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Comorbidities and increased mortality of COVID-19 among the elderly: A systematic review

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ABSTRACT

Purpose: The purpose of current review is to conduct a systematic overview of articles published between 2019 and 2021 on the relationship of comorbidities and mortality due to Coronavirus Disease 2019 (COVID-19) among the elderly population. *Methods:* We conducted a systematic search on PubMed for articles published between 2019 and 2021 to identify any cohort and case-control studies that investigated the relationship of comorbidities and COVID-19 mortality among the elderly, defined as 60 years of age and above. Databases were searched independently by two authors. Disagreements were resolved by the inclusion of a third investigator. Reviews, systematic reviews, and meta-analyses were excluded from our systematic review. *Results:* A total of 15 studies were selected for our systematic review. Of the included studies, 3 were case-control, 3 were prospective cohort studies and 9 were retrospective cohort studies. As for size, 10 studies were conducted on populations of <1000 participants, 3 ranging from 1001 to 10,000, and 2 on populations of >10,000 individuals. The included studies found that the presence of certain conditions, such as cardiovascular, respiratory, renal diseases, malignancies, diseases of the nervous system and diabetes are associated to increased mortality in populations that consisted of elderly patients. *Conclusion:* Results of our systematic review suggest that comorbidities contribute to increased COVID-19 mortality among the elderly. The detrimental effect of comorbidities and advanced age on the immune response could lead to a more frequent occurrence of symptomatic and severe infections with COVID-19.

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KEYWORDS

Coronavirus Disease 2019, coronavirus, pandemics, mortality, COVID-19, elderly, comorbidity

INTRODUCTION

On March 11th, the World Health Organization declared the Coronavirus Disease 2019 (COVID-19) as a global pandemic [1]. Since the beginning of the pandemic, more than 373 million people have contracted the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) globally, and a total of over 5.6 million people have lost their lives due to COVID-19 until now [2].

Studies indicate that the severity of COVID-19 increases with age and with the presence of certain comorbidities [1, 3–15]. Advanced age is often associated with a more serious manifestation of COVID-19, including higher mortality rates [16, 17]. Compared to the 5–17-year-old population, those between ages 65 and 74 have a 1,300-fold higher likelihood of dying as a result of a COVID-19 infection [18]. The same likelihood increases to 8,700-fold among the 75–84-year-old population [18]. Apart from older age, severe manifestations of COVID-19 are also linked to the presence of certain diseases, such as chronic kidney diseases, chronic obstructive pulmonary disease (COPD), cerebrovascular diseases, acute respiratory diseases, and coronary heart diseases [19]. Approximately 65% of people between ages 65 and 84 suffer from one or more concurrent conditions, the most frequent being cardiovascular and cerebrovascular diseases, respiratory diseases, and diseases affecting the central nervous system [20]. Among the elderly, the presence of comorbidities are linked to decreased immunity, higher mortality, reduced functional status, and increased health care utilization even without the presence of certain aggravating factors, such as an ongoing pandemic [20].

Advanced age and the number of concurrent comorbidities could have a synergistic adverse effect on the health status of elderly, explaining the higher COVID-19 mortality observed among elderly comorbid patients [6]. As the COVID-19 pandemic progresses, more and more studies are being published on the topic of comorbidities and mortality of elderly with sometimes contradictory evidence. Therefore, our aim was to conduct a systematic review of articles published to this date that investigate the relationship of comorbidities and COVID-19 mortality among the elderly population and synthetize their results to better elucidate the role of comorbidities in the mortality of COVID-19.

