

# Investigation of the Effect of Comorbidity on Mortality in Patients with COVID-19: A Systematic Review and Meta-Analysis

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**Abstract:** Comorbidity is the coexistence of two or more diseases in a certain period. Severe COVID-19 can occur in healthy individuals of any age but predominantly in adults of advanced age or with underlying medical comorbidity. Comorbidities are identified as the main determinants of poor outcomes. This meta-analysis aims to examine the effect of comorbidity on mortality in patients with a diagnosis of COVID-19. Materials and Methods: The studies published between 2019-2020 from Google Scholar, Pub Med, Medline, Scopus, Science Direct, and Web of Science databases were scanned. Inter-rater agreement was calculated with Kappa statistics, effect size "Odds Ratio", heterogeneity between studies with Cochran's Q statistics. The study's effect size and publication bias included in the meta-analysis were calculated using the CMA 3 (Comprehensive Meta-Analysis) program. Results: A total of 24 studies were included in the study. According to the random-effects model, the overall effect size of comorbid factors on mortality development in patients diagnosed with COVID-19 was found to be statistically significant with a value of 2.537 (G.A; 2.078-2.098;  $p < 0.05$ ). In conclusion, cancers, chronic respiratory diseases, diabetes, hypertension, and especially cardiovascular comorbidities are important risk factors for COVID-19 related mortality for COVID-19. There are controversial results in the literature; Further studies involving larger patient groups and examining the specific impact of certain comorbid conditions are needed in order to reach more precise conclusions.

**Keywords:** COVID-19; mortality; comorbidity.

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## 1. Introduction

Over the past two decades, the outbreak and prevalence of infectious diseases have been handled as one of the most serious dangers to global health. Among these diseases, the most common and effective diseases have been seen on the respiratory systems, such as SARS, MERS, etc. One of these infectious diseases that affected the respiratory system is the SARS-CoV-2 disease, first seen in Wuhan and spread rapidly worldwide. In March of 2020, the World Health Organization declared the SARS-CoV-2 diseases as a COVID-19 Pandemic. From the beginning of the COVID-19 Pandemic to 15 January of 2021, the number of COVID-19 cases exceeds 100 million, with a death toll crossing 2 million people around the world [1].

Previous outbreaks studies have shown an association between cardiovascular and metabolic diseases and SARS and MERS [2-4]. A systematic analysis of 637 MERS-CoV cases had shown that diabetes and hypertension were present in approximately 50% of patients and

heart disease in 30% of cases [4]. Besides this, diabetes had been seen as an independent predictor for mortality and morbidity in SARS patients [2]. Considering the prognosis of the COVID-19, studies have shown that the majority of these patients had some associated comorbid condition that affects the treatment progress worse, such as diabetes (DM), hypertension (HT) or cardiovascular diseases (CVD) etc. [5]. Within less than 10 months, COVID-19 has registered a higher mortality record than SARS and MERS combined. Predicting the risk factors associated with the need for poor prognosis are thus of utmost importance given the overwhelming number of critical patients. Studying the relation of various factors like demographics and comorbidities in COVID-19 mortality can help redirect the limited resources towards patients who require them the most and reduce the mortality rate. In this study, we aimed to perform a systematic review and meta-analysis in order to investigate the association between comorbidity and mortality in patients with COVID-19. Our hypothesis is that comorbidities are associated with the outcome of COVID-19 mortality.

## 2. Materials and Methods

### 2.1. Type, place, and duration of the study.

This research was conducted using the meta-analysis method, one of the quantitative research methods. The study was conducted in the Health Management Department of the Institute of Health Sciences foundation university between 1-31 December 2020. Since the research is a meta-analysis study, the literature review model was used. Since the literature search does not directly affect animals or humans, ethics committee approval was not obtained for the research.

### 2.2. The application steps of the study.

For the application steps of the study, the articles included in this meta-analysis were classified based on PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analysis) and MOOSE (Meta-analysis of Observational Studies in Epidemiology) criteria. Articles that meet these criteria were determined and presented in Fig.1.

