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SYSTEMATIC REVIEWS

Elderly adults with COVID-19 admitted to intensive care unit: A narrative review

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Abstract

BACKGROUND

In the context of the Coronavirus disease 2019 (COVID-19) pandemic, it has been reported that elderly patients are particularly at risk of developing severe illness and exhibiting increased mortality. While many studies on hospitalized elderly patients with COVID-19 have been published, limited information is available on the characteristics and clinical outcomes of those elderly patients admitted to intensive care unit (ICU).

AIM

To review the available evidence of the clinical data of elderly patients admitted to the ICU due to COVID-19.

METHODS

We searched for published articles available in English literature to identify those studies conducted in critically ill patients admitted to the ICU due to COVID-19, either exclusively designed for the elderly or for the whole ICU population with COVID-19, provided that analyses according to the patients' age had been conducted.

RESULTS

Only one study exclusively focusing on critically ill elderly patients admitted to the ICU due to COVID-19 was found. Eighteen additional studies involving 17011 ICU patients and providing information for elderly patients as a subset of the whole study population have also been included in the present review article. Among the whole patient population, included in these studies, 8310 patients were older than 65 years of age and 2630 patients were older than 70 years.



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Clinical manifestations were similar for all patients; however, compared to younger ones, they suffered from more comorbidities and showed a varied, albeit high mortality.

CONCLUSION

In summary, at present, although elderly patients constitute a considerable proportion of critically ill patients admitted to the ICU due to severe COVID-19, studies providing specific information are limited. The evidence so far suggests that advanced age and comorbidities are associated with worse clinical outcome. Future studies exclusively designed for this vulnerable group are needed.

Key Words: SARS-CoV-2; COVID-19; Elderly; Critically ill; Intensive care unit mortality; Respiratory failure

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Core Tip: Coronavirus disease 2019 (COVID-19) affects people of all ages; however, the risk for severe illness increases with age, with older adults being at highest risk. While many studies with regard to COVID-19 impact on elderly patients have been carried out, the information on characteristics and clinical outcome of critically ill elderly patients admitted to the intensive care unit (ICU) due to COVID-19 is scarce. Studies exclusively designed for these patients are limited. Data derived from these studies and additionally from studies analyzing critically ill elderly patients as a subset of the whole ICU population with COVID-19, support that advanced age along with comorbidities are associated with worse clinical outcome.

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INTRODUCTION

December 2019 was marked by the emergence of coronavirus disease 2019 (COVID-19), caused by the novel severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2)[1]. First detected in Wuhan, China, this infectious disease has spread rapidly worldwide, and it was declared a global pandemic by the World Health Organization on March 11, 2020[2].

The major clinical complication in patients with COVID-19 is respiratory failure and acute respiratory distress syndrome (ARDS) followed by sepsis, septic shock and multi-organ failure. The disease affects people of all ages; however, the incidence and the severity of COVID-19 consistently rises with increasing age[3-12]. Even if a completely understood pathophysiological mechanism for the severity of COVID-19 infection in the elderly has not been described, two major axes play a cornerstone role, multimorbidity such as hypertension, cardiovascular disease, diabetes, chronic respiratory and chronic kidney disease[13,14] as well as changes and dysregulation affecting organ systems of older adults. Specifically, changes affecting the immune system, processes known as immunosenescence and inflammaging[15-17] and anatomical and functional decline of the respiratory system[18], have been proposed to contribute to a more severe course of infection at advanced age. Furthermore, Santesmasses et al[19], have recently indicated an age-related increased ACE2 gene expression, which encodes the cell entry receptor for SARS-CoV-2, with increased levels of ACE2 protein in older individuals, highlighting that advanced age represents a major risk factor for disease severity.

A consequence of the increased incidence and severity of COVID-19 infection among elderly populations compared with younger adults is that the former will often need advanced medical care [20]. This fact, combined with the ongoing global population ageing[21], highlights the burden that this particular age group with severe COVID-19 infection puts on healthcare systems worldwide.

According to the available evidence, elderly patients are at an apparent increased risk of adverse outcome[22-27]. The mortality within older patient population could probably be further compounded by shortages of ICU beds and/or access to mechanical ventilatory support [28]. Indeed, in the context of COVID-19 pandemic, age and co-morbidities have been used as selection criteria to triage patients for ICU admission in order to prioritize the younger ones [29,30]. On the other hand, it could be suggested that in no overwhelmed ICU capacity, access to ICU for elderly patients with COVID-19 may be preserved and possibly could contribute to survival of severe forms of COVID-19.

