovascular disease also fell into this category.	
Rohith., et. al 2021 (India)	A total 1,977 patients were included. It was discerned that 52.9% of these patients suffered from both hypertension and diabetes, conditions associated with microvascular complications.	The study followed a cross-sectional design.	The study reported a total of 138 deaths.	Of the patients who passed away, 73 individuals or 52.9% were diagnosed with both diabetes and hypertension. The observed Case Fatality Rate (CFR) for patients with comorbid conditions stood at 12.38%. Chronic Kidney Disease (CKD) patients displayed the highest CFR of 32%, followed by patients concurrently suffering from diabetes and hypertension at 17.5%.	In conclusion, the data indicated that advanced age combined with a COVID-19 infection resulted in a higher mortality rate. Furthermore, patients with hypertension, diabetes, and associated macrovascular complications, as well as those with CKD, were found to have an elevated risk of death.

Table 1: ***Continue***

Author, year & country	Sample size	Study design	Death rate	Results	Conclusion
Huang., et.al 2020 China	A total of 310 patients were observed, with hypertension affecting 36.5%, diabetes 15.5%, and cerebrovascular diseases 6.8% and other didn't have any comorbidities.	The study followed a retrospective observational design.	The study reported a total of 59 deaths.	Based on the findings, COVID-19 patients with hypertension experienced more severe organ damage and inflammation compared to those without hypertension, suggesting a poorer prognosis.	In conclusion hypertensive COVID-19 patients have demonstrated higher mortality in previous clinical studies, indicating that hypertension is a risk factor for increased fatalities among infected individuals.
Tamura., et.al 2021 Brazil	This study observed a total of 1,170 COVID-19 patients, amongst which 188 were diagnosed with diabetes.	The study followed a cohort design.	The study reported a total of 49 deaths.	Patients aged 60 years or older, was a principal factor of mortality. Compared to the age group of 29 to 59, the older cohort had a 9.24 times higher risk of death, varying between 2.22 and 38.51. Another significant risk factor that contributed to the mortality rate, considering the various comorbidities, was diabetes.	In conclusion, a key association found in our uni and multivariate analysis was that the use of chloroquine/hydroxychloroquine significantly increased the risk of death and intubation. Conversely, the use of metformin during hospitalization showed better prognosis and a reduced mortality risk.

Table 1: ***Continue***

Author, year & country	Sample size	Study design	Death rate	Results	Conclusion
Oscar., et.al 2021 Mexico	This study observed 2,126 COVID-19 patients.	The study followed a cross-sectional design.	Not reported	It was observed that five factors had a significant correlation with patient outcomes, particularly the mortality rate amongst the migrant population diagnosed with COVID-19. These factors were pneumonia, age, nationality (groups classified as 'other'), HCMP, and intubated patients. A previous diagnosis of pneumonia raised a migrant's mortality risk from COVID-19 by 0.32 percentage points. Age also played a part - every additional year on a patient's age heralded a 0.001 percentage point increase in the risk of death from COVID-19.	In conclusion, migrant patients reported lower health service usage than the native-born population. The study also uncovered that comorbidity was less prevalent amongst migrants, and their prognoses were generally more favorable after contracting COVID-19 than those of the non-migrant population.
Jha., et al (2022) India	The data was gathered from 784 patients who tested positive for COVID-19. Notably, approximately 49.3% of these patients exhibited varying levels of anemia.	The study followed a Retrospective cross-sectional design.	The study reported a total of 509 deaths.	Out of these patients, a significant number of 509 unfortunately succumbed to COVID-19, whereas 277 patients were eventually discharged upon recovery. The composition of our study sample revealed that 441 patients did not suffer from any degree of anemia (mild, moderate, or severe), leaving 343 individuals who were plagued with anemia to varying extents. Upon analysis of the overall results (n = 784), a statistically significant correlation was deduced between the presence of anemia and increased severity of COVID-19, specifically evident in the death rate analysis of the study group.	In conclusion, the current study suggests initial assessments of COVID-19 patients to include evaluations of hemoglobin levels as a tool for risk stratification. It is plausible to suggest that improving these hemoglobin levels could be crucial in reducing the risk and potential severity of COVID-19 infections.