MATERIALS AND METHODS

For our present systematic review, we used the PRISMA statement guidelines as preferred reporting system for systematic reviews or meta-analyses [21]. We conducted a systematic search for articles published on PubMed including the following terms: („COVID-19" OR „coronavirus" OR „SARS-CoV-2" OR „SARS-nCoV-2" OR „nCoV" OR „2019-nCoV" OR „novel coronavirus") AND („comorbidit*" OR „morbidit*" OR „co-morbidit*" OR „underlying disease" OR „coexisting disease" OR „co-existing disease" OR „preexisting disease" OR

„pre-existing disease") AND („elderly" OR „aged, 60 and over" OR „Frail Elderly" OR „seniors" OR „aged 60") AND („mortality" OR „Age Specific Death Rate" OR „Age-Specific Death Rate" OR „CFR Case Fatality Rate" OR „Case Fatality Rate" OR „Crude Death Rate" OR „Crude Mortality Rate" OR „Death Rate" OR „Decline, Mortality" OR „Determinants, Mortality" OR „Differential Mortality" OR „Excess Mortality" OR „Mortality Decline" OR „Mortality Determinants" OR „Mortality Rate" OR „Mortality, Differential" OR „Mortality, Excess"). We also conducted a reference search of relevant articles to identify additional studies.

We decided to include studies that met the following inclusion criteria: 1) cohort and case-control studies 2) published in English 3) between December 1st, 2019, and August 31st, 2021, 4) focusing on the relationship of comorbidities and COVID-19 mortality 5) in the elderly population defined as 60 years of age and/or above. Reviews, systematic reviews, and meta-analyses were excluded from our study.

Databases were searched independently by two investigators (AP, AM). Articles were first filtered by reviewing their titles and abstracts, and this was followed by the full-text appraisal on a smaller number of articles. Articles chosen by at least one of the investigators were included in the final list of studies. Any disagreements were resolved by involving a third investigator (ZSSZ) in the article selection process.

After the list of selected studies was finalized, the following information was gathered from articles: author, year of publication, geographic location of study, study design, size of population, characteristics of examined populations, and the comorbidities identified by the study. Where available, both unadjusted and adjusted results were presented. Results were synthetized qualitatively. To facilitate the interpretation of results, all data was summarized in a table.

RESULTS

Initially, we identified a total of 539 publications on PubMed on the topic and 1 article with reference search. After review of titles and abstracts, 454 studies did not meet the eligibility criteria and were excluded. Full-text appraisal was hence conducted for 86 articles. A total of 71 articles were excluded because they did not include data on people older than 60 years ($n = 30$), they were meta-analyses ($n = 2$) or cross-sectional ($n = 5$) studies, or for other reasons ($n = 30$). Other reasons included no access to full-text, no data on mortality, or populations were grouped into age groups that did not coincide with our age group of interest (e.g. elderly data was only available for the 55+ population). Finally, four ($n = 4$) non-English articles with English abstracts were also excluded during the full-text assessment. As a result, a total of 15 studies were included in our systematic review. Study selection process is displayed in Fig. 1.

Of the included studies, 3 were case-control studies, 3 were prospective cohort studies and 9 were retrospective cohort studies. There was a total of 5 studies from Europe, 4 studies from Turkey, 3 studies published from China, and one study from USA and Brazil each. One additional study included data obtained from both certain European countries and Ecuador. As for sample size, 10 studies were conducted on populations of <1000 participants, 3 studies on populations ranging from 1001 to 10,000, and finally 2 studies on populations