Therefore, given the significant proportion of elderly patients putting pressure on health care systems, understanding the course of COVID-19 in this specific population is considered of major importance. The aim of this review is to present the existing literature and to provide a summary of the current evidence concerning characteristics and outcomes of elderly patients admitted to the ICU due to COVID-19, useful for the better management of this vulnerable population in the future.

MATERIALS AND METHODS

The search of the published medical literature was conducted across PubMed and Google Scholar databases using the keywords "COVID-19", "SARS-CoV-2", "critical care", "intensive care", "ICU", "mechanical ventilation", "elderly", "older patients", "death", "mortality", in order to find studies reporting characteristics and clinical outcome of critically ill elderly patients with laboratory- confirmed COVID-19 admitted to ICU, published in 2020 and in the early 2021. The last literature search was conducted on May 20, 2021. Only articles published in English were included; no limitations were applied to study design or country of origin. We also searched the reference lists of relevant articles to identify further articles. Studies were considered eligible if they included elderly patients with COVID-19 either exclusively or as a group among the whole study ICU population. Studies that did not analyse separately the subset of elderly patients were excluded.

The following data were extracted: first author, year of publication, country of origin, sample size of patients with COVID-19, mean or median age, number of elderly patients, number of deaths in each age group. Since there is no universally accepted age cut-off defining "elderly" [31], we followed each study's definition as it was used by the authors.

Our initial search did not identify studies exclusively designed for critically ill elderly patients with COVID -19 admitted to the ICU. Thus, we included those studies that provided separate data for elderly patients, as a subgroup, in the analyses of the whole study ICU population with COVID-19. However, during the revision process of the present review article, two additional studies have been recently released; therefore they have been added to the present review [32,33].

RESULTS

Description of the studies

Finally, a total of 19 studies fulfilling the inclusion criteria were included involving 18210 critically ill patients admitted to the ICU due to COVID-19. The proportion of elderly patients included in the whole studies population was considerable: 10646 patients were older than 60, 8310 patients older than 65 and 2630 patients older than 70 years of age. Table 1 lists the summary characteristics of the included studies. Five studies were conducted in China, three studies in the United States, one in Canada, one in Australia, one in Kuwait and eight in Europe (Italy, Germany, Sweden, the United Kingdom and the Netherlands). As the duration of mechanical ventilation and recovery from COVID-19 are often quite prolonged procedures, several articles included a substantial number of patients who were still in the ICU at the end of data collection.

Presence of comorbidities

In the large cohort study by Grasselli et al[23], including 1591 patients with COVID-19 admitted to ICUs of the Lombardy Region, Italy, 363 patients (23%) were older than 71 years. All patients older than 80 and 76% older than 60 had at least one comorbidity.

Table 1 Critically ill coronavirus disease-2019 elderly patients, included in observational clinical studies conducted in intensive care units

