REVIEW

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COVID-19 mortality and its predictors in the elderly: A systematic review

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Abstract

Background and Aims: Older people have higher rates of comorbidities and may experience more severe inflammatory responses; therefore, are at higher risk of death. Herein, we aimed to systematically review the mortality in coronavirus disease 2019 (COVID-19) patients and its predictors in this age group.

Methods: We searched PubMed, Web of Science, and Science Direct using relevant keywords. Retrieved records underwent a two-step screening process consisting of title/abstract and full-text screenings to identify the eligible studies.

Results: Summarizing findings of 35 studies demonstrated that older patients have higher mortality rates compared to the younger population. A review of articles revealed that increasing age, body mass index, a male gender, dementia, impairment or dependency in daily activities, presence of consolidations on chest X-ray, hypoxemic respiratory failure, and lower oxygen saturation at admission were risk factors for death. High D-dimer levels, 25-hydroxy vitamin D serum deficiencies, high C-reactive protein (≥5 mg/L) levels plus any other abnormalities of lymphocyte,

higher blood urea nitrogen or lactate dehydrogenase, and higher platelet count were predictors of poor prognosis and mortality in the elderly. Studies have also shown that previous treatment with renin–angiotensin–aldosterone system inhibitors, pharmacological treatments of respiratory disorders, antibiotics, corticosteroids, vitamin K antagonist, antihistamines, azithromycin, Itolizumab (an anti-CD6 monoclonal antibody) in combination with other antivirals reduces COVID-19 worsening and mortality. Vaccination against seasonal influenza might also reduce COVID-19 mortality.

Conclusion: Overall, a critical consideration is necessary for the care and management of COVID-19 in the aged population considering the drastic contrasts in manifestation and prognosis compared to other age groups. Mortality from COVID-19 is independently associated with the patient's age. Elderly patients with COVID-19 are more vulnerable to poor outcomes. Thus, strict preventive measures, timely diagnosis, and aggressive therapeutic/nontherapeutic care are of great importance to reduce acute respiratory distress syndrome and severe complications in older people.

KEYWORDS
aging, COVID-19, elderly, older people, SARS-CoV-2

1 | BACKGROUND AND AIMS

In the winter of 2019, an unknown infection was reported from Wuhan, China. Further investigations demonstrated its Coronaviridae origin.[1,2] Soon, many countries around the world reported cases of coronavirus disease 2019 (COVID-19).[3,4] After some months, the World Health Organization announced this outbreak as a pandemic.[5] The clinical spectrum of this disease ranges from asymptomatic infection to a severe disease turning into acute respiratory distress syndrome (ARDS) and death.[6,7] ARDS causes lungs to become stiff and precipitates hypoxemia and subsequent death in a considerable proportion of the patients if they do not receive adequate ventilation.[8] Since then, as of February 19th, more than 416.6 million confirmed cases and more than 5.8 million deaths were reported around the world.[9,10] There have been many efforts how to make COVID-19 diagnosis faster and more reliable; but still, real-time reverse transcription-polymerase chain reaction is the most helpful assay for COVID-19 diagnosis.[11] Severe acute respiratory syndrome-coronavirus-2 (SARS-CoV-2) can affect not only the respiratory system but also many vital human organs.[12] Few options exist for COVID-19 treatment and physicians mostly rely on symptomatic treatments.[13]

Aging can change the human body in many aspects and then affect the human immune system in many ways, such as a higher inflammatory response to antigens with lower efficacy to suppress infections.[14,15] On the other hand, older patients have more chronic diseases, such as hypertension, making them more susceptible to severe forms of COVID-19 based on some earlier reports.[16–18]

Therefore, older people have higher mortality rates compared to younger patients (the mortality of people over 60 years old is 4.5% in comparison to 1.4% in people under 60)[19,20] and therapeutic interventions may be less effective among them. Therefore, it has become an important challenge how to manage elderly people infected by COVID-19 to decrease the mortality rate.

In the present article, we aimed to systematically review the mortality rates in older patients compared to young patients. We also reviewed the factors increasing the mortality rate in the elderly, such as underlying diseases.

2 | METHODS

2.1 | Study design

This systematic review follows the preferred reporting items for systematic reviews and meta-analyses (PRISMA) 2020 guidelines (PRISMA 2020 checklist is mentioned in Supporting Information Material 1). We conducted this systematic review by searching the online databases of PubMed, Web of Science, and Science Direct for the relevant literature using keywords and operational phrases. The studies were retrieved and the duplicate records were removed. We followed a two-step screening process to sort the eligible results. First, we examined the title and abstract of the records and the ineligible studies were removed. Then, their full texts were evaluated based on their cohesion to the inclusion/exclusion criteria and the eligible ones were included

for qualitative synthesis. The screening process was performed by two researchers, and another independent researcher addressed any controversies between them.

