Statistical Evaluation of Comorbidities and Environmental Factors in COVID-19 Outcomes: Risk Measures and Predictive Analysis Using Odds and Hazard Ratios

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Abstract: In this study, we have reviewed studies that highlight the effects of common conditions like heart disease, high blood pressure, congestive heart failure, kidney problems, and emphysema, which offer the largest risk of death caused by COVID-19. Also, explored how physical activity can influence one's resistance to COVID-19, the effects of stat in medications on mortality rates, and the effectiveness of vaccines in reducing fatalities offer valuable avenues for tailored interventions and treatment strategies and the examination of the relationship between exposure to air contamination and the severity of COVID-19 highlights the task of environmental factors in shaping the outcomes of the illness. Primarily, we focused on how comorbidities affect COVID-19 patients and the associations between comorbidities, lifestyle factors, environmental influences, and COVID-19 outcomes, guiding healthcare strategies and future research, and refining responses to the ongoing pandemic. In this study, analysis of COVID-19 studies centered on compiling risk assessments, including 95% confidence intervals along with odds and hazard ratios. The analysis's goal was to gather and assess the different risk metrics provided in this study.

Keywords: COVID-19, Hazard Ratio, Odds Ratio, Comorbidity, Predictive Analysis.

INTRODUCTION

The global spread of COVID-19 marked a turning point in modern public health, prompting World Health Organization (WHO) Director-General to proclaim the epidemic a Public Health Emergency of International Concern on January 30, 2020. This seminal declaration, founded on the recommendations of the Emergency Committee, underscored the unprecedented nature and gravity of the situation, warranting urgent global attention and coordinated efforts. As of 8 November 2023, there have been 77,18,20,937 cases, including 69,78,175 deaths, reported globally [1]. Six (14.6%) of the 41 patients from Wuhan Jinyintan Hospital who had COVID-19 pneumonia in the first reported cohort got sick quickly & died of multiple organ failure [2]. Eleven (11.1%) of the 99 patients in the group died in another trial [3]. The total death rate among hospitalized patients with COVID-19 pneumonia in the Wuhan cohort was 4.3% (6/138) [4]. Considering the results of these three earlier studies, advanced age&among COVID-19 pneumonia cases, pre-existing medical conditions were linked to higher illness severity or fatality. Due to COVID-19, most individuals experience mild or asymptomatic cases, certain patients may develop critical health issues, such as severe pneumonia leading to life-threatening complications, multi-organ failure, and ultimately, death. Typically, individuals whose immune systems are weakened are deemed especially susceptible [5]. The majority of fatalities are thought to be linked to the presence of concurrent medical conditions. Ongoing investigations into potential factors contributing to COVID-19 mortality increasingly indicate that those with underlying multiple medical conditions, [6,7].

Moreover, as research deepens its exploration into the connection between COVID-19 and comorbidities, it is unveiling a clearer understanding that Individuals with underlying health issues stand an increased risk. This heightened susceptibility among those with pre-existing medical issues emphasizes the importance of

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E-ISSN: 1929-6029/25

targeted preventive measures and vigilant care for this vulnerable demographic. SARS-CoV-2 which is found in organs such as the kidneys, heart, and type II alveolar cells of the lungs [8].

There is a hypothesis, yet to be substantiated, suggesting that the presence of membrane-bound ACE2 may be increased by previous use of angiotensin II type 1 receptor blockers (ARBs)., potentially heightening the vulnerability of humans to virus entry [9]. As a result, persons using ARBs who have a history of chronic illness, such as hypertension or persistent heart failure, might be more vulnerable to the intensity of COVID-19 & related mortality. The recognition of primary risk factors, followed by the execution of appropriate clinical interventions could significantly contribute to saving lives. Healthcare systems worldwide, both in developed and developing nations, are under immense strain and fatigue due to the management of COVID-19 cases. Existing literature concerning COVID-19 offers limited directives for managing concurrent medical conditions [10, 11]. As a result, there exists a necessity to devise a treatment approach for various prevalent medical comorbidities. This strategy could aid healthcare providers in pinpointing high-risk patients during their admission to COVID-19 centers. Further, a general review has been given by Danish and Suhail [12]. Given the escalating number of patients during this pandemic, a deeper comprehension of high-risk comorbidities could greatly assist healthcare professionals. Providing safety guidelines to individuals with comorbidities, advising them to refrain from visiting infected areas, and avoiding contact with potentially infected individuals, could be a proactive measure.

NEED FOR THE REVIEW

Numerous research has centered on examining the health surveillance and medical features of individuals affected by COVID-19. Previous studies have emphasized specific pre-existing medical conditions like high BP, cerebrovascular disease, malignancies, renal issues, diabetes, and elevated cholesterol levels as notable factors linked to increased susceptibility to the virus. Yet not enough research has been done on the risk factors for mortality and severity [13]. Effective resource allocation during the pandemic depends on identifying risk variables to predict the seriousness of COVID-19 [14]. With the growing volume of published studies, discrepancies have emerged regarding the influence of existing simultaneous health conditionson COVID-19 fatality. Some research indicates that pre-existing conditions & COVID-19 mortality are related, while other research shows that they are not. These discrepancies may be explained by elements like the narrow focus of the examined research, diverse methodologies employed and unaccounted sources of bias within the research methodologies. Still, the highest burden of these pre-existing chronic illnesses is also found in areas with the highest mortality rates like China, Europe, and the United States [15].

Cardiovascular and cerebrovascular disorders were prevalent complications among COVID-19 patients, according to initial reports of COVID-19 cases in China [16]. Additional research has revealed that a greater prevalence of severe COVID-19, which requires intensive care unit (ICU) monitoring, was linked to both cardiovascular and cerebrovascular illnesses [14]. Cerebrovascular disease was linked to worsened disease severity in COVID-19 patients, according to Aggarwal *et al*. [17]. The researchers looked at typical estimates of risk based on unaltered effects and found no significant link between stroke &fatal outcomes in patients with COVID-19 (odds ratio (OR) = 2.33, 95% CI: 0.77-7.04), Chen *et al*. [18]. This showed the relationship between cerebrovascular disease and poor outcomes in COVID-19 patients may be influenced by a number of factors, including age, gender, and other illnesses [19-22].

Objective

The objective of this Review is to carry out a critical examination of the link between various pre-existing health issues and COVID-19 death rates.