Ref.	Country	Median age, yr	Sample size / No. of the elderly admitted to the ICU (proportion, %)	ICU mortality, No. of deaths (%), all ages	ICU mortality of the elderly, No. of deaths and proportion (%)	Comments
Yang et al[8], Lancet Respir Med	China	59.7 ¹	52 / 27 ≥ 60 yr (52)	32 (61.5)	20/27 (74.1) (≥ 60 yr)	-
Grasselli <i>et al</i> [23], <i>JAMA</i>	Italy	63	1591 / 961 ≥ 61 yr (60.4)	405 (60.3)	322/436 (73.9) (≥ 61 yr)	525/961 elderly patients still in ICU; 920/1591 patients (all ages) still in ICU
Richardson <i>et al</i> [24], <i>JAMA</i>	United States	N/A	1281 / 613 ≥ 65 yr (47.8)	291 (78)	182/200 (91) (≥ 65 yr)	413/613 patients \geq 65 yr old still in hospital; 908/1281 patients (all ages) still in hospital
Bhatraju et al[49], NEJM	United States	64 ¹	24 / N/A	12 (57.1)	62 (≥ 65 yr)	3 patients remained intubated at the end of the study
Karagiannidis et al[52], Lancet Respir Med	Germany	71	1727 / 1305 ≥ 60 yr (75.5)535, 70-79 yr; 388, ≥ 80 yr	906 (53)	174/382 (46), 60-69 yr; 335/535 (63), 70- 79 yr; 280/388 (72), ≥ 80 yr	ICU deaths in elderly with invasive and non-invasive mechanical ventilation are reported
Yu et al[47], Crit Care	China	64	226 / 149 ≥61 yr (65.9)	87 (41.2)	62/140 (44) (≥ 61 yr)	9/149 elderly patients still in hospital; 15/226 patients (all ages) still in hospital
Shi et al[34], Clin Lab Anal	China	59.4 ¹	161 / 83 ≥ 60 yr (51.5)	50 (39)	36 (60-74 yr)24.24 (> 74 yr)	Further comparison analysis revealed that no difference was found among the following age group patients: $\le 44, 45-59, 60-74$, and ≥ 75 yr; $33/161$ still in hospital- N/A if they were in ICU or in hospital's ward
Burrell <i>et al</i> [35], <i>MJA</i>	Australia	63.5	200 / 123 ≥ 60 yr (61.5); 97 ≥ 65 yr (48.5)	30 (15)	28/123 (22.8) (≥60 yr); 25/97 (25.8) (≥ 65 yr)	6/200 patients still in hospital wards
Aleva et al[36], J Crit Care	The Netherlands	65 ¹	50 / 30 ≥ 65 yr (60)	13 (32)	10/30 (33) (≥ 65 yr)	All survivors successfully discharged from the hospital
Mitra et al[37], CMAJ	Canada	69	117 / 76 ≥ 65 yr (64.9)	18 (17.1)	16/69 (23) (≥ 65 yr)	7/76 elderly patients still in ICU; 12/69 elderly patients still hospitalized; 12/117 patients (all ages) still in ICU
Alshukry et al [38], PLoS One	Kuwait	47	82 / 25 > 60 yr (30.4)	60 (73.1)	17/25 (68) (> 60 yr)	-
Larsson et al[39], Acta Anesthesiol Scand	Sweden	59	260 / 110 ≥ 60 yr (42.3); 28 ≥ 70 yr (10.7)	60 (30.3)	37/81 (45.7) (≥ 60 yr)	29/110 elderly patients still in ICU; 62/260 patients (all ages) still in ICU
Wang et al[42], AJRCCM	China	60	344 / 194 ≥ 60 yr (56.4)	133 (38.7)	101/194 (52.1) (≥ 60 yr)	-
Auld et al[46], Crit Care Med	United States	64	217 / 106 ≥ 65 yr (48.8)	62 (29.7)	45/103 (44) (≥ 65 yr)	3/106 elderly patients still in ICU; $8/217$ patients (all ages) still in ICU
Xu et al[48], Crit Care	China		239 / 112 ≥ 65 yr (46.9)	147 (61.5)	82/112 (73.2) (≥ 65 yr)	-
Thomson <i>et al</i> [50], <i>PLoS One</i>	United Kingdom	62	$156 / 89 \ge 60 \text{ yr (57)}$	38 (24.3)	31/89 (34.8) (≥ 60 yr)	-
Nachtigall et al [51], Clin Microbiol Infect	Germany	73	399 / 318 ≥ 60 yr (79.6)	109 (27.3)	102/318 (32) (≥ 60 yr)	
Guillon et al[32], Intensive Care Med	France	N/A	9885 / 5126 ≥ 65 yr (51.9); 480 ≥ 80 yr (4.9)	2914 (29.5)	1986/5126 (38.7) (≥ 65 yr); 300/480 (62.5) (≥ 80 yr)	
Dres et al[33], Ann Intensive Care	France, Switzerland, Belgium	74	1199 / 639 70-74 yr (53.3); 367 75-79 yr (30.6); 193 > 80 yr (16.1)	549 (45.8)	247/639 (38.7) (70-74 yr); 173/367 (47.1) (75-79 yr); 129/193 (66.8) (> 80 yr)	All patients were ≥ 70 yr old

 $^{^{1}}$ mean value. ICU: Intensive care unit; N/A: Not available.