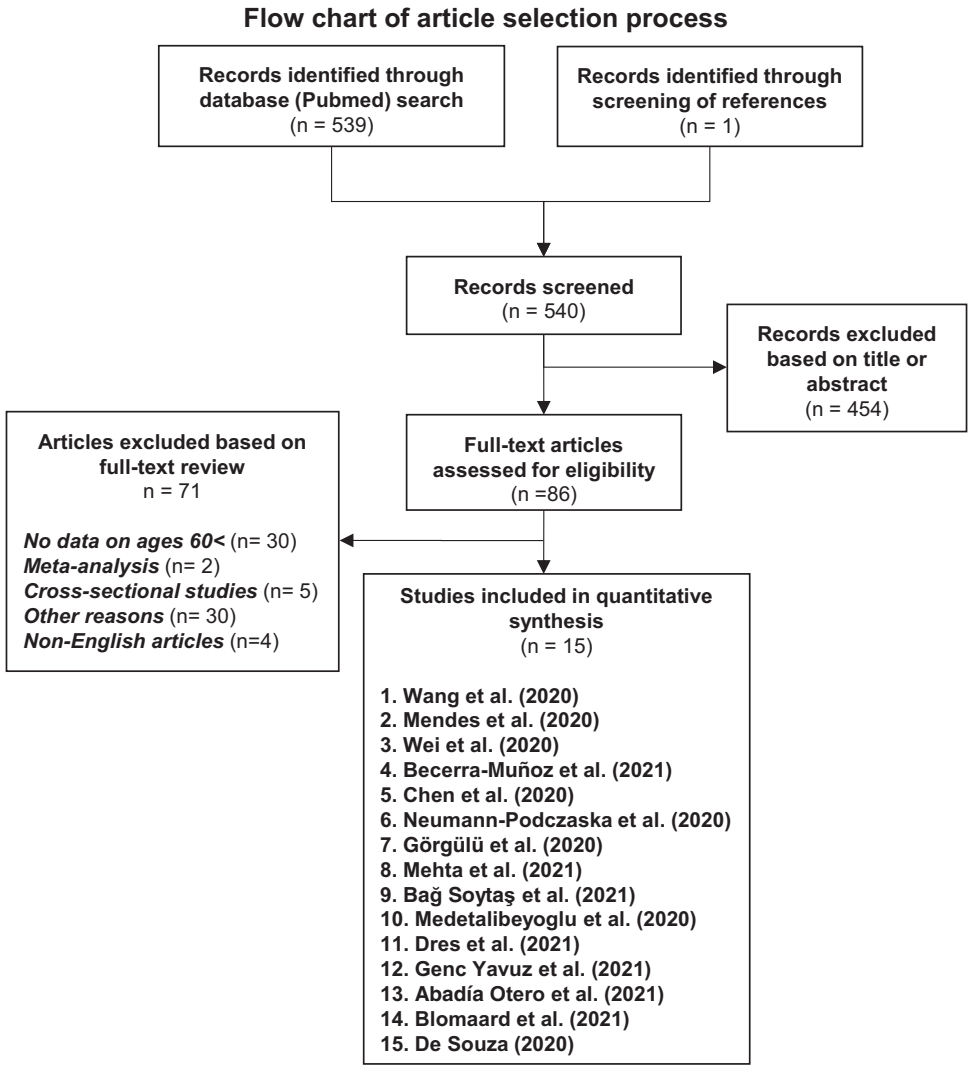

Fig. 1. A total of 540 articles were selected. 525 articles were excluded during the evaluation process, resulting in the inclusion of a total of 15 articles

of >10,000 individuals. A total of 8 studies published median ages, whereas 7 studies reported mean age. Median ages ranged from 61.5 to 82, while mean age ranged from 70 to 86 years. The proportion of female participants was between 30 and 68%. Regarding comorbidities, 6 studies identified cardiovascular diseases, 3 studies identified respiratory diseases, 3 studies identified renal diseases, 3 studies identified diabetes, 2 studies identified neurological and psychiatric conditions, while another 2 studies identified cancers as significant risk factors for increased COVID-19 mortality among elderly patients. A total of 3 studies found no relationship between

Table 1. Baseline characteristics and identified comorbidities of included studies

Author (year)	Country	Study design	Study size (deaths/total)	Population characteristics	Comorbidity	Unadjusted effect size (95% CI)	Adjusted effect size (95% CI)
Wang (2020)[22]	China	retrospective cohort	65/339	median age 69 years female 51%	cardiovascular disease	HR 2.87 (1.70–4.83)*	HR 1.86 (1.06–3.26)*
					COPD	HR 3.72 (1.94–7.13)*	HR 2.24 (1.12–4.46)*
Mendes (2020) [23]	Switzerland	retrospective cohort	76/235	mean age 86.3 years female 56.6%	peripheral artery disease*	HR 2.08 (1.18–3.66)*	HR 1.72 (0.97–3.05)
Wei (2020)[24]	China	retrospective cohort	66/566	median age 61.5 years female 52.8%	none	N/A	N/A
de Souza (2020) [25]	Brazil	retrospective cohort	1171/9807	mean age 70.2 years female 52.5%	hypertension	OR 2.20 (1.80–2.70)*	OR 1.53 (1.20–1.94)*
					diabetes	OR 2.57 (2.24–2.96)*	OR 2.33 (1.99–2.74)*
					chronic kidney disease	OR 2.02 (1.27–3.20)*	OR 2.02 (1.27–3.20)*
					cardiovascular disease	OR 1.49 (1.26–1.77)*	OR 1.15 (0.95–1.39)
					chronic lung disease	OR 1.75 (1.23–2.40)*	OR 1.27 (0.87–1.86)
					obesity	OR 3.45 (1.87–6.68)*	N/A
Becerra-Muñoz (2021)[26]	Ecuador, Germany, Italy, Spain	retrospective cohort	541/1520	median age 76 years female 39.7%	dementia	OR 4.21 (2.52–7.05)*	OR 8.06 (1.45–44.9)*
Chen (2020)[8]	China	retrospective cohort	19/55	median age 74 years female 48.2%	none	N/A	N/A