2.2 | Search terms

We performed a title search of the following keywords on the articles published until March 15th, 2021:

A. [Old patient] OR [Old] OR [Elder] OR [Elderly];
B. [SARS-CoV-2] OR [COVID-19];
C. [A] AND [B].

2.3 | Eligibility criteria

We included the original studies that evaluated the mortality in the elderly and/or reported the risk factors for higher mortality rates. The exclusion criteria were the following:

1) Nonoriginal studies, including reviews and non-original editorials;
2) pure laboratory or animal studies not conducted on humans;
3) case reports and case series;
4) studies not conducted on the elderly patients;
5) studies not related to the mortality of the patients; and
6) abstracts or conference abstracts, or not available full-text.

2.4 | Data extraction

Two researchers extracted and organized it into a word table. The extracted data consisted of the first author, type of study, country of study's origin, age of the participant (preferably mean age of the patients, if the studies reported), underlying diseases (categorized into neurological diseases, lung diseases, liver diseases, heart diseases, autoimmune diseases, kidney diseases, diabetes, hypertension, cancer, and other diseases), and preventive and care measures that decrease the mortality of the patients. Another independent researcher reviewed the extracted data and solved any discrepancies and issues among the other researchers. After the data for each of the variables were extracted into the table, two researchers read and compare them and used them for the qualitative synthesis.

2.5 | Quality assessment

We used the Newcastle–Ottawa scale (NOS) to analyze the risk of bias in the studies.[21] NOS provides a maximum score of 9 for each study in three categories of selection, comparability, and exposure. We defined a score of 4 or below as "poor," and above that as "acceptable."

2.6 | Certainty of evidence

We used the recommendations of the Cochrane handbook of systematic reviews chapter 14.2 to assess the certainty of the evidence for this study.[22]

3 | RESULTS

After removing irrelevant and duplicates, the title and abstract of the remaining 110 articles were reviewed. Applying the eligibility criteria, 23 articles were excluded, and 35 full-text articles that met the inclusion criteria were included in the final review (Figure 1).

The included studies were conducted in 10 countries (China = 14, Italy = 5, Spain = 5, France = 2, South Korea = 2, Cuba = 2, and one study from Germany, Australia, Brazil, and Japan). One of the articles was also a report on multinational scientific collaborations. Table 1 shows a summary of the findings. All the studies had acceptable scores in the risk of bias assessment (Table 2). Certainty of evidence analysis results is mentioned in Table 3, demonstrating acceptable evidence certainty for most of the parameters, except for the lack of matching the control groups of several studies for confounders.

We summarized each study's main findings. Studies have revealed that increasing age, dementia, and impairment in dependency in activities of daily living were strong risk factors for in-hospital death, regardless of disease severity. D-dimer level was also an independent predictor of mortality.

According to the findings, body mass index had an association with severe COVID-19. Moreover, 25-hydroxy vitamin D deficiency is associated with more severe lung involvement, longer disease duration, and risk of death in the elderly.

The review of articles showed that predicting survival factors were female sex, previous treatment with renin–angiotensin–aldosterone system inhibitors, higher oxygen saturation at admission, and a greater platelet count.

The presence of consolidations at chest x-ray along with hypoxemic respiratory failure, high C-reactive protein (CRP ≥5 mg/L) level plus any other abnormalities of lymphocyte, high blood urea nitrogen, or lactate dehydrogenase were significant predictors of poor prognosis.

Studies have demonstrated that pharmacological treatments of respiratory disorders, antibiotics, corticosteroids, use of vitamin K antagonist, antihistamines, azithromycin, and itolizumab (an anti-CD6 monoclonal antibody) in combination with other antivirals reduce COVID-19 worsening and mortality. Vaccination against seasonal influenza might also reduce COVID-19 mortality.