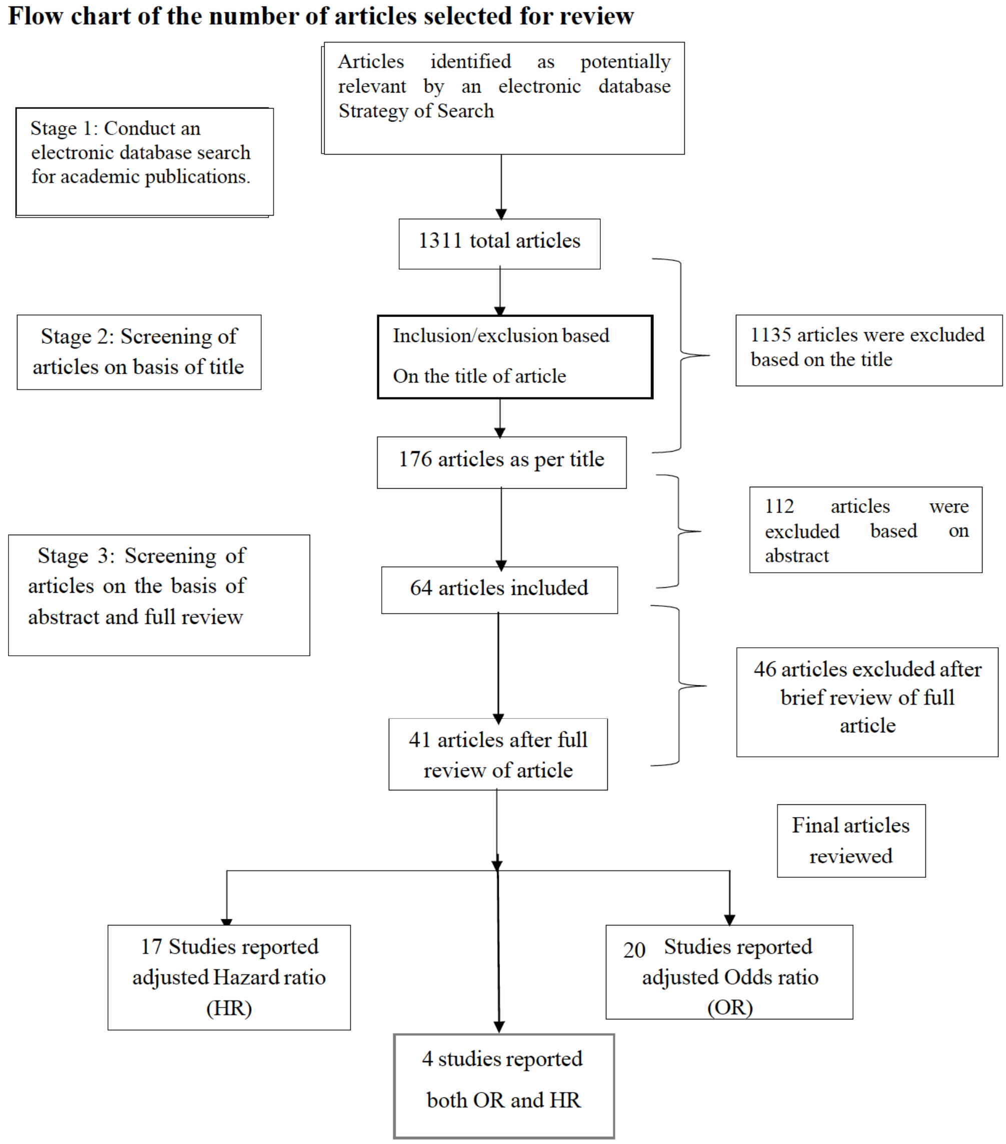
METHODOLOGY

For conducting such review, the literature was systematically looked on online to identify published studies on contraceptive discontinuation, switching patterns, and its association with fertility preferences. The searches were conducted using the following online databases: SCOPUS, Google Scholar, PubMed, Jstor, Springer Link, and Cochrane Library.

The predefined search criteria, directed by Medical Subject Headings and keywords, covered a wide array of variations, including ("COVID-19"/"coronavirus"/ "SARS-CoV-2"/"2019-nCoV"/"SARS-nCoV2") and ("mor-tality"/"outcome"/"prognosis") and ("comor-bidities"/"chronic illness"/"chronic disease"/"cardiovas-cular disease"/"chronic obstructive pulmonary disease"/ "asthma"/"coronary heart disease"/"coronary artery disease"/"hypertension"/"diabetes"/ "congestive heart failure"/"malignancy"/"cancer"/"chronic kidney disease"/"chronic liver disease"/"cerebrovascular disorders"/"stroke").

Inclusion and Exclusion Criteria

Qualified studies comprised Studies with cohorts, clinical trials with randomized designs, study designs



with case controls, and case series (involving at least 20 patients). This encompassed research involving hospitalized COVID-19 patients, irrespective of age. The focus was on major underlying health conditions like heart-related ailments, high blood pressure, diabetes, heart failure, cancer, stroke-related conditions, Chronic renal issues, breathing problems, chronic bronchitis, as well as liver diseases. Selection of original papers involved reviewing the study titles and assessing the abstracts' keywords.

Criteria of Inclusion

COVID-19 was identified following the WHO protocols. The studies explored the relationship between any of the specified comorbidities and COVID-19 assessed how engaging in physical activities affects an individual's immunity against COVID-19, examined the effect of statin medication on patient mortality, evaluated examined the relationship between exposure to air pollutants and the prevalence of COVID-19, as well as the efficacy of vaccines in lowering mortality, also studied proportion of malnutrition among COVID survivors along with factors contributing to it. Risk estimates were presented as ORs or HRs with 95% CIs. Only articles published in English and freely accessible online before October 30, 2023, were considered for inclusion in this review.

Criteria of Exclusion

Individual cases or series of cases involving fewer than 20 patients are omitted from this study. Research not done on human beings, review articles, synthesis studies, systematic reviews, and opinions. Additionally, studies that reported unadjusted estimates of association were excluded from the review. Simulation studies were not considered. Furthermore, studies exclusively encompassing COVID-19 suspected cases were excluded from this review.

The Papers were Selected in Three Steps

Initially, articles were chosen based on their titles. Subsequently, abstracts were reviewed to identify articles that aligned with the research criteria. 112 articles were excluded after additional screening because they were thought to be irrelevant based on their abstracts. Following this step, 46 articles were excluded after a brief assessment of the full article. In the end, 18 articles under went rigorous selection for comprehensive review and inclusion in the study.

Findings from the Review Articles

A comprehensive review is needed to analyze studies examining the link between specific comorbidities and COVID-19 susceptibility, shedding light on risk factors influencing disease severity. Additionally, investigating dominance of engaging in individual work on COVID-19 resistance and assessing the impacts of stat in medication son patient mortality is crucial.

Understanding vaccine efficacy in reducing mortality rates and exploring the relation between air pollution exposure & COVID-19 severity are essential for informed public health interventions. Furthermore, Examining the incidence of inadequate nourishment among COVID survivors and its contributing factors is vital for addressing long-term health implications. Synthesizing risk estimates like ORs or HRs with 95% CIs from these studies will provide a comprehensive overview. This review would aid in understanding the associations between comorbidities, lifestyle factors, environmental influences, and COVID-19 outcomes, guiding healthcare strategies and future research, and refining responses to the ongoing pandemic. Numerous Studies indicate that a substantial percentage of individuals diagnosed with COVID-19 also presented pre-existing chronic conditions. For instance, Zhang *et al.* [23] conducted a review involving Diabetes (adjusted Using the Cox proportional hazard model, they found that fasting blood glucose (HR = 1.19; 95% CI: 1.08 - 1.31) and heart rate (HR = 3.64; 95% CI: 1.09 - 12.21) were associated with the risk of dying from COVID-19. The scientists arrived at the conclusion that diabetes mellitus (DM) is related with high prevalence.

