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Review Article

Manifestations and Management of COVID-19 in Older Patients with Frailty

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SUMMARY

Frailty is a major prognostic factor for COVID-19 in older individuals, associated with an increased risk of in-hospital mortality. This study broadly explores the pathophysiology, epidemiology, and clinical features of COVID-19 in older patients, as well as the associations of frailty with the progression and management of COVID-19. During the COVID-19 pandemic, older individuals consistently manifested severe symptoms. Comprehensive geriatric assessments can help identify the risk factors for frailty. Physical limitations may increase the risk of COVID-19-related mortality in older individuals with frailty. Immunosenescence or inflammaging are potential mechanisms underlying older individuals' increased susceptibility to COVID-19 and mortality risks. Vaccine efficacy varies across older individuals with frailty. COVID-19 can be potentially treated using corticosteroids and antiviral agents such as remdesivir, nirmatrelvir/ritonavir, and molnupiravir, as well as immunomodulatory agents such as baricitinib and tocilizumab. However, most reports of clinical trials on corticosteroids and new antiviral agents did not specifically address older patients, further limiting the discussion on frailty. Thorough clinical assessments and effective communication with healthcare providers aid in timely detection of disease worsening. In conclusion, our study underscores the complex interplay between age, frailty, and COVID-19 outcomes, but we refrain from making speculative assertions due to insufficient evidence. Further studies are necessary to optimize the outcomes of COVID-19 in individuals with frailty.

1. Introduction

Coronavirus disease 2019 (COVID-19) is an infectious disease caused by a coronavirus.[1] The World Health Organization (WHO) declared COVID-19 a pandemic in January 2020, till date, COVID-19 has resulted in approximately 6.9 million deaths worldwide.[2] The causative agent of COVID-19 is SARS-CoV-2, which is an enveloped virus with a large, single-strand, positive RNA genome. Generally, the SARS-CoV-2 viral transmission works through the inhalation of small respiratory droplets.[3] COVID-19 is associated with the risks of respiratory failure, pneumonia, multiple organ failure, and death, particularly among older adults. This review was conducted to summarize the pathophysiology, epidemiology, and clinical features of COVID-19 in older patients and to highlight effective interventions or treatment options for reducing the rates of complications and mortality in this population.

2. Method

All candidate studies were initially identified by conducting a literature review of online databases, namely PubMed, Cochrane Library, and Embase, from late 2019 to December 31, 2023. The following search terms were used in various combinations: 'Frailty', 'Elderly', 'older adult', 'geriatric', 'Tocilizumab', 'SARS-CoV-2', 'corona-virus', 'nCoV', 'pneumonia', 'corona-virus', and 'COVID-19'.

For studies involving vaccines or agents, only pivotal studies were included, excluding smaller scale, single-arm, or single-country studies. Studies lacking a control group, not reporting on comorbidities or adverse outcomes, or not published in English were also excluded. A detailed flowchart (Figure 1) illustrates the inclusion and exclusion criteria used in the review process.

3. Frailty increases the risk of COVID-19-related mortality

Frailty is a heterogeneous syndrome characterized by increased vulnerability across health domains, leading to adverse health outcomes.[4] Risk factors for frailty include malnutrition, insufficient physical activity, comorbidities, and polypharmacy; these risk factors result in adverse clinical outcomes in individuals with frailty.[5] The symptoms of frailty include overall weakness, fatigue, slow gait, poor balance, reduced physical activity, cognitive impairment, and weight loss.[6] Frailty has been diagnosed in approximately 15% and 25% of all individuals aged ≥ 65 years and those aged > 85 years, respectively.[7]

The risk of in-hospital mortality of COVID-19 was approximately 51% higher in older individuals with frailty than in those without frailty.[8] Since the onset of the pandemic, the older population has consistently manifested severe COVID-19 symptoms, because of age-related decline in immune function, older individuals are at substantially elevated risks of contracting and succumbing to COVID-19. A population-based study reported a COVID-19 case fatality rate of 24% among older individuals and projected that this rate would in-