4 | DISCUSSION

Considerable differences in the clinical course and risk predictors for COVID-19 exist between the elderly and other age groups patients.[53] Our knowledge of the COVID-19 infection implies that the elderly, in
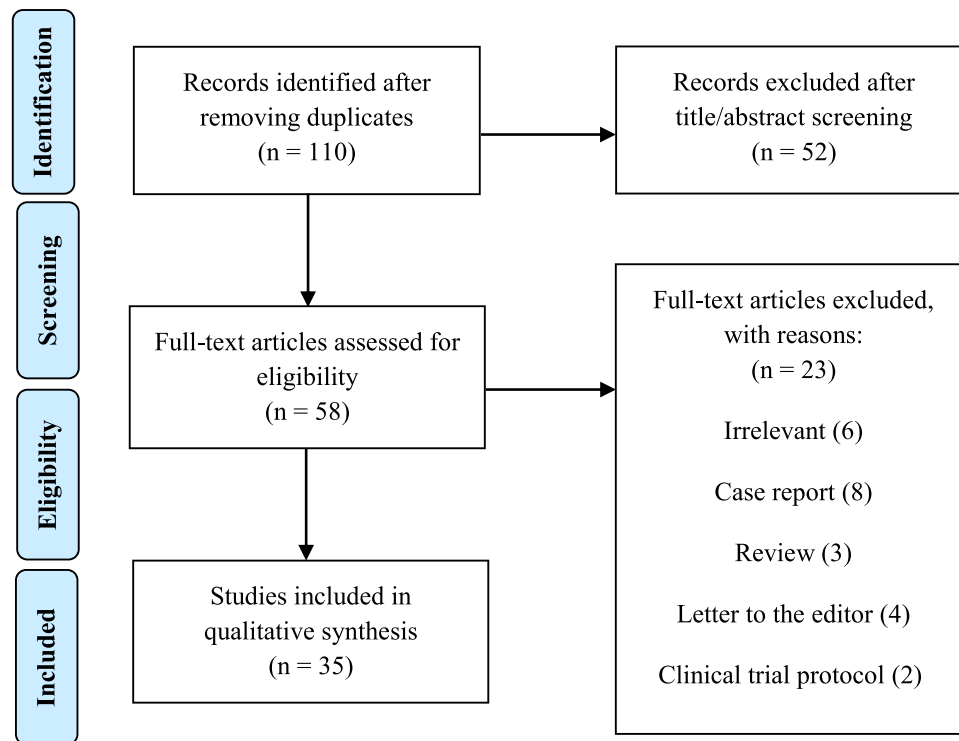
FIGURE 1 Preferred reporting items for systematic reviews and meta-analyses flow diagram of the selection process.

contrast to young- and middle-aged patients, are more susceptible to severe clinical outcomes of the disease and fatality. In fact, old age is a significant predictor of poor prognosis, suggesting that aging-related mechanisms may be integral elements in disease severity.[51] A gradual age-associated increase in the COVID-19 mortality rate has been demonstrated in previous literature. For instance, a study showed a 10.5% fatality ratio for the elderly versus 0.43% for younger patients.[58] Another study demonstrated a 1.55-fold increase in the mortality rate for every 5 years increase in age.[46] To date, both predictors for in-hospital mortality of the elderly and some survival factors have been identified. The mortality predictors include hypernatremia, lymphopenia, high interleukin 6 (IL-6) and CRP serum levels, elevated D-dimer, dyspnea, dementia, and so forth.[24,39,46,52] Also, in a study on the elderly population, men had higher mortality than women.[34] On the other hand, survival factors such as interferon atmotherapy and reduced metabolic pathway activities were also identified.[31]

Subject to advanced age and comorbidities, the elderly are considered a high-risk group for developing severe manifestations and complications, some of which are discussed as follows. They are more likely to be hospitalized or admitted to the intensive care unit. Also, compared with younger people, they have a longer hospitalized time, and their duration of the disease has a positive correlation with age.[28] From the pulmonary aspect, they are more likely to develop critical pneumonia and ARDS. A study found more grade IV and V pneumonia, based on the pneumonia severity index, among the elderly than younger COVID patients.[53] These severe complications can be traced back to lung muscle atrophy, reduced airway clearance,

lung reserve, and defense barrier function.[28] Heart failure and acute cardiac injury are other complications of COVID-19 that are more common in the elderly. The reason for their higher frequency could be underlying chronic cardiovascular diseases.[49] Moreover, fungal and bacterial infections were more prevalent among the elderly based on the increased number of white blood cells and neutrophils in their laboratory tests.[51,53] Furthermore, gastrointestinal symptoms interfering with feeding can make the elderly more vulnerable to malnutrition.[36,59] Acute liver and kidney injuries, septic shock, and multiple organs dysfunction syndrome are other complications quite common in this age group.[49,51,53]

