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Narrative review

Caring for older adults during the COVID-19 pandemic

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ABSTRACT

Background: Elderly patients represent a high-risk group with increased risk of death from COVID-19. Despite the number of published studies, several unmet needs in care for older adults exist.
Objectives: To discuss unmet needs of COVID-19 in this special population.
Sources: A literature review for studies on COVID-19 in elderly patients published between December 2019 and November 2021 was performed. Clinical questions were formulated to guide the literature search. The search was conducted in the MEDLINE database, combining specific search terms. Two reviewers independently conducted the search and selected the studies according to the prespecified clinical questions.
Content: Elderly patients with COVID-19 have peculiar characteristics. They may have atypical clinical presentation, with no fever and with delirium or neurological manifestations as the most common signs, with potential delayed diagnosis and increased risk of death. The reported fatality rates among elderly patients with COVID-19 are extremely high. Several factors, including comorbidities, atypical presentation, and exclusion from intensive care unit care, contribute to this excess of mortality. Age alone is frequently used as a key factor to exclude the elderly from intensive care, but there is evidence that frailty rather than age better predicts the risk of poor outcome in this category. Durability of vaccine efficacy in the elderly remains debated, and the need for a third booster dose is becoming increasingly evident. Finally, efforts to care for elderly patients who have survived after acute COVID-19 should be implemented, considering the high rates of long COVID sequelae and the risk of longitudinal functional and cognitive decline.
Implications: We highlight peculiar aspects of COVID-19 in elderly patients and factors contributing to high risk of poor outcome in this category. We also illuminated gaps in current evidence, suggesting future research directions and underlining the need for further studies on the optimal management of elderly patients with COVID-19. **Virginie Prendki, Clin Microbiol Infect 2022;28:785**
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Introduction and rationale for the review

Since the start of the COVID-19 pandemic, elderly patients have been identified as one of the most vulnerable categories [1]. Several studies investigating this population have been published, but the currently available evidence provides contrasting and heterogeneous data.

Elderly patients with COVID-19 are known to present with atypical clinical features, such as delirium or neurological signs in the absence of fever or productive cough [2]. Moreover, the elderly are usually underrepresented in clinical trials, limiting current knowledge about their response to treatments and vaccines. Finally, criteria for deciding to forgo intensive care unit (ICU) care are not clear, and frequently age itself (and not performance status) is considered a key factor in whether to admit a patient to the ICU.

This paper aims to underline the peculiarity of COVID-19 in elderly patients and to discuss some critical points that clinicians should know when caring for this special population. The current

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evidence and its limitations have been summarized and implications for the future have been highlighted to guide the clinical research in this field.

Methods and sources

We reviewed the medical literature for studies on COVID-19 in the specific population of elderly patients, published between December 2019 and November 2021. This review is structured around the following clinical questions:

1. What is the epidemiology of COVID-19 in elderly patients?
2. Do elderly patients with COVID-19 have a peculiar clinical presentation?
3. Do elderly patients with COVID-19 have a higher risk of mortality compared to younger ones?
4. Does frailty affect access to care and the outcome of elderly patients?
5. What are the knowledge gaps on the efficacy and safety of drugs to treat COVID-19 in elderly patients?
6. What is the efficacy of vaccines in the elderly?
7. What is the impact of long COVID-19 in the elderly?

The search was conducted in the MEDLINE database combining the following search terms: (COVID-19 OR SARS-CoV-2) AND (elderly OR older OR nursing home). Considering the huge number of published articles, we also added the filter 'age≥65 years'. English language restriction was applied. Systematic reviews, meta-analyses, randomized clinical trials, and observational studies were considered. Case series and clinical cases were not included. Two reviewers independently conducted the search (VP and GT) and reviewed the studies. Any discrepancies were resolved by a third reviewer (MF). The reviewers conducted an initial screening of titles and abstracts of published articles and reviewed full articles to assess each study's eligibility for inclusion. A study was included if it was considered likely to provide valid and useful information and met the clinical questions previously discussed.