Table 1: *Continue*

Author, year & country	Sample size	Study design	Death rate	Results	Conclusion
Hartantri., et.al (2023) Indonesia	A total of 689 COVID-19 patients were observed. Among these patients, various comorbid conditions were noted; 71 had coronary heart disease, 187 displayed symptoms of Hypertension, 121 had manifested Diabetes Mellitus, and 42 suffered from chronic kidney disease.	The study followed a Retrospective cohort design.	The study reported a total of 103 deaths.	The current study results found a significant linkage between the severity of the disease leading to an elevated mortality rate, older age, and comorbidities. Secondary bacterial infections were identified as potential contributors to increased mortality, typically after the second week of hospitalization. Consequently, it was noted that comorbidities heightened the risk of death in patients suffering from COVID-19.	In conclusion, this study identifies key risk factors contributing to the mortality rate among COVID-19 patients in a referral hospital in Bandung. Crucially, older age and the presence of comorbidities, notably chronic kidney disease (CKD), Diabetes Mellitus (DM), Hypertension, and coronary heart disease, stood out as prevalent factors. These elements were observed to lead to a severe progression of COVID-19, subsequently resulting in a higher mortality rate.
Mehta et al., (2021) India	A total of 186 COVID-19 patients. Among them, 11 suffered from cardiovascular disease, 2 had Chronic Obstructive Pulmonary Disease, 34 were diagnosed with Diabetes, and 30 had Thyroid conditions (Hypo/Hyper).	The study followed a Retrospective cohort design.	The study reported a total of 27 deaths.	The current study results indicated a prevalent occurrence of COVID-19 in cancer patients. However, recent cancer treatments seemed to have little influence on mortality rates. The factors strongly associated with death from COVID-19 in our study group were the presence of multiple comorbidities, particularly diabetes, severe initial symptoms, and pre-existing health conditions.	In conclusion, current study noted that the presence of comorbidities, like diabetes, and the presence of more than one comorbidity played a significant role in the severity of initial symptoms of COVID-19. As such, these were linked to an increased patient mortality rate.

Table 1: *Continue*

Author, year & country	Sample size	Study design	Death rate	Results	Conclusion
Andres I. Vecino-Ortiz et. al.(2021) Colombia	A sizable cohort of primary COVID-19 patients was analyzed, totaling 54,931 individuals. In addition, a secondary sample group of 112,279 patients was also studied.	The study followed a cross-sectional design.	Out of the initial primary batch, unfortunate fatalities numbered 1,853, whereas the secondary group witnessed an alarming 3,738 deaths.	Results indicate that a total of 54,931 and 112,279 confirmed COVID-19 cases from March 2 to June 16. The distribution of daily cases per department varied between 1 and 567 cases, yielding a mean value of 26.54 cases. Regarding active cases, the upper limit observed was 608, while the corresponding mean was 15.08. Notably, the total number of deaths recorded for each department by June 16 spanned from a minimum of 1 to a peak of 24, averaging at 2.65 deaths.	In conclusion, this study is the first to utilize empirical data to pinpoint the significant reductions in mortality linked with contact tracing for COVID-19. Our findings underline the crucial role of contact tracing in managing and mitigating the impact of the pandemic.
José Sifuentes-Osornio et.al., (2022) Mexico	The health composition of the study group revealed that 8.6% had Diabetes Mellitus (DM), 11.6% struggled with Arterial Hypertension (AHP), and 9.7% wrestled with obesity. Notably, 29.5% (or 666,694 individuals) out of the entire group tested positive for COVID-19.	The study followed a cross-sectional design.	The study reported a total of 42797 deaths.	The current study results reported that the likelihood of death surged among hospitalized individuals who suffered from DM, AHP, or Obesity. This risk eventually elevated when the demand at the hospitals was higher. Moreover, this level of increased risk was consistently observed across all age brackets, irrespective of the existence or non-existence of comorbidities in the individuals.	In conclusion, a higher mortality rate was observed in hospitalized patients battling comorbidities such as DM, Obesity, and AHP. The increment in mortality rates was indiscriminate of age groups, further boosting the urgency for managing healthcare resources and improving patient care in the fight against COVID-19.