The general pattern of signs and symptoms in COVID-19 infection among the elderly is almost similar to that of young- and middle-aged patients. However, a few differences may be noticed. A study reported fever, cough, and dyspnea as the most common symptoms.[46] Also, it has been reported that symptoms in the elderly begin with fever and cough, followed by shortness of breath and admission in 2–7 days. Then, they can be developed into respiratory failure, ARDS, and death in the following days.[34] COVID-19 signs and symptoms in the elderly differ from others in some aspects. The time from onset of the infection to confirmed diagnosis has been reported longer than that nonelderly patients. A study has attributed this to the atypical manifestation of clinical symptoms.[47] Another study has found that anorexia is more common in the elderly, while younger patients are more likely to develop a fever. Also, the elderly showed a higher systolic blood pressure and slower heart rate than the younger patients.[51] Substantial risk factors for poor prognosis among the elderly include fever during hospitalization and severe initial

TABLE 1 Summary of the findings of the included studies

ID	The first author (reference)	Type of study	Country	Age	Mortality rate (N (%))	Neurological disease	Lung disease	Liver diseases	Heart damage	Autoimmune	Kidney disease	Diabetes	Hypertension	Cancer	Other	Prevention and care
1	Hwang J.[23]	Cohort	South Korea	≥60	15										Dependency in activities of daily living (ADL) impairment, comorbidity, fever during hospitalization, and initial increased C-reactive protein (CRP)	Antiviral or antibiotic agents, oxygen supply, ventilator, dialysis, and even extracorporeal membrane oxygenation
2	Lee J.[24]	Cohort	South Korea	≥65	20.4	*	*					*			Nosocomial acquisition, diabetes, chronic lung diseases, and chronic neurologic diseases	MV/HFNC laboratory abnormalities, especially high CRP
3	Li P.[25]	Cohort	China	60	54 patients were discharged and 76 died.										Hypertension, diabetes, cardiovascular disease (CVD), and chronic obstructive pulmonary disease (COPD)	Dyspnea (hazards ratio), older age, neutrophilia, and elevated ultrasensitive cardiac troponin
4	Li G.[26]	Cohort	China, European regions, and North America	Males ≥70	High										Cerebrovascular disease and chronic obstructive pulmonary disease	Neither dexamethasone nor remdesivir
5	Li Q.[27]	Cohort	China	The median age 70 (64–78)	47.7						*				Kidney injury[28]	
6	Liu K.[29]	Cohort (Retrospective)	China	68	5.3										PSI grades IV and V Lower lymphocytes and ARDS	Lopinavir and ritonavir tablets, Chinese medicine, oxygen therapy, and mechanical ventilation
7	Liu Z.[30]	Cohort	China	>60	–								*		Higher hypertension The median systolic blood pressure The levels of proBNP & cTnI Lower hemoglobin, nine lymphocyte percentages, ALT levels, albumin levels higher neutrophil percentages, total bilirubin levels, direct bilirubin levels	Cardiovascular protection

Underlying diseases

(Continues)

TABLE 1 (Continued)

ID	The first author (reference)	Type of study	Country	Age	Mortality rate (N (%))	Neurological disease	Lung disease	Liver diseases	Heart damage	Autoimmune	Kidney disease	Diabetes	Hypertension	Cancer	Other	Prevention and care
						Underlying diseases										
8	Mei Q.[31]	Cohort	China	≥65	59.2										Decreased hsCRP during hospitalization and higher proBNP values.	Phenylalanine, fatty acid, and pyruvate showed a consistently lower flux
9	Ménager P.[32]	Cohort	France	88.8	Shorter survival times than those not using VKA											Use of VKA
10	Blanco J. I. M.[33]	Cohort	Spain	85	0% while comparator retirement homes had a mortality rate of 28%.											Antihistamines and azithromycin
11	Mostaza J.[34]	Cohort	Spain	≥75 years	(35.9%)										Age, heart rate, a decline in renal function during hospitalization, and worsening dyspnea during hospitalization	Factors predicting survival was female gender, previous treatment with RAAS inhibitors, higher oxygen saturation at admission, and a greater platelet count
12	Mori H.[28]	Cohort	Japan	72 (67–76)	Unable to address the relationship between the										Silent pneumonia, lung anatomy, including muscle atrophy	
13	Annweiler G.[35]	RCT	France	84–93	2–10				*				*	*		Pharmacological treatments of respiratory disorders, antibiotics, corticosteroids
14	Araújo, M. P. D.[36]	Cross-sectional	Brazil	>80	-	*	*		*			*	*		Asthma	Showed an association between severe Covid-19 and BMI
15	Bongiovanni, M. M.[37]	Cohort	Italy	<70 >80	3–22											Use of antivirals and hydroxychloroquine was associated with a higher risk of death. D-dimer levelwasan independent predictor of mortality

TABLE 1 (Continued)

