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ASSESSMENT OF RISK FACTORS OF COVID-19 SEVERITY AND MORTALITY USING META-ANALYSIS

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Abstract
Coronavirus Disease 2019 (COVID-19) became widespread in December 2019, causing a Public Health Emergency. It was a cause of great anxiety for a variety of reasons. Since it was a new virus, no one was immune, and there was no antidote or vaccine. Because of its uniqueness, scientists were unsure of how it acts and had no historical data to go on. Mild, moderate, and serious or critical COVID-19 cases were classified. The comprehensive analysis in this text combines findings from multiple studies, shedding light on the numerous factors influencing COVID-19 outcomes. This study focuses on identifying different risk factors for COVID-19 by applying rigorous statistical analyses to a comprehensive dataset encompassing demographic, clinical, and socio-economic variables. A systematic approach is employed for literature review and data extraction, ensuring the inclusion of studies with high methodological quality. Through this comprehensive assessment, we try to identify high-risk populations and factors amenable to intervention. A critical part of this investigation is to explore the death rate among patients who were admitted to the hospital as diagnosed patient of COVID-19 and to identify specific risk factors that can lead to fatal outcomes. More specifically, the study explores the impact of prevalent comorbidities on the mortality rate among COVID-19 patients, hypothesizing that the presence of such conditions could potentially elevate the risk of death.

Keywords: COVID-19, Odds Ratio, Meta-Analysis, Risk assessment,

INTRODUCTION

The COVID-19 pandemic not only caused millions of casualties but also changed lives and life style of human beings worldwide. Numerous studies have been conducted for the identification of the risk factors associated with severe, critical, and fatal cases due to this fatal disease (Zhu et al., 2020). Some risk factors have been consistently identified as being associated with a higher risk of severe and mortal cases of COVID-19. These risk factors include older age, male gender, and the presence of some critical health conditions such as diabetes, hypertension, cardiovascular disease, and respiratory diseases (Richardson et al., 2020). In addition, an association between obesity and the severity of COVID-19 disease has also been highlighted. It has been shown that people with obesity face more difficulties and they are at an increased likelihood of developing severe difficulties from COVID-19 (Goyal et al., 2020; Kass et al., 2020). Furthermore, socioeconomic factors such as poverty, crowded living conditions, and limited access to health care have also been associated with an increased risk of critical and mortal COVID-19 cases (Patel et al., 2020; Niedzwiedz et al., 2020).

Advanced statistical modeling, machine learning, and artificial intelligence (AI) techniques have been employed to identify and quantify risk factors, predict disease spread, and evaluate the effectiveness of interventions (Alimadadi et al., 2020, Faisal and Tutz, 2021). These approaches enable the integration of multi-dimensional data sources, including epidemiological, clinical, and genomic data, offering insights into the multifaceted nature of the disease and informing public health responses (Zahid and Ramzan, 2012).

Meta-analysis has been widely utilized in medical research to assess the strength of evidence regarding risk factors and treatment outcomes across diverse studies (Li et al., 2020, Zahid et al., 2024). In the context of COVID-19, several meta-analyses have aimed to consolidate findings related to its epidemiology, transmission dynamics, and clinical characteristics (Borenstein, et al, 2020; Galbadage 2020). However, there remains a need for comprehensive meta-analyses that specifically address the broad spectrum of risk factors for COVID-19, incorporating the latest research and covering various populations and settings. The objective of this study is to bridge this gap by conducting a rigorous meta-analysis of the literature to get an estimate of how different risk factors are associated with COVID-19 infection and intensity of this association. By providing a synthesized view of risk factors, this research contributes to the ongoing efforts to combat COVID-19, guiding public health policies, and informing individual and community-level preventive measures.
The COVID-19 pandemic affected the society and human life badly throughout the world. It left its impact on education, research activities, all religious, political, and entertainment gatherings, economy, and corporations (Onyema (2020). COVID-19 is linked to several different risk factors. Comorbidities are widely mentioned in COVID-19 outcomes as risk variables that are severe. However, is controversial the extent to which exact comorbidities affect the condition. (Ng et al. 2021).