Epidemiology

Since the end of 2019, SARS-CoV-2 has caused over 6 million deaths worldwide, especially in the older population [3]. Epidemiological data on COVID-19 in elderly patients are heterogeneous across countries. The organization and resilience of healthcare systems, variations in aged populations in different countries, criteria to establish COVID-19–attributable deaths, and sociocultural practices for elderly care lead to substantial variability in reported data. Data from Europe showed that during the first wave of the pandemic, COVID-19 was responsible for 41.6% of deaths for men over 80 years of age [4]. Despite a reduction in COVID-19 mortality during the second wave, poor outcomes still remained high in this category of patients.

COVID-19 represents a challenge in nursing home/long-term care facilities (LTCF), which registered a disproportionally high number of deaths during the pandemic [5]. A study conducted in South Carolina showed that LTCF residents with COVID-19 were more likely to be hospitalized and die compared to older adults living in the community (hospitalization rates: 1953/7366 (26.5%) vs 7007/47 148 (14.9%); mortality rates: 1760/7366 (23.9%) vs 2839/47 148 [6%]) [6].

Epidemiology of COVID-19 in the elderly continues to change, according to restriction measures adopted by governments and vaccine access, and data need to be continually updated according to the spread of variants of concern (VOCs) all over the world.

Clinical presentation and risk of death

A growing number of studies have highlighted that elderly patients may have atypical clinical presentation [7], with fever occurring less frequently in older patients compared to younger ones [8]. Mounting evidence supports a high frequency of delirium and neuropsychiatric manifestations in this category of patients [9]. Confusion at hospital admission is significantly more common in COVID-19 patients ≥70 years old compared to younger ones ($n = 30/152$ (19.9%) vs $n = 2/188$ (1.1%); $p < 0.001$) [10], and in a recent meta-analysis conducted on 9031 patients with COVID-19 the prevalence of delirium was 28.2% (25/5490) in patients over 65 years old compared to 15.7% (12/3293) in younger adults [11]. The occurrence of delirium in elderly patients with COVID-19 has been associated with a mortality rate of 48.4% [11]. Other atypical presentations may include falls, generalized weakness, diminished food intake, changes in behaviour, malaise, and functional decline [12].

Accurate screening for typical and atypical symptoms of COVID-19 in elderly patients is crucial to avoid diagnostic errors both in the emergency department and in special contexts such as nursing homes or LTCFs [13]; the underreporting of symptoms in such structures contributes to a delayed diagnosis with consequent spread of the virus [13].

A meta-analysis including more than 600 000 individuals showed that mortality changes across age categories, ranging from 9.5% (8073/85 358) in patients 60 to 69 years old up to 29.6% (41 958/141 745) in those aged >80 years [1]. Tables 1 and 2 summarize mortality rates extrapolated from clinical studies conducted in elderly patients with COVID-19 and factors associated with poor outcome [14–31]. Among biomarkers of infection, an increase in procalcitonin values was associated with increased risk of hospital death in patients >75 years old, but not in younger ones [32]. Further studies are warranted to investigate patients' related factors and biomarkers independently associated with death in this population.

The highest mortality rates (40%–80%) are reported in elderly patients admitted to the ICU [14,15,31]. Because of this finding, some intensivists were initially discouraged from admitting elderly patients to the ICU and used age as an exclusion criterion for ICU care [33]. This choice was justified by ethical consideration to prioritize younger patients in a time of reduced ICU capacity. However, an interesting study by the COVIP group unexpectedly showed that elderly patients admitted to the ICU during the second wave had higher short- and long-term mortality compared to the first wave [14]. Among the other potential explanations, the worse outcome might have been caused by the increased length of time spent in other departments before ICU admission, a hypothesis supported by decreased PaO_2/FiO_2 ratio at ICU admission in the second period [14]. Specific parameters to take into consideration for deciding whether an elderly patient should be admitted to ICU are discussed in the following.

