


# Frailty in Elderly Patients with Covid-19: A Narrative Review

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## Abstract

**Introduction:** The SARS CoV-2 pandemic still generates a very high number of affected patients and a significant mortality rate. It is essential to establish objective criteria to stratify COVID-19 death risk. Frailty has been identified as a potential determinant of increased vulnerability in older adults affected by COVID-19, because it may suggest alterations of physical performance and functional autonomy.

**Methods:** We have conducted a narrative review of the literature on the evidences regarding COVID-19 and the frailty condition. Thirteen observational studies were included.

**Conclusion:** Data emerging from the studies indicate that older COVID-19 patients with a frailty condition have an increased risk of mortality compared with non-frail patients, and this association is independent of other clinical and demographic factors. A frailty evaluation is required to help clinicians to better stratify the overall risk of death for older patients with COVID-19.

## Keywords

older adults, frailty, COVID-19, multi-morbidity

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## Introduction

Although vaccination campaigns have already started and are proceeding quickly in many countries around the world, the SARS CoV-2 pandemic, with the consequent respiratory illness named COVID-19, still generates a very high number of affected patients and a significant mortality rate.

Every day the number of new positive cases is increasing and so does the number of hospitalizations (WHO Coronavirus Disease Dashboard).

Several countries are facing new waves caused by variants, high number of unvaccinated subjects, and increased incidence of breakthrough infections in vaccinated people.

COVID-19 may present either as an asymptomatic or paucisymptomatic disease (with non-severe symptoms as asthenia, fever, diarrhea, anosmia, ageusia, etc.) up to severe pneumonia. Respiratory failure may require mechanical ventilation in 12% of patients (Grasselli et al., 2020; Guan et al., 2020).

The high number of patients in need of medical assistance requires clear and objective criteria to stratify COVID-19 death risk.

In Italy, one of the most affected countries, the mortality rate and the number of deaths are still particularly high

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and Open Access pages (<https://us.sagepub.com/en-us/nam/open-access-at-sage>).

(<http://www.salute.gov.it/portale/nuovocoronavirus>). The mortality rate is higher in older adults, particularly in those with pre-existing diseases (Onder et al., 2020).

In this situation, the attention of researchers was directed to the impact of age and multi-morbidity on the prognosis of these patients. It was subsequently evident that these conditions cannot comprehensively predict the adverse outcomes observed in older COVID-19 patients because these are not relevant factors when not associated to other conditions (e.g., severe dementia, ADL impairment, fever during hospitalization, initial increased CRP or lactate dehydrogenase, and low oxygen saturation at emergency department admission) (Becerra-Muñoz et al., 2021; Blagosklonny, 2020; Covino et al., 2020; Covino, De Matteis et al., 2021; Covino, Russo et al., 2021; Grasselli et al., 2020; Hwang et al., 2020; Zuccaro et al., 2021; Mueller et al., 2020; Weiss & Murdoch, 2020).

Looking for other explanations to justify what was described, the frailty condition has been identified as a potential determinant of increased vulnerability.

Frailty is defined as a condition characterized by a progressive decline in physiologic function resulting in a reduced ability to respond to stress factors. This is caused by a decline in homeostatic mechanisms, which results in an increased risk of adverse events (Vermeiren et al., 2016). This condition becomes more evident with advanced age and additional comorbidities. Frailty synergistically acts with both age and comorbidities in determining the state of the complexity of the specific patient. The increased vulnerability associated with the frailty condition is partially explained by the fact that in frailty patients' conditions that favor negative outcomes do coexist. Among these, we can find deterioration in the physiological capacity of organs and systems, cognitive impairment, malnutrition, and functional impedance. Moreover, frailty implicates a condition of chronic inflammation (Soysal et al., 2016) with consequent release of proinflammatory cytokines and it has now been made clear that cytokines role is decisive in determining lung damage in COVID-19, increasing the risk of mortality (Fara et al., 2020). Finally, it is important to emphasize how the frailty condition impairs patients' capability to tolerate high-invasive treatments such as mechanical ventilation, extracorporeal circulation or drugs administration with consequent risk of adverse events and interactions (Muscedere et al., 2017).