The primary goal of this study is to understand how different risk factors contribute to the severity of COVID-19, aiming to help lower the chance of serious illness. It also looks into the death rates of COVID-19 patients who have been hospitalized, focusing on identifying which risk factors might increase the likelihood of death. Additionally, the research examines if having common health problems, known as comorbidities, can make the situation worse for COVID-19 patients, potentially leading to higher death rates. This study is designed to uncover important information that could guide efforts to better manage and treat COVID-19, aiming to save lives and reduce the disease's impact.

MATERIALS AND METHODS

The awareness and understanding of possible risk factors associated with COVID-19 or that can boost the severity of the disease is important for developing effective prevention and management strategies. While numerous studies have identified potential risk factors, the variability in study design, populations, and methodologies has resulted in a wide range of findings. To address these disparities and provide a comprehensive overview, meta-analysis emerges as a powerful tool. By aggregating and synthesizing data from multiple studies, meta-analysis enables the identification of consistent risk factors and the quantification of their effects, offering valuable insights into disease mechanisms and potential targets for intervention.

Effect Size Based on Binary Data

When the data is taken from a prospective study with binary outcomes such as disease severity or mortality, it is typically presented in the form of contingency tables. For two mutually exclusive groups of occurance and non-occurrence of COVID-19 , the intensity of association of each risk factor with the outcome can be computed with different measures like risk ratio, odds ratio, and/or risk difference. The classic 2×2 table is shown as Table 1, this data can be represented by the cells W, X, Y, and Z.

Table 2: contingency table showing the events for control and treated group

	Events	Non-Events	M
Treated	W	X	m_1
Control	Y	Z	m_2

Odds Ratio

The odds ratio represents the relationship between two odds, while the risk ratio signifies the relationship between two risks. Despite the statistical attributes that render the odds ratio as the optimal selection for meta-analysis, it may appear more complex to individuals compared to the risk ratio. In situations where the risk of an event is minimal, the odds ratio is expected to closely mirror the risk ratio. The odds ratio is computed as

$$\text{Odds-Ratio} = \frac{WZ}{XY}$$

The log Odds-Ratio is

$$\text{log Odds-Ratio} = \ln\left(\frac{WZ}{XY}\right)$$

with estimated variance defined by

$$V_{\log Odds-Ratio} = \frac{1}{W} + \frac{1}{X} + \frac{1}{Y} + \frac{1}{Z}$$

and estimated standard error as

$$SE_{\log Odds-Ratio} = \sqrt{V_{\log Odds-Ratio}}$$

Subsequently, these values are converted back into odds ratios using the odds ratio method.

$$\text{Odds-Ratio} = \exp(\text{log Odds-Ratio})$$

$$UL_{Odds-Ratio} = \exp(UL_{\log Odds-Ratio})$$

$$LL_{Odds-Ratio} = \exp(LL_{\log Odds-Ratio})$$

where UL and LL denote the upper and lower limits.

Random Effect Meta-Analysis

A single true effect size can characterize all the studies included in the analysis, with possible variations in observed effects attributed solely to sampling error within the fixed effect model. Since all studies under a fixed effect model have the same true effect, we utilize standard error to measure the influence. However, in some cases, the aforementioned assumption may be too strong to hold. This may lead us to assume that there is no reason to suppose that all studies are identical and so share the same true effect size in such cases.

We have another method for dealing with such cases, which is known as random effect meta-analysis. The inverse of variance is similarly employed as a weight in the random effect model, although here variance is the sum of within-study and between-study variance (τ^2).