ID	The first author (reference)	Type of study	Country	Age	Mortality rate (N (%))	Neurological disease	Lung disease	Liver diseases	Heart damage	Autoimmune	Kidney disease	Diabetes	Hypertension	Cancer	Other	Prevention and care
									Underlying diseases							
16	Cocco P.[38]	Observational	Italy	>65	—											Vaccination against seasonal influenza might reduce COVID-19 mortality
17	Covino M.[39]	Observational (Prospective)	Italy	≥80		*									Increasing age, dementia, and impairment in ADL were strong risk factors for in-hospital death, regardless of disease severity.	Presence of consolidations at chest X-ray and the hypoxemic respiratory failure were significant predictors of poor prognosis
18	Dai S. P.[40]	Observational (retrospective)	China	>60			*		*				*		Low immune function (the cell counts of T lymphocyte subsets, B and NK cells of them were significantly decreased)	
19	Díaz Y.[41]	Clinical trial	Cuba	77–79	7.1–42.4		*		*		*	*	*	*	Obesity	Itolizumab (an anti-CD6 monoclonal antibody) in combination with other antivirals reduces COVID-19 worsening and mortality
20	Franchini M.[42]	RCT	Italy	≥65	13.6–38.3											Convalescent plasma transfusion
21	Gao S.[43]	Observational (retrospective)	China	≥65	20	*	*				*		*			Higher CRP (≥5 mg/L) plus any other abnormalities of lymphocyte, blood urea nitrogen or lactate dehydrogenase (LDH) significantly predicted poor prognosis
22	Pratt N.[44]	Observational	Australia	≥70			*		*	*		*	*		Chronic renal failure, chronic airways disease (including asthma and chronic obstructive pulmonary disease), cerebrovascular disease	Antihypertensive medication, atrial fibrillation, long-acting beta-agonists, muscarinic antagonists alone or in combination

(Continues)

TABLE 1 (Continued)

ID	The first author (reference)	Type of study	Country	Age	Mortality rate (N (%))	Underlying diseases									Other	Prevention and care
						Neurological disease	Lung disease	Liver diseases	Heart damage	Autoimmune	Kidney disease	Diabetes	Hypertension	Cancer		
23	Ramos-Rincon J. M.[45]	Original	Spain	≥80	46.9	*	*					*		*	Age and gender, Charlson comorbidity index (CCI), mean (SD), dyslipidemia, nonatherosclerotic CVDs, atherosclerotic CVDs, dementia, moderate-to-severe renal disease, symptoms (shortness of breath, cough, fatigue, anorexia, diarrhea, vomiting)	-Antimicrobial therapy: Beta-lactam antibiotics, hydroxychloroquine, azithromycin, lopinavir/ritonavir– -Immunomodulatory therapy: Systemic corticosteroids, Interferon beta-1b, tocilizumab, colchicine, anakinra, baricitinib, immunoglobuLIN - Ventilation therapy: High-flow nasal cannula oxygen, noninvasive mechanical ventilation, invasive mechanical ventilation - Anticoagulant therapy: Oral anticoagulants, low-molecular-weight heparin
24	Recinella G.[46]	Original	Italy	≥65	higher	*	*	*	*			*			Age and gender, CCI, cognitive impairment, previous stroke, arterial hypertension, atrial fibrillation, coronary heart disease (CHD), chronic heart failure, COPD, CKD, symptoms (fever, dyspnea, cough, asthenia), lymphocytes, CRP, LDH, D-dimer, GRF, albumin, PaO$_2$/FiO$_2$, BMI, GNRI (moderate–severe risk)	Assessment of nutritional status
25	Rui L.[47]	Original	China	≥87		*	*		*			*	*	*	Age and gender, BMI, smoking history, Barthel ADL index, cerebrovascular disease, dementia, long-term bedridden, symptoms: (fever, dry cough,	Analysis of laboratory results, chest computed tomography manifestation

TABLE 1 (Continued)