In this context, frailty was found to be a possible independent predictor of death in hospitalized patients with different acute conditions as well as COVID-19 (Aliberti et al., 2021; De Smet et al., 2020; Laosa et al., 2020; Pranata et al., n.d.; Zhang et al., 2021).

This narrative review aims to summarize the available evidences on the assessment of frailty in COVID-19 geriatric patients.

## Materials and Methods

### Search strategy

We have conducted a narrative review of the literature on the evidences regarding COVID-19 and the frailty condition.

Sources were identified using PubMed and Web of Science through a comprehensive search using key terms.

We used a combination of keywords and medical subject headings (MeSH). The search strategy was (Frail or Frailty or Frail condition [MeSH]) and (“COVID-19” OR “Coronavirus Infection” OR “Coronavirus Infection Disease 2019” OR Coronavirus [MeSH]) and (mortality or death or survival).

### Inclusion and exclusion criteria

We considered all observational studies describing the associations between frailty and COVID-19. We excluded comments, reviews, conferences, correspondence, editorials, letters to the editor, and case reports. Only studies published in English language were selected for evaluation. We also excluded studies with fewer than two hundred patients (as a general criterion in order to ensure mid-to-large number of patients reports), studies concerning not purely geriatric ( $\geq 65$  y.o.) population and studies in which the findings did not include a compatible age subgroup. No full text available was not an exclusion criterion.

### Study selection process

Two reviewers performed the literature search, selecting titles and abstracts before reviewing the full texts. Subsequently, some studies were excluded either because they were duplicates or did not meet the established inclusion criteria. Other reviewers were consulted in the event of disagreements between reviewers.

### Study characteristics

Last search was performed in November 2021. We found 29 articles. Thirteen studies were included in terms of the predefined inclusion criteria. We excluded 16 articles (3 because of small study population, 6 because of the age range, 3 because of non-English language, and 4 because of non-related objectives).

Table 1 shows the main characteristics of included studies.

All the studies date from January 2020—when the pandemic began—to November 2021.

Regarding the study design, we found six prospective cohort studies (Aw et al., 2020; Chinnadurai et al., 2020; Hägg et al., 2020; Kundi et al., 2020; Miles et al., 2020; Tehrani et al., 2021) and seven retrospective (Bielza et al., 2021; Blomaard et al., 2021; Brill et al., 2020; Covino, De Matteis et al., 2021; Covino, Russo et al., 2021; Darvall et al., 2019; Mendes et al., 2020; Owen et al., 2021). The largest sample size was in Turkey (Kundi et al., 2020), with 18,234 patients, and the smallest was in the UK (Chinnadurai et al., 2020), with 215 patients. To assess frailty, 12 studies used the clinical frailty scale (CFS) (Hägg et al., 2020; Aw et al., 2020; Miles et al., 2020; Chinnadurai et al., 2020; Tehrani et al., 2021; (Owen et al., 2021; Bielza et al., 2021; Mendes et al.,