Estimation of τ^2

The between-study variance (τ^2) is calculated by

$$\tau^2 = \frac{Q - d.f}{C}$$

The number of studies that are included in the main analysis is denoted by *k*.

$$Q = \sum_{i=1}^{k} W_i Y_i^2 - \frac{\left(\sum_{i=1}^{k} W_i Y_i\right)^2}{\sum_{i=1}^{k} W_i}$$

and

$$C = \sum_{i=1}^{k} W_i - \frac{\sum_{i=1}^{k} W_i^2}{\sum_{i=1}^{k} W_i}$$

RESULTS AND DISCUSSION

In this section, the results for the fitted models are presented for various risk factors. The comorbidities contribute to a higher risk of severe illness, such as diseases related to the lungs, kidneys, heart or respiratory system, and diabetes. The older age and severe obesity, also contribute to this condition. These factors increase the risk of having severe disease among the patients (Petrakis et al. (2020)). There have been reports about specific comorbidities that can increase the risk of infection and leading to dreadful outcomes with the progression of lung damage severity and mortality. As per another investigation, hypertension, diabetes, and cardiovascular disease emerged as the prevailing comorbidities among COVID-19 patients experiencing acute respiratory distress syndrome (Schiffrin et al. 2020).

The focused meta-analysis in the current study uses the findings of several independent studies to study different risk factors and their impact on COVID-19 infection. The aggregate data is visualized using a forest plot which indicates a range of associations, with the log odds ratio. A noticeable diversity in findings can be observed clearly. The negative values of associations in some studies (e.g., Rodriguez-Nava et al., 2021) show that certain risk factors may be linked to reduced odds of severe outcomes or mortality in COVID-19. Conversely, other studies (e.g., Fukushima K et al., 2021) present positive associations, indicating an increased risk. The width of the confidence intervals (CI) varies significantly, reflecting the precision of each study's estimate. For example, Lv & Lv, 2021 demonstrate a notably wide CI, suggesting a lower level of precision in their findings. The pooled estimate, obtained from a random effects (RE) model and shown by a diamond, indicates a Log[OR] of 0.60 with a 95% CI of [0.31, 0.89]. The association is statistically significant thus the examined risk factors are linked with increased odds of severity or mortality due to COVID-19. This collective insight underscores the importance of identifying and understanding these risk factors to inform targeted interventions and healthcare strategies.

The meta-analysis reveals that overall male individuals have a greater chance of having severe COVID-19. These are the combined results of 15 studies using fixed-effect meta-analysis. The proportion of male patients is higher in the severe disease group of coronavirus patients as compared to the non-severe group of coronavirus patients [male: OR = 1.593, 95% confidence interval (1.404, 1.807). It means that male has a 59.3% higher chance of having severe coronavirus disease 2019. The associated p-value (after combining studies) pointed out that this coefficient is statistically significant.

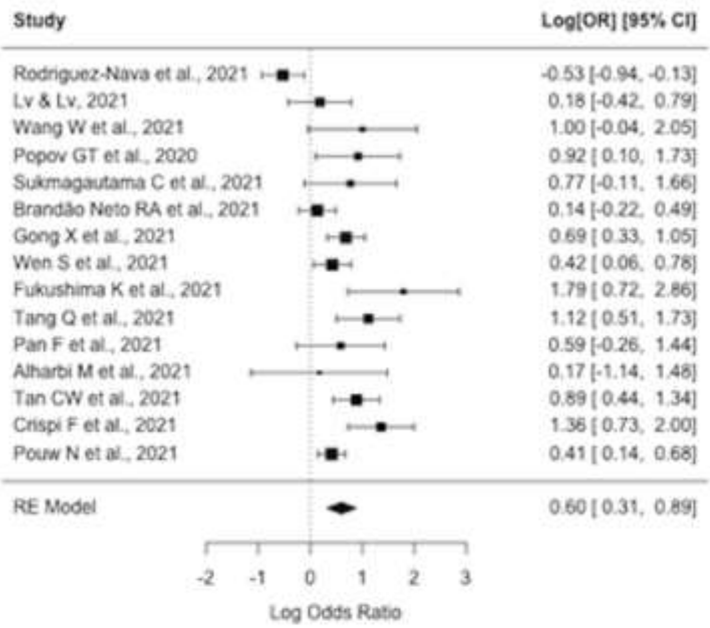
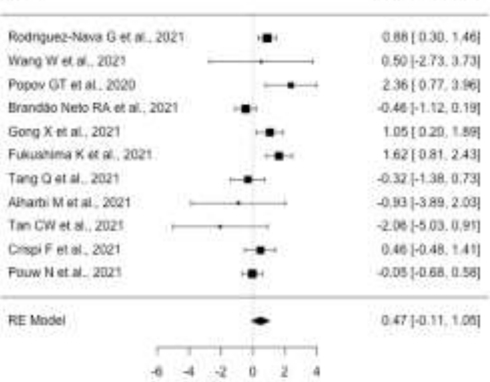


