


Factors Associated for Mortality of Older People With COVID 19: A Systematic Review and Meta-analysis

Gerontology & Geriatric Medicine
Volume 7: 1–12
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DOI: 10.1177/23337214211057392
journals.sagepub.com/home/ggm


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Abstract

Background: Whilst people of all ages are affected in some way by COVID-19 virus, older people are at a high mortality risk. This study aimed to systematically review the numerous factors associated with mortality among COVID-19 infected older people.

Method: PubMed and Science Direct were searched from inception to the April 15, 2021. We followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 statement and Joanna Briggs Institute critical appraisal tool to assess the methodological quality of the included studies.

Results: Of the 4957 studies identified, 20 were included in the qualitative analysis, while 10 were included in the quantitative analysis. Male sex (OR = 2.22, 95% CI = 1.23–3.99), age (over 75 years old) (OR = 3.36, 95% CI = 2.30–4.90), Dementia (OR = 3.69, 95% CI = 1.99–6.83) and Dyspnoea (OR = 3.16, 95% CI = 2.61–3.82), were found to be significantly associated with mortality. There is no significant association between Diabetes, or Hypertension.

Conclusion: Older age, male gender, dyspnoea and dementia were associated with a greater risk of death of older people from COVID-19 infection. These findings may help health care professionals to identify high-risk groups, facilitate appropriate remedial measures, and control mortality among older people.

Keywords

aging, community, gerontology, long-term care, nursing

Manuscript received: June 16, 2021; **final revision received:** September 28, 2021.

Introduction

Globally, people of all ages are affected in some way by the severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) (also known as COVID-19) pandemic since it was reported in Wuhan, China, in December 2019 (Chen et al., 2021). Among all age groups, older people who were defined as those of age 60 or above are at a risk of getting the infection and are at a higher risk of dying from the illness (Leung, 2020; Lithander et al., 2020). In May 2021, Centres for Disease Control and Prevention highlighted that older people

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are at a greater risk of hospitalization or dying with COVID-19 infection due to age-related decline in immune function (Centers for Disease Control and Prevention, 2021; Kang & Jung, 2020; Yang & Li, 2020). The majority of deaths associated with COVID-19 were due to a respiratory failure, sepsis, cardiac failure, kidney injury, or coagulopathy (Yang & Li, 2020).

Globally, older people are at a higher risk of getting COVID-19. Eighty percent of deaths reported in the U.S. have been in adults 65 and older (Centres for Disease Control and Prevention, 2021). By May 14, 2021, in Australia, most deaths have been reported in people aged 70 years and over (Health, 2021). Further, the likelihood of mortality in this age group was comparatively higher in the Asian region (Susilowati et al., 2020).

Numerous published studies focused on factors affecting the mortality of older people diagnosed with COVID-19. Identified factors related to the increased risk of mortality are demographic characteristics, pre-existing diseases or clinical aspects, and social factors (Tarteret et al., 2021; Williamson et al., 2020). Yanez et al. (2020) found that persons aged 65 or older had strikingly higher COVID-19 mortality rates than younger individuals. Severe cognitive decline, respiratory symptoms, low Barthel index, and lymphocytopenia were identified as factors associated with mortality (Heras et al., 2020). Living with someone of working age, living in a care home, living in neighbourhoods with the highest population density were found to be social factors associated with the mortality of older people diagnosed with COVID-19 (Brandén et al., 2020).

It is essential to summarize the significant factors associated with mortality to provide reliable evidence for clinical decision-makers, public health officials, researchers, and the general public to better control the pandemic and reduce the mortality of older people who diagnosed with COVID-19 (Sepandi et al., 2020; Tian et al., 2021). Further, identifying factors related to mortality is very important when the demand for health care is surging and resources are limited (Rosenbaum, 2020). Hence, systematic reviews can be used to summarize and synthesize evidence accurately and reliably (Ejiri et al., 2021). Up to now, no studies have systematically reviewed the factors associated with the mortality of older people with COVID-19. Therefore, this systematic review aimed to identify various factors associated with mortality among older people infected with COVID-19.

Methods

Design

The authors performed a systematic searching following the updated Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement 2020 (Moher et al., 2009; Page et al., 2021) for evidence synthesis and Joanna Briggs Institute's manual in methodological quality assessment (Aromataris & Riitano, 2014).

Search Strategy

The authors searched two online databases of PubMed, and Science Direct from inception to April 15, 2021. These two databases were chosen for the purpose of data search, because authors have free access to these two databases, while other databases are only accessible via paid subscription. Keywords used in this search were 'factors', 'predictors', 'mortality', 'fatal' 'death', 'elderly', 'older', 'geriatric', 'COVID-19', 'coronavirus disease'. Boolean operators were used for the advanced search strategy with the following combined text in Title/Abstract in PubMed: ('factors' OR 'predictors') AND ('mortality' OR 'fatal' OR 'death') AND ('elderly' OR 'older' OR 'geriatric') AND ('COVID-19' OR 'coronavirus disease'). These search terms were adapted to search the other database (Table 1). In addition, we included some more studies from citation tracking related to the aim of the review, and Google Scholar searching was done as a secondary source. The protocol for this systematic review was registered in PROSPERO (CRD42021252946) on May 5, 2021.