### 2.3. Detailed literature review.

A preliminary literature search was conducted to identify keywords on the internet access network of a foundation university. Turkish keyword combinations with screening are "Coronavirus and mortality and death and comorbidity". In English, the keyword combinations 'Coronavirus and mortality and death and comorbidity and COVID-19 and 'SARS-CoV-2' were used. Full-text articles published in scientific journals between 2019-2020 were scanned from electronic databases of Google Scholar, Web of Science, Scopus, Science Direct, Google Academic, MEDLINE, PUBMED. As a result of the literature review within the scope of the research, 1061 studies were found that examined the effect of comorbidity on mortality in patients diagnosed with COVID-19. 24 studies were eligible for inclusion in the meta-analysis. The included studies were evaluated by two separate evaluators using the quality assessment criteria suggested by Polit and Beck [6], and the kappa compliance rate was calculated in the SPSS 25 program. The protocol of the study was recorded in the "PROSPERO" database (ID = CRD42017054228), which provides systematic reviews and meta-analyses in the world (APPENDIX-A). No study with a similar title was found. After the title and summary readings,

the articles to be included in the full-text reading were determined. The article search and screening diagram for the inclusion flow of the articles in the study Figure 1. presented.

2.4. Searching articles and inclusion criteria in meta-analysis.

1. Studies with original articles (excluding qualitative studies, thesis, book, review, letter, case, and reports).
2. Randomized controlled studies, experimental and descriptive, full-text research articles written only in English and Turkish in order to prevent linguistic bias in the relevant subject.
3. Articles that are accessible within the university and published in a national/international refereed journal.
4. Full-text articles about the effects of comorbidity on mortality in patients diagnosed with COVID-19 and articles from 2019-2020 were evaluated (Figure 1).