Figure 1: Funnel Plot of Gender (male)

Figure 2 shows the forest plot of cancer patients which shows quite interesting results. For instance, Popov GT et al., 2020 reported a log(OR) of 2.36, with a 95% confidence interval (CI) (0.77,3.96), suggesting a strong positive correlation between cancer and increased severity or mortality in COVID-19 patients. Similarly, Fukushima K et al., 2021 exhibit a log(OR) of 1.62, supporting that cancer as a comorbidity may worsen the risk of severe COVID-19 outcomes. Conversely, Tan CW et al., 2021 provided a log(OR) of -2.06, which interestingly suggests a significant negative association, potentially indicating a lower risk or a protective effect in the context of COVID-19, though this calls for a deeper investigation due to the complexity of the disease interactions.

Figure 3 depicts a forest plot for a meta-analysis evaluating the impact of cardiovascular disease (CVD) on the severity and mortality of COVID-19 patients. This plot integrates the effect sizes, in the form of log odds ratios, and their 95% confidence intervals (CIs) from multiple studies. The pooled result shows a combined log(OR) of 0.56 with a 95% CI of (0.24, 0.88). This implies that overall cardiovascular disease is associated with a statistically significant increase in the risk of severe COVID-19. The position of the diamond entirely to the right of the no-effect line and its narrow confidence interval underscores the robustness of this association across the included studies.



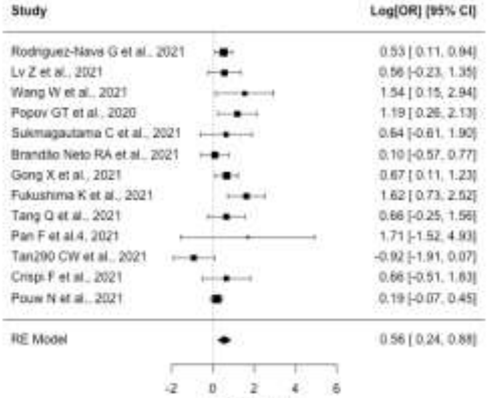
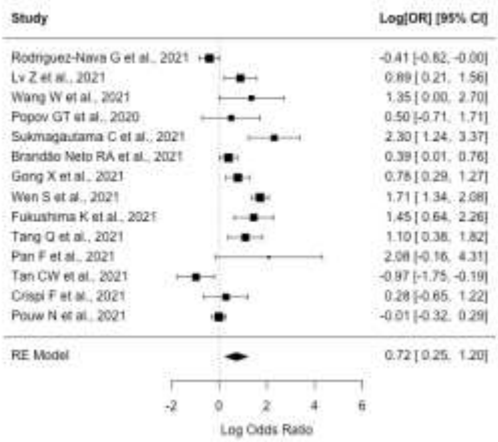