Table 1: *Continue*

Author, year & country	Sample size	Study design	Death rate	Results	Conclusion
Koya et al., (2021) India	Not mentioned	The study followed a cross-sectional design.	A total of 2,000 COVID-19-related fatalities were reported.	Approximately 73% were males and 72% received treatment in public medical facilities. Acute Respiratory Distress Syndrome (ARDS) following pneumonia was identified as the immediate cause of death in about 54% of these cases. Details on symptoms were available for 624 cases: around 39% displayed three simultaneous symptoms (dyspnea, fever, and cough), while 16% manifested only one symptom. Dyspnea was the most prevalent symptom, affecting 77% of these individuals, followed by fever in 75% and cough in 55% of individuals. Comorbidities were recorded in a vast majority, 96%, of the cases.	In conclusion, young adults without concurrent health conditions had a shorter survival duration from the onset of symptoms. This trend was observed irrespective of when they were admitted to the hospital. A concurrently performed meta-analysis suggested an elevated risk for severe COVID-19 outcomes in patients suffering from hypothyroidism.

Dimova et.al., (2022) Bulgaria	The study encompassed 5,200 patients suffering from COVID-19. Cardiovascular disorders were present in 1,583 patients, making it the most common comorbidity. Endocrine and other metabolic disorders were found in 275 patients, while lung disorders were encountered in 94 patients.	The study followed a cross-sectional design.	N	The result from this study reported that 41.5% of the total patients had no pre-existing medical conditions, and the other 58.5% were diagnosed with between one and five comorbidities. Of the total patients, one-third (approximately 1,470) had fatal outcomes, while the remaining 71.7% were able to recover from the infection and were subsequently discharged from the hospital.	In conclusion, this study affirmed that various patient-specific comorbidities and factors influence the severity of the infection. Higher mortality rates were recorded among men, older individuals, and those requiring hospitalization. Superior medical treatments and robust healthcare system organization play a critical role in controlling the spread of the infection.

Table 1: ***Continue***

Author, year & country	Sample size	Study design	Death rate	Results	Conclusion
Jassat et al., (202 South Africa	A total of 41,877 COVID-19 patients were included; among them, 36.9% had hypertension, 29.6% had diabetes, 19.78% had obesity, and 8.7% had HIV.	The study followed an RCT design.	The study reported a total of 7662 deaths.	Results from this study indicate that comorbidities, along with gender, race, and concurrent illnesses, emerged as strong predictors of COVID-19 mortality in South Africa. The study indicated that death rates were slightly elevated for those with HIV and hypertension, particularly among HIV-positive individuals who were not receiving antiretroviral therapy (ART)	In conclusion, the study revealed that comorbidities are crucial in predicting hospital mortality. COVID-19 death rates in South Africa demonstrated a positive increase among HIV and TB patients, emphasizing the need for targeted resource allocation in response to the ongoing crisis.