ID	The first author (reference)	Type of study	Country	Age	Mortality rate (N (%))	Underlying diseases									Other	Prevention and care
						Neurological disease	Lung disease	Liver diseases	Heart damage	Autoimmune	Kidney disease	Diabetes	Hypertension	Cancer		
26	Saavedra D.[48]	Original	Cuba	≥73	6.48		*		*			*	*	*	Age and Gender, COPD	expectoration, lethargic, fatigue, shortness of breath, -Serum cytokines -An anti-CD6 monoclonal antibody(itolizumab)
27	Song J.[49]	Original	China	≥60	5.3		*		*			*	*	*	Age and gender, smoking history, cerebrovascular disease, fever, dry cough, fatigue, diarrhea, expectorant, muscle ache, sore throat, anorexia, runny nose, chest pain, headache, asymptomatic	Antiviral treatment, arbidol, lopinavir/ritonavir, oseltamivir, interferon alpha inhalation, traditional Chinese medicine, antibiotics, corticosteroid, gamma globulin
28	Sulli A.[50]	Original	Italy	≥76	–		*	*	*		*	*	*	*	Age and gender, smoking history, BMI, ethnicity, cerebral ischemic vasculopathy, recent hip or vertebral fracture, dysthyroidism, colic diverticulosis, chronic arthritis (rheumatoid or psoriatic), epilepsy, allergic asthma, liver cirrhosis, hepatitis B infection	Confirms that 25-OH-vitamin D serum deficiency is associated with more severe lung involvement, longer disease duration, and risk of death, in the elderly.
29	Tan X.[51]	Original	China	≥70	12.12		*	*	*			*	*	*	Age and gender, chronic hepatic disease, chronic renal disease, cerebrovascular disease, anemia, symptoms (fever, cough, fatigue, myalgia, sputum production, dyspnea, nausea, vomiting, abdominal pain, diarrhea, headache, anorexia, shortness of breath	–
30	Trecarichi E.[52]	Cohort	Italy	≥80	49–64	*	*	*	*		*	*	*	*	Hypernatremia, lymphopenia, CVD other than hypertension, psychiatric disorders, obesity, neurologic diseases, >2	Combination therapy with hydroxychloroquine plus azithromycin, electrocardiographic

(Continues)

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TABLE 1 (Continued)

ID	The first author (reference)	Type of study	Country	Age	Mortality rate (N (%))	Underlying diseases — Neurological disease	Lung disease	Liver diseases	Heart damage	Autoimmune	Kidney disease	Diabetes	Hypertension	Cancer	Other	Prevention and care
															coexisting comorbidities, bedridden status, polypharmacy	monitoring, anticoagulant therapy with enoxaparin or fondaparinux, corticosteroid therapy with intravenous methylprednisolone, high IL-6 levels, with tocilizumab single dose (162 mg) administered subcutaneously
31	Wang L.[53]	Cohort	China	≥65	15.74		*		*			*	*	*	Cerebrovascular disease,	–
32	Wassenaar T. M.[54]	Original	Germany	≥70								*	*	*	Cardiovascular disease, obesity	BCG vaccination
33	Yan F.[55]	Cohort	China	≥65			*	*	*		*	*	*	*	Cerebrovascular disease, fatigue, dyspnea	Antihypertensive drugs
34	Zeng F.[56]	Cohort	China	≥66			*	*	*		*	*	*	*	Chronic respiratory disease. Symptoms are fever, expectoration, fatigue, myalgia, pharyngalgia, nausea, vomiting, pectoralgia, rhinorrhoea, diarrhoea	--
35	Zhang P.[57]	Cohort	China	≥67			*	*	*		*	*	*	*	CHD, cerebrovascular disease, COPD, symptoms (fever, cough, fatigue, myalgia, expectoration, nausea, vomiting, shortness of breath, rhinorrhoea, haemoptysis, diarrhoea, arrhythmias, dizziness, palpitation)	–

Abbreviations: ALT, alanine transaminase; ARDS, acute respiratory distress syndrome; BCG, bacille Calmette-Guérin; BMI, body mass index; CKD, chronic kidney disease; COVID-19, coronavirus disease 2019; cTnI, cardiac troponin-I; GNRI, geriatric nutritional risk index; GRF, glomerular filtration rate; HFNC, high-flow nasal cannula; hsCRP, high-sensitivity C-reactive protein; IL-6, interleukin-6; MV, mechanical ventilation; proBNP, pro-B-type natriuretic peptide; PSI, pneumonia severity index; RAAS, renin-angiotensin-aldosterone system; VKA, vitamin K antagonist.

