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Clinical Features of SARS-CoV-2 Infection in Older Adults



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KEYWORDS

- SARS-CoV-2 • Aged • Symptoms • Symptom clusters • Comorbidity • Frailty
- Mortality

KEY POINTS

- In older people, COVID-19 clinical presentation is extremely heterogeneous, especially the atypical symptoms, as delirium, which are more likely than in younger age classes.
- COVID-19 presenting symptoms are not simply influenced by chronologic age, but by common health-related conditions in advanced age, as comorbidity and frailty.
- COVID-19 symptoms tend to aggregate in clusters, and this approach appears to better describe the clinical complexity of COVID-19 disease.
- The prognostic value of clinical presentation is poorly investigated: in older people, COVID-19 atypical symptoms, such as delirium and falls, seem to correlate with adverse outcomes.

INTRODUCTION

In April 2020, the SARS-CoV-2 (COVID-19) infection was declared a pandemic emergency by the World Health Organization,¹ and after 2 years, in January 2022, the virus had already caused more than 357 million confirmed cases and 5.6 million deaths globally.² Older people have been described as extremely vulnerable to SARS-CoV-2, reporting a high probability of adverse outcomes, such as hospitalization, intensive care unit admission, and mortality.³ In the first phases of the pandemic, in older patients the fatality rate was almost 8 times higher than in younger age groups.⁴ Although advanced age has been correlated with higher mortality risk, the presence of specific health-related and clinical conditions (ie, multimorbidity, disability, and frailty), common in older people, may explain the main age-related differences in susceptibility

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during SARS-CoV-2 infection.^{5,6} Moreover, these conditions could also modify the clinical presentation of COVID-19, with a higher frequency of atypical symptoms and signs in older than younger age, such as hyporexia and delirium.⁷

This narrative review aims to describe the current knowledge on the clinical features of SARS-CoV-2 infection in older adults, focusing on the heterogeneity of clinical presentation and the health-related conditions that might determine a different clinical picture of this disease in advanced age. Moreover, the authors discuss the prognostic value of specific symptoms at COVID-19 presentation in older people.

HETEROGENEITY OF CLINICAL PRESENTATION OF COVID-19 DISEASE

The clinical presentation of COVID-19 disease is extremely heterogeneous (Fig. 1): in a Cochrane systematic review published in 2020, up to 27 symptoms and signs of SARS-CoV-2 infection were described.⁸ Based on the current literature, however, it is still unclear whether this high symptoms variability depends exclusively on the characteristics of the virus or, in addition to age and sex, also on the presence of the host's health-related conditions, such as comorbidities, disability, and frailty.⁷ Among patients with COVID-19 infection, the most commonly reported symptoms were fever, cough, and dyspnea; other frequent symptoms were headache, sore throat, fatigue, myalgia, gastrointestinal symptoms (such as nausea, vomiting, and diarrhea), anosmia, and ageusia.⁹ Of note, in studies of older patients, anosmia and ageusia have been described more rarely, probably because they are poorly reported by the patient, as a consequence of cognitive decline, age-related sensory impairments, and because of the presence of the confounding effect of medications taken.¹⁰ In addition, the prevalence of asymptomatic and paucisymptomatic patients is not irrelevant and may hamper the application of measures to contain the virus's diffusion.² A retrospective study on 141 individuals aged 50 years or older with SARS-CoV-2 infection confirmed that also in older people the most common clinical presentation of COVID-19 disease included typical symptoms, especially fever (79.5%), cough (61.4%), and dyspnea (31.8%) for those between 65 and 79 years; and fever (75.0%), cough (43.8%), dyspnea (25.5%), and fatigue (25.5%) for those aged 80 years and over.¹¹ Indeed, in advanced age, the variability in the clinical presentation of COVID-19 is wider owing to the higher prevalence of atypical symptoms and signs, such as gastrointestinal ones (nausea,

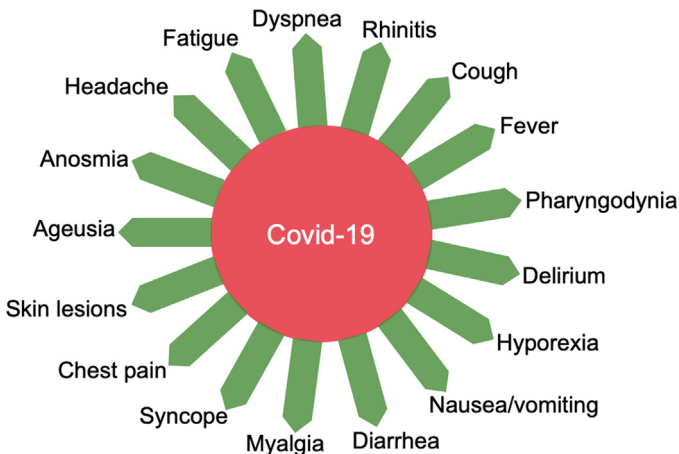


Fig. 1. Symptoms and signs of SARS-CoV-2 infection.

vomiting, and diarrhea), hyporexia, delirium, and falls.^{12,13} These findings confirm previous studies that focused on the clinical presentation of common diseases in geriatric patients and observed that about one-third of older individuals admitted to the Emergency Department (ED) had atypical symptoms of the underlying disease, with the absence of fever being the most common described atypia.¹⁴