Impact of frailty on access to intensive care and outcome

The mortality rate associated with COVID-19 is directly related to the classes of age of patients [19]. However, age alone is not a good predictor of survival when other factors such as frailty, comorbidity, gender, and disease severity are considered [19]. Several studies have showed that in elderly patients, outcomes are better predicted by frailty, using a clinical frailty scale (CFS), than by age itself [34–36]. The UK National Institute for Health and Care Excellence has advocated the use of CFS in clinical decisions in patients aged ≥65 years with COVID-19 [37]. In the context of COVID-19, a score of 1 to 3 is considered a lower risk of mortality, a score of 4 to 5 moderate risk, and a score of 6 to 9 high risk [38]. A

Table 1
Reported mortality rates of elderly patients with COVID-19 from clinical studies

Study	Design	Population	Period	No.	Mortality rates
Jung C [14]	Prospective	ICU pts ≥70 y old	March–December 2020	2625	30-d mortality: 42.6% first surge; 40.9% second surge 90-day mortality: 49.2% first surge; 59.7% second surge
Guillon A [15]	Cross-sectional	ICU pts ≥80 y old	March–May 2020	480	ICU mortality: 62.5% 6-mo mortality: 72.1%
Aw D [16]	Retrospective	Pts ≥65 y old	March–April 2020	677	30-d mortality: 40.8%
Blomaard L [17]	Retrospective	Pts ≥70 y old	February–March 2020	1530	In-hospital mortality: 38.4%
Singhal S [18]	Meta-analysis	Pts ≥60 y old	December 2019–May 2020	13 624	Mortality: 11% (weighted pooled prevalence)
Covino M [19]	Prospective	Pts ≥80 y old	April 2020–March 2021	729	In-hospital mortality: - 34.4% in pts 80–84 y old - 42% in pts 85–89 y old - 61.5% in pts 90–94 y old
Guo Y [20]	Retrospective	Pts >65 y old	December 2019–March 2020	14 238	Case fatality ratio: 19.4%
Meis-Pinheiro U [21]	Retrospective	Residents in LTCF	March–April 2020	2092	Mortality: 21.7%
Brill S [22]	Retrospective	Pts >80 y old (subgroup)	March–April 2020	150	In-hospital mortality: 60%
Chinnadurai R [23]	Retrospective	Pts ≥65 y old (subgroup)	March–April 2020	150	In-hospital mortality: - 65–75 y: 37% - 75–85 y: 53% - >85 y: 62%
Miles A [24]	Retrospective	Pts ≥70 y old	March–April 2020	217	In-hospital mortality: 51.2%
Kundi H [25]	Nationwide cohort	Pts ≥65 y old	March–June 2020	18 234	In-hospital mortality: 18.2%
Mendes A [26]	Retrospective	Pts ≥65 y old	March–April 2020	234	In-hospital mortality: 32%
Owen R K [27]	Retrospective	Pts ≥65 y old	March–April 2020	285	In-hospital mortality: 43%
Steinmeyer Z [28]	Retrospective	Older pts	March–May 2020	94	In-hospital mortality: 18%
Blanc F [29]	Retrospective	Pts ≥65 y old	March–April 2020	89	In-hospital mortality: 29.2%
Silva NJ [30]	Cross-sectional	Pts ≥60 y old (subgroup)	March–June 2020	12 925	In-hospital mortality: 76.9%
Dres M [31]	Prospective	ICU pts >60 y old	February–May 2020	1199	28-d mortality 41% 60-d mortality 45% 90-d mortality 46%

ICU, intensive care unit; pts, patients.

recent meta-analysis showed that each one-point increase in CFS is associated with a 12% increase in mortality [39]. Therefore, it should be considered that mildly frail older adults may still have enough intrinsic capacity to withstand the stressors of hospitalization and make a good recovery; in patients at intermediate risk, an individualized evaluation is necessary.

Unfortunately, an internet-based survey showed that the main reason to exclude patients from ICU care was an individual decision by an intensivist, whilst comorbidity scores, such as CFS, were not used by the majority of clinicians [40]. The allocation of patients based only on age may generate ethical concerns, and age should not be the only determining factor in ICU triage decisions.