Figure 2: Funnel Plot of Cancer Disease

Figure 3: Funnel Plot of Heart Diseases



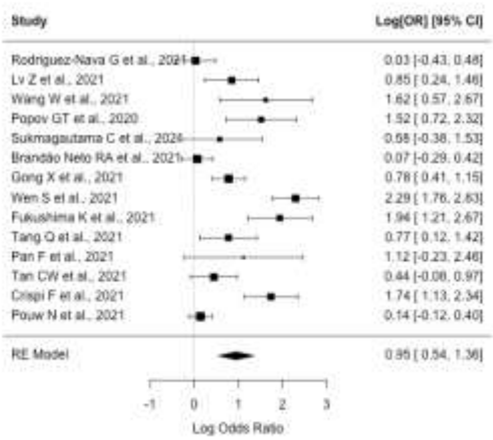
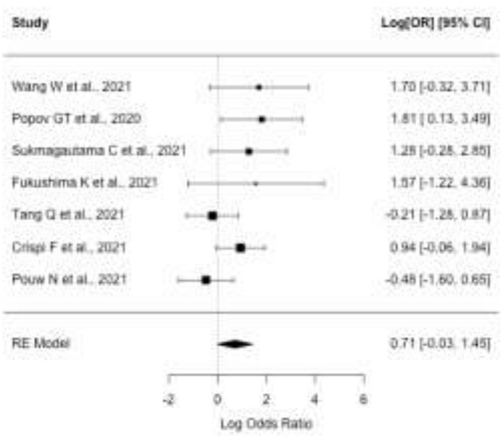


Figure 4: Funnel Plot of Diabetes

Figure 5: Funnel Plot of hypertension



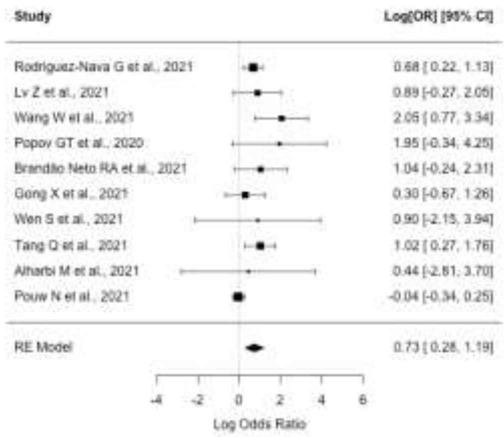
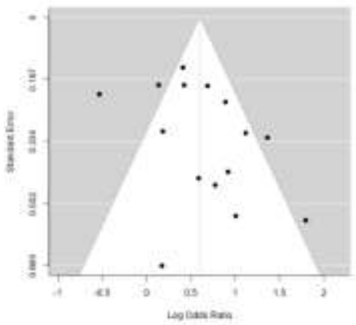


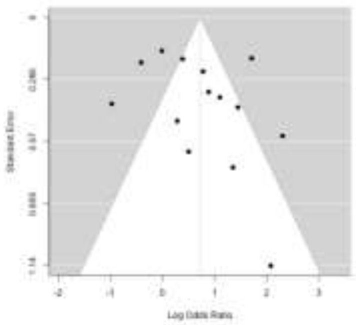
Figure 6: Funnel Plot of kidney disease

Figure 7: Funnel Plot of respiratory diseases

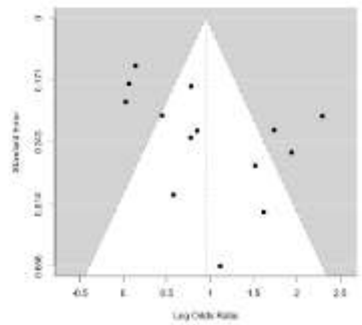
Figure 4 presents the forest plot from a meta-analysis examining the role of diabetes as a risk factor in the severity and mortality of COVID-19 patients. The plot aggregates the effect sizes from individual studies, quantified by log odds ratios, alongside their respective 95% confidence intervals (CIs). The results are based on the random-effects model to account for between-study variability and to calculate a pooled estimate. The value of log(OR) is 0.72, with a 95% CI of (0.25, 1.20). This indicates that diabetic patients have higher odds of experiencing severe or fatal COVID-19 compared to those without diabetes, although the lower limit of the confidence interval is relatively close to the no-effect line, indicating moderate certainty. The position of the diamond, which represents the pooled estimate and spans to the right of the no-effect line but does not include it, confirms the association is statistically significant. However, the width of the confidence interval points to a certain degree of uncertainty around the exact strength of this association, which may be influenced by the varying characteristics and methodologies of the included studies.