Eligibility criteria

All clinical studies evaluating factors associated with mortality of older people aged 60 years or over and diagnosed with COVID-19 were included (World Health Organization, 2001). Given that there were no much studies published on COVID-19 at the time of the search, we included the studies if authors identified their study sample as COVID-19 infected. All included articles were published in English. Both peer and non-peer reviewed papers were included to ensure the inclusion of all or majority of the available published data assessing the interested outcomes. We excluded article types such as comments, reviews and editorials.

Study selection

Authors exported the search identified through databases into the EndNote reference management software. All duplicates were removed. Two reviewers then independently screened the studies based on their titles and abstracts for eligibility, against a pre-defined inclusion and exclusion criteria explained above (HDWT and KIPP). Similarly, the full-text screening was carried out (HDWT and KIPP). Any discrepancies between the authors were resolved by consensus.

Methodological quality assessment

The authors used Joanna Briggs institute's (JBI) critical appraisal tool for descriptive/case series studies to assess the quality of the selected studies (Joanna Briggs Institute, 2017; Kiljunen et al., 2017). Two authors (HDWT and KIPP) independently assessed the included studies and resolved discrepancies by consensus.

Table 1. Example of search strategy in PubMed.

(((((Factors [Title/Abstract]) OR (Predictors [Title/Abstract])) AND (mortality [Title/Abstract])) OR (fatal [Title/Abstract])) OR (death [Title/Abstract])) AND (elderly [Title/Abstract]) OR (older [Title/Abstract]) OR (geriatric [Title/Abstract])) AND (COVID-19 [Title/Abstract]) OR (Corona virus disease [Title/Abstract])

Factors' [Title/Abstract] OR "Predictors"[Title/Abstract] AND "mortality"[Title/Abstract] OR "fatal"[Title/Abstract] OR "death"[Title/Abstract] AND "elderly"[Title/Abstract] OR "older"[Title/Abstract] OR "geriatric"[Title/Abstract] AND "COVID-19"[Title/Abstract] OR "corona virus disease"[Title/Abstract]

Narrow by publication year: January 1, 2020, to March 31, 2021

Narrow by language: English

Search modes: Boolean

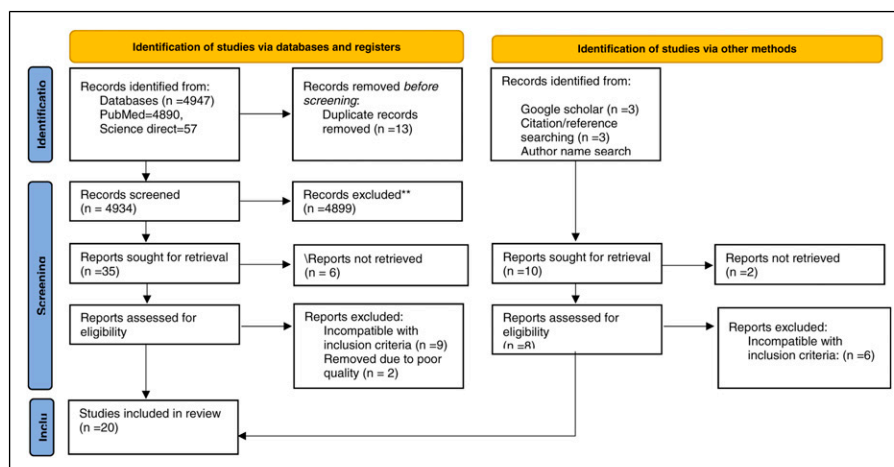


Fig. 1 Flowchart – study selection process.*Consider, if feasible to do so, reporting the number of records identified from each database or register searched (rather than the total number across all databases/registers).**If automation tools were used, indicate how many records were excluded by a human and how many were excluded by automation tools.

Data extraction

The authors used a pre-defined data extraction table for the data extraction. The extracted data included details of authors' names, publication year, mean age/age range, gender of participants, country, setting, sample size, the method for diagnosing COVID-19 and factors associated for mortality such as pre-existing diseases.

Analysis of results

The extracted data were summarized and tabulated to address the research objectives. The authors used hazard ratios (HRs), odds ratios (ORs), relative risks (RRs) (and their 95% confidence intervals) reported for the association between risk factors and mortality from COVID-19 infection.

When the data is available to pool together as heterogeneity between studies allowed, they were quantitatively analysed with meta-analyses. All the meta-analyses were conducted in the Review Manager Software 5.4 (Review Manager [RevMan] [Computer program]). Version 5.4. The Cochrane Collaboration, 2020). Odd Ratios (OR) were used to describe risks between people with the identified risk factor and people without those risk factors. Random-effects model was used

when there was a considerable heterogeneity ($I^2 > 30\%$) among studies. Otherwise, fixed-effects model was used. The overall effects were presented by a combined Z value, with indicating statistical significance ($p < 0.05$).

Results

Studies included in the review

The initial database search identified 4947 articles. A total of 4934 potentially relevant articles were screened after the removal of 13 duplicates. Based on title screening, 4899 articles were excluded. Ten articles were identified via other sources and added for screening (Google scholar, and citation tracking). Thirty-seven articles were selected for evaluation at the full-text screening process. Based on JBI criteria, two studies were excluded because of not defining inclusion criteria, objectives of the study and not identifying confounding factors properly in those studies.