Efficacy of therapy specifically directed against SARS-COV-2

Some therapeutic strategies may have peculiar effects and are usually associated with increased risk of side effects in elderly patients. A recent study including patients with a median age of 69 years suggests that remdesivir is efficacious in preventing the progression of disease if administered within 5 days from the onset of symptoms [41]. Remdesivir demonstrated good safety in patients >80 years old [42], but some conditions, such as renal kidney disease, may represent common contraindications to use of this antiviral in elderly patients [43]. Although studies on the convalescent plasma against SARS-CoV-2 in adult patients are not fully conclusive [44], an RCT demonstrated that early administration of high-titre convalescent plasma in mildly ill older adults reduced the progression of COVID-19 [45]. Monoclonal antibodies (mAbs) showed efficacy in reducing the risk of disease progression and death and are now recommended in both outpatients and hospitalized patients with negative serology [46]. Although mAbs represent a promising therapeutic option, no data in elderly patients are available. Of note, some are not efficient against new variants (i.e. casirivimab/imdevimab is effective against Delta but loses its effectiveness against Omicron, unlike sotrovimab) [47].

Dexamethasone has been established as the standard of care in patients with severe COVID-19, but data in the elderly are controversial. The RECOVERY trial showed no effect of dexamethasone in the subgroup of patients >70 years of age [48]. Moreover, a secondary analysis of the COVIP study conducted in critically ill elderly patients with COVID-19 found an independent association of steroid use with increased mortality [49]. Conversely, corticosteroids were associated with a significant increase in overall survival at day 14 in patients aged >80 years hospitalized for severe COVID-19 in a recent study conducted in 36 hospitals in France and Luxembourg [50]. Hyperglycaemia is a potentially dangerous effect of steroid therapy and may be associated with poor outcome [51]. The available data suggest using steroids according to disease severity and comorbidities, with strict monitoring of potential adverse effects in the elderly.

Anticytokine antibodies such as tocilizumab were demonstrated to be an effective and safe therapeutic option in elderly patients with severe COVID-19, also in combination with steroids [52]. However, elderly patients treated with these drugs should be carefully monitored during the postdischarge phase because of a higher vulnerability to superinfections [53]. The dosage of low-molecular-weight heparin should be balanced according to the individual risk of bleeding in these patients [54]. Finally, antibiotic therapy should not be systematically prescribed on admission as initial bacterial pulmonary coinfections are rare. A study in elderly patients with COVID-19 pneumonia showed that early antibiotic treatment was not associated with decreased in-hospital mortality [55].

The lack of knowledge about the efficacy and safety of these treatments in elderly patients is also a consequence of their

Table 2
Potential reasons explaining the higher risk of poor outcomes in elderly patients with COVID-19

Factors	Consequences
Comorbidities	• Higher risk of mortality in COVID-19 patients with multiple comorbidities. • Limited access to treatments (remdesivir, immunosuppressants). • Risk of decompensated underlying disease after start of treatments (e.g. steroids in patients with diabetes mellitus).
Ageing	• Dysregulation of immune function: T-cell polarization and immune cell gene expression signature shifts toward an inflammatory type, increasing the cytokine storm and the risk of severe COVID-19. • Poor nutritional status may lead to alterations in the innate and adaptive immune systems, resulting in worse outcomes in elderly patients with COVID-19.
Atypical clinical presentation	• Delay in diagnosis and hospital admission. • Delirium associated with high risk of poor outcome.
Exclusion of elderly patients from ICU	• Limited access to noninvasive ventilation and intensive care.
Underrepresentation of elderly in RCTs	• Limited data about efficacy and safety of therapeutic options in elderly patients.

ICU, intensive care unit; RCT, randomized clinical trial.

underrepresentation in clinical trials [56]. Major barriers for their inclusion in clinical trials are the comorbidities and cognitive disorders highly prevalent in these patients.

Efficacy of vaccines

There is general consensus that the elderly represent a high-risk group that should be offered vaccination with priority. However, compared to younger individuals, antibody response after vaccination is generally lower because of a gradual deterioration of the immune system with age, and neutralizing antibody immune response after vaccination declines more precipitously in elderly individuals [57]. Thus, the following knowledge gaps exist in vaccination in elderly individuals:

1. The efficacy of vaccines in elderly compared to younger adults, especially against VOCs;
2. The durability of immune response after a booster dose of vaccine; and
3. The need for further booster doses.