AGE-RELATED DIFFERENCES IN CLINICAL FEATURES

Age-related differences in the clinical presentation of COVID-19 have been widely described across the literature of the last 2 years.^{15,16} In a multicenter study conducted on 107 hospitalized individuals ≥ 60 years old with SARS-CoV-2 infection, the oldest group of patients (>75 years old) was more likely to present atypical symptoms, such as apyrexia and hyporexia, than the youngest one. Of note, however, the most frequent clinical presentation of COVID-19 disease was characterized by typical symptoms, including fever and cough, in both age classes.¹⁵ For example, a study sample of 788 people with COVID-19, of which more than 80% were middle-aged adults, provided similar results, and the most reported presenting symptoms on hospital admission were typical (ie, fever and dyspnea).¹⁷ Consistently, several studies highlighted the presence of opposite trends in the frequency of typical and atypical symptoms across age classes^{13,16,18}: atypical symptoms became more likely with increasing age with a parallel reduction in typical ones, although the latter remained the most frequent within the single age classes. Among atypical clinical presentations, Martín-Sánchez and colleagues¹³ showed that older individuals with COVID-19 presented a higher rate of confusion (5.7% vs 0.3%) and presyncope or syncope (7.9% vs 2.4%) than adults at ED admission. The prevalence of confusion at COVID-19 onset reaches 11.7% in a sample of 103 older patients aged ≥ 80 years.¹⁸ Like other infections,¹⁹ the risk of developing delirium was higher in patients with SARS-CoV-2 infection aged 80 years and over than those 70 to 79 years old (28.4% vs 21.4%).²⁰ As mentioned above, when compared with older people, middle-aged adults showed atypical signs of COVID-19 disease more rarely, except for gastrointestinal symptoms. Indeed, in a prospective study performed in China in 2020 on young adults with suspected SARS-CoV-2 pneumonia, only vomiting and abdominal pain were described as atypical clinical presentations of the disease,²¹ whereas no atypical signs were reported in other works involving adult individuals.²² Of note, because of the young age of both samples (37 and 46.7 years old, respectively), no associated comorbidities were described.^{21,22}

FACTORS INFLUENCING COVID-19 CLINICAL PRESENTATION

Whether the peculiar clinical features of COVID-19 in older people exclusively depends on advanced age, or rather on the presence of health-related conditions, common in geriatric individuals, such as comorbidities, motor disability, and frailty, is still uncertain. Indeed, several studies showed that older people with COVID-19 can develop different clinical pictures and degrees of severity of the disease, also within the same age class (**Table 1**).^{11,23–25} In a mentioned study conducted on older patients with COVID-19,¹⁵ almost 20% of the enrolled populations reported several complications of COVID-19 disease during their hospital stay, including acute respiratory distress syndrome, sepsis, acute renal failure, and acute heart failure. Regardless of age, for example, important clinical differences were reported based on sex, inasmuch as men more frequently develop severe COVID-19 disease than women.²⁶

Moreover, a widespread hypothesis supported by the scientific community is that the presence of typical geriatric syndromes (eg, multimorbidity, disability) can

Table 1
Studies about clinical features of COVID-19 disease

Author/Year	Cohort (Country)	Study Design (Duration)	Population Characteristics	Age (y)	Sex (F)	SARS-CoV-2 Patients	3 Most Frequent Comorbidity	3 Most Frequent Symptoms and Signs of Presentation of COVID-19	Atypical Symptom of Presentation	Mortality	Conclusions
Ai et al, ²¹ 2020	China	Prospective (3 wk)	53 individuals with suspected SARS-CoV-2 pneumonia	COVID-19 patients: median 37.0 (IQR 33.75–50.5) Non-COVID-19 patients: median 39.0 (IQR 30.5–43.0)	50.9%	37.7%	N/A	Fever (80%) Cough (55%) Diarrhea (15%) and headache (15%)	Nausea/ vomiting (5%) Abdominal pain (5%)	N/A	Symptoms were not specific for the diagnosis of COVID-19, because similar to other viral pneumonia
Andrés-Esteban et al, ³⁷ 2021	Spain	Retrospective (2 wk)	254 individuals ≥65 y with SARS-CoV-2 infection	Robust patients: median 69.5 (IQR 55.0–79.0) Frail patients: median 76.0 (IQR 66.5–82.5)	37.8%	100%	Hypertension (35.5%) Diabetes (17.5%) Cardiomyopathy (17.2%)	Cough (56.2%) Fever (53.6%) Dyspnea (34.5%)	Diarrhea (12.5%) Nausea/vomiting (11.1%) Abdominal pain (6.1%)	27.6%	Frailty was associated with adverse outcomes, as death, in older people with COVID-19
Anweiler et al, ²⁰ 2020	France	Cross-sectional	103 individuals ≥70 y with SARS-CoV-2 infection	Mean 84.7 (SD ± 7.0)	54.7%	100%	Hypertension (66.3%) Cardiomyopathy (45.0%) Dementia (38.0%)	Fever (77.4%) Cough (58.9%) Polypnea (39.9%)	Delirium (26.7%) Diarrhea (21.8%) Falls (18.7%) Nausea/ vomiting (6.2%)	N/A	Like in young adults, in older people the clinical presentation of COVID-19 included general and respiratory symptoms, but also atypical signs, for example, delirium, falls, and gastrointestinal ones