Against the eligibility criteria, 20 articles met the inclusion criteria for systematic review (qualitative analysis). During qualitative synthesis, we were able to pool 10 studies together for meta-analyses (Figure 1). The included studies were published during the time between January 1, 2020 and March 31, 2021.

Table 2. Key characteristics of studies included in the systematic review.

No	Authors and Year	Study Design	Mean age/Age range (years)	Country	Setting	Sample (n)	Diagnosis method-COVID-19	*Overall Quality Appraisal
1	Baktash et al. (2020)	Prospective cohort study	81 years, range 65–102; male (n = 57) Female (n = 48)	UK	Hospital	105	Viral reverse transcriptase-polymerase chain reaction (PCR) swab or supporting radiological evidence	Fair
2	Bavaro et al. (2021)	Multicentre-retrospective-case-series	Mean age 80 (IQR 72–86)	Italy	Hospitals	206	Real-time reverse transcriptase-polymerase chain reaction (RT-PCR)	Good
3	Becerra-Muñoz et al. (2021)	Post-hoc analysis	Median age of 76 (IQR 71–83) Male = 60.3%	Spain	Hospitals	1520	RT-PCR	Good
4	Bianchetti et al. (2020)	Retrospective study	Dementia Mean age 82.6 (SD 5.3) Female = 57.3% No dementia Mean age 68.9 (SD 12.7) Female = 52.8%	Italy	Hospitals	627	RT-PCR	Good
5	Brandén et al. (2020)	Population-based, observational study	Female = 55.8%	Sweden	Residing in Stockholm Cause-of-death register held by the Swedish national board of health and welfare	274 712	Not clearly mentioned about the diagnosis method	Fair
6	Covino et al. (2020)	Single-centre, retrospective, observational study	84 years (IQR 82–89) Male = 53.6%	Italy	Hospital	69	COVID-19 was diagnosed based on the World Health Organization interim guidance	Good
7	Covino et al. (2021)	Single-centre prospective study	Median age 85 (IQR 82–89) Males = 46.9%	Italy	Hospital	239	RT-PCR	Good
8	De Smet et al. (2020)	Retrospective single-centre observational study	Median age 85 (Range 65–97) Female = 59%	Belgium	Long-term care residence	48	RT-PCR	Fair
9	de Souza et al. (2020)	Cross-sectional observational study	Average age 70.21	Brazil	State of Alagoas, Brazil	5145	RT-PCR	Good
10	Fagard et al. (2021)	Retrospective observational cohort study	Median age 82	Belgium	Hospital	105	A PCR test or based on the clinical picture and a chest C.T. scan	Good
11	Heras et al. (2020)	Retrospective analysis	Median age 85 Female:62%	Spain	Long-term care centre	100	RT-PCR	Good
12	Lee et al. (2020)	Retrospective study	Median age 72 Female = 55.1%	Korea	Hospitals	98	RT-PCR assay of a nasopharyngeal swab or sputum referring to the national guidelines	Fair

(continued)

Table 2. (continued)

No	Authors and Year	Study Design	Mean age/Age range (years)	Country	Setting	Sample (n)	Diagnosis method-COVID-19	*Overall Quality Appraisal
13	Leung (2020)	Clinical review	Deceased group Median age 75 Surviving group Median age 68	China	Hospitals	154	Not clearly mentioned about the diagnosis method	Fair
14	Mendes et al. (2020)	Retrospective study	86.5(SD:6.5) Male = 43%	Switzerland	Hospital	235	RT-PCR	Fair
15	Owen et al. (2021)	Retrospective observational	79.7 Female = 49.4%	United Kingdom	Hospital	1,071	RT-PCR	Fair
16	Sun et al. (2020)	Retrospective case-control	Discharged patient group median age 67 Female = 58.5% Diseased group Median age 72 Female = 32.2%	China	Hospital	244	Diagnosis and treatment guideline for COVID-19 published by the national health commission of People's republic of China	Good
17	Trecarichi et al. (2020)	Retrospective, observational cohort study	80 (SD 12) Male = 57.1%	Italy	long-term care facilities	50	SARS-CoV-2 molecular test	Fair
18	Yu et al. (2020)	Retrospective	Median age 81 Female = 59.6%	China	Hospital	141	Nucleic acid of the SARS-CoV-2 virus	Fair
19	Zhang et al. (2020)	Retrospective cohort study	Median 55.6 (IQR 44–69) Male: 48.4%	China	Hospital	663	RT-PCR for the presence of SARS-CoV-2 in both nasal and pharyngeal swab specimens	Fair
20	Zhou et al. (2020)	Retrospective	Survivors 70.6 (SD 6.9) Female = 67.2% No-survivors 73.1 (SD ± 7.3) Female = 39.2%	China	Hospital	118	RT-PCR	Fair

IQR, interquartile range; RT-PCR, real-time reverse transcriptase-polymerase chain reaction; SD, standard deviation.

*Joanna Briggs institute critical appraisal tool.