Guan *et al*. [24] examined the 1590 laboratory-confirmed hospitalized patients. People with COPD had a greater chance of achieving composite end-points after controlling for age and smoking status. (95% CI: 1.42–5.05; HR = 2.68. Similarly, patients with malignancy (3.50: 1.60–7.64), hypertension (1.58: 1.07–2.32), and diabetes (1.59:1.03–2.45) were also more susceptible to achieving these combine dend points in contrast to individuals lacking these conditions. When compared to patients without any underlying health issues, (HR=1.79; 95% CI: 1.16–2.77) among those accompanied by at least one illness and notably higherat (2.59:1.61–4.17) among patients with two or more comorbidities. From December 30, 2019, to February 17, 2020, Yu *et al*. [25] examined the medical records of different patients including demographic, clinical, and treatment information. Individuals diagnosed with cancer and residing in People living in the focal point of a widespread pandemic were found to be significantly more susceptible to getting sick with SARSCoV-2 (OR= 2.31; 95% CI: 1.89-3.02) than the general population. Du *et al*. [26] prospectively collected clinical and findings from a study of 179 COVID-19 pneumonia patients and obtained that multiple factors were linked to a higher likelihood of mortality caused by COVID-19 pneumonia. Notably, individuals aged greater than 65 years (OR= 3.765; 95% CI, 1.146–17.394; P = 0.023) and those with preexisting concurrent cardiovascular or cerebrovascular diseases (OR = 2.464; 0.755–8.044; P = 0.007) were among these factors were identified as factors linked to an elevated risk of mortality. Shi *et al.* [7] demonstrated that mortality and cardiac injury in COVID-19 patients are statistically significantly correlated. In The final analysis included 416 admitted patients with a COVID-19 diagnosis from the cohort study. According to a Cox regression model, individuals with cardiac injury, as compared to those without, faced a marked lyelevated risk of death. This increased risk was seen both at the time of symptom start (HR =4.26; 95%CI, 1.92-9.49) and when they were admitted to the endpoint (HR=3.41; 95% CI, 1.62-7.16) whereas cardiovascular diseases, cerebrovascular diseases, diabetes, and cancer found statistically not significant. Mehra *et al.* [27] used to evaluate the connection between the prevalence of cardiovascular conditions as well as pharmaceutical treatment with death during hospitalization within those receiving treatment in Covid-19. as well as currently smoking (OR = 1.79; 95% CI, 1.29 - 2.47), cardiac failure (OR = 2.48; 95% CI, 1.62 - 3.79), and COPD (OR = 2.96; 95% CI, 2.00 - 4.40) and cardiac arrhythmia (OR = 1.95; 95% CI, 1.33 - 2.86) were identified as factors independently linked to a heightened likelihood of death during hospitalization. Suleyman *et al*. [28] reported on the medical features and results of 463 consecutive COVID-19 patients. Later, in multivariate logistic regression, he discovered that age over 60. The presence of the mentioned factor (OR, 5.3; 95% CI, 2.9-9.7; P = .001) demonstrated a major connection in mortality. However, being of African American race didnotexhibita significant association (OR, 0.98; 95% CI, 0.54-1.8; P= .86) with the result. Chen *et al.* [29] did a retrospective analysis of 904 COVID-19 patients (136 of whom had diabetes, primarily type 2 diabetes), clinical and laboratory data were gathered and contrasted between the diabetes and non-diabetic groups. Factors that increased the likelihood of mortality in individuals affected by both diabetes and COVID-19, factors such as increasing age (adjusted odds ratio [aOR] of C-reactive protein levels were also higher (aOR = 1.12 [95% CI 1.00, 1.24]; P = 0.043) and increased by 1.09 [95% CI 1.04 - 1.15] annually; P = 0.001 were found to be influential.

The multivariable regression analysis revealed higher odds of in-hospital fatality connected with several factors: more years of age (OR=1.10; 95% CI 1.03–1.17, on an annual basis; p=0.0043), indicating a significant association with each year's increase by Zhou *et al.* [13]. In a prospective observational cohort study, Cumming *et al*. [30] examined 1150 adults with laboratory-confirmed COVID-19 who were admitted to two New York Presbyterian hospitals connected to the Irving Medical Center of Columbia University in northern Manhattan. Of these, 257 (22%) were seriously ill. Multivariable Cox model analysis unveiled several independent factors intricately linked to in-hospital mortality. Notably, advancing age showed a notable association, demonstrating an adjusted hazard ratio (HR) of 1.31 (95% CI 1.09–1.57) per 10-year increment. Additionally, chronic cardiac disease and chronic pulmonary disease showcased elevated risks, with (HR=1.76; 95% CI: 1.08–2.86) and (HR=2.94; 95% CI: 1.48–5.84) respectively. Moreover, increased levels of interleukin-6 displayed an independent association, reflecting (HR= 1.11; 95% CI:1.02–1.20) for each tenth percentile increase. Similarly, elevated levels of D-dimer were linked independently, exhibiting a HR of 1.10 (95% CI 1.01–1.19) per decile rise. These findings underscore the intricate interplay of age, chronic health conditions, and specific biomarkers in influencing the in-hospital mortality risk among the analyze dcohort. Wang *et al.* [31] 339 consecutive cases of COVID-19 in patients over 60 were examined at Wuhan University's Renmin Hospital in order to look into the traits and prognostic factors of the elderly patients, China. In the analysis considering multiple factors, comorbidities such as cardiovascular diseases COPD (HR 2.24, CI 1.12–4.50, P = 0.023) and (HR 1.86, CI 1.06–3.26,P= 0.031). One significant indicator of mortality was found to be acute respiratory distress syndrome (ARDS) (HR 29.33, CI 12.37–69.58, P < 0.001).

Smet *et al.* [32] a retrospective single-center observational study was conducted to as certain the relationship between frailty and mortality in older adults admitted to hospitals due to coronavirus disease 2019 (COVID-19). Multivariable logistic regression analyses identified associations, revealing that the Clinical Frailty Scale (CFS) held an (OR=1.752; 95% CI:1.096-3.435), However, lactate dehydrogenase (LDH) continued to be independently linked to mortality, exhibiting an OR=1.005; 95% CI: 1.00-1.011. The goal of Fu *et al*. [33] was to investigate the factors that affect the risk of death in 200 COVID-19 patients. In a Chinese cohort study, 200 patients with a confirmed SARS-CoV-2 infection were included. The researchers used logistic regression with multiple variables to assess the correlation among biochemical indicators and probability of expire in COVID-19 individuals while controlling for any confounders. Only serum total bilirubin showed a positive connection with the chance of expire (OR=1.062; 95% CI: 1.007, 1.120; P0.05) among the biochemical indicators studied. Additionally, urea nitrogen (OR=1.589; 95% CI:1.273, 1.984; P0.001), lactate dehydrogenase (OR=10.395; 95% CI:2.163, 49.957; P0.01), and the amino transferase or alanine amino transferase ratio (OR=3.224; 95% CI: 1.586, 6.555; P0.001).