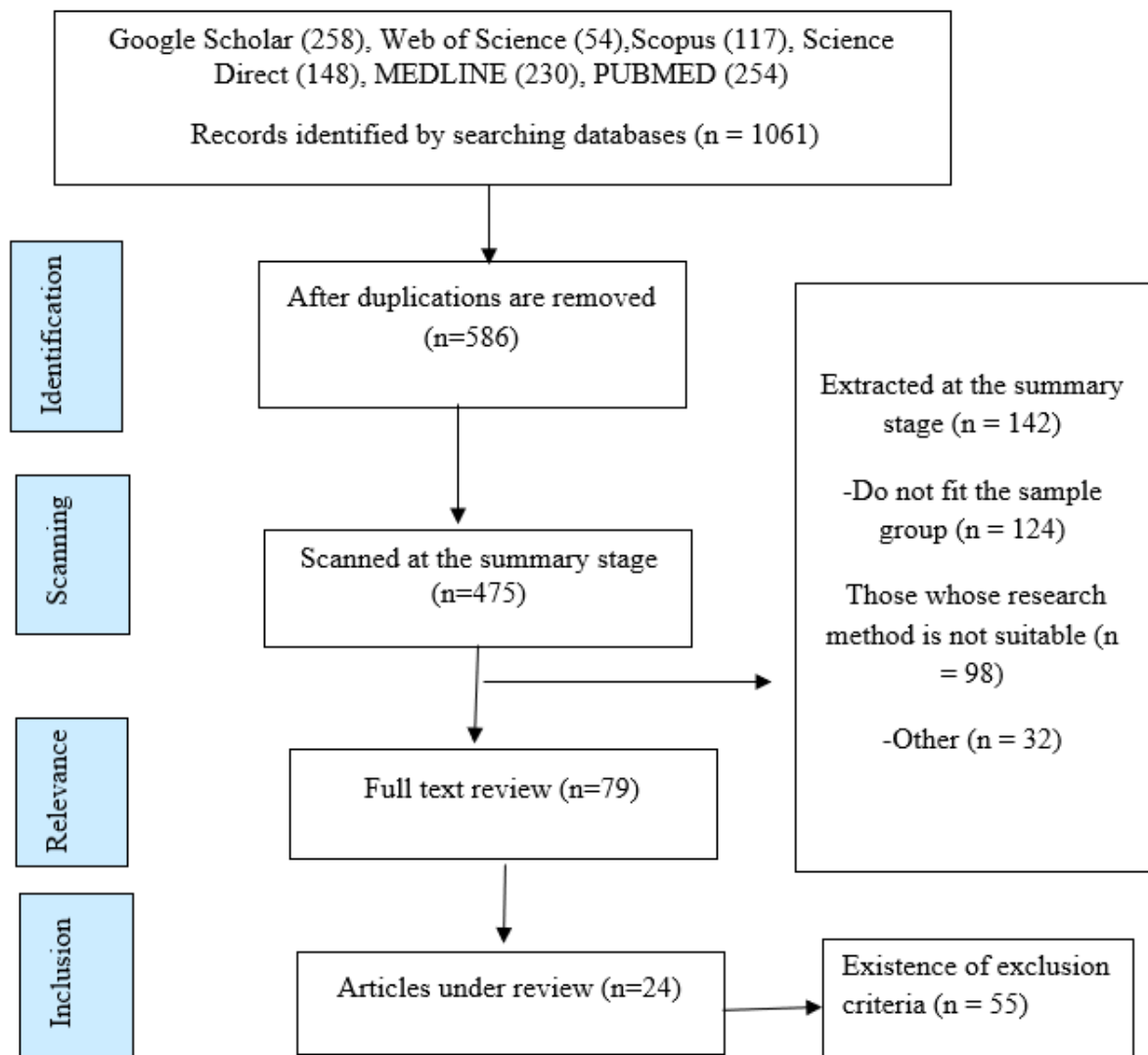


Figure 1. PRISMA 2 (Preferred Reporting Items for Systematic Reviews and Meta-Analyzes Statement) Flowchart.

*2.5. Methodological quality assessment according to the review, coding, and inclusion criteria of articles.*

Independent and detailed abstract and full-text readings of the articles were completed by two researchers/experts in order to prevent publication bias. The articles evaluated were coded according to their descriptive features. These defining features; The name and date of the study, its purpose, sample size, comorbid disease diagnoses, research design, basic findings (main output), and quality evaluation score for the results of the diagnosis of COVID-19. Twelve of the research quality evaluation criteria proposed by Polit and Beck were used for the remaining 24 publications after the review of the studies [6]. Each study was evaluated on all criteria and separately by the researchers, and if each item did not meet "1 point", a score of "0" was given. The scores that the study can get according to the criteria range from 0 to 12. In the study, two researchers independently examined articles belonging to all subgroups, and articles scoring 7 or more in the quality evaluation were evaluated as quality. Two of the studies (n = 26) whose quality was evaluated by independent evaluators were evaluated as "poor" and 1 as "moderate". A total of 24 studies were included in the meta-analysis since studies were evaluated as strong and medium-quality.

*2.6. The data analysis.*

The "Comprehensive Meta-Analysis Academic (Version 3)" licensed software was used to analyze the frequency and percentage values of the combined sample numbers of the 24 studies included in the meta-analysis, according to the sample content and the effects of comorbidities of patients diagnosed with COVID-19 on mortality. The data of all articles meeting the inclusion criteria and decided to be included in the study were entered into the CMA software, and the heterogeneity of the articles was evaluated. In the first stage, scattering in the funnel plot was examined to determine whether publication bias was in the studies conducted with meta-analysis. In the research, after the effect size value of each study was calculated, a heterogeneity test was performed. According to the results of this test, two models, fixed effects and random effects, are used in meta-analysis. Random effects model in group analysis with  $p \leq 0.05$  in heterogeneity test, effect sizes of all studies under the fixed-effects model in group analyzes with  $p > 0.05$ , study weights, 95% confidence intervals, and overall effect size were calculated. The statistical significance limit was accepted as  $p \leq 0.05$  in the evaluation of the overall effect. FunnelPlot analysis was performed to test the publication bias, and the results of Classic Fail-Safe N and Tau coefficient calculations were used.

### **3. Results and Discussion**

Studies used in the meta-analysis were identified as 18 descriptive observational retrospectives, four observational prospective, and two cross-sectional studies. The sample size in the studies included in the study is between 92 and 2821. In this study, kappa values ranged from 0.741 to 0.872 based on inter-rater reliability agreement analysis articles. The general fit rate kappa value was found to be 0.878, which was good [7].