TABLE 2 Newcastle–Ottawa scale quality assessment for the included studies

ID	First author	Selection (out of 4)	Comparability (out of 2)	Outcome (out of 3)	Total (out of 9)
1	Hwang J.[23]	***	–	***	6
2	Lee J.[24]	***	–	***	6
3	Li P.[25]	***	**	***	8
4	Li G.[26]	****	–	***	7
5	Li Q.[27]	****	**	***	9
6	Liu K.[29]	****	–	***	7
7	Liu Z.[30]	****	–	***	7
8	Mei Q.[31]	****	**	***	9
9	Ménager P.[32]	****	**	**	8
10	Blanco J. I. M.[33]	****	–	***	7
11	Mostaza J.[34]	****	–	***	7
12	Mori H.[28]	****	–	***	7
13	Annweiler G.[35]	****	**	***	9
14	Araújo, M. P. D.[36]	***	–	***	6
15	Bongiovanni M.[37]	***	*	***	7
16	Cocco P.[38]	***	**	**	7
17	Covino M.[39]	***	**	***	8
18	Dai S. P.[40]	****	–	***	7
19	Díaz Y.[41]	***	–	***	6
20	FranchiniM.[42]	***	–	***	6
21	Gao, S.[43]	***	–	***	6
22	Pratt N.[44]	***	–	***	6
23	Ramos-Rincon J. M.[45]	***	**	***	8
24	Recinella G.[46]	***	**	***	8
25	Rui L.[47]	***	–	**	5
26	Saavedra D.[48]	***	–	**	5
27	Song J.[49]	****	–	***	7
28	Sulli A.[50]	****	**	***	9
29	Tan X.[51]	***	–	***	6
30	Trecarichi E.[52]	***	**	***	8
31	Wang L.[53]	***	*	***	7
32	Wassenaar T. M.[54]	***	–	***	6
33	Yan F.[55]	****	**	***	9
34	Zeng F.[56]	****	*	***	8
35	Zhang P.[57]	****	**	***	9

presentations, such as dyspnea, tachypnea, hypoxia, altered mental status, and hypotension.[23,24] Of interest, the elderly are more often asymptomatic and afebrile while having a similar viral load to the symptomatic patients; therefore, they can be a significant source of viral spread.[28]

Considering that the elderly usually have different underlying comorbidities and are more susceptible to severe complications of COVID-19 infection, comprehensive care for them is of great importance. Early diagnosis and supportive care may prevent severe outcomes.[46] Also, particular attention should be paid to a thorough

TABLE 3 Certainty of evidence analysis of the included studies.

	Risk of bias	Inconsistency	Indirectness	Large effects	Dose response	Opposing plausible residual bias and confounding
Results section	The studies had an acceptable risk of bias, particularly in the selection and outcome parameters. However, most of the studies lacked adequate measures in the comparability section, as several of them did not match their participants based on gender, comorbidities, or other confounders.	Most of the studies used and found similar outcomes, the increased severity of COVID-19 in the elderly. Furthermore, this outcome is also empowered and regenerated by other systematic reviews and meta-analyses.	The PICO of the studies was similar, to the COVID-19 outcomes of the elderly.	Several of the cohorts had a high number of participants. Furthermore, besides our study, other systematic reviews and meta-analyses demonstrated increased COVID-19 mortality with increased age.	Several studies found an increasing trend of mortality with an increase in decades of life.	Several studies did not match the participants based on various confounders, as mentioned in the risk of bias section. The studies were mostly observational and not RCTs, but this is not a weakness due to the subject of the study, and even could be a strength as a high portion of the studies were cohorts.
Reasons for lowering or increasing the certainty of the evidence	Downgraded because several studies lacked matching the groups for confounders.	Not downgraded due to inconsistency.	Not downgraded due to indirectness.	Upgraded, due to high participant numbers in the studies.	Upgraded, because of the increased mortality with an increase in age.	Not downgraded as the problem was mentioned earlier.

Abbreviations: COVID-19, coronavirus disease 2019; PICO, population, intervention, control, and outcome; RCT, randomized controlled trial.

assessment of them while they are admitted since they are more prone to severe illness. Different aspects that need to be focused on include advanced respiratory support due to more susceptibility to ARDS and cardiac monitoring due to the possibility of acute cardiac injury.[49] Other strategies for improving the health condition of the elderly include minimizing exposure to the virus as a preventive measure, implementing telemedicine methods, having multidisciplinary teams and multicomponent programs for geriatric units, maintaining good nutritional status and healthy eating habits, and influenza vaccination resulting in a reduced impact of COVID-19 epidemic waves.[36,38,39]

Having multiple comorbidities such as diabetes mellitus (DM), hypertension, heart disease, lung disease, and so forth, are predictive factors of poor prognosis, higher mortality, and morbidity in the elderly.[40,43,60] Elderly patients with COVID-19 demonstrated a significantly higher prevalence of comorbidities.[40] Although senility is a distinct risk factor for COVID-19 severity and fatality rate,[24,45,61–63] pre-existing conditions will exacerbate the disease course.[60] The relationship between comorbidities and COVID fatality was not confounded by age.[3,64,65] Despite compelling evidence for the association of various comorbidities with COVID-19 mortality, in very old inpatients (age > 80 years) this relationship does not stand.[45]