Cheng *et al.* [34] wanted to see the link between COVID-19 patients' in-hospital deaths and renal failure. A study with a possible group was carried out, involving 701 patients that had been admitted to a Chinese tertiary institution after receiving a COVID-19 diagnosis. The study utilized multivariable to discover independent risk factors, and utilize Cox proportional hazard regression. associated with in-hospital death. The analysis stated increased baseline serum creatinine (HR= 2.10, 95% CI:1.36-3.26) and elevated baseline blood urea nitrogen (HR= 3.97; 95% CI:2.57-6.14), as well as Acute Kidney Injury stage 2 (HR= 3.51; 95% CI: 1.49-8.26) and stage 3 (HR= 4.38; 95% CI: 2.31-8.31), were identified as independent risk factors contributing to hospitalized mortality. Once leukocyte count, comorbidities, disease severity, age, and gender were taken into account, these associations persisted. In addition, Nepogodiev *et al*. [35] carried out a global, multicenter cohort study at 235 hospitals across 24 countries, accounting for all surgical patients who had a confirmed SARS-CoV-2 infection within seven days prior to or thirty days following surgery. This study's main focus was 30-day afterwards death from the disease, which assessed every individual involved in the trial. Two predictors of death after thirty days were discovered after controlling for multivariable logistic regression: people aged 70 years or above in comparison to those under the age of 70, showed an (OR=2.30; 95% CI:1.65–3.22, p<0.0001), indicating a critical related with higher mortality risk. Furthermore, patients diagnosed with malignancies, rather than benign or obstetric conditions, displayed an OR of 1.55 (95% CI:1.01–2.39, p=0.046), signifying an enhanced risk of 30-day mortality. Patients with one or two comorbidities were not found significant with 30 days mortality among patients with COVID-19. Zhang *et al*. [36] discussed about the cardiac injury and in-hospital mortality. The multivariate Cox regression analysis revealed independent associations between certain factors and in-hospital mortality. Specifically, on admission, a decrease in pulse oximetry of oxygen saturation (SpO2) showed (HR= 0.704; 95% CI: 0.546-0.909, per 1% decrease, p=0.007), indicating an association with increased mortality risk. Additionally, elevated levels of hs-cTnI exhibited (HR=10.902; 95% CI:1.279-92.927, p=0.029), while increased levels of d-dimer displayed (HR =1.1030; 95% CI:1.0340-1.1760, 1mg/L enhanced, p=0.0030), both inception and death while in the hospital were linked independently.

Li *et al*. [37] sought to assess COVID-19 patients' admission extent, difficulties, medication, and outcomes. Patients with COVID-19 were brought to Tongji Hospital were part of a retrospective enrolment and subsequent follow-up study. The study employed a Cox PH model analysis of survival, particularly focusing on individuals categorized as severe illness. The multivariable Cox proportional hazards regression analysis found many significant risk factors associated with death in severe COVID-19 cases. Risk factors included experiencing cardiac injury (HR, 2.9; 95% CI:1.8-4.8), having an LDH level higher than 445 U/L at admission (HR, 2.0; 95% CI:1.2-3.3), being 65 years or older (HR, 1.7; 95% CI:1.1-2.7), and having hyperglycemia while in the hospital (HR, 1.8; 95% CI:1.1-2.8). These variables were found to be important predictors of mortality in cases of severe COVID-19. The possible risk factors linked to COVID-19-related deaths were later examined by Chen *et al*. [20] using a retrospective cohort of 1,590 hospitalized COVID-19 patients over China came into being. The impact on forecasting in various factors, encompassing both techniques KM and Cox PH models were utilized to examine medical and laboratory data. Upon conducting multivariate Cox regression analysis, several variables were found as independent risk factors for catastrophic outcomes. These included age groups: individuals aged 75 and over (HR=7.86; 95% CI:2.44-25.35) as well as those aged between 65 and 74 years of age (HR, 3.43; 95% CI:1.24-9.5). Additionally, those who suffer from cerebrovascular disease (HR, 3.1; 95% CI:1.07-8.94), coronary heart disease (HR, 4.28; 95% CI:1.14-16.13), and dyspnea (HR, 3.96; 95% CI:1.42-11) were found to be independent risk variables that were significantly related with fatal results. Further, Chesnut *et al.* [38] investigated the impact of reducing added sugars and increasing physical activity on individual COVID-19 resistance. A meta-analysis examining 35 studies suggested that preserving a healthy way of life, which includes a healthy diet and physical activity, could potentially alleviate the seriousness of SARS-CoV-2 infection. The analysis indicated that with each 1 mmol/Lrise in fasting blood glucose (FBG), there was a 33% rise in COVID-19 severity, denoted by (risk ratio=1.33; 95% CI: 1.26-1.40). FBG levels of 5.5-6.9 mmol/L showed an odds ratio of 1.69for ICU admission, soaring to 19.21 at levels surpassing 7.0 mmol/L. Hyperglycaemia correlated with mechanical ventilation, ICU stays, and mortality, exhibiting (HR=1.50; 95% CI:1.31-1.73) for 180mg/dL and (HR=1.48; 95% CI:1.29-1.70) for140-180 mg/dL glucose levels. Elevated blood glucose corresponded to severe SARS-CoV-2 symptoms (weighted mean deviation 2.21 [95% CI:1.30-3.13, P< 0.001]). Additionally, Kollias *et al.* [39] carried out a thorough meta-analysis and comprehensive review to evaluate the effects for stat in medication on COVID-19 patient mortality. Analyzing 10 studies, among individuals using statins was found to be (aHR=0.65; 95% CI:0.53, 0.81). Among six papers focusing on statin consecutively during hospitalization, the pooled hazard ratio, determined from theanalysis, was 0.54 (95% CI:0.47, 0.62). Moreover, in a meta-analysis involving twelve papers, the combined modified odds ratio for mortality among statin consumers was found to be 0.65 (95% CI:0.55, 0.78). Norelation between ratios for death and various factors across the studies, including gender, age, and comorbidities using multivariable meta-regression analysis. The analysis encompassed the studies that were considered in the research and accounted for numerous confounders by adjusting for demographics, comorbidities, medications, and biochemical indices.