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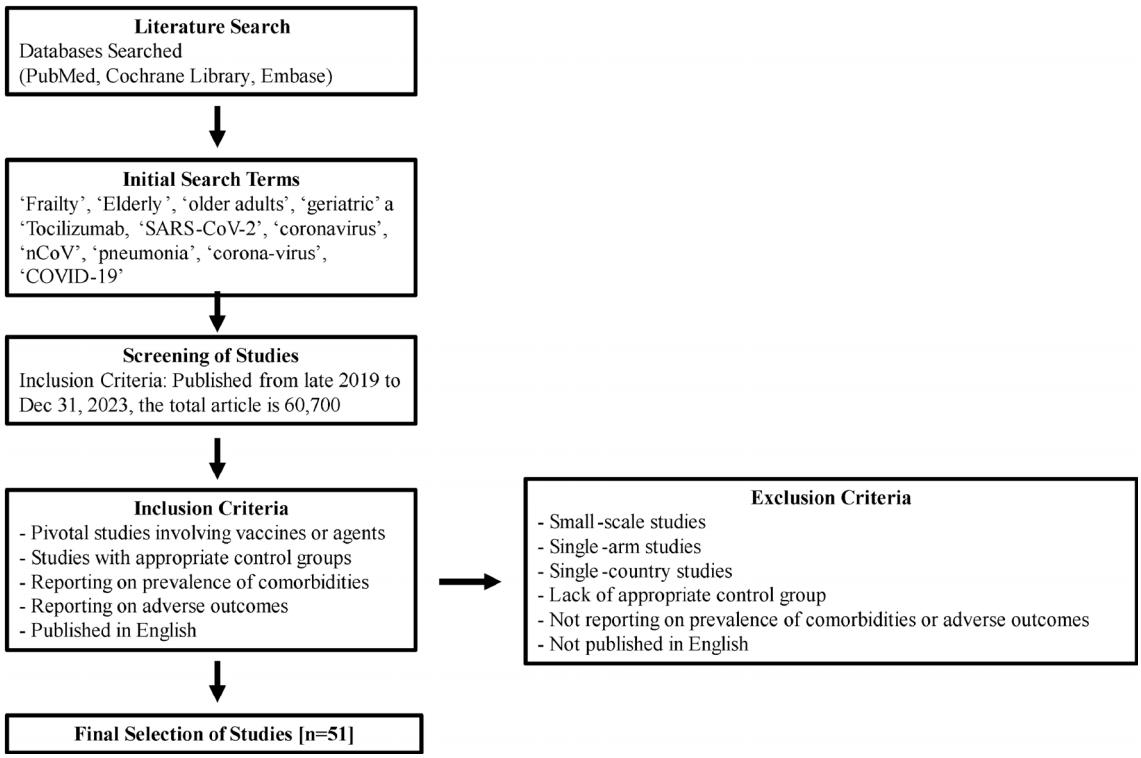

Figure 1. Flowchart of research participants. This flowchart outlines the selection process of studies, including identification, screening, and final inclusion based on predefined criteria.

crease by 70% in individuals aged ≥ 85 years.[9] A systematic review revealed a significant association between frailty and COVID-19-related the parameters, these studies have indicated strong associations between frailty and high COVID-19-related mortality risk.[10]

The severity of COVID-19 impacts the long-term functionality of older survivors. Post-acute sequelae, or "long COVID," cause chronic symptoms affecting daily life and may lead to frailty. In a retrospective study of hospitalized patients aged 65 and older, about 9% developed long COVID.[11]

4. Assessment of frailty in patients with COVID-19

Comprehensive geriatric assessment is a multidisciplinary evaluation method for assessing various domains in diverse patients; these domains include functional capacity; physical, cognitive, and mental health; and other factors such as financial status, social support, and environmental factors. There are 2 models are primarily used for this purpose: the Fried phenotype model[12] and the cumulative deficit model or frailty index.[13] The Fried phenotype model categorizes frailty based on five components: weight loss, fatigue, poor grip strength, low physical activity, and slow walking speed.[12] The cumulative deficit model includes symptoms, signs, disabilities, and comorbidities in frailty assessment. Certain methods are particularly useful for evaluating frailty in patients with COVID-19; among these, the Clinical Frailty Scale is of utmost importance.[13] A meta-analysis of fifteen studies identified frailty to be an independent predictor of COVID-19-related mortality.[14]

5. Pathophysiology of COVID-19 in older patients

Several hypothetical models have been proposed to explain the differences between older and younger individuals in terms of COVID-19 susceptibility and mortality risks. Potential mechanisms include immunosenescence and inflammaging.