Bavaro et al. ³⁹ 2020	Italy	Retrospective (4 mo)	206 individuals ≥65 y with SARS-CoV-2 infection	Median 80.0 (IQR 72.0-86.0)	52.0%	100%	Hypertension (60.0%) Cardiomyopathy (45.0%) Diabetes (24.0%)	Dyspnea (61.0%) Fever (55.0%) Cough (40.0%)	Confusion (39.0%)	23.0%	Frail older people with COVID-19 presented frequently extrapulmonary symptoms of disease, such as confusion
Chen et al. ²² 2020	China	Retrospective (5 wk)	136 individuals with suspected SARS-CoV-2 infection	COVID-19 patients: mean 42.9 (SD ± 13.3) Non-COVID-19 patients: mean 46.7 (SD ± 25.0)	38.2%	51.5%	N/A	Cough (68.6%) Fatigue (31.4%) Sore throat (12.9%)	N/A	N/A	A diagnostic model that included chest CT, clinical and blood test features resulted predictive for COVID-19 diagnosis
Chen et al. ⁴³ 2020	China	Retrospective (6 wk)	203 individuals ≥18 y with SARS-CoV-2 infection	Median 54.0 (IQR 20.0-91.0)	46.8%	100%	Hypertension (21.2%) Diabetes (7.9%) Cardiovascular diseases (7.9%)	Fever (89.2%) Cough (60.1%) Chest distress (35.5%)	Diarrhea (4.9%) Nausea/vomiting (3.0%) Hyporexia (3.0%) Dizziness (2.0%) Abdominal pain (2.0%)	12.8%	In the subgroup of patients ≥65 y, no COVID-19 symptoms were correlated with mortality risk
Gálvez-Barrón et al. ¹⁸ 2021	Spain	Ambispective (8 wk)	103 individuals ≥80 y with SARS-CoV-2 infection	Mean 86.8 (SD ± 4.7)	59.2%	100%	Hypertension (81.6%) Dyslipidemia (40.8%) Dementia (35.0%)	Fever (68.9%) Dyspnea (60.2%) Cough (39.8%)	Diarrhea (15.5%) Confusion (11.7%)	57.3%	The typical COVID-19 presentation was less likely in the oldest-old, while the atypical symptoms were more frequently described
Gómez-Belda et al. ⁴⁶ 2020	Spain	Retrospective (6 wk)	340 individuals ≥18 y with SARS-CoV-2 infection	Mean 65.5 (SD ± 15.0)	43.4%	100%	Hypertension (47.8%) Obesity (27.5%) Diabetes (17.4%)	Cough (63.2%) Fever (60.3%) Fatigue (42.9%)	Diarrhea (23.0%) Confusion (17.4%) Hyporexia (15.3%) Nausea/vomiting (11.5%)	16.2%	In patients >70 y, oxygen saturation <93% was associated with mortality
Guo et al. ¹⁵ 2020	China	Retrospective (4 wk)	107 individuals ≥60 y with SARS-CoV-2 infection	Median 67.0 (IQR 64.0- 74.0)	54.3%	100%	Hypertension (43.8%) Diabetes (25.7%) Cardiovascular diseases (16.2%)	Fever (66.7%) Cough (64.8%) Fatigue (33.3%)	Diarrhea (9.5%) Hyporexia (8.6%) Nausea/vomiting (5.7%)	2.8% 60-d mortality	Patients >70 y showed more likely an atypical clinical presentation and complications of COVID-19 than younger patients

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Table 1
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Author/Year	Cohort (Country)	Study Design (Duration)	Population Characteristics	Age (y)	Sex (F)	SARS-CoV-2 Patients	3 Most Frequent Comorbidity	3 Most Frequent Symptoms and Signs of Presentation of COVID-19	Atypical Symptom of Presentation	Mortality	Conclusions
Herwitt et al, ³³ 2020	United Kingdom, Italy	Observational study (2 mo)	1,564 individuals ≥18 y with SARS-CoV-2 infection	Median 74.0 (IQR 61.0–83.0)	42.3%	100%	Hypertension (51.4%) Diabetes (26.5%) CHD (22.1%)	N/A	N/A	27.2% 60-d mortality	In hospitalized COVID-19 patients, frailty better predicted the mortality risk than age or comorbidities
Karlsson et al, ⁴⁵ 2020	Denmark	Retrospective (3 mo)	102 individuals ≥80 y with SARS-CoV-2 infection	Median 84.0 (IQR 82–88)	53.0%	100%	Hypertension (53.0%) Cardiomyopathy (53.0%) Respiratory disease (45.0%)	Fever (74.0%) Cough (62.0%) Dyspnea (54.0%)	Confusion (29.0%) Difficulty walking (13.0%) Falls (8.0%)	31.4% in-hospital mortality 41.2% 30-d mortality	Older patients with atypical symptoms of COVID-19 (confusion and falls) reported higher mortality
Lian et al, ¹⁷ 2020	China	Retrospective (4 wk)	788 individuals with SARS-CoV-2 infection	Patients <60 y: mean 41.2 (SD ± 11.4) Patients ≥60 y: mean 68.3 (SD ± 7.3)	48.4%	100%	Patients <60 y: Hypertension (11.2%) Diabetes (5.0%) CLD (3.8%) Patients ≥60 y: Hypertension (55.2%) Diabetes (39.0%) CHD (4.1%)	Patients <60 y: Fever (79.9%) Cough (64.6%) Sputum production (33.1%) Patients ≥60 y: Fever (84.6%) Cough (62.5%) Dyspnea (36.0%)	Patients <60 y: Gastrointestinal symptoms (11.8%) Patients ≥60 y: Gastrointestinal symptoms (8.1%)	0% 30-d mortality	Older COVID-19 patients presented more likely fever and critical disease
Malara et al, ²⁵ 2021	Italy	Prospective (10 mo)	586 individuals ≥60 y with suspected SARS-CoV-2 infection	COVID-19 patients: mean 85.5 (SD ± 8.1) Non-COVID-19 patients: mean 84.4 (SD ± 8.6)	COVID-19 patients: 72.7% Non-COVID-19 patients: 73.0%	35.7%	COVID-19 patients: Nervous system disorders (68.2%) Osteoarthritis (54.1%) Hypertension (46.6%)	COVID-19 patients: Fever (74.9%) Delirium (41.2%) Sudden worsening of health status (35.0%)	Delirium (41.2%) Hypoxemia (27.0%) Diarrhea (21.6%) Nausea/vomiting (7.2%) Fall (0.9%)	COVID-19 patients: 21.6% Asymptomatic non-COVID-19 patients: 1.8% Symptomatic non-COVID-19 patients: 10.8%	Comorbidities influenced the mortality in SARS-CoV-2-positive residents in long-term care, especially the presence of dementia