Larvin *et al.* [40] worked on 58,897 UK Biobank subjects and found that overweight individuals had (OR=1.18; 95% CI:1.12 to 1.24) for COVID-19, and obese individuals had a higher (OR=1.33; 95% CI:1.26 to 1.41) compared to those with usual weight. However, periodontal disease did not significantly impact COVID-19 infection. Within the population classified as obese, individuals with periodontal disease exhibited a 57% higher rate of hospital admission (HR=1.57; 95% CI:1.25 to 1.97) compared to those without this condition. The hospital admission rates showed an incremental increase across varying BMI classifications: 4.4% in healthy weight, 6.8% in above ideal weight, and 10.1% in obese individuals. Furthermore, mortality rates were observed to rise with increasing BMI: 1.9% in a healthy weight, 3.17% above ideal weight, and 4.5% in the obese group. Particularly note worthy was the substantially elevated mortality rate (HR=3.11; 95% CI:1.91 to 5.06) among individuals with obesity and periodontal illness in comparison to those with no periodontal issues. Later, Namendys-Silva *et al.* [41] evaluated the clinical features and outcomes of critically ill individuals alongside severe COVID-19 who were brought to intensive care units (ICUs) in Mexico.Age demonstrated a significant connection with a heightened risk of death during hospitalization (OR=1.05; 95% CI:1.02-1.08; p<0.001). Additionally, C-reactive protein levels at ICU admission were also linked to a heightened risk of in-hospital death (OR, 1.008; 95% CI:1.003- 1.012; p<0.001). The duration of time spent in the ICU demonstrated an association with a reduced risk of hospital death rate (OR=0.89; 95% CI:0.84-0.94; p<0.001). Further, Rahmani *et al.* [42] carried out a meta-analysis and systematic review to evaluate how well COVID vaccinations reduce the disease's incidence, hospitalization, and mortality. This meta-analysis comprised 54 studies in total. The first dose of the vaccine showed a 71% effectiveness (OR = 0.29; 95% CI:0.23-0.36) against SARS-CoV-2 infection, 87% effective during the administration of the second dose (OR = 0.13; 95% CI:0.08-0.21). To prevent COVID-19-related hospital admissions, the first dose was 73% effective (OR = 0.27; 95% CI: 0.18-0.41), increasing to 89% effectiveness after the second dose (OR = 0.11; 95% CI:0.07- 0.17). In terms of vaccine types, mRNA-1273 and combined studies were highly effective after the initial dose, while ChAdOx1 and mRNA-1273 were effective after the following dose for infection prevention. The initial dose exhibited a 68% effectiveness (HR= 0.32; 95% CI:0.23- 0.45) in preventing deaths caused by COVID-19, while the following dose showed a remarkable 92% effectiveness (HR = 0.08; 95% CI:0.02-0.29).

Bramante *et al.* [43] aimed to assess if early outpatient therapy for COVID-19 with met form in, ivermect in, or fluvoxamine following SARS-CoV-2 infection could lower the likelihood of long-term COVID-19 infection. HR values for several treatment groups are provided in the paper. The HR comparing patients receiving metformin to those given a placebo was 0.59, with a 95% CI ranging from 0.39 to 0.89,and a significance indicated by ap-value of 0.012. Metformin consistently demonstrated therapeutic efficacy across all pre-established subgroups. Initiating metformin within 3 days of symptom onset resulted (HR=0.37;95% CI:0.15–0.95). In comparison to a placebo, there was no significant variation observed in the aggregate prevalence of extended COVID-19 with either fluvoxamine (HR=1.36; 95% CI:0.78–2.34) or ivermectin (HR= 0.99; 95% CI:0.59–1.64). Later, El-Qushayri *et al.* [44] about COVID-19. Compared to negative controls, patients with ACS and COVID-19 exhibited a significantly EMR (OR= 4.95; 95% CI:3.92-6.36; p < 0.01). Moreover, COVID-19 patients, when compared to negative controls, showed a significantly lower TIMI 3 post-test result (OR=0.55; 95% CI:0.41-0.73; p 0.01). Nevertheless, unrelateated in the prevalence of thrombus aspiration were reported (OR: 1.88; 95% CI:0.97-3.65; p = 0.06). The OR numbers represent the association between COVID-19 and results mentioned with values greater than one indicating a higher risk or prevalence in COVID-19 patients and values less than one indicating a lower risk or prevalence of COVID-19victims. Further, Evans *et al.* [45] examined how well sotrovimab, nirmatrelvir-ritonavir, and molnupiravir worked in lowering hospitalization or mortality rates among high-risk SARS-CoV-2 patients versus no treatment in the community. The study used HR and aHR. To evaluate the effectiveness of treatments in diminishing hospitalization or mortality after a positive SARS-CoV-2 test, within 28 days. An adjusted hazard rate in treated subjects was 35% lower than in non-treated participants. The adjusted HR for patients with two or more comorbidities was 0.45, demonstrating a 55% decrease in risk following treatment. Sensitivity analysis revealed that treated people had lower hazard ratios than untreated participants, both in adjusted and unadjusted analyses. The paper did not offer hazard ratio statistics for different treatment types or time periods. Later, Gul *et al.* [46] investigated predictors and outcomes of acute pulmonary embolism (PE) in individuals with COVID-19, assessing a value of d-dimerin predicting PE. Results reveal higher comorbidity prevalence (atrial fibrillation, hypertension, diabetes, etc.) in PE patients (OR data). COVID-19 individuals with severe PE have a higher 90-day death rate (adjusted HR = 1.36 [1.20-1.55]) and intubation rates (adjusted HR = 1.38 [1.18-1.61]) based on HR findings. Additionally, patients with acute PE exhibit elevated D-dimer at admission (OR = 1.13). These results emphasize the significance of promptly identifying and addressing pulmonary embolism (PE) in individuals with COVID- 19, as it is associated with worse results and higher death rates.

Isla *et al.* [47] investigated the relationship between COVID-19 infection and short-term mortality in patients with hip fractures who tested positive for COVID-19 using a systematic review and meta-analysis. The odds ratio for short-term death among patients with hip fractures who tested positive for COVID-19 were found to be 7.16 (95% CI:4.99-10.27) in studies that included both COVID-positive and negative individuals. A likelihood ratio for short-term mortality stood at 4.08(95% confidence interval, 2.31-7.22) for studies that screened all patients and 8.32 (95% confidence interval, 5.68-12.18) for studies that conditionally screened patients when stratified by hospital screening type. A statistically observation was fetched in OR between two screening methods (P= 0.04). Later, Kwok *et al.* [48] sought to investigate the effectiveness of inactivated whole virus and COVID-19 mRNA vaccines in patients with chronic respiratory conditions. However, no statistically not able distinction was detected between those who received a minimum of two doses of Corona Vac and those who received a minimum of two doses of BNT162b2 concerning their likelihood of being hospitalized with COVID-19 and suffering from respiratory failure.