*3.1. Analytical findings affect sizes and heterogeneity.*

In the study, a heterogeneity test was applied to determine the general effect of the disease on death in patients diagnosed with COVID-19. As a result of the heterogeneity test, the p-value was found to be less than 0.05. The Q (528,802) value was found to be greater than <https://biointerfaceresearch.com/>

the value corresponding to the df value. As a result of the individual studies included in the analysis, it was determined that the studies evaluated in the meta-analysis application were heterogeneous. The  $I^2$  statistic value was calculated as 99,565. As the result of the calculations, the effect size distribution was evaluated according to the random effects model (Table 1).

**Table 1.** Heterogeneity test results for General Mortality  
**Effect size and 95% interval**

Model	Number Studies	Point Estimate	Lower Estimate	Upper Limit
Fixed	24	0.134	0.128	0.141
Random	24	0.075	0.034	0.165
Test Of Null (2-Tail)				
Model	Z-Value	P-Value		
Fixed	-81.363	0,000		
Random	-6.400	0,000		
Heterogeneity				
Model	Q-Value	Df (Q)	P-Value	I-Squared
Fixed	5288.802	23	0,000	99.565
Random				
Tau-Squared				
Model	Tau Squared	Standard Error	Variance	Tau
Fixed	3.864	2.244	5.037	1.966
Random				

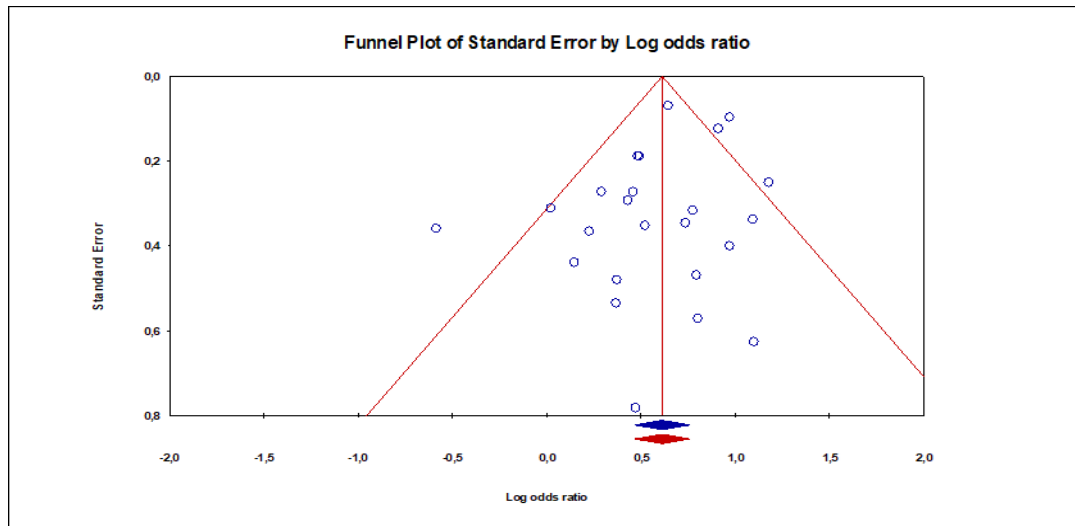
In Table 2, the meta-analysis results of 24 studies examining the general effect of the disease on mortality in patients with COVID-19 diagnosis and included in the study are shown with a forest plot.

**Table 2.** The effect of COVID-19 diagnosis on overall mortality.

Study Name	Statistics for each study				
	Odds ratio	Lower limit	Upper limit	Z-Value	p-Value
[8]	0,895	0,564	1,420	-0,471	0,637
[9]	0,004	0,001	0,011	-9,502	0,000
[10]	0,157	0,091	0,270	-6,661	0,000
[11]	0,031	0,018	0,055	-11,984	0,000
[12]	0,002	0,001	0,003	-28,217	0,000
[13]	0,883	0,610	1,278	-0,660	0,509
[14]	0,155	0,100	0,243	-8,194	0,000
[15]	0,067	0,043	0,105	-11,779	0,000
[16]	0,001	0,001	0,002	-33,732	0,000
[17]	0,119	0,079	0,179	-10,147	0,000
[18]	0,872	0,799	0,953	-3,045	0,002
[19]	0,300	0,265	0,340	-19,151	0,000
[20]	0,066	0,033	0,132	-7,679	0,000
[21]	0,028	0,017	0,048	-13,390	0,000
[22]	0,045	0,040	0,050	-55,375	0,000
[23]	0,013	0,011	0,015	-50,634	0,000
[24]	0,059	0,036	0,096	-11,371	0,000
[25]	2,560	1,162	5,641	2,332	0,020
[26]	0,346	0,115	1,044	-1,883	0,060
[27]	0,091	0,069	0,121	-16,595	0,000
[28]	0,493	0,351	0,692	-4,080	0,000
[29]	0,030	0,014	0,065	-8,892	0,000
[30]	0,165	0,087	0,314	-5,478	0,000
[31]	0,008	0,006	0,009	-51,019	0,000
<b>The general effect size</b>	<b>0,075</b>	<b>0,034</b>	<b>0,165</b>	<b>-6,400</b>	<b>0,000</b>