**Table 1.** Main characteristics of the reviewed studies.

Authors	Year	Study Design	NO. Of Patients	Age	Frailty Criteria	Setting	Findings	Conclusions
Kundi	2020	PCS	18,234	≥65	HFRS	Hospital	In-hospital mortality	The HFRS is a standardized tool for an effective grading of frailty in patients in COVID-19
Hägg	2020	PCS	250	≥65	CFSHFRS	Hospital	In-hospital mortality	The level of frailty is a useful predictor of short-term COVID-19 outcomes in geriatric patients
Aw	2020	PCS	677	≥65	CFS	Hospital	In-hospital mortality	Frailty is associated with all-cause mortality risk in older inpatients with COVID-19
Owen	2021	RCS	285	≥65	CFS	Hospital	In-hospital mortality	Frailty measured using the CFS appeared to make little incremental contribution to the hazard of dying in older people hospitalized with COVID-19 infection
Bielza	2021	RCS	630	≥70	CFS	Nursing home	30-day mortality	A severe form of the disease was associated with mortality, apart from the male sex, CFS ≥6, dementia, and dyspnea, whereas age and care setting were not
Mendes	2020	RCS	235	≥70	CFS	Hospital	In-hospital mortality	Non-survivors were more often frail
Blomaard	2021	RCS	1376	≥70	CFS	Hospital	In-hospital mortality	Frailty was independently associated with higher in-hospital mortality, even though COVID-19 patients with frailty presented earlier to the hospital with less severe symptoms
Covino	2021	RCS	729	≥80	CFS	Hospital	In-hospital mortality	An evaluation based on clinical severity, multi-morbidity, and frailty could effectively predict the clinical risk of in-hospital death for COVID-19 patients ≥80 years since ED admission
Darvall	2020	RCS	5607	≥65	CFS	ICU	In-hospital mortality and ICU bed days	Patients with severe and very severe frailty account for relatively few ICU bed days as a result of pneumonia, whilst adjusted mortality analysis indicated little difference in risk between patients in vulnerable, mild, and moderate frailty categories
Chinnadurai	2020	PCS	215	—	CFS	Hospital	In-hospital mortality	Older age and frailty are chief risk factors associated with mortality in COVID-19 patients hospitalized to an acute medical unit of a secondary level care
Tehrani	2021	PCS	255	≥20	CFS	Hospital	60-day mortality	In patients aged 65 years or older, CFS level was the strongest prognostic factor for death
Brill	2020	RCS	450	≥56	CFS	Hospital	In-hospital mortality	Patients who died had greater median frailty compared to survivors. Such difference was more evident among patients aged 80 or more
Miles	2020	PCS	377	≥70	CFS	Hospital	All-cause mortality	For frailty, differences in effect size were evident between cases and non-COVID-19 controls, with an interaction term suggesting that frailty is not a good discriminator of prognosis in COVID-19

Prospective cohort study (PCS); Retrospective cohort study (RCS); Clinical frailty scale (CFS); Hospital frailty risk score (HFRS); Intensive care unit (ICU); Emergency department (ED).

2020; Blomaard et al., 2021; Covino, Russo et al., 2021; Darvall et al., 2019; Brill et al., 2020), 2 studies used the hospital frailty risk score (HFRS) (Kundi et al., 2020; Hägg et al., 2020). In terms of AVG age, 10 studies had a geriatric population (≥65 y.o.) (Kundi et al., 2020; Hägg et al., 2020;

Aw et al., 2020; Miles et al., 2020; Owen et al., 2021; Bielza et al., 2021; Mendes et al., 2020; Blomaard et al., 2021; Covino, Russo et al., 2021; Darvall et al., 2019) while 3 studies had findings that include a compatible age subgroup (Chinnadurai et al., 2020; Tehrani et al., 2021; Brill et al., 2020).

Ten trials had in-hospital mortality as primary outcome (Kundi et al., 2020; Hägg et al., 2020; Aw et al., 2020; Chinnadurai et al., 2020; Owen et al., 2021; Mendes et al., 2020; Blomaard et al., 2021; Covino, Russo et al., 2021; Darvall et al., 2019; Brill et al., 2020), one trial had 30-day mortality (Bielza et al., 2021), one had 60-day mortality (Tehrani et al., 2021), and one had all causes of mortality (Miles et al., 2020).

Charlson Comorbidity Index was used for screening comorbidity in 2 studies (Hägg et al., 2020; Blomaard et al., 2021).

## Results

Studies evaluated conclude that mortality risk correlates significantly with frailty status, regardless of study design, country, or care setting.

The studies analyzed confirm that frailty seems to be associated with all causes of mortality in patients hospitalized with COVID-19 (Aw et al., 2020; Brill et al., 2020; Chinnadurai et al., 2020; Hägg et al., 2020; Kundi et al., 2020) and becomes the strongest prognostic factor in patients aged >65 (Tehrani et al., 2021; Blomaard et al., 2021). In some cases, CFS value was also associated with lower probability of home discharge (Hägg et al., 2020).

In some of these studies, frailty does not appear to be an independent condition, but appears to contribute, along with other factors, to the increased risk of mortality both in hospitalized patients (Owen et al., 2021; Mendes et al., 2020) and in patients residing in nursing homes (Bielza et al., 2021) (in which advanced age, comorbidities, and frailty often coexist).