Marengoni et al., ³⁵ 2020	Italy	Retrospective (5 wk)	165 individuals ≥65 y with SARS-CoV-2 infection	Mean 69.3 (SD ± 14.5)	39.4%	100%	Hypertension (59.4%) Diabetes (30.9%) Obesity (16.4%)	Fever (89.1%) Cough (50.3%) Dyspnea (42.4%)	Gastrointestinal signs (18.8%)	25.5%	Older patients already frail pre-COVID-19 reported a higher risk to die during the acute disease
Martín-Sánchez et al., ¹³ 2020	Spain	Retrospective (4 wk)	1379 individuals ≥18 y with SARS-CoV-2 infection	Median 63.0 (IQR 48.0–77.0)	46.4%	100%	Hypertension (40.5%) Dyslipidemia (37.9%) Diabetes (19.2%)	Fever (80.0%) Cough (71.1%) Dyspnea (33.3%)	Diarrhea (19.9%) Nausea/vomiting (9.9%) Pre/syncope (4.9%) Confusion (2.8%)	17.7% 30-d mortality	With increasing age, the frequency of atypical symptoms raised as the risk of the short-term mortality
Miles et al., ³⁴ 2020	United Kingdom	Retrospective (4 wk)	377 individuals ≥70 y with or without SARS-CoV-2 infection	COVID-19 patients: mean 80.0 (SD ± 6.8)	38.0%	57.6%	N/A	N/A	N/A	37.7%	In hospitalized COVID-19 older patients, frailty was not a reliable prognostic factor
Niu et al., ¹¹ 2020	China	Retrospective (5 wk)	141 individuals ≥50 y with SARS-CoV-2 infection	50–64 y: 57.5% 65–79 y: 31.2% ≥80 y: 11.3%	50.4%	100%	Patients 50–64 y: Hypertension (28.0%) COPD (12.0%) Cerebrovascular disease (12.0%) Patients ≥65 y: Hypertension (48.8%) COPD (29.0%) CHD (16.1%)	Patients 50–64 y: Fever (77.8%) Cough (45.7%) Fatigue (32.1%) Patients ≥65 y: Fever (78.3%) Cough (56.7%) Dyspnea (30%)	N/A	Patients 50–64 y: 1.2% Patients ≥65 y: 8.3%	Older patients with COVID-19 had a higher risk of severe disease and death
Rozzini et al., ¹⁹ 2020	Italy	Prospective (N/A)	14 individuals ≥70 y with SARS-CoV-2 infection developing delirium	Mean 78.2 (SD N/A)	21.4%	100%	Hypertension (85.7%) Cardiovascular diseases (64.3%) Diabetes (57.1%)	Dyspnea (85.7%) Fever (50.0%) Cough (28.6%)	Fall and syncope (7.1%)	71.0%	Delirium subtypes identified in individuals with different prognosis, especially those with hypokinetic forms revealed the worst outcome