Discussion

The COVID-19 pandemic has led to extensive morbidity and mortality worldwide; however, the correlation between comorbidities, age, and mortality has not been thoroughly examined with larger effect sizes in consideration. The majority of papers analyzed in this systematic review demonstrated that factors such as old age and the presence of specific comorbidities, including peripheral artery disease, hypertension, coronary heart disease, heart failure, COPD, asthma, bronchitis, dementia, cognitive impairment, and diabetes contributed to increased mortality among hospitalized COVID-19 patients. While cardiovascular diseases were the most commonly studied comorbidities in the reviewed articles, other conditions received comparatively less attention. The associations between comorbidities and COVID-19 mortality observed in our study are supported by systematic reviews that found chronic kidney diseases, dementia, familial hypercholesterolemia, cardiovascular diseases, diabetes, and hypertension significantly increased mortality among elderly COVID-19 patients [35, 36]. A plausible explanation for these findings might involve the SARS-CoV-2 virus infecting endothelial cells, causing damage to small vessels, and promoting microvascular dysfunction, inflammation, and thrombosis [35, 37-40]. SARS-CoV-2 can also invade other cardiovascular system cell types expressing SARS-CoV-2 entry genes (angiotensin-converting enzyme 2, basigin), including cardiomyocytes and renal cells [41-43]. In patients with comorbidities impacting the microvasculature or myocardium, COVID-19-associated vascular and myocardial pathologies may become aggravated. Moreover, both aging and several comorbidities have been shown to elevate the expression of cellular entry receptors for SARS-CoV-2, which directly influences COVID-19 severity [43-46]. The adipokine enzyme DPP4 could represent another potential entry receptor for COVID-19 [47]. The adipokine enzyme DPP4 could represent another potential entry receptor for COVID-19 [47]. This could serve as an indicator of more severe disease manifestations [47].

A number of comorbidities, such as heart failure (HF), a history of deep vein thrombosis (DVT) and, pulmonary embolism (PE), and malignancy, have been remarkably identified as factors associated with increased mortality in COVID-19 patients across numerous studies. The current study data analysis further reveals a higher risk of severe COVID-19 in patients with pre-existing cancer. It's worth noting that infections are the primary cause of mortality in malignancy [9, 20]. The predisposition to infections in these patients is generally attributed to the initial disease, treatments related to malignancy, and concurrent comorbidities. The malignant conditions and associated

treatments inevitably compromise the immune system, escalating infection risks [9, 20]. Many research studies confirm an important finding: Among different age groups, the highest rate of COVID-19 infections was observed in people aged 18 to 59, who mainly work and contribute to the economy. However, when looking at the death rates, it was discovered that individuals who were 60 years old and above and had underlying health issues had the highest risk of disease severity and lethality.

This trend suggests that the elevated infection rate in the younger population may be attributable to their active lifestyle and work commitments outside the home, contrasted by the increased severity and mortality in the older demographic. Advanced age itself, exhibiting an effect termed "immunosenescence," also detrimentally influences the immune response by impairing monocytes and lymphocytes' functionality [48-54]. These factors, coupled with the impact of comorbidities, could lead to diminished protection against SARS-CoV-2 infection in older individuals. Immunosenescence also correlates with reduced vaccine responses in the elderly [49, 55, 56]. In addition to immunosenescence, aging also intensifies cellular senescence and the production of inflammatory cytokines, resulting in inflammasome upregulation and promoting genomic instability and mitochondrial malfunction. All these factors could contribute to the heightening susceptibility to organ failure associated with SARS-CoV-2 infectio [54, 57, 58]. Moreover, the prothrombotic environment correlated with advanced age might incite severe tissue damage, vascular leakage, thrombosis, and a systemic cytokine storm. These risks may further contribute to a higher COVID-19 mortality rate among elderly patients with comorbidities [49, 59, 60]. The World Health Organization found that COVID-19 patients had underlying medical issues that were high risk. It had been discovered that patients who were put into intensive care had more comorbidities than those who were not [61]. Despite considering various comorbidities, all reviewed studies consistently indicated that cardiovascular diseases and diabetes were associated with increased mortality in patients with COVID-19, attributable to more than half of the fatal outcomes. According to one such study, among hospitalized COVID-19 patients, those with diabetes exhibited a higher mortality rate than their non-diabetic counterparts. Additional risk factors, such as end-stage kidney disease, heart failure, malignancy, immunosuppression, obesity, and the presence of pneumonia, were more commonly observed among deceased patients than among COVID-19 survivors. Based on the current review study's findings, hospital admissions of patients with comorbidities were more likely to lead to severe outcomes than patients without underlying health conditions. The mortality rates were almost doubled for COVID-19 patients with the most lethal comorbidities diabetes and hypertension. Most patients who didn't have pre-existing illnesses upon hospital admission survived COVID-19. So, the current review overwhelmingly supports a strong correlation between comorbidities and mortality rates in patients with COVID-19 [62-65].