Later, Mak *et al.* [49] examined the connection between death and weakness, readmission, and length of stayin older COVID-19 patients, as well as to evaluate the electronic frailty index's (eFI) prediction accuracy in relation to other frailty and comorbidity indicators. The odds ratio (OR) for in-hospital mortality per 10 rise in the electronic frailty index (eFI) was 2.95 (95% CI:2.42-3.62).The OR for 30-dayreadmission was 1.22(95% CI:1.07-1.39) per point increase on the Clinical Frailty Scale (CFS). Cox proportional-hazards models were used to compute the HR to 30-day and 6-month mortality. Particular values for these hazard ratios, however, were not disclosed in the publications cited. Further, Miyashita *et al.* [50] investigated the evolution of COVID-19 patient characteristics, outcomes, and risk factors, concentrating on the shift from early pandemic waves to waves dominated by delta variants. Examining a sizable dataset from a nationwide claims database in Japan (937,758 patients), the study calculates odds ratios for various factors that elevate the possibility of severe complications from COVID-19 and death across different pandemic phases. Accounting for age, gender, and comorbidities, specific odds ratios for diverse risk variables and age groups are provided. During the delta-predominant phase in comparison to the phase of wild-type predominance, for extreme COVID-19 (OR= 0.78; 95% CI:0.71-0.85), while for mortality, it was 0.56 (95% CI: 0.51-0.62). The study utilized multivariable logistic regression analysis to present adjusted ORs and 95% CIs to illustrate how severe COVID-19 is linked to death across different waves.

Hulme *et al.* [51] shows mRNA-1273's HR for positive SARS-CoV-2 tests is 0.95 (95% CI:0.95 to 0.96) vs. BNT162b2. Hospital admission HR for mRNA-1273 vs. BNT162b2 is 0.89 (95% CI:0.82 to 0.95), and COVID-19 mortality (HR = 0.83; 95% CI:0.58 to 1.19). For BNT162b2 recipients, OR infection of SARS- CoV-2 tests is 0.93 (95% CI 0.92 to 0.94). In those with prior infection, mRNA-1273 vs. BNT162b2 has a hospitalization HR of 0.61 (95% CI:0.42 to 0.89). At 28 weeks, non-COVID- 19-related mortality HR for mRNA-1273 vs. BNT162b2 is 0.92 (95% CI:0.86 to 0.99). Later, The relationship between chronic exposure to air pollution and the severity of COVID-19 was examined by Hyman *et al*. [52]. Additive generalized models using a 5-degree freedom regression spline function were employed to illustrate the relationship. The relationship between 2019 annual levels of PM2.5, PM10, O3, NO2, SO2, and benzene and the severity of COVID-19 (hospitalizations and mortality) was examined using multivariate logistic regression. Hospitalizations for COVID-19 were positively correlated with PM2.5, PM10, NO2, SO2, and benzene.Furthermore, PM2.5, PM10, SO2,and benzene displayed significant positive relationships with COVID-19 deaths yielding Ors (95%CI) of 1.62(1.52-1.72), 1.18(1.12-1.24), 1.39(1.31-1.48) and 1.23(1.17- 1.30) printer quartilerange (IQR).

Further, Huang *et al.* [53] explored the relationship between different right ventricular (RV) involvement phenotypes and intensive care unit (ICU) mortality among COVID-19-induced ARDS patients. Acute cor pulmonale (ACP) in all examinations resulted in a 0.479 times shorter survival time compare d to those without ACP (P=0.005). RV failure (RVF) was associated with a 0.642 factor for a shorter survival time of Pis 0.059, and RV dys function's impact on the duration of survival did not show a conclusive impact (P = 0.451). However, patients with acute cor pulmonale (ACP) identified during their final critical care echocardiography (CCE) assessment exhibited the greatest mortality risk, with an HR of3.25 (P<0.001) according to a multistate analysis. The RV involvement phenotype in the last echocardiography was similarly linked to ICU mortality, with acute cor pulmonale indicating a worse prognosis. Reis *et al*. [54] investigated The effectiveness of pegylated interferon lambda in averting serious adverse reactions in outpatient care with acute symptoms COVID-19.The cohort receiving pegy late dinter fer on lambda demonstrated that when compared to the placebo group, there was an HR of 0.57 (95% Bayesian credible interval, 0.33 to 0.95) for the duration until Covid-19 hospitalization and an HR of 0.59 (95% Bayesian credible interval, 0.35 to 0.97) for Covid-19-related patients admitted to hospitals or death rate. Individuals with an elevated viral loadat the beginning showed amore significant reduction in viral load on day7 (median log 10 decline: 8.29 vs. 5.16 within the placebo group). Furthermore, a greater proportion of patients in the interferon group (50.5% vs. 32.9% in the placebo group; OR= 2.13; 95% Bayes iancredible interval, 1.14 to 4.00) attained a load of viruses below the quantitation limit by day 7.

Later, Surendra *et al*. [55] assessed the COVID-19 pandemic's effects on Indonesia's national TB program, with particular attention to mortality rates, treatment coverage, and case notification. Models of bivariate and multivariable logistic regression were utilized for pin point factors linked with noteworthy reductions, exhibited as Ors alongside their

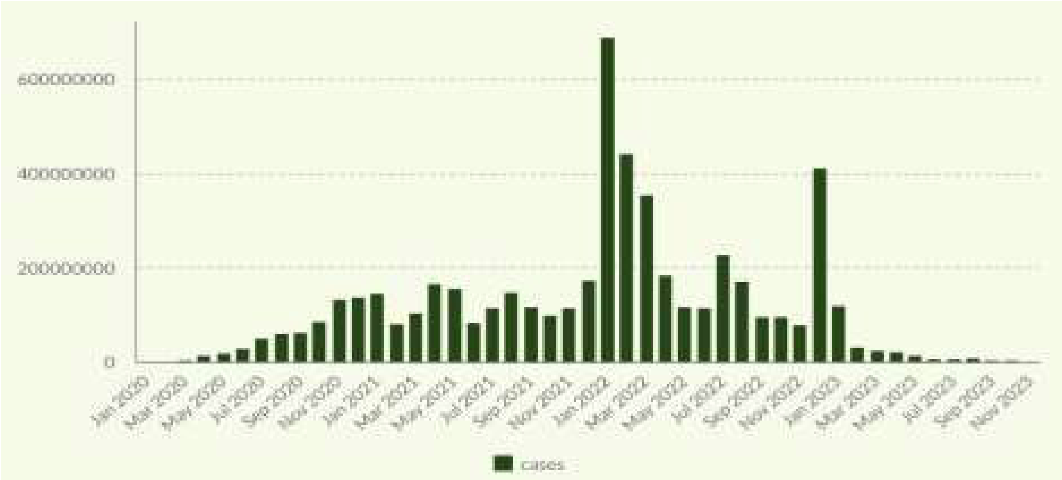


Figure 1: Global COVID case count from January 2020 to November 2023.