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Table 1
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Author/Year	Cohort (Country)	Study Design (Duration)	Population Characteristics	Age (y)	Sex (F)	SARS-CoV-2 Patients	3 Most Frequent Comorbidity	3 Most Frequent Symptoms and Signs of Presentation of COVID-19	Atypical Symptom of Presentation	Mortality	Conclusions
Wang et al, ⁵ 2020	China	Retrospective (4 wk)	339 individuals ≥60 y with SARS-CoV-2 infection	Median 71.0 (IQR 65.0–76.0)	51.0%	100%	Hypertension (40.8%) Diabetes (16.0%) Cardiovascular diseases (14.2%)	Fever (92.0%) Cough (53.0%) Dyspnea (40.8%)	Diarrhea (12.7%) Nausea/vomiting (3.8%) Dizziness (3.8%)	19.2%	COVID-19 patients with comorbidities (ie, COPD, cardiovascular and cerebrovascular diseases) reported a higher risk of severe disease and death
Zazzara et al, ⁴⁰ 2021	United Kingdom, Italy	Observational (4 wk)	448 individuals ≥65 y with SARS-CoV-2 infection	Hospital cohort: mean 77.9 (SD ± 6.8) Community cohort: mean 73.0 (SD ± 5.9)	36.6%	100%	Hospital cohort: Cardiovascular diseases (66.0%) Diabetes (40.4%) Respiratory disease (40.0%) Community cohort: Respiratory disease (21.0%) Diabetes (16.0%) Cardiovascular diseases (15.5%)	Hospital cohort: Cough (60.0%) Fever (39.0%) Delirium (25.2%) Community cohort: Fatigue (69.5%) Dyspnea (49.2%) Delirium (35.6%)	Hospital cohort: Delirium (25.2%) Community cohort: Delirium (35.6%)	N/A	Delirium might be the unique COVID-19 presenting symptom in older people, especially in frail patients

Zhou et al., ⁴⁴ 2020	China	Retrospective (6 wk)	108 individuals ≥ 60 y with SARS- CoV-2 infection	Survivors: mean 70.6 (SD ± 6.9) Nonsurvivors: mean 73.1 (SD ± 7.3)	60.2%	100%	Hypertension (59.3%) Diabetes (25.0%) CHD (21.3%)	Fever (75.9%) Cough (75.0%) Polypnea (64.8%)	Vomiting or hyporexia (35.2%) Dizziness (13.9%) Diarrhea (4.6%) Disturbance of consciousness (4.6%)	47.2%	No differences in COVID-19 presenting symptoms were highlighted between survivors and nonsurvivors
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Abbreviations: CHD, coronary heart disease; CLD, chronic liver disease; CT, computed tomography; IQR, interquartile range; N/A, data not available; SD, standard deviation.

influence the COVID-19 clinical presentation (Fig. 2). Indeed, most of the hospitalized patients with COVID-19 reported more than one chronic disease (such as diabetes, hypertension, and coronary heart diseases)²⁷ and were more likely to develop a severe form of the disease.²⁴ In the study of Lian and colleagues,¹⁷ older individuals showed a higher number of comorbidities than the younger group (55.15% vs 21.93%), as well as a greater risk to develop a critical COVID-19 disease. These findings were confirmed also by Niu and colleagues,¹¹ that reported a higher prevalence of severe COVID-19 disease in older patients and higher mortality among people ≥ 80 years old than in the 50 to 64 years olds (18.8% vs 1.2%, respectively). In a study on 319 patients with COVID-19 aged 60 years and over, comorbidities, such as chronic obstructive pulmonary disease (COPD) and cardiovascular and cerebrovascular diseases, increased the probability to develop a severe disease.⁵ Finally, a similar picture was observed in 586 residents of long-term care facilities with suspected SARS-CoV-2 infection, with 88.8% of positive patients ($n = 159$) reporting 3 or more comorbidities, and this influenced the severity of COVID-19 disease (especially the presence of dementia).²⁵

Several studies investigated the possible link between frailty and COVID-19 clinical presentation. It is widely known that in older patients the presence of frailty, either defined according to the Fried²⁸ or Rockwood criteria,²⁹ is strongly correlated with adverse outcomes.^{30–32} Indeed, through the assessment of frailty, a better stratification of the individual's biological reserve and risk profile can be achieved, as compared with the simple assessment of chronologic age.³³ Therefore, several studies were conducted to evaluate the role of frailty in older patients with SARS-CoV-2 infection. Although the reported results are not uniform, most of the available studies support the usefulness to assess frailty in older people with COVID-19 disease.^{33–37} In an observational study on 165 individuals with COVID-19 admitted in a Geriatrics Unit, Marengoni and colleagues³⁵ demonstrated that patients who were more likely to die during the hospitalization were already frail before COVID-19 onset (37.5% vs 4.1%).³⁵ In addition, every unit increment on the Clinical Frailty Scale (CFS)³⁸ was associated with a 30% increased risk of death, regardless of age. Despite some contrasting results,³⁴ in a multicenter study published in *Lancet* and including 1564 inpatients with COVID-19 with a mean age of 74 years, frailty was associated with an 83% increased risk of death in people with a CFS of 5 to 6, and with more

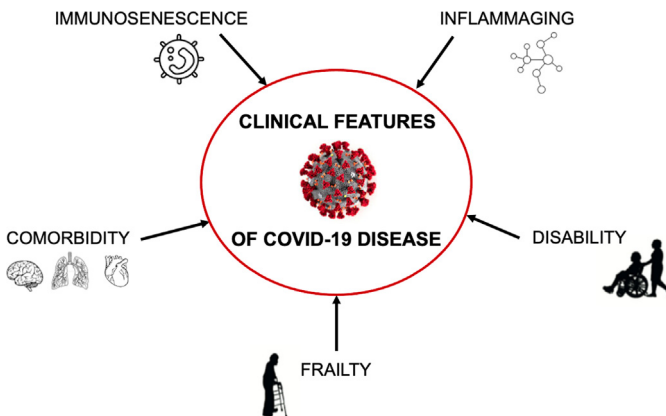


Fig. 2. Influencing factors of COVID-19 clinical presentation.