(continued)

Table 1. Continued

Author (year)	Country	Study design	Study size (deaths/total)	Population characteristics	Comorbidity	Unadjusted effect size (95% CI)	Adjusted effect size (95% CI)
Neumann-Podczaska (2020)[27]	Poland	retrospective cohort	20/50	mean age 74.8 years female 30%	heart disease*	HR 3.49 (1.27–9.63)*	HR 2.61 (0.92–7.39)
Görgülü (2020) [28]	Turkey	case-controll	81/483	mean age 74.4 years female 57.6%	COPD-asthma-bronchitis	N/A	OR 0.38 (0.19–0.76)*
Mehta (2021)[29]	U.S.A.	retrospective cohort	26384/482323	mean age 82.7 years female 67.8%	mild CI	N/A	HR 1.17 (1.14–1.21)*
					moderate CI	N/A	HR 1.45 (1.41–1.50)*
					severe CI	N/A	HR 1.79 (1.71–1.86)*
					cancer	N/A	HR 1.17 (1.12–1.21)*
					heart disease	N/A	HR 1.07 (1.04–1.11)*
					renal disease	N/A	HR 1.23 (1.20–1.26)*
					diabetes	N/A	HR 1.16 (1.13–1.19)*
					repsiratory conditions	N/A	HR 1.11 (1.08–1.14)*
					neurologic conditions	N/A	HR 0.94 (0.92–0.97)*
					extreme BMI (>45)	N/A	HR 1.19 (1.14–1.24)*

(continued)

Table 1. Continued

Author (year)	Country	Study design	Study size (deaths/total)	Population characteristics	Comorbidity	Unadjusted effect size (95% CI)	Adjusted effect size (95% CI)
Bağ Soytaş (2021) [30]	Turkey	case-controll	52/218	mean age 75.3 years female 48.6%	cancer	OR 5.75 (2.61–12.6)*	OR 4.82 (1.11–21.0)*
Medetalibeyoglu (2020)[31]	Turkey	retrospective cohort	24/104	median age 73 years elderly female 38.1%	none	N/A	N/A
Dres,M (2021)[32]	France Switzerland	prospective cohort	549/1199	median age 74 years female 27%	diabetes	HR 1.43 (1.20–1.71)*	HR 1.42 (1.10–1.82)*
Genc Yavuz (2021) [33]	Turkey	case-controll	22/113	mean age 70.7 years female 35.4%	renal disease history*	OR 3.35 (1.0–12.5)*	N/A
Abadía Otero (2021)[34]	Spain	prospective cohort	24/83	median age 82 years female 57.8%	malnutrition	N/A	OR 3.22 (1.03–10.1)*
Blomaard (2021) [35]	Netherlands	retrospective cohort	499/1376	median age 78 years female 39.6%	diabetes*	OR 1.50 (1.10–1.80)*	N/A
					history of myocardial infarction*	OR 1.60 (1.20–2.10)*	N/A

*Significant results $P < 0.05$.

Abbreviations: CI: cognitive impairment; COPD: chronic obstructive pulmonary disease; HR: hazards ratio, N/A: not available; OR: odds ratio.

comorbidities and mortality of COVID-19 among the elderly. Results are summarized in Table 1.