The general effect size was found to be 0.075 (G.A; 0.034-0.165), with the analysis performed according to the random-effects model. This result determined that although  $p < 0.050$ , COVID-19 disease did not affect mortality, the Odds ratio was found to be 0.075, and the effect size was insignificant (Table 2).





**Figure 2.** Funnel Scatter Plot.

#### 4. Conclusions

Previous literature has documented the increased risk of worse clinical outcomes in patients with avian influenza [34-38], SARS-CoV [39], and MERS-CoV infections [40-48]. Among the most common comorbidities related with poor prognosis are hypertension [48], diabetes [41, 45], respiratory diseases [39, 49], heart disease [35, 44], pregnancy [32], kidney disease [48], and malignancy [39]. According to studies on SARS-CoV, comorbidities, such as cardiovascular diseases, HT, diabetes, were the most important components to predict negative outcomes and increased death risk [50]. Cardiac disease and diabetes increased the risk of death by twice as much as other risk factors [50]. Thus, it is necessary to evaluate the comorbidity diseases in COVID-19 prognosis.

Literature showed that the limited time so far and the sample size with data collection are not complete for the overall world. Most of the studies have not analyzed comorbidities in mortality cases. So the relationship between COVID-19 related mortality and comorbidities such as cardiovascular diseases, metabolic diseases had not been determined. In this study, comparing the results of Covid-19 related publications, people with comorbidities were more sensitive to COVID-19 infection in this meta-analysis. The presence of comorbid diseases such as cerebrovascular disease, cardiovascular disease, chronic liver disease is associated with an increased likelihood of mortality in COVID-19 patients. The results in this study are similar to this meta-analysis results' [51,52]. The general approach for comorbidities is that they often coexist and that such patients are more likely to have poor health, and this is the case with COVID-19 [13,14,53-55]. Guan *et al.* found that comorbidities such as diabetes, hypertension, chronic obstructive diseases, and malignancy are inclined to adverse clinical consequences in COVID-19 patients, similar to other severe acute respiratory outbreaks [16]. They also reported that serious cases were presumably to have hypertension, cardiovascular diseases, cerebrovascular diseases, and diabetes than non-serious cases. Inciardi *et al.* revealed that patients with a history of heart disease had an extremely poor prognosis, such as greater septic shock, thromboembolic events, and mortality rates than patients without a history of heart disease [56]. Patel *et al.* Reported that COVID-19 patients with ARDS complications had a higher risk of mortality than patients without ARDS [57]. Another study reported that diabetes disease and obesity may have contributed to disease severity and mortality in COVID-19 patients [30]. Yang *et al.* reported that the epidemiology of COVID-19 incidence, the severity

of disease, and mortality appears to be directed towards older people with diabetes, hypertension, and cardiovascular disease in particular [58]. Another study reported that age and comorbidities, especially hypertension, were independent risk factors for mortality in Bolivia [9]. Our study revealed that in COVID-19 prognosis with presence comorbidities such as diabetes, cardiovascular disease, the cerebrovascular disease had associated with COVID-19 Mortality. COVID-19 patients with at least one comorbidity had a significantly increased risk of poor outcome or greater than patients without comorbidity, and this study may help the clinicians in the COVID-19 prognosis with identifying high-risk patients to reduce the mortality.

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## Conflicts of Interest

The authors declare that they have no competing interests.

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