than a twofold risk in the case of a CFS of 7 to 9, regardless of age.³³ Consistent findings emerged from a prospective study on 254 older inpatients admitted for COVID-19, where frail patients were more likely to develop in-hospital delirium (43.2% vs 8.2%) and to die compared with their nonfrail counterparts.³⁷

Concerning clinical presentation, Bavaro and colleagues³⁹ demonstrated that frail patients with COVID-19 reported a higher risk of low oxygen saturation and extrapulmonary signs at disease onset, such as electrolytes disturbances, dehydration, and confusion. In an observational study conducted on 2 cohorts in the hospital and community settings, delirium was reported as a very likely presenting symptom of COVID-19 in frail older individuals.⁴⁰ Considering that the presence of dementia is strictly connected with frailty, Annweiler and colleagues²⁰ showed that older patients affected by dementia had a higher risk of developing delirium at COVID-19 onset. These results were strengthened by a position paper published in 2020 by Bianchetti and colleagues,⁴¹ where it was reported that 67% of older people with dementia developed delirium as a unique presenting symptom of COVID-19.

In conclusion, in older people, the simple chronologic age appears poorly predictive of the COVID-19 severity and health-related outcomes. For this reason, the implementation of the Comprehensive Geriatric Assessment in these patients would allow better evaluation of the presence of comorbidities, disability, and frailty, and improvement in prognostic estimation.

SYMPTOM CLUSTERS

Because of its high clinical heterogeneity, the clustering approach has been proposed to better describe the presenting symptoms of COVID-19, increase the accuracy of clinical diagnosis, and forecast the progress toward more severe forms of the disease. Indeed, some researchers observed the tendency of some symptoms and signs to aggregate, identifying specific symptom clusters of COVID-19 disease (**Table 2**).^{2,10} Dixon and colleagues² published in March 2021 a study on community-dwelling individuals screened for SARS-CoV-2 infection, with the purpose of identifying specific symptom clusters linked to the infection presence. The investigators identified 5 symptom clusters at COVID-19 onset. Specifically, cluster 1 was characterized by the copresence of ageusia, anosmia, and fever; cluster 2 was characterized by dyspnea, cough, and chest pain; cluster 3 was characterized by asthenia, myalgia, and headache; cluster 4 was characterized by diarrhea and vomiting; and cluster 5 was characterized by rhinitis and pharyngodynia. Clusters 1 and 2 were the most strictly associated with SARS-CoV-2 infection. However, this study did not perform any subanalysis on different age groups (about one-third were >60 years old), and no information on comorbidity and preacute physical performance was reported.

In a similar study, Trevisan and colleagues¹⁰ considered 6680 patients aged 18 years and over screened for SARS-CoV-2 infection between February and June 2020. This study aimed to identify specific symptom clusters associated with a positive SARS-CoV-2 nasopharyngeal swab and recognized 4 symptom clusters, that is, cluster 1 was characterized by flulike symptoms (rhinitis, pharyngodynia, cough, fever, myalgia, headache, gastrointestinal symptoms, anosmia/ageusia), in 40.6% of the recruited individuals; cluster 2 was characterized by generic symptoms, in 1.7% of the sample; cluster 3 was characterized by flulike + generic symptoms, in 31.5% of individuals; and cluster 4 was characterized by asymptomatic patients, involving 26.2% of the sample. At the stratified analysis, after adjusting for potential confounders (including major comorbidities), older adults belonging to the flulike

Table 2
Main characteristics of the identified studies on symptom clusters in patients with COVID-19

Author/Year	Cohort (Country)	Study Design (Duration)	Population Characteristics	Age (y)	Sex (F)	SARS-CoV-2 Patients	N. Symptom Cluster	Outcome	Results	Conclusions
Dixon et al, ² 2021	United States	Prospective (3 mo)	8.214 individuals ≥12 y screened for SARS-CoV-2 infection	<40 y: 29.0% 40–59 y: 37.0% ≥60 y: 34.1%	55.6%	4.5%	5	SARS-CoV-2 positivity	The symptoms clusters associated with SARS-CoV-2 positivity were: (1) ageusia, anosmia, and fever; (2) dyspnea, cough, and chest pain	Anosmia and ageusia were the key symptoms for SARS-CoV-2 positivity, especially if associated with fever. The cluster characterized by severe respiratory symptoms is also strictly related to the outcome

Sudre et al, ⁴² 2021	United Kingdom, United States, Sweden	Cross-sectional	1.653 individuals ≥16 y with SARS-CoV-2 infection	Mean (±SD) C.1: 41.1 (±11.6) C.2: 43.2 (SD ± 12.1) C.3: 41.0 (SD ± 12.4) C.4: 43.0 (SD ± 11.9) C.5: 43.7 (SD ± 13.2) C.6: 43.8 (SD ± 12.2)	C.1: 70.6% C.2: 73.7% C.3: 80.1% C.4: 83.2% C.5: 72.3% C.6: 71.9%	100%	6	Need for respiratory support	C.4 (flulike symptoms), C.5 (combined respiratory symptoms), and C.6 (nonspecific symptoms) were associated with the necessity of respiratory support	Specific symptom clusters predicted the necessity of respiratory support in COVID-19 patients
Trevisan et al, ¹⁰ 2021	Italy	Cross-sectional	6.688 individuals ≥18 y screened for SARS-CoV-2 infection	Mean (SD) 47.9 ± 14.0	65.7%	25.1%	4	SARS-CoV-2 positivity	Flulike symptoms cluster was associated with SARS-CoV-2 positivity	COVID-19 symptoms differently aggregated in specific clusters, influenced by age and comorbidities