Hwang et al.[60] and Lee et al.[24] studies claimed that patients with DM required more intensive care and experienced higher mortality. This is in line with previous studies in more wide populations and not only in the elderly, in which evidence reported DM more frequently in critical patients than noncritical.[63,64,66] However, some studies[31,34,67,68] did not find an association for DM. This inconsistency may stem from the fact that well-controlled blood glucose protects diabetic patients from COVID-19 mortality and severe course compared to poor-controlled blood glucose patients.[69]

Neurologic comorbidities also play a role in the COVID-19 clinical course. Poblador-Plou et al.[62] and Li et al.[25] revealed cerebrovascular disease as a mortality-related risk factor for the disease. Covino et al.[39] and Ramos-Rincon et al.[45] studies also showed dementia deteriorates the disease prognosis as an independent risk factor. This statement confirms previous studies about the association between dementia and COVID-19.[70]

The cardiovascular disturbance may alternate the outcome of the disease. Tan et al.[51] and Poblador-Plou et al's.[62] studies assumed chronic cardiovascular comorbidities as a leading risk factor for COVID-19 mortality in the elderly. Also, Covino et al.[39] and Li et al.[25] suggested congestive heart failure as a strong predictor of mortality among the elderly. On the other hand, Mei et al.[31] did not find an association for coronary disease. As the most prevalent comorbidity among the elderly,[44,45] hypertension has been significantly associated with mortality in Mei et al.[31] and Li et al.[25] studies. In addition, elderly deceased patients have shown more prevalent hypertension compared to the young deceased.[51] In contrast, in Lee et al.[24] study, hypertension was not a statistically meaningful risk factor for COVID-19 mortality among the elderly. Also, some studies confirm a lack of association for hypertension.[43,45] Hypertension

introduces an additional risk for acute kidney injury and renal complications in elderly patients.[52]

Contrary to intuitive beliefs, carcinoma was not associated with survivorship among elderly COVID-19 patients.[31,45,68] On the other hand, lung disease and COPD impose higher mortality on senescent patients with COVID-19 (hazards ratio [HR] = 3.1).[34,51,68] Besides, in the case of kidney disease, elderly patients with chronic renal failure are also at higher risk of mortality (HR = 4.2).[45]

Due to the retrospective nature of a significant fraction of included studies, the results of this review study should be interpreted with caution. The limited population enrolled in the included studies in which only the elderly were included was another drawback and limited our ability in making valid comparisons between this age group with the younger population. We not only faced heterogeneity in the sample population of selected studies but also, may include some duplicate data from case studies that are shared with another study chosen from the same setting.

5 | CONCLUSION

A critical consideration is necessary for the care and management of COVID-19 in the aged population considering the drastic contrasts in manifestation and prognosis compared to other age groups. Mortality from COVID-19 is independently associated with the patient's age. Specific blood and serum elements (hypernatremia, lymphopenia, high IL-6 and CRP serum levels, and elevated D-dimer), symptoms (severe initial presentations, e.g., dyspnea), and comorbidities (dementia, DM, and cardiac disease) are predictive of the severe form of the disease. Being asymptomatic with a capable viral load to disseminate, make the elderly a potential source of viral spread. Old-aged patients with COVID-19 are more vulnerable to poor outcomes. Thus, strict preventive measures, timely diagnosis, and aggressive therapeutic and nontherapeutic care should be considered in the elderly to reduce ARDS and severe complications. Further prospective investigations are necessary to eliminate confounding variables and to elucidate the predictive risk factors that contribute to the patients' mortality and morbidity.

AUTHOR CONTRIBUTIONS

Esmaeil Mehraeen and SeyedAhmad SeyedAlinaghi: Conception and design of the study. **Esmaeil Mehraeen, SeyedAhmad SeyedAlinaghi, Amirali Karimi, and Shiva A. Azar**: Methodology. **Kowsar Qaderi, Maryam Ramezani, Solmaz Saeidi, and Amirali Karimi**: Acquisition of data. **Ahmadreza Shamsabadi and Farzin Vahedi**: Analysis and interpretation of data. **Alireza Shojaei, Seyed Peyman Mirghaderi, Sara Mahdiabadi, and Amirali Karimi**: Writing – original draft preparation. **SeyedAhmad SeyedAlinaghi, Omid Dadras, and Mohammad Mehrtak**: Writing – review & editing. **Esmaeil Mehraeen, Omid Dadras, Fabrício A. Voltarelli, and SeyedAhmad SeyedAlinaghi**: Validation.

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