Hypertension was the most common, followed by diabetes, hypercholesterolemia, ca



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Similarly, in the large study of 5700 hospitalized patients with COVID-19 in the United States, including a subgroup of 373 ICU patients, older persons and those with pre-existing hypertension and/or diabetes were highly prevalent[24]. Other chronic conditions, such as smoking, malignancy, chronic kidney disease and chronic liver disease were less reported elsewhere [34-36]. In another study by Mitra et al [37] in critically ill patients with COVID-19 admitted to ICU, the majority were older than 65 and 73.5% of patients had at least one medical comorbidity. Seventeen (94.4%) out of the 18 patients who died (with a median age of 75 years), had at least one comorbid disease[37]. In addition, Burrell et al[35], have shown that the number of comorbidities was associated with increased risk of ICU admission, need for mechanical ventilation or death. Similarly, older patients with comorbidities and ARDS were found at increased risk of death[8,38], though such an association was not observed elsewhere [36,39].

Clinical features

Based on the data collected from the selected studies, fever, cough, and shortness of breath were the most commonly developed symptoms among patients with COVID-19, including older adults[40]. Compared to younger patients, older ones more frequently presented shortness of breath; a factor related to dismal prognosis[41,42]. Other clinical manifestations in the elderly included fatigue, myalgia, nasal congestion, sore throat, diarrhea, nausea, anorexia, headache, and dizziness[43-45]. Other atypical presentations of the infection in elderly patients included absence or low-grade fever [36], abdominal pain and delirium[16,45]. Interestingly, in the cohort study of Kennedy et al[43], delirium symptoms, such as impaired consciousness, disorientation and inattention were found to be among the most common clinical manifestations in patients aged over 65. Additionally, 37% of patients presented delirium in the absence of fever or shortness of breath, while delirium was correlated with adverse clinical outcomes, including ICU admission or even death[43].

Mechanical ventilation

Among the 19 included studies, only seven report on mechanical ventilation use in older individuals. In the study by Grasselli et al[23], the majority (89%) of elderly patients admitted to the ICU received invasive mechanical ventilation with high levels of positive end expiratory pressure (PEEP). There was need for higher fraction of inspired oxygen (FiO₂) in the group aged \geq 64 years compared to the group aged \leq 63 years (70% vs 60% respectively, P = 0.006); the ratio of the partial pressure of oxygen in arterial blood (Pao₂) to Fio₂ was higher in the younger patients compared to older ones (163 vs 156, P = 0.02). In addition, patients with hypertension were significantly older and had higher PEEP levels and lower PaO2/FiO2 compared with patients without hypertension[23].

In the studies by Auld et al [46], Yu et al [47] and Richardson et al [24], the proportion of elderly patients requiring mechanical ventilation was 52%, 89% and 91% respectively. In the large study by Richardson et al[24], which included 5700 patients hospitalized with COVID-19 in the New York City area, 373 patients (14.2%) were admitted to the ICU and 320 (12.2%) of them received invasive mechanical ventilation. An intriguing find was that older and frailer patients were less likely to receive ventilatory support compared to younger ones (< 65 years old); however, it could be attributed, at least in part, to incomplete outcome data, since 413 out of 613 patients were still hospitalized at the study end.

Clinical outcome

Usually, mortality rates were calculated based on the number of patients who had an outcome or had been discharged from the ICU, thus, excluding patients who were still in ICU. In all studies without exception, older patients with COVID-19 admitted to the ICU had a higher mortality rate compared to younger patients. In the study by Yang et al[8], 20 out of 27 (74.1%) patients \geq 60 years old died. Similarly, in the study by Xu et al[48], among 112 critically ill patients \geq 65 years old, mortality rate was 73.2 %. Alshukry et al[38], in their study included 82 patients admitted to the ICU; 17 out of 25 (68%) patients \geq 60 years old died, while Bhatraju et al[49] reported similar mortality rates in patients \geq 65 years (62%). Other studies, namely those by Auld et al[46], Yu et al[47], and Larsson et al[39], which included, 106, 149 and 110 elderly patients respectively, among the whole ICU study population, reported mortality rates of 44%, 44% and 45.7% respectively. Comparable mortality rates were reported by Shi et al [34], 36%, Burrell et al[35], 25.8%, Aleva et al[36], 33% and Mitra et al[37], 23%, though, not all patients had reached an outcome at the study end. Finally, Thomson et al[50], in 89 patients ≥ 60 years old admitted to the ICU with COVID-19 reported a mortality

rate of 31.3%.