5.1. Immunosenescence

Immunosenescence, characterized by alterations in both innate and adaptive immunity with age, is a significant risk factor for most age-related diseases. It reduces the phagocytic capacity of neutrophils and the functions of macrophages, including microbicidal activity, phagocytic function, and cytotoxicity of immune cells. For adaptive immunity, aging is associated with reductions in the generation of naïve B cells and their responsiveness to new antigens. Aging diminishes the naïve T-cell receptor repertoire, making it difficult for dendritic cells (DCs) to access SARS-CoV-2-specific T cells, thereby delaying immune responses. With aging, levels of cytokines such as IFN-γ, IL-2, and TNF-α increase in CD8+ cells; additionally, levels of IL-4, IL-6, and IL-10, which are strongly associated with humoral immunity and cytokine release syndrome, also increase.[15,16]

5.2. Inflammaging

In the older population, the immune system is consistently overactive but less efficient and specific, which may explain the severe outcomes of SARS-CoV-2 infection in older adults. Severe COVID-19 symptoms are correlated with reduced type I IFN responses, exacerbated by age-related defects in IFN signaling and fewer plasmacytoid DCs in severe cases.[17] Aging reduces the ability of plasmacytoid DCs to produce type I IFN and desensitizes immune signaling. These signals activate the nuclear factor-κB pathway, promoting the production of proinflammatory cytokines. Damage-associated molecular patterns associated with aging and viral infections lead to the activation of inflammasomes, inducing cytokine production and cell death.[18] The immune environment predisposes older individuals to a prothrombotic state, creating a feed-forward loop with inflammation. This exacerbates the hyperinflammatory response to severe COVID-19 and contributes to its devastating outcomes.

6. Vaccination of older individuals against COVID-19

Vaccination campaigns against SARS-CoV-2 have markedly reduced mortality and severe COVID-19 worldwide.[19] However, vaccination outcomes remain uncertain in older individuals, particularly those with frailty. Very few studies have focused on the efficacy of SARS-CoV-2 vaccines in older individuals with frailty.[20] Real-world evidence suggests that some older individuals require hospitalization for severe COVID-19 despite vaccination, posing a considerable risk of mortality.[21] In a study involving 136,493 veterans, vaccine efficacy against symptomatic infection was 71.8%, varying with the degree of frailty. Efficacy was lower in the frail group and decreased with age, declining to 57.3% over five months.[22] The study indicated significant reductions in infection rates and mortality among frail older adults following vaccination.[23] It also found frailty progression higher in unvaccinated older adults, underscoring vaccination's importance.[24] Additionally, vaccination improved mental health and allowed for a return to pre-pandemic activities.[25] The previous studies emphasized the role of vaccination and physical activity in mitigating frailty and improving health outcomes.[26] In a trial of SARS-CoV-2 mRNA vaccination involving 82 older adults, aging and frailty were associated with reduced post-vaccination antibody responses in males but not females.[27] These findings highlight the need for targeted vaccination strategies to protect frail older individuals from severe COVID-19 outcomes.

7. Treatment of older patients with COVID-19

Since the onset of the pandemic, researchers have been striving to devise strategies to reduce the risks of clinical deterioration, hospitalization, and mortality in patients with COVID-19. Before effective vaccination campaigns, clinicians resorted to emergency assessments and existing medications to improve the outcomes of COVID-19, particularly in the older population.

7.1. Corticosteroids

The RECOVERY trial and various other trials have endorsed corticosteroid therapy, particularly dexamethasone, educing mortality among patients with severe COVID-19 requiring oxygen support.[28] Despite these endorsements, the effects of corticosteroid therapy on COVID-19 mortality remain debatable. A pooled analysis involving a total of 96852 patients revealed that mortality was significantly higher among patients receiving corticosteroid intervention than among control patients. Although methylprednisolone significantly increased mortality, the effects of dexamethasone on mortality were nonsignificant.[29] These findings imply an unfavorable prognosis in patients receiving corticosteroid therapy for COVID-19. Potential causes could include a delay in clearing the virus and secondary infections resulting from the early-stage use of high doses of corticosteroids.[29] Notably, these studies did not perform the stratified analysis to consider the age, nor frailty. Therefore, there is no evidence to prove the benefits or disadvantages in the use of steroids for the older patients with frailty.