Abbreviations: C.1, cluster 1; C.2, cluster 2; C.3, cluster 3; C.4, cluster 4; C.5, cluster 5; C.6, cluster 6.

symptoms cluster had a 73% higher probability of SARS-CoV-2 infection, whereas the cluster more strongly associated with a positive swab in younger people was that with flulike + generic symptoms. In both the abovementioned studies,^{2,10} the investigators investigated the association between the single symptoms and the outcome identifying anosmia and ageusia as the symptoms most associated with SARS-CoV-2 infection, although the clustering approach resulted more effectively to capture the clinical complexity of COVID-19.

A third study performed using the clustering approach was conducted by Sudre and colleagues⁴²: their purpose was to identify specific symptom clusters to predict the prognosis of COVID-19 disease, specifically, the necessity of respiratory support. This work is discussed in the next paragraph.

PROGNOSTIC VALUE OF COVID-19 CLINICAL PRESENTATION

Regarding the prognostic significance of COVID-19 presenting symptoms in older patients, the available literature is still not uniform. In 2 Chinese studies performed in 2020 on older individuals with SARS-CoV-2 infection, no differences in mortality were observed based on the clinical characteristics at disease onset.^{43,44} On the other hand, in an Italian study conducted on 14 hospitalized older individuals with delirium during the COVID-19 disease, the investigators found that all patients who developed hypokinetic delirium died compared with the 50% of those with hyperkinetic form. These results supported the role of delirium as a negative prognostic factor in older patients with COVID-19 disease, especially the hypokinetic form.¹⁹ These findings are consistent with those described by previous geriatric literature,¹⁴ inasmuch delirium appeared strictly associated with a higher risk of death, regardless of clinical respiratory severity, preacute cognitive status, and motor disability. In a multicenter retrospective study in patients aged 80 years and over with COVID-19, mortality was 24% higher in those experiencing falls and 12% higher in those with confusion at the disease onset.⁴⁵ In addition to these symptoms, Gómez-Belda and colleagues⁴⁶ found that the presence of oxygen saturation $\leq 93\%$ at COVID-19 onset was associated with increased mortality (odds ratio = 11.65, 95% confidence interval: 3.26–41.66) in patients ≥ 70 years old.

Concerning the prognostic significance of symptom clusters, to the authors' knowledge, only one study investigated the need for respiratory support (supplemental oxygen and ventilation) in patients with COVID-19.⁴² This work was conducted by Sudre and colleagues⁴² and included 1047 individuals with SARS-CoV-2 infection. The tendency of symptoms to aggregate in clusters was analyzed in the first 5 days from disease onset. Six symptom clusters were identified, namely: cluster 1, characterized by the presence of cough, myalgia, and anosmia; cluster 2, characterized by cough, fever, anosmia, and headache; cluster 3, characterized by gastrointestinal signs (hyporexia and diarrhea); cluster 4, characterized by flulike symptoms (cough, fever, and headache); cluster 5, characterized by combined respiratory symptoms (cough, pharyngodynia, and dyspnea); cluster 6, characterized by nonspecific symptoms (confusion and abdominal pain). When evaluating the prognostic value of symptom clusters, cluster 4 (flulike symptoms), cluster 5 (combined respiratory symptoms), and cluster 6 (nonspecific symptoms) were associated with a higher risk of needing respiratory support during the acute disease. Of note, this study involved young individuals (mean age 44 years old) and did not investigate possible age-related differences. Currently, therefore, data on the COVID-19 symptom clusters that may be more strongly associated with higher mortality are still lacking, especially as concerns older people.

FUTURE RESEARCH DIRECTIONS

Severe health-related and social effects of the SARS-CoV-2 pandemic affect especially older people, because of the high risk of social isolation, hospitalization, disability, and death. In addition, the heterogeneity of clinical presentation in this age class has often led to a delay in diagnosis, and, consequently, of treatment. Thus, based on the available studies on COVID-19 symptoms and signs in advanced age, standardized questionnaires should be created and administrated at disease onset and, in case of hospitalization, at admission; in this context, the clustering approach may help to improve the diagnostic phase of the disease. Moreover, the prognostic value of COVID-19 presenting symptoms may be extremely useful to discriminate high-risk patients; therefore, it should be deeply investigated with special attention to the older population.

SUMMARY

The COVID-19 clinical presentation is extremely heterogenous and, in older people, it is influenced not simply by chronologic age but also by common geriatric syndromes, such as multimorbidity, motor disability, and frailty. Consequently, although typical respiratory symptoms remain the most frequent clinical presentation of COVID-19 in all age classes, in older patients, atypical symptoms (including but not limited to delirium and hyporexia) are more common than in middle-aged adults and have been associated with adverse outcomes. Moreover, some studies described the tendency of COVID-19 presenting symptoms to aggregate in clusters, and this approach seems to better capture the complexity of COVID-19 disease. The prognostic value of COVID-19 symptom clusters, however, is currently poorly investigated, especially in the older population.