In accordance with the aforementioned observational small-scale studies, large studies have reported similar findings. Indicatively, in the study by Richardson et al [24] mortality rates for those who received mechanical ventilation in the 18-to-65 and older-than-65 age groups were 76.4% and 97.2%, respectively. Mortality rate for those in the 18-to-65 and older-than-65 years age groups who did not receive mechanical ventilation was 1.98% and 26.6%, respectively.

In the earlier study by Wang et al [42], which included 344 patients admitted to ICU due to COVID-19, older patients (> 60 years) with comorbidities were at dramatically increased risk of death, having a mortality of 75.9% (101/194), whereas a 24.1% mortality was observed in patients ≤ 60 years old. A lower mortality of 32% has been recently reported by Nachtigall et al[51], who analyzed 318 critically ill patients \geq 60 years old with COVID-19 in German ICUs.

In the large retrospective analysis by Grasselli et al[23], older age was, among others, an independent risk factor associated with increased mortality. Specifically, 322 out of 436 (73.9%) ICU patients over 60 years of age died. Again, as commented above, a considerable number of patients (525 out of the 1521 study patients) were still in the ICU at the end of the study. Possibly for the same reason, the reported mortality of 91% among older patients in the study by Richardson et al[24], may have been overestimated, as it was calculated only for 413 out of 613 patients ≥ 65 years old who were either discharged alive or died by the end of the study.

The German nationwide cohort study by Karagiannidis et al[52] comprised 1727 mechanically ventilated patients, 75.5% of them aged ≥60 years. The mortality rate of 60.5% in this age group was remarkably higher compared to the observed mortality rate of 28% in the 18-to-59 age group. Further stratifying elderly patients (≥ 60 years) by age (60-69, 70-79, \geq 80 years old), the risk for death increased with each successive age group (46%, 63%, 72% respectively). Moreover, comparison between mechanically ventilated patients and non-ventilated ones revealed that the latter presented significantly lower mortality rates regardless of age (1% and 22.5% in the 18-to-59 and \geq 60-age group respectively).

Finally, two recently published large-scale studies by Guillon et al[32] and Dres et al [33], the latter focusing exclusively on elderly patients over 70 years old, demonstrated similar results with reported mortality rates 38.7% in patients ≥ 65 years and 45.8% in patients ≥ 70 years, respectively. Moreover, both studies showed that elderly patients over 80 years old were remarkably more susceptible to death (62.5% and 66.8%) compared to young- and middle-old patients.

DISCUSSION

Despite the large number of COVID-19- related publications, and despite the impact of COVID-19 on the elderly population, we found only a limited number of relevant studies being conducted in ICU, providing evidence on characteristics, clinical course and outcomes of critically ill elderly patients with COVID-19. In most of the studies, elderly patients comprised a substantial proportion of the study population, ranging approximately from 30.4% to 79.6%, indicating, thus, the high burden of advanced age on ICU beds capacity.

Although limited evidence on elderly patients in the ICU setting is available, accumulating observational data show a varied, albeit high mortality. This variability could partially be explained by management heterogeneity of these patients, the diversity in sample size and the incomplete outcome data due to rapid publication of results, while a substantial number of these patients were still in the ICU or the hospital at the time their outcome was evaluated. Another factor possibly influencing the reported mortality is a trend towards improvement of the disease clinical outcome. During the initial surge of the pandemic, reports of critically ill COVID-19 patients in China, Italy and the United States have reported a high mortality, whereas recent analyses are reassuring that ICU mortality is lower than earlier reports suggested[53]. Similarly, according to a systematic review and metanalysis of patients with severe COVID-19, the overall estimate for the reported case fatality rate was 45% (95%CI, 38%-52%); nevertheless, significant variability was observed by age, among other parameters[54]. Specifically, the reported case fatality ratio was higher in older patients and in early pandemic epicenters, which may have been influenced by limited ICU resources.