7.2. Antiviral agents

7.2.1. Remdesivir

COVID-19 trials provided mixed results for remdesivir, an agent that inhibits SARS-CoV-2 RNA polymerase.[30] Initial trials indicated rapid recovery but no survival benefits.[31] Large trials (Solidarity and DisCoVeRy) including hospitalized patients revealed no clear advantages, although some cohorts exhibited improved clinical outcomes.[32] Another study involving high-risk outpatients reported an 87% reduction in the risk of mortality or hospitalization in patients receiving a 3-day course of remdesivir.[33] Although this agent has been approved for hospitalized patients with specific oxygen requirements, its efficacy and safety in older adults with moderate to severe COVID-19 are inconsistent.

A Spanish retrospective cohort study included unvaccinated older patients (≥ 80 years) with COVID-19 to investigate the efficacy of remdesivir.[34] Compared with patients who did not receive remdesivir, those who received this agent were slightly young, had relatively few hospitalizations, and exhibited low dependency levels, dementia prevalence, and comorbidity scores. Both groups exhibited similar oxygen saturation levels and tachypnea prevalence. Patients who received remdesivir exhibited more bilateral infiltrates on chest X-ray, had lower D-dimer levels, and received systemic corticosteroids and tocilizumab more frequently but beta-lactams and macrolides less frequently than did those who did not receive this agent. Furthermore, the high-flow nasal cannula oxygen requirement was higher among patients who received remdesivir than among those who did not.[34]

7.2.2. Paxlovid™ (nirmatrelvir/ritonavir) and Lagevrio Paxlovid™ (Molnupiravir)

Two additional agents have been approved for treating severe disease in patients with COVID-19 who are not hospitalized: Paxlovid Paxlovid™ (nirmatrelvir/ritonavir) and Lagevrio Paxlovid™ (molnupiravir). Both agents are suitable for patients not requiring supplemental oxygen therapy, and they should be administered within 5 days of symptom onset. A systematic review of one interventional study and three observational studies reported the efficacy of nirmatrelvir/ritonavir for the treatment of COVID-19.[35] Evidence-based RCT have indicated that the oral administration of nirmatrelvir/ritonavir within 5 days of symptom onset reduced the risks of all-cause mortality and hospitalization, affirming its safety. Patients receiving nirmatrelvir/ritonavir exhibited significantly reduced HRs for all-cause mortality and hospitalization. Relevant cohort studies have indicated the efficacy of nirmatrelvir/ritonavir in reducing the risks of mortality, hospitalization, and disease progression among hospitalized or non-hospitalized patients aged > 65 years.[1,36] This agent potentially improves clinical outcomes such as oxygen therapy requirement and disease progression but does not significantly affect hospital stay, mechanical ventilation, or intensive care unit admission. Unlike randomized controlled trials, observational studies have demonstrated the benefits of nirmatrelvir/ritonavir for older individuals (> 65 years), but not for younger individuals (< 65 years).[37] This discrepancy highlights the need for exercising caution when prescribing nirmatrelvir/ritonavir to patients < 65 years. Observational evidence supports the early administration of nirmatrelvir/ritonavir in high-risk patients with COVID-19; this recommendation is based on the relevant results for different ethnic groups infected with different Omicron variants.[38]

The phase 3 MOVe-OUT trial confirmed the efficacy of molnupiravir in non-hospitalized, symptomatic, high-risk patients with COVID-19.[39] A Japanese retrospective study assessed the efficacy of molnupiravir in 102 patients with COVID-19 (46.1% aged ≥ 80 years [older group] and 53.9% aged < 80 years [younger group]).[40] Most patients (95.1%) were initially hospitalized. The prevalence of moderate disease was higher in the older group than in the younger group. Both groups were similar in terms of comorbidities, vaccination history, and disease status. Concomitant medication use, particularly corticosteroid use, was more prevalent in the older group

than in the younger group. The rates of medication discontinuation due to disease exacerbation or dysgeusia were similar between the groups. Adverse events occurred in 38.2% of all patients; no age-related differences were noted. The study highlight the safety and efficacy of molnupiravir in patients with COVID-19, revealing similar tolerability levels across age groups despite variations in the frequencies of concomitant medications.[40] Overall, these trials on antiviral agents involving older patients did not consider the frailty status.