Among the included studies, 15 were retrospective (Bavaro et al., 2021; Bianchetti et al., 2020; Covino et al., 2021; De Smet et al., 2020; Fagard et al., 2021; Heras et al., 2020; Lee et al., 2020; Mendes et al., 2020; Owen et al., 2021; Sun et al., 2020; Trecarichi et al., 2020; Yu et al., 2020; Zhang et al., 2020; Zhou et al., 2020), while two studies were prospective designs (Baktash et al., 2020; Covino et al., 2020). The remaining four studies used a post-hoc analysis (Becerra-Muñoz et al., 2021), cross-sectional observational study (de Souza et al., 2020), and population-based observational study (Brandén et al., 2020) and clinical data review of geriatric patients infected with COVID-19 (Leung, 2020).

Five studies were conducted in China (Leung, 2020; Sun et al., 2020; Yu et al., 2020; Zhang et al., 2020; Zhou et al., 2020), five in Italy (Bavaro et al., 2021; Bianchetti et al., 2020; Covino et al., 2020, 2021; Trecarichi et al., 2020), 2 in the United Kingdom (Baktash et al., 2020; Owen et al., 2021), 2 in Spain (Becerra-Muñoz et al., 2021; Heras et al., 2020), 2 in Belgium (De Smet et al., 2020; Fagard et al., 2021) and

each one in Sweden (Brandén et al., 2020), Korea (Lee et al., 2020), Switzerland (Mendes et al., 2020) and Brazil (de Souza et al., 2020).

Thirteen studies (Baktash et al., 2020; Bavaro et al., 2021; Becerra-Muñoz et al., 2021; Covino et al., 2020, 2021; Fagard et al., 2021; Lee et al., 2020; Mendes et al., 2020; Owen et al., 2021; Sun et al., 2020; Yu et al., 2020; Zhang et al., 2020; Zhou et al., 2020) were conducted in hospital settings. Three of the included studies were from long-term care centres (De Smet et al., 2020; Heras et al., 2020; Trecarichi et al., 2020), while two other studies were particular states in Sweden (Brandén et al., 2020) and Brazil (de Souza et al., 2020).

The sample size of the studies in this review ranged from 48 to 274,712. Seventeen studies used real-time reverse transcriptase-polymerase chain reaction (RT-PCR) to confirm COVID-19 infection (Baktash et al., 2020; Bavaro et al., 2021; Becerra-Muñoz et al., 2021; Bianchetti et al., 2020; Covino et al., 2020; De Smet et al., 2020; de Souza et al., 2020; Fagard et al., 2021; Heras et al., 2020; Lee et al., 2020;

Table 3. Factors associated with mortality.