DISCUSSION

In our systematic review, cardiovascular diseases, respiratory diseases, diseases of the nervous system, renal conditions, and malignancies were associated with a higher mortality of elderly patients affected by COVID-19. Among specific diseases, the following conditions increased the mortality of elderly COVID-19 patients: peripheral artery diseases, hypertension, coronary heart diseases, heart failure, hypertension, COPD, asthma, bronchitis, dementia, cognitive impairment, diabetes, and both low (<18.5 kg m^{-2}) and high (>35 kg m^{-2}) body mass index.

The most frequently studied comorbidities were cardiovascular diseases in reviewed articles, while other conditions were comparatively underrepresented. Our observations on comorbidities and COVID-19 mortality are confirmed by two meta-analyses which found that chronic kidney diseases (RR: 3.96), dementia (RR: 3.67), familial hypercholesterolemia (RR: 3.27), cardiovascular diseases (OR: 2.46), COPD (RR: 2.19), diabetes (RR: 1.90 and OR: 1.76), and hypertension (RR: 1.37 and OR: 2.10) significantly increased the mortality among elderly patients with COVID-19 [36, 37].

A possible explanation for these findings could be that the SARS-CoV-2 virus infects endothelial cells, damaging small vessels and promoting microvascular dysfunction, inflammation, and thrombosis [38–46]. Additionally, SARS-CoV-2 can also infect other cell types in the cardiovascular system that express SARS-CoV-2 entry genes (angiotensin-converting enzyme 2, basigin), including cardiomyocytes and renal cells [47–49]. In patients with comorbidities that affect the microvasculature or the myocardium, COVID-19-related vascular and myocardial pathologies can be exacerbated. Furthermore, both aging and several comorbidities were shown to increase the expression of the cellular entry receptors of SARS-CoV-2, which directly affect the severity of COVID-19 [49–52]. A possible entry receptor of COVID-19 could also be the adipokine enzyme DPP4 [53]. Cells of both the elderly and of patients affected by certain conditions, such as diabetes, obesity, and metabolic syndrome, express higher levels of the DPP4 enzyme [53]. This could act as a predictor for more severe manifestations of the disease [53]. Moreover, comorbidities also lead to a less coordinated and thus less effective response to COVID-19 offering another explanation between the worse outcomes of comorbid COVID-19 patients [54]. In addition, comorbidities and medications used to treat them may both have a negative effect on the immune function of patients and the expression of SARS-CoV-2 entry genes, which may also contribute to increased morbidity and mortality [55, 56].

Studies also indicate that advanced aging per se also negatively affects the immune response ("immunosenescence"), impairing the function of both monocytes and lymphocytes [6, 18, 57–61]. The elderly often exhibit a dysregulated innate immune system, delayed viral sensing, and impaired antigen presentation [18, 62]. This, in combination with the effect of comorbidities, could lead to a weaker protection against SARS-CoV-2 infection among the elderly population. Importantly, immunosenescence is also associated with poor vaccine responses in older adults [63]. Additionally, aging also exacerbates cellular senescence and inflammatory cytokine production, up-regulates inflammasomes, promotes genomic instability and mitochondrial dysfunction, all of which may contribute to the increased susceptibility to organ

failure associated with SARS-CoV-2 infection [61, 64, 65]. Furthermore, the pro-thrombotic environment seen in advanced age may also lead to more severe tissue damage, vascular leakage, thrombosis, and systemic cytokine storm, contributing to the higher mortality of COVID-19 among elderly comorbid patients [18, 66, 67].