7.3. Immunomodulatory therapy

In addition to factors such as age, sex, and obesity, the irregulated of immune status, particularly elevated levels of cytokines of IL-1, IL-6, and TNF-α, in patients with SARS-CoV-2 infection increase the risk of mortality, necessitating urgent intervention to prevent severe outcomes. Therefore, immunotherapies targeting IL-6, IL-1, and TNF-α must be explored to mitigate the increased inflammatory response in patients with SARS-CoV-2 infection, thereby facilitating virus management.[41]

7.3.1. Baricitinib

Baricitinib belongs to a class of agent known as inhibitors of JAK, a surface receptors of various cytokines and growth factors linked to inflammation and immune responses.[42] Among several JAK inhibitors, only baricitinib have approved to treat COVID-19.[43] In the ACTT-2 trial, combining baricitinib with remdesivir increased the rate of recovery by 1 day (from 7 to 8 days) compared with the rate noted for remdesivir alone; nonetheless, slight overall improvements, although nonsignificant, were observed by day 15 in patients receiving the combination therapy.[44] Subsequent studies, including the COV-BARRIER trial, have corroborated the benefits of baricitinib when used in conjunction with standard treatment, particularly corticosteroids.[45] The COV-BARRIER trial revealed that although baricitinib did not influence overall disease progression (defined as an increase in the requirement of oxygen therapy such as mechanical ventilation), it reduced the rate of 28-day all-cause mortality.[45]

7.3.2. Tocilizumab

As an IL-6 receptor inhibitor, Tocilizumab was widely used in the United States after 2021 to prevent severe complications and death post COVID-19 infection, although its beneficial understanding among COVID-19 patients at that time was limited.[46] The case-control retrospective studies reported that Tocilizumab reduces mortality rates in most COVID-19 patients with ARDS and could potentially improve survival outcomes.[47] In patients with severe COVID-19 pneumonia, the use of Tocilizumab has been been proven to be associated with a reduced risk of death requiring oxygen therapy.[48] Consequently, after 2021, the safety and efficacy of Tocilizumab have been extensively evaluated among different groups of COVID-19 patients in various stages of infection. The most notable randomized controlled trials include the groundbreaking RECOVERY trial and EMPACTA trial.[49,50] These trials showed vastly different results in the efficacy of Tocilizumab among patients with varying disease severity. Therefore, these conflicting outcomes may be due to the timing of Tocilizumab administration affecting the observed clinical outcomes. The available clinical evidence collectively suggests that Tocilizumab is a promising treatment for COVID-19 hospitalized patients with disease progression and high oxygen requirements. However, there is currently no necessity for widespread use of Tocilizumab in mild disease or in patients requiring long-term invasive mechanical ventilation.[50] In a multicenter retrospective study on older adults found lower in-hospital deaths with Tocilizumab treatment compared to those untreated. While 30-day mortality did not show significant difference, in-hospital deaths decreased significantly with Tocilizumab. Tocilizumab also reduced respiratory failure needing ventilation in COVID-19 ICU patients.[51] This is the only study of immunomodulatory therapy focusing on older patients, frailty was not mentioned.

8. Conclusion

Frailty significantly affects the immune response and outcomes of COVID-19 in older adults. Vaccination is crucial but less effective in those with frailty or comorbidities, leaving them vulnerable to severe illness and hospitalization. Current treatments carefully balance immunosuppressants' safety and efficacy, especially for unvaccinated and elderly patients. However, most reports of clinical trials on corticosteroids, antiviral agents and immunomodulatory therapy did not specifically address older patients, further limiting the discussion on frailty, and we refrain from making speculative assertions without sufficient evidence. The limitations include a focus on pivotal studies, potential publication bias, variability in defining risk factors, and a bias towards severely ill hospitalized populations. Since these treatments are still being used as first-line therapies for this vulnerable group in practical settings specific trials targeting older patients with frailty are essential to evaluate COVID-19 effects on this vulnerable group. Comprehensive assessments and tailored interventions are necessary to improve outcomes, given the emerging understanding of frailty mechanisms in COVID-19.

Declaration of any potential financial and nonfinancial conflicts of interest

None declared. The authors do not have an actual or potential conflict of interest and do not have any interest to declare with regard to this study.

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