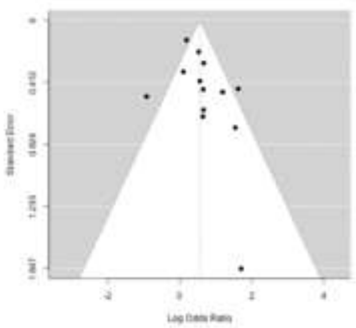
(a) Gender



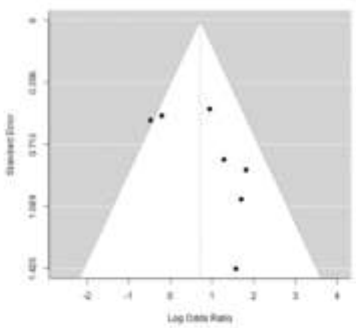
(b) Diabetes



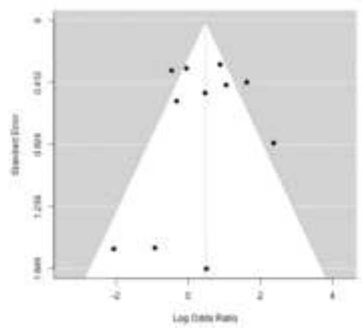
(c) Hypertension



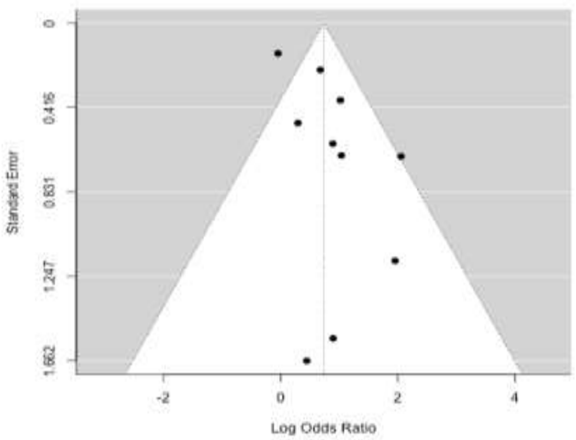
(d) Cardiovascular Disease



(e) Kidney Disease



(f) Cancer Disease



(g) Respiratory Diseases

Figure 8: Funnel Plots showing the results for all factors under study

Figure 5 illustrates the forest plot from a meta-analysis that assesses hypertension as a potential risk factor influencing the severity and mortality of COVID-19 patients. The pooled estimate using a random-effects (RE) model yielded a log(OR) value of 0.95 and 95% confidence limits (0.54, 1.36)). This value of combined effect size suggests that patients with hypertension are more likely to experience severe or fatal outcomes when infected with COVID-19 compared to those without hypertension.

Similarly, Figures 6 and 7 present the results of the impact of kidney and respiratory diseases respectively on the severity and mortality outcomes in COVID-19 patients. Kidney disease presents a non-significant trend toward increased severity of COVID-19, with a pooled log(OR) of 0.71 with 95% CI (-0.03, 1.45). It indicates a possibly increased risk for severe COVID-19 in affected patients (Figure 6). Whereas, respiratory diseases show a more noticeable risk for COVID-19 severity, with a log(OR) of 0.73 and 95% CI (0.28, 1.19). This shows a statistically significant association (Figure 7).

Collectively, these findings suggest that while kidney disease's impact on COVID-19 severity requires further investigation due to the non-significant statistical association, respiratory diseases are a clear risk factor for exacerbating COVID-19 severity. This combined interpretation emphasizes the importance of closely monitoring and managing patients with these comorbidities within the spectrum of COVID-19 care.
The funnel plots corresponding to all these risk factors are collectively shown in Figure 8. Inspection of these plots confirms the integrity of the reported findings, suggesting that the outcomes and associations mentioned are supported by the data visualized.