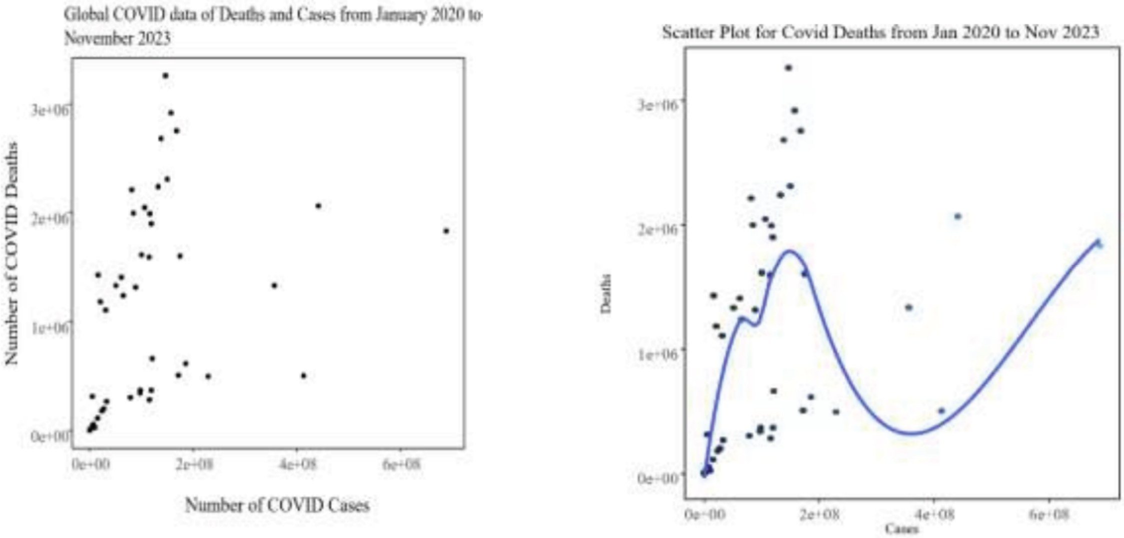


Figure 2: Global COVID deaths fromJanuary2020toNovember2023.

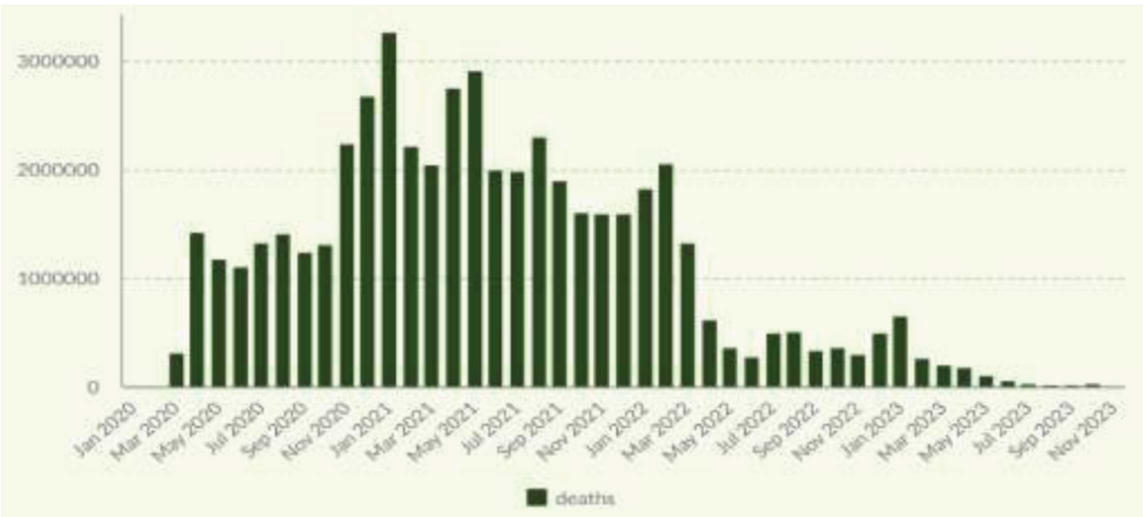


Figure 3: Global COVID death count from January2020 to November 2023.

associated 95% CIs. Higher COVID-19 incidence and each population has fewer Gene Xpert machines relate to lower tuber culos is notifications. Notably, during the wave with the delta variant majority, (OR=11.7; 95% CI: 1.5-93.4), and factors such as fewer primary health centers showed an OR of 10.6 (95% CI: 4.1-28.0), both associated with reduced treatment coverage. However, no factors were

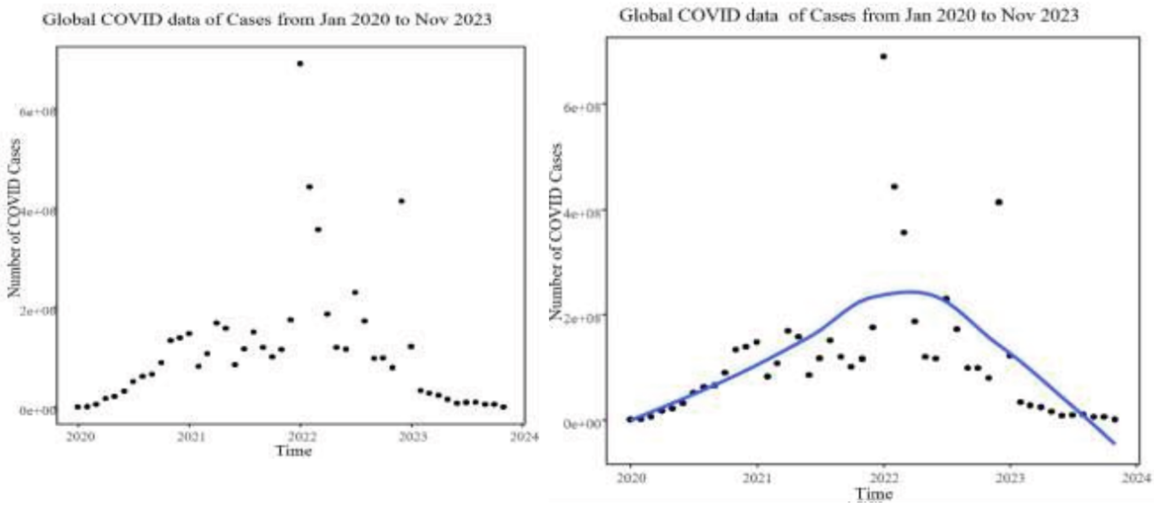


Figure 4: Global COVID case count from January 2020 to November 2023.