No	Authors and Year	Main Findings
1	Baktash et al. (2020)	Comparing to the replete group, there was a higher peak D-dimer level among patients with vitamin D deficiency (1914.00 µgFEU/L vs. 1268.00 µgFEU/L) ($p = 0.034$) and higher incidence of non-invasive ventilation support and high dependency unit admission (30.77% vs. 9.68%) ($p = 0.042$). No increased mortality was observed between groups
2	Bavaro et al. (2021)	Male sex (aOR = 2.87, 95% CI: 1.15–7.18), CFS 7–9 (aOR = 9.97, 95% CI: 1.82–52.99), dehydration at admission (aOR = 4.27, 95% CI: 1.72–10.57) and non-invasive/invasive ventilation (aOR = 4.88, 95% CI: 1.94–12.26) were independent predictors of mortality
3	Becerra-Muñoz et al. (2021)	Age ≥ 75 (OR = 3.54, 95% CI: 1.76–8.38), (OR = 3.36, 95% CI: 1.00–11.33), dementia (OR = 8.06, 95% CI: 1.45–44.85), peripheral oxygen saturation $< 92\%$ (OR = 5.85, 95% CI: 2.89–11.84), (Becerra-Muñoz et al., 2021) (OR = 3.36, 95% CI: 1.53–7.38) and qSOFA > 1 (OR = 8.31, 95% CI: 2.29–30.16) were independent predictors of mortality
4	Bianchetti et al. (2020)	Dementia independently associated with a higher mortality (OR = 1.84, 95% CI: 1.09–3.13, $p < 0.05$)
5	Brandén et al. (2020)	Household and neighbourhood characteristics were associated with COVID-19 mortality among older people. Living with someone of working age (< 66 years) (HR = 1.6, 95% CI: 1.3–2.0) and living in a care home were associated with an increased risk of COVID-19 mortality (HR = 4.1, 95% CI: 3.5–4.9) compared with living in independent housing. Living in neighbourhoods with the highest population density (≥ 5000 individuals per km ²) was associated with higher COVID-19 mortality (HR = 1.7, 95% CI: 1.7–2.7) compared with living in the least densely populated neighbourhoods (0 to < 150 individuals per km ²)
6	Covino et al. (2020)	Severe dementia (HR = 3.87, 95% CI: 1.23–12.17), pO ₂ ≤ 90 at admission (HR = 2.98, 95% CI: 0.68–13.11) and lactate dehydrogenase > 464 U/L (HR = 4.11, 95% CI: 1.34–12.63) were independent risk factors for mortality
7	Covino et al. (2021)	Age ≥ 85 years (HR = 2.40, 95% CI: 1.32–4.35), dependency in activities of daily living (ADL) (HR = 2.57, 95% CI: 1.14–5.82), and dementia (HR = 2.34, 95% CI: 1.33–4.12), congestive heart failure (HR = 1.94, 95% CI: 1.06–3.53), LDH > 489 (U/L) (HR = 2.08, 95% CI: 1.19–3.64), CRP > 121 (mg/L) (HR = 2.40, 95% CI: 1.39–4.15), serum lactate > 1.5 (mmol/L) (HR = 1.66, 95% CI: 1.02–2.72), PaO ₂ /FiO ₂ < 261 (HR = 1.67, 95% CI: 1.03–2.72) were risk factors for death
8	De Smet et al. (2020)	Mortality was associated with age (Spearman $r = 0.241$, $p = 0.03$), CFS score ($r = 0.282$, $p = 0.011$), baseline lactate dehydrogenase ($r = 0.301$, $p = 0.009$), lymphocyte count ($r = 0.262$, $p = 0.02$) and RT-PCR cycle threshold ($r = 0.285$, $p = 0.015$)
9	de Souza et al. (2020)	Male gender (OR = 1.54, 95% CI: 1.35–1.76), age ≥ 75 years (OR 2.40, 95% CI: 2.10–2.74), dyspnoea (OR 2.92, 95% CI: 2.34–3.64), chronic diseases such as diabetes (OR 2.33, 95% CI: 1.99–2.74), hypertension (OR 1.53, 95% CI: 1.20–1.94) and kidney disease (OR 2.02, 95% CI: 1.27–3.20) were associated with mortality
10	Fagard et al. (2021)	Clinical Frailty Scale/CFS (OR = 2.325, 95% CI: 1.10–4.94) and cognitive decline (OR = 11.50, 95% CI: 1.32–100.35) were independently associated with in-hospital mortality
11	Heras et al. (2020)	Male gender (OR = 38.1, $p = 0.001$), low Barthel index (OR = 0.92, $p = 0.006$), pharmacological treatment/hydroxychloroquine plus azithromycin (OR = 0.045, $p = 0.004$) and lymphocytopenia (OR = 6.55, $p = 0.039$) were identified as independent factors for mortality
12	Lee et al. (2020)	Nosocomial acquisition (OR = 7.86, 95% CI: 2.16–28.57), diabetes (OR = 4.74, 95% CI: 1.68–13.38), chronic lung diseases (OR = 8.33, 95% CI: 1.80–38.68), chronic neurologic diseases (OR = 8.00, 95% CI: 2.36–27.16), a higher white blood cell count: Neutrophil count $> 4,500$ /mm ³ (OR = 14.48, 95% CI: 3.83–54.78), blood urea nitrogen level > 20 mg/dL (OR = 6.77, 95% CI: 2.29–19.99), serum creatinine level > 1.0 mg/dL (OR = 14.42, 95% CI: 3.84–54.14), lymphocyte count < 900 /mm ³ (OR = 10.88, 95% CI: 3.23–36.63) and C-reactive protein > 8.0 mg/dL (OR = 27.95, 95% CI: 5.93–131.63) were associated with mortality
13	Leung (2020)	Age (OR = 1.04, 95% CI: 1.00, 1.10), fever (OR = 0.23, 95% CI: 0.08, 0.64), diarrhoea (OR = 8.62, 95% CI: 0.97, 76.78) were associated with mortality
14	Mendes et al. (2020)	Male gender (HR = 4.00, 95% CI: 2.08–7.71), increased fraction of inspired oxygen (HR = 1.06, 95% CI: 1.03–1.09), and crackles (HR = 2.42, 95% CI: 1.15–6.06) were the best predictors of mortality, while better functional status was protective (HR = 0.98, 95% CI: 0.97–0.99)
15	Owen et al. (2021)	Age (HR = 1.03, 95% CI: 1.01, 1.04), male sex (HR = 1.40, 95% CI: 1.09, 1.79), Early Warning Score EWS (HR = 1.16, 95% CI: 1.12, 1.20) and Charlson scores (HR = 1.09, 95% CI: 1.03, 1.15) were all associated with relatively minor increases in mortality hazard in the adjusted model
16	Sun et al. (2020)	Lymphocyte count (OR = 0.01, 95% CI: 0.001–0.138), older age (OR = 1.122, 95% CI: 1.007–1.249) and white blood cell count (OR = 1.28, 95% CI: 1.00–1.64) were risk factors

(continued)

Table 3. (continued)