With regard to the efficacy of vaccination in elderly patients, contrasting data emerged from the literature (Table 3) [58–63]. Phase II and III studies are limited by small sample sizes, exclusion of older people with frailty, and a relatively short follow-up. Real-world data from LTCF residents confirmed that mRNA vaccines had an estimated effectiveness of 71%, 88%, and 97% against SARS-CoV-2 infection, COVID-19 hospitalization, and death, respectively [64]. More specifically, the proportion of vaccinated patients with SARS-CoV-2 infection from the total number of infected patients was 292 of 8379 (3.5%), the proportion of vaccinated patients who were hospitalized from the total number of patients with COVID-19 who were hospitalized was 49 of 2509 (2%), and the proportion of vaccinated patients with COVID-19 who died compared with the total number of patients with COVID-19 who died was 16 of 1602 (1%).

However, a recent study showed a nonlinear relationship between age and immune response after the BNT162b2 vaccine, with a marked drop around the age of 80 years [57]. After the first dose, the geometric mean neutralization titre was lower in participants aged ≥80 years than in younger individuals (48.2 vs 104.1; $p = 0.004$). When individuals aged 80 years or more were tested between 3 and 12 weeks after their first dose, around half showed no evidence of neutralization [57]. Moreover, compared to the latter, patients ≥80 years old had a lower neutralizing activity to P.1 and B.1.1.7 variants [57].

In a study from Israel involving participants ≥60 years old, the rates of confirmed COVID-19 and severe illness were substantially lower (by a factor of 11.3% and 19.5%, respectively) among those who received a third booster dose of the BNT162b2 vaccine compared to the nonbooster group [65]. Current data suggest efficacy of mRNA-based COVID-19 vaccine boosters against the B.1.1.529 variant (Omicron) [66], but data on elderly are limited.

Long covid

Several studies confirmed the presence of persistent symptoms after acute COVID-19, a condition known as long COVID, post-COVID, or long-haul COVID [67]. Long COVID in the elderly may include a huge spectrum of manifestations, ranging from cognitive

Table 3
Data from phase I–II and III studies on COVID-19 vaccines in the elderly

Vaccine (type)	Phase I and II studies in the elderly	Phase III inclusion criteria	Phase III exclusion criteria	Proportion of elderly in phase III	Limitations
Pfizer/BioNTech BNT162b2 (mRNA) [58,61]	Phase I clinical study showed that the GMT after the second dose was 149 in patients 65–85 y old	Adults ≥16 y old Healthy or with stable medical conditions	Immunosuppressive therapy, or immunocompromising condition	42% ≥ 55 y old	Low sample size of phase I and II studies Underrepresentation of elderly and patients with frailty
Moderna mRNA-1273 (mRNA) [60,62]	Phase II clinical study in patients >55 yold showed that antibody response of elderly was similar to that observed in younger people	Adults ≥18 y old Increased risk of SARS-CoV-2 infection	Immunosuppressive therapy, or immunocompromising condition	24.8% ≥ 65 y old	Relatively short follow-up No data about VOCs
AstraZeneca AZD-1222 (adenovirus vector) [59,63]	Analysis of a phase II study showed that neutralizing antibody titres were similar across all age groups	Adults ≥18 y old Increased risk of SARS-CoV-2 infection Healthy or stable medical condition	Immunosuppressive or immunodeficient state Significant disease	22.4% ≥ 65 y old	