Although, in general, the results of reviewed studies identify common diseases that adversely affect the COVID-19 mortality of elderly patients, there are also uncertainties. For instance, negative effects of cardiovascular diseases, chronic lung diseases, peripheral artery disease, diabetes, and kidney diseases were often significant in the univariate regression analysis [23, 25, 27, 33, 35], whereas statistical significance was weakened after adjustment for confounders. In certain studies, the association between comorbidities and increase mortality of COVID-19 in older adults was less clear [8, 24, 31]. However, these studies were conducted on relatively small populations with a younger age distribution, so caution should be applied when interpreting their results. Other studies found contradictory evidence for the effect of comorbidities and COVID-19 mortality among the elderly, namely that the presence of certain diseases could indeed be a protective factor, such as in the case of COPD, asthma, or bronchitis [28]. The authors of these studies suggested that their surprising results may be caused by the higher prevalence of pneumococcal vaccination and self-protective behavior among patients with lung diseases [28]. In our opinion, however, the very low effect estimate is more likely caused by the lack of statistical power or the effect of unadjusted confounding factors. Another study found similar observations for certain neurologic conditions, such as stroke, hemiplegia, and paraplegia collapsed into a single group [29]. The researchers did not comment on these findings in the same study [29]. A possible explanation could be that these patients may have been observed more closely due to their condition and were more likely to be prioritized in vaccination programs as a result of their advanced age and chronic conditions, resulting in better survival rates. Furthermore, patients suffering from stroke, hemiplegia, or paraplegia may have a more restricted mobility resulting in less frequent occurrence in public spaces and areas where the likelihood of infection is also higher. It cannot be ruled out, however, that these results may have been also caused by the effect of certain uncontrolled confounding factors.

The relationship of comorbidities and COVID-19 mortality of elderly may change as a condition worsens with stronger observed effect sizes as the disease progresses. For instance, cognitive impairment was linked to higher hazard ratios as the disease progressed from mild to moderate and to severe [29]. In the case of BMI, it is difficult to define whether mortality increases parallel with BMI, or whether there is a *U*-shaped relationship between BMI and mortality with higher mortality rates at both ends of the BMI spectrum. Higher BMI seems to be associated with higher COVID-19 mortality among the elderly, the results for low BMI however are inconclusive as studies found either significant or non-significant results [29, 34].

A major limitation of our systematic review is the relatively high number of studies with small sample sizes, which seriously affect the reliability of our conclusion. Moreover, studies merged different diseases into a single group making it impossible to disentangle the effect of individual comorbidities [28, 29]. Another study furthermore decided to merge diseases (e.g. COPD, respiratory failure) and symptoms (e.g. shortness of breath) into a single group making the interpretation of results even more difficult [29]. The results mostly point in the direction that these comorbidities significantly contribute to COVID-19 mortality. However, contradictory evidence is also available, and systematic reviews do not allow for the quantitative synthesis of results to resolve these inconsistencies. Another limitation is caused by the fact that the

studies were published from countries greatly differing in respect of their sociodemographic characteristics, health parameters, and other factors, such as quality of and access to health care. A subsequent limitation could be that odds ratios tend to overestimate risk ratios in case of frequent diseases. As several of these comorbidities are fairly frequent, odds ratios may indeed overestimate the potential role of these diseases in the mortality of COVID-19-positive elderly patients. A final limitation is linked to the exclusion of non-English language articles and the fact that we searched only PubMed, and thus, we cannot exclude that certain studies may have been omitted that were published elsewhere.

Overall, it is likely that a range of comorbidities contribute to COVID-19 mortality in older adults, however, large-scale studies are still needed to quantify the effect sizes more precisely. Alternatively, smaller studies where confounders are uniformly controlled could also lead to a better understanding of the association of comorbidities to COVID-19-related deaths. Such studies could have greater impact on the planning and allocation of healthcare resources during the COVID-19 pandemic. This, in turn may positively affect the survival rates of patients and also allow more efficient use of healthcare facilities. The latter is crucial during a pandemic when the overloading of health care systems is a serious threat.

In conclusion, our systematic review suggests that comorbidities increase the mortality of COVID-19 among older adults. Since comorbidities and advanced age have a detrimental effect of the immune system and affect the cellular entry mechanisms of SARS-CoV-2 too, this could lead to a higher proportion of symptomatic and severe COVID-19 manifestations among the elderly. This, combined with impaired resilience and functional reserve of older adults and the increased vulnerability of the aged microcirculation to SARS-CoV-2-related injury contributes to more severe manifestations of the disease, including elevated mortality. Further studies are needed to determine how the implementation of preventive programs for the most important cardiovascular risk factors affects the outcome of COVID-19 among the elderly.

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