Limitations

While this study provides compelling evidence regarding the association of comorbidities with elevated mortality rates in COVID-19 patients, several limitations warrant consideration. Primarily, a high level of heterogeneity was observed, likely due to variations in study designs, patient characteristics, treatments, ethnicity, and unadjusted variables among the included studies. Secondly, the study's scope was limited by the geographical span of the included research publications. These studies originated from countries with significantly diverse sociodemographic characteristics and health parameters, as well as differing qualities of and access to healthcare. These disparities could potentially impact the generalizability of our findings. Lastly, as we restricted our review to English language articles, relevant studies published in non-English languages were excluded. This linguistic restriction could potentially limit the breadth of data in our review and consequently impact the study's representativeness. Despite these limitations, the persuasive findings of this study may play a crucial role in informing stakeholders, policymakers, and healthcare professionals, potentially shaping responses to one of the most formidable infectious and health challenges of the 21st century. By enhancing our understanding of the epidemiologic features, disease progression, and clinical outcomes associated with SARS-CoV-2 infection, our findings can guide strategies to mitigate COVID-19's global toll.

Conclusion

In conclusion, the mortality risk substantially escalated with age, implying that older patients face significantly greater risk than younger ones. The mortality rate was also noticeably higher in patients with comorbidities such as kidney disease, cardiovascular disease, respiratory disease, diabetes, hypertension, and cancer. This heightened risk can be attributed to factors such as the decreased resilience and functional reserve typically associated with older adults and the increased susceptibility of an aged microcirculation system to injury caused by the SARS-CoV-2 virus. These factors contribute to more severe disease manifestations, including increased mortality. Implementing adequate protective measures and targeted interventions for COVID-19 patients, particularly older individuals with comorbidities, could significantly reduce the associated mortality risk. Furthermore, additional research is required to understand how establishing preventive programs for key cardiovascular risk factors impacts COVID-19 outcomes in the elderly demographic.

Further research and future implications

Despite the abundance of existing research, the relationship between comorbidities, age, and mortality in COVID-19 patients requires continued examination with larger effect sizes and diverse patient populations in mind. Most current studies primarily focus on cardiovascular diseases concerning COVID-19 mortality, while other conditions warrant further investigation. One potential direction for future research involves exploring how the SARS-CoV-2 virus interacts with the cardiovascular system, endothelial cells, and other cell types. Further investigation could illuminate the interplay between the virus, comorbidities, and microvascular dysfunction, inflammation, thrombosis, and other complications. Another research approach pertains to understanding the cellular entry receptors for SARS-CoV-2 and their influence on COVID-19 severity in the presence of various comorbidities. Additionally, studies should consider examining the role of the immunosenescence process in COVID-19 severity, particularly in relation to vaccine responses and the development of targeted interventions for older adults. The evolving incidence patterns and risk factors of COVID-19 infections among different age groups necessitate ongoing observation and reevaluation. This information can help inform policymaking and healthcare interventions. In particular, developing strategies to minimize the impact of COVID-19 among vulnerable older adults with various predisposing factors is crucial. Implementing preventive programs that address key cardiovascular risks and other comorbidities in more aged individuals could go a long way in mitigating the overall mortality rate associated with COVID-19.

Statement of ethics

The paper is exempt from ethical Committee approval since it is a systematic review.

Conflict of interest statement

The authors declare no conflict of interest.

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