significantly linked to all- cause mortality. Later, Tran *et al.* [56] investigated the connection between mortality risk and pre-cannulation prognostic factors in adults receiving venovenous extracorporeal membrane oxygenation (ECMO) for ARDS linked to COVID-19. Significant factors linked with higher mortality include older age (aHR 2.27), male gender (uOR 1.34), and long-term lung conditions (aHR 1.55). Longer symptom duration (mean difference 1.51 days), extended intrusive mechanical ventilation (uOR 1.94), higher carbon dioxide levels in the blood (mean difference 4.04 mm Hg), increased driving pressure (aHR 2.36), and less prior ECMO experience (a OR 2.27) are also associated with elevated mortality. The study highlights potential bias risk in adjusted analyses if methodological requirements are not met during statistical analysis. The odds and hazard ratios provide insights into death risk factors in patients receiving venovenous ECMO for ARDS associated with COVID-19. Additionally, Tosato *et al.* [57] investigated the rate of malnutrition and the factors that contribute to it in COVID-19 survivors. They investigated the connection between the incidence of malnutrition and diagnostic and functional parameters during acute COVID-19 using logistic regression models. Following adjustments for multiple variables, the risk of malnutrition exhibited a gradual and independent increase with age (OR 1.02; 95% CI 1.01-1.03). Men in the study were also shown to be at significantly greater risk (OR 5.56; 95% CI: 3.53-8.74). Lack of nutrition detected during the study visit was linked to two symptoms indicated by individuals with COVID-19 in the acute stage: decreased appetite (OR 2.50; 95% CI 1.73-3.62) and dysgeusia (OR 4.05; 95% CI 2.30-7.21). Further, Watanabe *et al.* [58] evaluated the connection between COVID-19 vaccination and long-term COVID.Compared to those who did not receive vaccination (OR, 0.64; 95% CI, 0.45–0.92), those who received a single dose of the two-dose vaccination had a lower incidence of delayed COVID of the vaccine (OR, 0.60; 95% CI, 0.43-0.83). A decreased incidence of respiratory illness (OR, 0.50; 95%CI, 0.47-0.52) and persistent fatigue (OR, 0.62; 95%CI, 0.41- 0.93) was linked to two vaccination doses as opposed to not any immunization. After receiving the COVID-19 immunization, 20.3% (95% CI, 8.1-42.4%) of people with persistent long-term COVID symptoms reported improvement in their symptoms, whereas 54.4% (95% CI, 34.3- 73.1%) of those without such alterations did not report any changes in their symptoms.

Zeymer *et al.* [59] provided a thorough description of acute myocardial infarction (AMI) Individuals' hospitalizations and in-hospital deaths during Germany's initial COVID-19 outbreak. The study presents 95% CI and OR and incidence rate ratios (IRR) for comparingdata from various time periods. The odds ratios for under going percutaneous coronary intervention in ST-elevation myocardial infarction cases were 1.26 (95% CI:1.10-1.43) & non-ST-elevation myocardial infarction cases were 1.13 (95% CI:1.06-1.21), according to the analysis of in-hospital treatment conducted between 2020 and 2019. Conversely, there were no observed changes in the OR for Heat bypass surgeries over the course of these years. Further, Zuin *et al.* [60] evaluated the risk for deep vein thrombosis (DVT) and higher pulmonaryembolism (PE) in COVID-19 recovered people relative to non-infected patients, and identified the variables linked to this risk. When comparing Patients recovered from COVID-19 to non-infected individuals, the HR for acute pulmonary embolism (PE) was 3.16 (95% CI:2.63-3.79, I2: 90.1%). When comparing COVID-19 recovered individuals to non-infected patients, the hazard ratio (HR) for deep vein thrombosis (DVT) was 2.55 (95% CI:2.09-3.11, I2: 92.6%). When comparing COVID-19 recovered individuals to non-infected patients, the combined hazard ratio (HR) for Pe and DVT varied from 2.32 (95% CI:1.95-2.76) to 2.82 (95% CI:2.14-3.70).

According to the sensitivity analysis, the HR for PE with a range between 2.90 (95% CI:2.45- 3.43) and 3.43 (95% CI:2.85-4.13). Figure **1** and **2** displays the temporal evolution of COVID- 19 cases and fatalities from Jan 2020 to Nov 2023, revealing a pronounced surge in cases during specific periods, notably at the time of inception of COVID and subsequent waves.

CONCLUSION

The studies discussed in this review have explored the influence of significant underlying conditions, including cardiovascular disease, kidney issues, hypertension, congestive heart failure and chronic obstructive pulmonary disease. These conditions have been associated with the greatest risk of mortality due to COVID-19. Additionally, there is a need for further investigation into other comorbidities like cancer, diabetes, stroke, asthma, and HIV/AIDS to establish a stronger correlation with COVID-19 mortality. Identifying these comorbidities is crucial for COVID-19 patients to be more successfully classified as an increased risk, allowing for a more specific strategy in preventing tragic consequences. Furthermore, this review has explored how physical activity impacts COVID-19 resistance, the effects of statin medications on mortality rates, and the effectiveness of vaccines in reducing fatalities. These areas offer promising avenues for tailored interventions and treatment strategies. Additionally, investigating the correlation between pollution from the air exposure and COVID-19 severity sheds light on environmental factors influencing disease outcomes. Understanding the prevalence and determinants of malnutrition among COVID survivors provides critical insights for long-term care and rehabilitation. The synthesis of risk estimates, such as ORs or HRs with 95% CIs, from diverse studies has provided a thorough grasp of the complex features of COVID-19 and how it interacts with different environmental and health components. This research underscores the importance of focusing on customizing treatment approaches to meet the needs of populations with particular underlying health conditions. However, regardless of definitive measurements, prioritizing patient care and research remains crucial in combating this deadly pandemic.

STRENGTHS AND LIMITATIONS

This review consolidates recent findings on how comorbidities impact the elevated risk of death in COVID-19 patients by examining a significant amount of recently released research. There search involved a varied demographic drawn from multiple regions spanning Europe, Asia, Africa, and North America. However, this analysis faced several constraints. While some studies contained details regarding the racial and ethnic background of subjects, others provided limited or no information. Consequently, we were unable to investigate the possible impact of ethnic background and race, which might have contributed to variations observed among the studies.

The limitations within the reviewed studies revolved around potential inherent biases, particularly regarding patient selection and the diversity of medical treatment approaches. Caution is advised when interpreting the results due to inconsistent criteria used to differentiate severe & non-severe cases. Notably, Every individual with pneumonia who was admitted to the intensive care unit and needed mechanical ventilation, suffering from ARDS, or facing mortality were collectively classified as having undergone severe events. Moreover, the presence of multiple comorbidities in some patients might have compounded their impact on these serious events.

IMPLICATIONS FOR CLINICAL PRACTICE AND RESEARCH

As the race to create a vaccine against SARS-CoV-2 intensifies, the findings strongly advocate for prioritizing immunization among individuals identified to be at elevated risk. Those with pre-existing conditions like heart-related ailments, high BP, diabetic conditions, heart conditions causing fluid build-up, long-term kidney problems, and malignant illnesses confront a heigh tened risk of mortality due to the virus. Hence, they must be granted precedence to vaccination, particularly in situations where the vaccine supply is limited. Historically, the Advisory Committee on Immunization Practices recommends targeted public health vaccination intervention strategy for influenza vaccination against seasonal influenza [61]. In the population with chronic comorbidities, annual influenza vaccination significantly reduces mortality and morbidity [62]. Mounting evidence postulates that SARS-CoV-2 may become seasonal requiring annual vaccination [63].

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Received on 08-06-2025 Accepted on 07-07-2025 Published on 04-08-2025

https://doi.org/10.6000/1929-6029.2025.14.40