Two recent studies confirm the evolution of clinical outcome over time in adults with COVID-19-related critical illness admitted to ICU. The first study shows that

among patients with COVID-19-related critical illness admitted to ICUs in the United States, mortality seemed to decrease over time despite stable patient characteristics [55]. According to the second study, among more than 4000 critically ill patients with COVID-19 admitted to ICUs located at central Europe, 90 d mortality decreased from 42% to 25% over the study period. Although detailed information on elderly population is not provided in this study, mortality was higher in older patients as well as in those with diabetes, obesity and severe ARDS[56]. Probably, more studies are necessary to confirm these results and to investigate the causal mechanisms in the elderly subset of patients.

The impact of age on mortality of critically ill patients has been already demonstrated in earlier studies in the pre-COVID-19 era[57-60]. However, important factors, such as severity of acute illness, comorbidities, as well as functional status of very old patients before ICU admission might be of more importance for the prognosis than age alone[61]. Similarly, according to a recent metanalysis, in the context of COVID-19, age-related comorbidities seem to have a more important effect than age itself; though this metanalysis refers to the whole population of hospitalized elderly patients with COVID-19 and not exclusively to those admitted to the ICU[62]. A currently ongoing clinical trial (ClinicalTrials.gov identifier NCT04321265) has planned to study the outcome of elderly ICU patients (≥ 70 years) suffering from COVID-19 using a multi-centre and multi-national approach.

Clinical manifestation of the disease was common in all age groups, however, quite often, elderly patients seem to present insidious symptom onset, as low-grade fever or altered mental status with confusion or delirium, indicating the necessity for increased suspicion by clinicians for prompt diagnosis and appropriate interventions. Notably, dyspnea as presenting symptom in older individuals seemed to correlate with dismal prognosis, at least according to one study[42]. Regarding comorbidities, as they are more likely to occur in adults ≥ 60 years old, and as advanced age is associated with immune system dysfunction, a possible correlation between the particular high risk for severe disease of elderly population and the pre-existing diseases may be explained. Specifically, the majority of studies indicated hypertension, diabetes, COPD and obesity as the most commonly identified diseases, which could predict poor prognosis.

Although in some studies the type of ventilatory support, i.e., invasive or noninvasive, in elderly patients is not clear, mechanical ventilation was associated with high mortality. As limited data is available on ventilation strategies used in elderly ICU patients with COVID-19, further research is needed as more comprehensive clinical insights concerning ICU treatment strategies in this population may be offered, in order to improve survival.

CONCLUSION

In this narrative review we summarize the current evidence for the characteristics and outcomes of elderly patients admitted to the ICU due to COVID-19. The cumulative data so far show that severe COVID-19 has a direct health impact on the elderly population, putting that at increased risk of mortality. Until effective treatments emerge, supportive care, including appropriate ventilator support for the acute respiratory failure along with co-morbidities clinical management, should be followed in the ICU so that survival of elderly patients with severe form of COVID-19 be improved. To this end, future studies exclusively designed for this vulnerable group are absolutely necessary.

ARTICLE HIGHLIGHTS

Research background

Coronavirus disease-2019 (COVID-19) affects people of all ages; however, in particular the elderly is at higher risk of severe illness.

Research motivation

Although many studies on elderly adults with COVID-19 admitted to hospital wards have been published, the information on characteristics and clinical outcome of critically ill elderly patients admitted to the intensive care unit (ICU) due to COVID-19 is limited.

Research objectives

To provide information about clinical features and outcomes of elderly critically ill patients admitted to the ICU due to COVID-19, by carrying out a review of the existing literature.

Research methods

PubMed and Google Scholar databases were searched up to May 20, 2021, while reference lists were explored for relevant articles, to identify studies either focusing on this patient population or studies in which age-stratified results were reported.

Research results

A total of 19 studies, involving 10646 patients older than 60, 8310 patients older than 65 and 2630 patients older than 70 years of age, were included. Only one study exclusively focusing on critically ill elderly patients admitted to the ICU due to COVID-19 was found. Although clinical manifestations were similar for all ICU patients, compared to younger ones, elderly patients suffered from more comorbidities and showed a varied, albeit high mortality, up to 91%.

Research conclusions

Studies exclusively designed for elderly ICU population with COVID-19 are currently limited. The current evidence suggests that elderly patients admitted to the ICU with COVID-19 are at increased risk of death.

Research perspectives

Future studies focused on elderly patients admitted to the ICU due to COVID-19 are worthwhile.

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