Risk Factors and Mortality
This analysis reveals that certain conditions markedly elevate the risk of mortality among infected individuals. The impact of comorbidities on the death rate due to COVID-19 has been a critical area of investigation since the beginning of the pandemic. Our meta-analysis of 29 studies between 2019 and 2022 provides compelling evidence of the impact of various comorbidities. It is clear from Table 2 that cardiovascular disease increases the likelihood of casualty among the patients, (OR: 2.354, 95% CI: (1.703, 3.255)), and 32.615% of the patients with this condition died from the disease. Similarly, cerebrovascular and chronic kidney diseases were distinct by the highest ORs of 3.522 (95% CI: (2.390-5.190)) and 3.514 (95% CI: (2.748, 4.495)), respectively. It shows that these conditions are significant risk factors for mortality, with roughly one-third of affected patients dying.

Table 2: Summary information, Odds ratio and proportion of patients who died (2019-2022)

Risk facors	Number of studies (n=29)	Number of dead patients	Number of alive patients	Odds Ratio (95% CI)	Proportion of dead (%)
Cardiovascular disease	24	2437	5035	2.354(1.703-3.255)	32.615
Diabetes	28	17606	47058	1.816(1.511-2.183)	27.227
Smoking	8	3314	21391	1.590(1.122-2.254)	13.414
Respiratory Disease	16	4033	12860	2.195(1.600-3.012)	23.874
Cerebrovascular Disease	8	1067	2225	3.522(2.390-5.190)	32.412
Cancer	14	663	1512	1.910(1.412-2.584)	30.483
Chronic kidney disease	13	5653	10966	3.514(2.748-4.495)	34.015
Chronic Liver Disease	7	117	349	1.452(0.815-2.587)	24.947
Gender (Male)	28	32059	186774	1.476(1.320-1.651)	14.650
Hypertension	28	24438	78260	2.063(1.709-2.490)	23.796

Diabetes and hypertension also indicated a significant relationship with COVID-19 mortality, with ORs of 1.816 (95% CI: (1.511, 2.183)) and 2.063 (95% CI: (1.709, 2.490)) respectively. The proportions of mortality is 27.227% and 23.796% respectively. These values indicate the serious nature of these chronic conditions in the context of COVID-19. Smoking and respiratory diseases were associated with an increased risk of death (ORs of 1.590 with 95% CI (1.122, 2.254)] and 2.195 with 95% CI (1.600, 3.012), respectively). While the proportion of deaths among smokers was lower (13.414%) compared to other comorbidities, it nevertheless represents a significant risk factor. Respiratory diseases led to death in 23.874% of the cases.

Cancer and chronic liver disease showed increased mortality risks with ORs of 1.910 (95% CI: (1.412, 2.584)) and 1.452 (95% CI (0.815, 2.587)), although with wider confidence intervals, especially for liver disease, indicating variability in the impact of these conditions. Finally, the analysis showed that the male patients have a higher likelihood of mortality with an OR of 1.476 (95% CI: (1.320, 1.651)). However, the proportion of deaths was 14.650% lower as compared to other risk factors.

Overall, the results of this study reinforce the critical nature of comorbidities in the mortality of COVID-19 patients, with cardiovascular, cerebrovascular, and chronic kidney diseases being the most significant predictors of fatal outcomes.

Risk Factors and Disease Severity

The results in the disease severity of patients, their summary information, proportion and odds ratio along with their 95% confidence intervals are provided in Table 3. Cardiovascular disease notably stood out, almost tripling the odds of severe disease manifestation (OR: 2.875, 95% CI: (2.183, 3.786)). This pronounced impact calls for an enhanced clinical focus on patients with cardiovascular histories who are navigating the complexities of COVID-19. Similarly, diabetes was implicated as a significant risk enhancer, with a marked increase in the odds of severe disease (OR: 2.658, 95% CI: (2.112, 3.344)), underscoring the critical need for stringent glycemic control among affected patients.