No	Authors and Year	Main Findings
17	Trecarichi et al. (2020)	Hypnatraemia (HR = 9.12, 95% CI: 2.15–38.52), lymphocyte count <1000 cells/ μ L (HR = 7.45, 95% CI: 1.81–30.68), cardiovascular diseases other than hypertension (HR = 6.41, 95% CI: 1.51–27.22) and higher levels of serum interleukin-6 (IL-6, pg/mL) (HR = 1.005, 95% CI: 1.001–1.009) were significant predictors of mortality
18	Yu et al. (2020)	Male sex (OR = 13.1, 95% CI: 1.1–160.1), body temperature >37.3°C (OR = 80.5, 95% CI: 4.6–1407.6), SpO ₂ \leq 90% (OR = 70.1, 95% CI: 4.6–1060.4), and NT-proBNP > 1800 ng/L (OR = 273.595% CI: 14.7–5104.8) were independent risk factors of in-hospital death
19	Zhang et al. (2020)	Older people (>60 years) were more likely to die in hospital than those 60 years old (p 0.004). Dyspnoea (Respiratory symptoms) and unconsciousness (neurological symptoms) were the only two symptoms that were associated with mortality
20	Zhou et al. (2020)	Neutrophil to lymphocyte ratio (OR = 31.2, 95% CI: 6.7–144.5), lactate dehydrogenase (OR = 73.4, 95% CI: 11.8–456.8), albumin (OR < 0.1, 95% CI: <0.1–0.2, p < 0.0001), D-dimer (OR = 13.6, 95% CI: 3.4–54.9) and urea nitrogen (OR = 12.0, 95% CI: 3.0–48.4)

ADL, activities of daily living; aOR, adjusted odds ratio; CI, confidence interval; CRP, C – reactive protein; HR, hazard ratio; ICU, intensive care units; NT-proBNP, N-terminal pro hormone BNP; OR, odds ratio; PaO₂/FiO₂, ratio of arterial oxygen partial pressure to fractional inspired oxygen; qSOFA, quick sepsis related organ failure assessment; RT-PCR, real-time reverse transcriptase-polymerase chain reaction; p , significance level was set at 0.05.

Mendes et al., 2020; Owen et al., 2021; Trecarichi et al., 2020; Yu et al., 2020; Zhang et al., 2020; Zhou et al., 2020). One study used World Health Organization interim guidance to diagnose the infection (Covino et al., 2021), whereas another two studies did not clearly mention the diagnostic method of the participants in their studies (Brandén et al., 2020; Leung, 2020). The abstracted data are presented in Table 2.

Related to JBI critical appraisal tool, nine studies (Bavaro et al., 2021; Becerra-Muñoz et al., 2021; Bianchetti et al., 2020; Covino et al., 2020, 2021; de Souza et al., 2020; Fagard et al., 2021; Heras et al., 2020; Sun et al., 2020) can be categorized as ‘good’ while 11 studies (Baktash et al., 2020; Brandén et al., 2020; De Smet et al., 2020; Lee et al., 2020; Leung, 2020; Mendes et al., 2020; Owen et al., 2021; Trecarichi et al., 2020; Yu et al., 2020; Zhang et al., 2020; Zhou et al., 2020) can be categorized as ‘fair’.

Results of the reviewed studies

The qualitative synthesis was presented as a tabulated summary. The main findings on the factors associated with mortality among older people with COVID-19 were presented under three main categories, after careful evaluation of the factors associated with mortality; sociodemographic characteristics, comorbidity factors and haematologic and biochemical indicators associated with mortality. The summary of the qualitative analysis is depicted in Table 3.

Meta-analysis of risk factors of mortality

Several factors were able to pool together for meta-analyses, including age, sex, Dementia, Dyspnoea, Diabetes and Hypertension. The other identified risk factors were not able to pool together for meta-analyses mainly due to lack of studies for those outcomes (less than two studies reported) (Baktash et al., 2020; Fagard et al., 2021; Trecarichi et al., 2020) or due

to the inability to locate the raw data (indicated odds ratios and hazard ratios were reported instead) (Bavaro et al., 2021; Brandén et al., 2020; De Smet et al., 2020; Heras et al., 2020; Owen et al., 2021; Sun et al., 2020; Zhou et al., 2020).

Three articles (de Souza et al., 2020; Mendes et al., 2020; Yu et al., 2020) that included older people with COVID-19 were pooled together. We analysed 10,683 (males = 4831, females = 5362) people to find any significant difference between the two sexes. Male sex was found to be significantly higher in reported deaths (p < 0.001, OR = 2.22 [95% CI = 1.23–3.99], and I^2 = 73%) (Figure 2 (a)). Two articles (Becerra-Muñoz et al., 2021; de Souza et al., 2020) were pooled together with 11,327 (over 75 years = 3294, less than 75 years = 8033) older people with COVID-19 to find any significant difference in advanced age. Deaths in advanced age (over 75 years old) were significantly high (p < 0.001, OR = 3.36 [95% CI = 2.30–4.90], and I^2 = 87%) (Figure 2(b)). To find any significant difference of deaths in older people with and without Dementia, three studies (Bianchetti et al., 2020; Covino et al., 2020, 2021) with 935 (people with Dementia = 130, people with no Dementia = 805) were pooled together. Deaths were significantly higher in people with Dementia (p < 0.001, OR = 3.69 [95% CI = 1.99–6.83], and I^2 = 46%) (Figure 2(c)). There was a significantly higher incidence of deaths in people with Dyspnoea when two available studies (de Souza et al., 2020; Zhang et al., 2020) pooled together, with 10,470 (people with Dyspnoea = 720, people without Dyspnoea = 9750) older people with COVID-19 (p < 0.001, OR = 3.16 [95% CI = 2.61–3.82], and I^2 = 0%) (Figure 2(d)). Three studies (de Souza et al., 2020; Lee et al., 2020; Leung, 2020) were pooled together with 10,059 older people with COVID-19 (with Diabetes = 1629, without Diabetes = 8430), and found to be there is no significant difference in deaths between people with and without Diabetes (p = 0.77, OR = 1.31 [95% CI = 0.22–7.83], and I^2 = 96%) (Figure 2(e)). Two articles (de Souza et al., 2020; Leung, 2020) were pooled together with 9961