In some cases, however, the analysis conducted showed that frailty may not be useful for stratification of prognosis in COVID-19 and different mechanisms may underlie pathways to death depending on pre-morbid frailty (Miles et al., 2020).

Regarding ICU bed days, it was registered, a little difference in risk between patients in vulnerable, mild, and moderate frailty categories. Therefore, CFS does not seem to be a determinant score for access to intensive care (Darvall et al., 2019).

The best prognostic confidence is obtained by combined risk stratification, associating frailty status with multi-morbidity status and disease severity (Aw et al., 2020; Covino, Russo, et al., 2021; Owen et al., 2021). This evaluation is effective for risk stratification since ED admission of hospitalized COVID-19 patients (Covino, Russo, et al., 2021).

## Discussion

The task force of the International Conference of Frailty and Sarcopenia Research (ICFSR) recommended to perform frailty screening using validated scales (Dent et al., 2019).

Guidelines have been published recommending the Clinical Frailty Scale as an assessment tool for COVID-19

patients (The National Institute for Health and Care Excellence [NICE]—COVID-19 rapid guideline: Managing COVID-19, 2021) in an attempt to stratify the risk of mortality in these patients and to implement interventions to prevent, when possible, the occurrence of complications related to hospitalization.

The Clinical Frailty Scale (Rockwood et al., 2005) is an easy and rapid but also sensitive and valid frailty assessment scale.

It quickly became apparent that age and comorbidity are correlated with adverse outcomes, but cannot comprehensively predict them if not associated to other conditions.

Consequently, frailty screening has been incorporated into the evaluation of these patients.

Performing a geriatric multidimensional assessment, especially in the emergency department, is rather difficult, as emergency physicians have to deal with the acute phase and the time available to them for a multidimensional assessment is limited. Moreover, the clinical complexity of the older patient is often due to the coexistence of multiple factors that make the patient frail, including functional and cognitive impairment, multi-morbidity, and polypharmacotherapy. Nevertheless, using a simple frailty scale such as the CFS, frailty could be effectively assessed even in the emergency department, ensuring an early frailty evaluation for all patients.

Several studies suggest that frailty is a key prognostic factor in the evolution of COVID-19 disease. So, although it could not be the sole prognostic factor for mortality, frailty assessment is crucial for patients  $\geq 65$  years, even in those affected by Covid-19, to better stratify the risk for the single patient and to allow a better overall assessment in terms of prognosis and therapeutic intervention.

## Study limitations

Although the trend of results is in favor of assessing frailty, all reviewed studies have some limitations. Since most studies used CFS, it could be necessary to evaluate if different frailty scales, or a more comprehensive frailty assessment led to identical prognostic results.

Moreover, since mortality was the most commonly considered outcome, we could not evaluate the effectiveness of frailty assessment for the prediction of different relevant outcomes such as effects of COVID-19 on quality of life, functional status, and frailty itself. It could be also interesting to evaluate the response to treatments, the tailored care and the allocation of available resources.

In addition, more research is needed to focus on possible correlation between the frailty condition and the manifestation of symptoms (which can be atypical in the older, comorbid, and frail patient) (Poco et al., 2021).

Moreover, although the importance of such screening seems clear, only observational studies have been conducted and there are no studies that clarify how knowing that the patient has a high risk of death can change the prognosis.

Finally, once the frailty patient has been identified, it is still unclear if that patient needs a protected discharge for the continuity of care, ensuring an appropriate follow-up and a dedicated cognitive-functional rehabilitation path.

## Conclusion

This systematic review summarizes the evidence of the impact of frailty on COVID-19 patients showing that adults  $\geq 65$  years with frailty have an increased risk of mortality compared with non-frail ones, and this association is independent of other clinical variables.

Frailty assessment may help clinicians to better stratify the risk of death for elderly patients with COVID-19. This allows the identification of patients deserving of an integrated multidimensional assessment that better reflects their complexity. Further studies are needed to better characterize the impact of frailty in COVID-19 patients, particularly regarding other outcomes and the effectiveness of a possible personalized approach to reduce mortality and long-term disability.

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