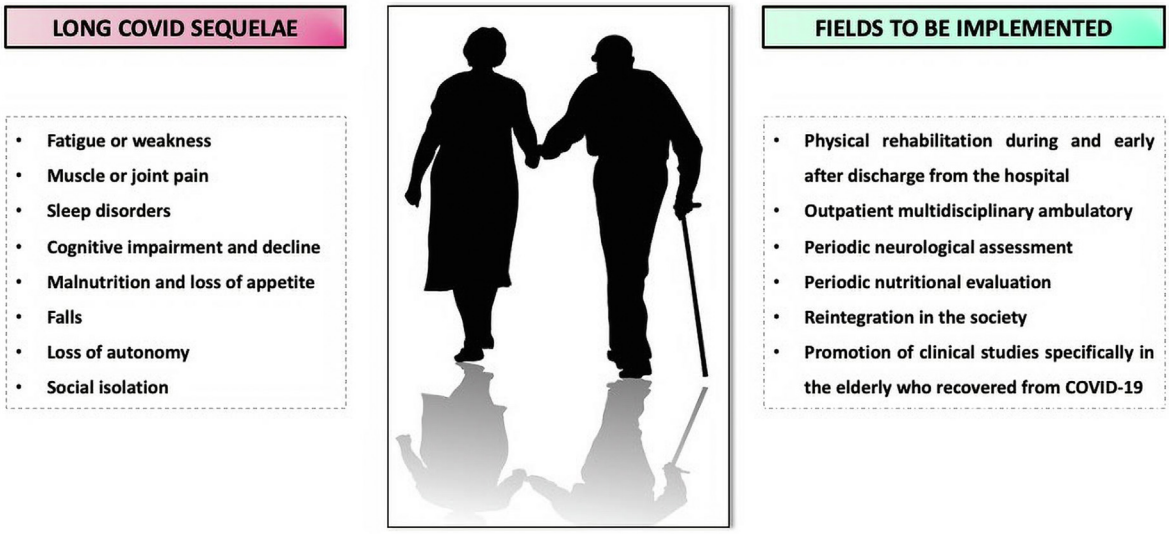

Fig. 1. Long COVID sequelae frequently reported in the elderly and actions to be implemented.

decline to altered nutritional status (Fig. 1). In a large observational study, 76% (1265/1655) of patients reported long COVID symptoms [67]. In another study, 1095 of 2433 (45%) reported at least one symptom at 1-year follow-up, and older age was one of the strongest risk factors for reporting at least three symptoms [68]. Of note, 83% (137/165) of recovered elderly patients reported at least one persistent symptom, with fatigue as the most prevalent [69]. An increased risk of long-term cognitive decline after COVID-19 has been described in elderly individuals, particularly in patients recovered from severe COVID-19, among whom 59% (141/238) reported cognitive decline [70].

Some aspects of COVID-19 sequelae in elderly patients remain unknown, with ongoing studies evaluating the decline of respiratory function 1 year or more after COVID-19 pneumonia and changes in the functional status of elderly patients with COVID-19 after discharge from the ICU.

Implication for patient management and future research

Management of elderly patients with COVID-19 is becoming increasingly diverse and complex, in relation to the spread of VOC, reduced vaccine response, and availability of early immunotherapy and new antivirals. Available data are sparse and not sufficient to delineate a tailored management of elderly patients with COVID-19. Importantly, there are few and contrasting data on the efficacy and safety of treatments currently used against COVID-19 in this special population. Although our understanding is still evolving, some treatments currently used against COVID-19, such as steroids, have a high risk of side effects in elderly patients; alternative strategies, including early immunotherapy (e.g. mAbs) and anticytokine antibodies (e.g. tocilizumab), should be preferred in mild-to-moderate and severe COVID-19, respectively. Occurrence of adverse events should be carefully monitored in these patients.

Because this is not a systematic review, some limitations should be acknowledged. The determination of which studies to include and the conclusions may be subjective; no assessment of the quality of evidences has been performed; and selection bias and subjective weighting of the included studies may have occurred.

Future research should focus on specific therapeutic approaches and factors associated with survival to better allocate patients, maximizing their opportunity of clinical success. A more effective regulatory framework to ensure equitable inclusion of elderly patients in research is clearly needed. For high-quality trials, some authors have brought to light the need for creating a national network of skilled facilities engaged in interventional clinical trials. Logistic challenges may be overcome, implementing dedicated skilled staff and facilitating the consent procedures and methods for obtaining biospecimen and clinical data.

Transparency declaration

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Author contributions

VP and GT revised the literature and wrote the manuscript; MF revised the final manuscript and supervised the activities.

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