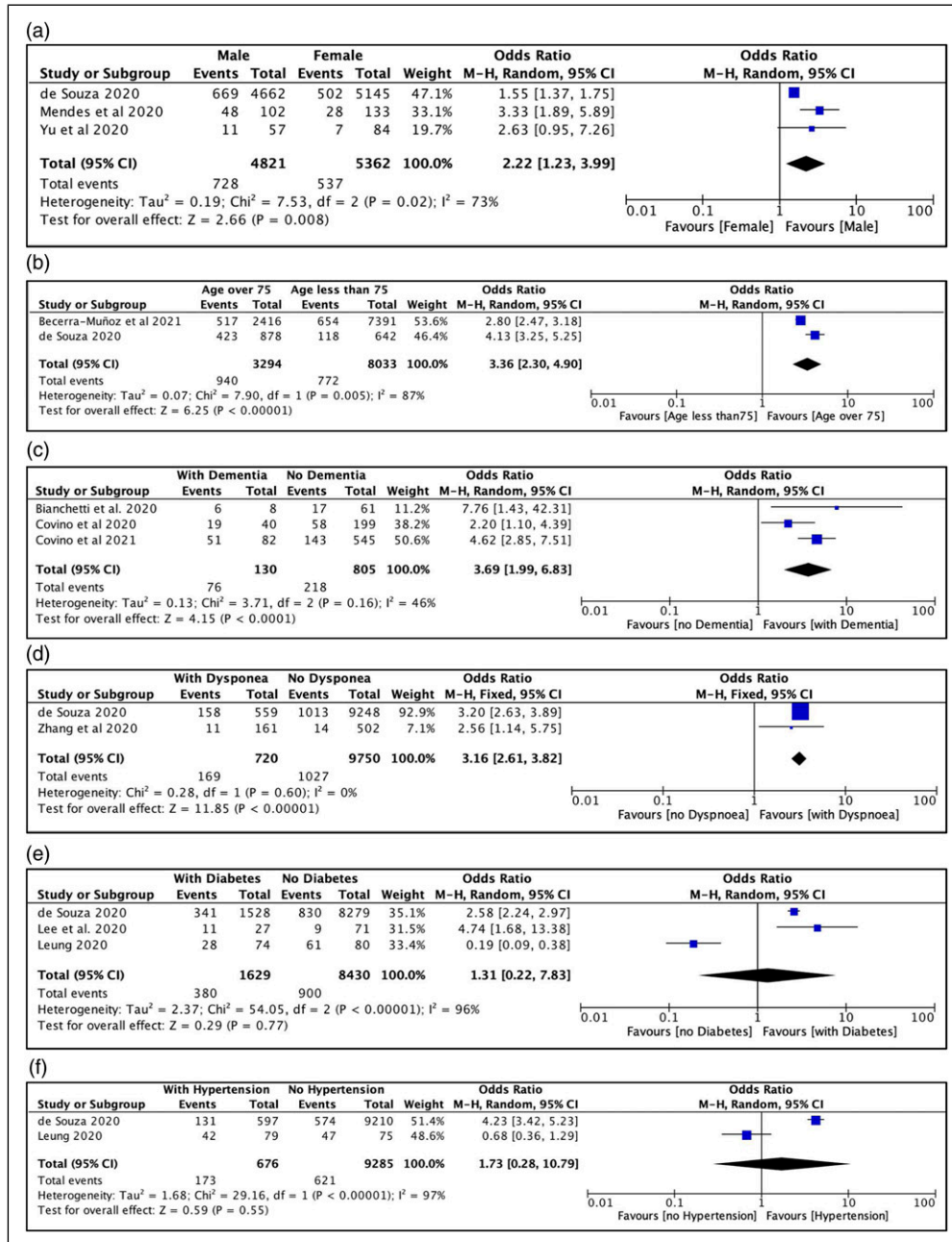


Figure 2. Meta-analysis findings of the association between risk factors and deaths in older people with COVID-19 (a) sex, (b) advanced age, (c) Dementia, (d) Dyspnoea, (e) Diabetes and (f) Hypertension.

(with Hypertension = 676, with no Hypertension = 9285) older people with COVID-19 to find any significant difference in advanced age. There were no significant differences in deaths in people with Hypertension and without ($p = 0.55$, OR = 1.73 [95% CI = 0.28–10.79], and $I^2 = 97%$) (Figure 2 (f)).