Table 3: Summary information, Odds ratio and proportion of of Severe patients (2019-2022)

Risk facors	Number of studies (n=29)	Number of severe disease patients	Number of non-severe disease patients	Odds Ratio (95% Cl)
Cardiovascular disease	25	413	343	2.875(2.183-3.786)
Diabetes	28	1064	975	2.658(2.112-3.344)
Smoking	12	156	182	1.170(0.677-1.484)
Respiratory Disease	20	230	155	2.781(1.757-4.402)
Cerebrovascular Disease	10	159	112	2.623(1.692-4.066)
Cancer	17	190	195	2.176(1.567-3.022)
Chronic kidney disease	9	68	28	3.269(1.633-6.543)
Chronic Liver Disease	10	80	83	1.965(1.076-3.588)
Gender (Male)	28	2749	4509	1.547(1.337-1.788)
Hypertension	26	1665	1636	2.507(2.116-2.970)

Smoking, a modifiable risk factor, presented a comparatively modest increase in risk (OR: 1.170, 95% CI: (0.677, 1.484)), highlighting the potential benefits of smoking cessation initiatives as part of public health strategies against COVID-19. Chronic kidney disease emerged as a particularly potent risk factor, with an OR of 3.269 (95% CI: (1.633, 6.543)), suggesting that individuals with renal impairments require meticulous care when confronted with SARS-CoV-2 infection. Furthermore, gender was identified as a significant risk factor where the odds of males are 54.7% higher to be infected as compared to females with OR=1.547 and limits of 95% CI are (1.337, 1.788). These findings are aligned with the global trends that suggest a gender disparity in disease outcomes. The analysis showed that the presence of hypertension increases the risk of COVID-19 infection 150% times than non-sufferers of hypertension. The resulting OR and corresponding 95% CI are 2.507 and (2.116, 2.970) respectively. The results highlighted hypertension as a potential comorbidity of COVID-19.

The investigation into chronic liver disease (CLD) by Kulkarni et al. (2020) reveals a nuanced relationship between CLD and COVID-19, underscoring that while CLD prevalence among COVID-19 patients was notable, it did not significantly exacerbate the progression to critical illness, suggesting that liver chemistry alterations may serve as more pivotal indicators of COVID-19 severity than the presence of CLD itself. Concurrently, the meta-analysis by L. Quan Li et al. (2020) catalogs the common clinical manifestations of COVID-19, establishing a baseline for clinical prognosis with a particular focus on discharge and fatality rates, thus emphasizing the disease's clinical trajectory from presentation to outcome.

Further exploration into specific risk factors such as gender, comorbidities (cardiovascular, cerebrovascular, diabetes), lifestyle choices (smoking), and demographic characteristics (age, sex) across several studies (e.g., Galbadage et al., 2020; Pranata et al., 2020; Z. Zheng et al., 2020) consistently highlights their substantial impact on disease severity and mortality. Notably, obesity emerged as a significant risk factor for severe COVID-19 outcomes, including increased hospitalization, ICU admission, and mortality rates, as evidenced by Yang1 & Le (2021). These findings collectively underscore the critical role of pre-existing health conditions and lifestyle factors in dictating COVID-19 prognosis, advocating for targeted preventive and management strategies that address these risk factors to mitigate disease progression and improve patient outcomes. The synthesized evidence suggests a complex interplay of demographic, clinical, and lifestyle factors in influencing COVID-19 severity, necessitating a multifaceted approach to patient care and intervention strategies tailored to individual risk profiles.

CONCLUSION

This study evaluated the risk factors that contributed to COVID-19 patients developing critical illness, to aid in assessing patient status and an early detection of critical patients. To reduce the chances of death, strict attention is needed to be paid to these risk factors. According to the findings of a meta-analysis, male patients may have a higher chance of acquiring a severe illness. The comorbidities such as hypertension, diabetes, cardiovascular disease, cancer, chronic liver disease, and chronic kidney disease may cause to intensify the severity of risk of COVID-19. Respiratory disease is also more likely to progress to severe illness, according to our findings. Patients with fundamental diseases such as diabetes and hypertension go through a lot of stress over time, and as a result their immunity decreases. Furthermore, a long history of diabetes and hypertension affects the vascular anatomy, causing the infection more likely to occur.

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