Discussion

This systematic review provides current evidence of associations between various factors and mortality based on 20 studies

assessing older people infected with COVID-19. The quality of the searched studies is in the acceptable range (fair or good) according to Joanna Briggs institute’s critical appraisal tool (Joanna Briggs Institute, 2017) for descriptive/case series studies. The majority of the articles in this review contained a clear description about the diagnosis method of COVID-19 that is ‘real-time reverse transcriptase-polymerase chain reaction’ (RT-PCR) (Borges do Nascimento et al., 2020) or any other acceptable method which may follow the triple algorithm (epidemiological history, clinical symptoms and laboratory or

radiological findings), a standard procedure proposed by the World Health Organization (Borges do Nascimento et al., 2020).

Different types of study designs identified in this review may be one of the possible reasons for different findings for a similar research question (Peinemann et al., 2013). Although the different methodologies caused methodological heterogeneity, several factors were able to pool to identify the association with mortality.

Further, this review consists of studies from nine countries; China, Italy, United Kingdom, Spain, Belgium, Sweden, Korea, Switzerland and Brazil. Navar et al. (2021) and Deeb et al. (2021) found significant difference in mortality between race and ethnicity. However, no study included in our review elaborated such an association.

The result of the current meta-analyses showed that male sex, advanced age, Dementia and Dyspnoea significantly increase the risk of deaths in older people with COVID-19, while there were no significant risks of deaths by having Diabetes or Hypertension.

Older age has been recognized as an important risk factor of mortality in COVID-19 among the studied population (Lithander et al., 2020). This may be because ageing leads impaired functioning of various systems, including the immune system. Two reasons need to be considered related to the immune system; 1) the gradual decline in the immune function called immunosenescence and, 2) chronic increase in systemic inflammation called inflammaging (Mueller et al., 2020). Both immunosenescence and inflammaging are considered vital features of the ageing immune system that cause immune dysfunction in older people (Bajaj et al., 2021). Further, the increased prevalence of comorbidities in older people may be another reason for ageing as a high mortality risk (Cho et al., 2021).

Male gender has been found as a risk factor of mortality among older people diagnosed with COVID-19. This might be related to the action of angiotensin-converting enzyme 2 (ACE-2). This acts as a functional receptor for COVID-19 (Moradi et al., 2020). It has been reported that males may have a higher expression of angiotensin-converting enzyme 2 (ACE-2) levels rendering them at more risk for COVID-19 infection as well as mortality (La Vignera et al., 2020). In addition, the androgen-mediated expression of ACE-2 among males could be another possibility (Moradi et al., 2020). However, Naaraayan et al. (2020) found no difference in the odds of mortality between males and females. This disparity of findings warrants future clinical studies assessing gender differences in the mortality of COVID-19.

The findings of this study were in line with the conclusion made by Legris et al. (2021) and showed Dementia as a risk factor for mortality. The nature of this association has not yet been clearly evaluated from a global perspective (Azarpazhooh et al., 2020). However, patients with Dementia are immunocompromised and may present with non-respiratory symptoms such as delirium or isolated functional decline. These situations may reduce early disease recognition and increase patients'

mortality (Azarpazhooh et al., 2020; Saragih et al., 2021). In addition, the current review found that dyspnoea was associated with the mortality of older people with COVID-19. Dyspnoea is a subjective symptom, and it suggests poor lung function and lacking oxygen which deteriorates patients' conditions (Pesola & Ahsan, 2016; Zheng et al., 2020). In this review, comorbidity factors such as hypertension and diabetes were not associated with the risk of mortality. This might be due to the possible confounding effect of other comorbidities of this vulnerable population. The effect of unreported comorbidities such as neurodegenerative diseases is common among institutionalized older people (Legris et al., 2021; Martín-Jiménez et al., 2020; Woolcott & Castilla-Bancayán, 2021).

This review has several limitations. The main limitation is using a few online databases for literature searching. Moreover, there are a limited number of studies for certain outcomes, and it would be difficult to provide meta-analysis. Another limitation is the restriction of the language to English, which limits potential inclusion of related studies in other languages. Next, we did not consider the mechanisms to confirm COVID-19 in inclusion of articles which directly affect the credibility of the included studies. There were three different types of study designs were included in this review. While this broadly collect all the available evidence, it is encouraged to implement more quality observational studies. Finally, it was unable to perform funnel plots given that there were two to three studies included in the meta-analysis. One of the strengths of this review is that this review gives a broad overview of factors associated with mortality among older people. Another strength of the study is that JBI evaluation indicated that all the included studies were in the acceptable level and included into the analysis. In terms of future research, it is interesting to explore the country-wise differences in reported mortalities. We found that there is a lack of studies for some outcomes to pool together for a meta-analysis, and quality studies are encouraged on those outcomes with future research.

Conclusion

Older age, male gender, dyspnoea and dementia were associated with a greater risk of death of older people from COVID-19 infection. The results of the present review could help health care professionals to identify high-risk groups, facilitate appropriate remedial measures and help control mortality among this vulnerable population. In addition, using prognostic information identified in this search could be helpful to selecting old patients in most need of medical attention and resources.

Author Contributions

H.D.W.T.D. conceived the study idea, performed searches, primary data extraction, and quality assessment aided by K.I.P.P., H.D.W.T.D., and I.W. were involved in data analysis and manuscript preparation. All the authors read the final version of the manuscript and approved it.

Conflict of interest

The authors of the study declare that there is no conflict of interest

Funding sources

This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

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