CLINICS CARE POINTS

- The diagnosis of COVID-19 in older patients is extremely challenging, owing to the possible presence of atypical clinical presentation, such as delirium, hyporexia, and falls.
- Older patients with comorbidity, disability, and frailty reported a higher risk of atypical presenting symptoms of COVID-19.
- The symptom cluster approach could be useful to identify COVID-19 patients with higher certainty.
- Older patients with atypical presenting symptoms and signs have a greater risk to develop a severe case of COVID-19 and to die.

DISCLOSURE

The authors have nothing to disclose.

REFERENCES

1. World Health Organization. Coronavirus disease 2019 (COVID-19) situation report-97. Geneva: World Health Organization; 2020.
2. Dixon BE, Wools-Kaloustian KK, Fadel WF, et al. Symptoms and symptom clusters associated with SARS-CoV-2 infection in community-based populations:

- results from a statewide epidemiological study. *PLoS ONE* 2021;16(3 March). <https://doi.org/10.1371/journal.pone.0241875>.
3. Onder G, Rezza G, Brusaferro S. Case-fatality rate and characteristics of patients dying in relation to COVID-19 in Italy. *JAMA - J Am Med Assoc* 2020;323(18): 1775–6. <https://doi.org/10.1001/jama.2020.4683>.
 4. Characteristics of COVID-19 patients dying in Italy. Available at: <https://www.epicentro.iss.it/en/coronavirus/sars-cov-2-analysis-of-deaths>.
 5. Wang L, He W, Yu X, et al. Coronavirus disease 2019 in elderly patients: characteristics and prognostic factors based on 4-week follow-up. *J Infect* 2020;80(6): 639–45. <https://doi.org/10.1016/j.jinf.2020.03.019>.
 6. Nickel CH, Rueegg M, Pargge H, et al. Age, comorbidity, frailty status: effects on disposition and resource allocation during the COVID-19 pandemic. *Swiss Med Wkly* 2020;150:20169.
 7. Richardson S, Hirsch JS, Narasimhan M, et al. Presenting characteristics, comorbidities, and outcomes among 5700 patients hospitalized with COVID-19 in the New York City Area. *JAMA - J Am Med Assoc* 2020;323(20):2052–9. <https://doi.org/10.1001/jama.2020.6775>.
 8. Struyf T, Deeks JJ, Dinnes J, et al. Signs and symptoms to determine if a patient presenting in primary care or hospital outpatient settings has COVID-19 disease. *Cochrane Database Syst Rev* 2020;(7):2020. <https://doi.org/10.1002/14651858.CD013665>.
 9. Yang J, Zheng Y, Gou X, et al. Prevalence of comorbidities and its effects in coronavirus disease 2019 patients: a systematic review and meta-analysis. *Int J Infect Dis* 2020;94:91–5. <https://doi.org/10.1016/j.ijid.2020.03.017>.
 10. Trevisan C, Noale M, Prinelli F, et al. Age-related changes in clinical presentation of Covid-19: the EPICoVID19 web-based survey. *Eur J Intern Med* 2021;86:41–7. <https://doi.org/10.1016/j.ejim.2021.01.028>.
 11. Niu S, Tian S, Lou J, et al. Clinical characteristics of older patients infected with COVID-19: a descriptive study. *Arch Gerontol Geriatr* 2020;89. <https://doi.org/10.1016/j.archger.2020.104058>.
 12. Mueller AL, Mcnamara MS, Sinclair DA. Why does COVID-19 disproportionately affect the elderly? *Preprints* 2020;1–32.
 13. Martín-Sánchez FJ, del Toro E, Cardassay E, et al. Clinical presentation and outcome across age categories among patients with COVID-19 admitted to a Spanish Emergency Department. *Eur Geriatr Med* 2020;11(5):829–41. <https://doi.org/10.1007/s41999-020-00359-2>.
 14. Limpawattana P, Phungoen P, Mitsungnern T, et al. Atypical presentations of older adults at the emergency department and associated factors. *Arch Gerontol Geriatr* 2016;62:97–102.
 15. Guo T, Shen Q, Guo W, et al. Clinical characteristics of elderly patients with COVID-19 in Hunan Province, China: a multicenter, retrospective study. *Gerontology* 2020;66(5):467–75. <https://doi.org/10.1159/000508734>.
 16. Chow EJ, Schwartz NG, Tobolowsky FA, et al. Symptom screening at illness onset of health care personnel with SARS-CoV-2 infection in King County, Washington. *JAMA - J Am Med Assoc* 2020;323(20):2087–9. <https://doi.org/10.1001/jama.2020.6637>.
 17. Lian J, Jin X, Hao S, et al. Analysis of epidemiological and clinical features in older patients with coronavirus disease 2019 (COVID-19) outside Wuhan. *Clin Infect Dis* 2020;71(15):740–7. <https://doi.org/10.1093/cid/ciaa242>.
 18. Gálvez-Barrón C, Arroyo-Huidobro M, Miñarro A, et al. COVID-19: clinical presentation and prognostic factors of severe disease and mortality in the oldest-old

- population: a cohort study. *Gerontology* 2021;1–14. <https://doi.org/10.1159/000515159>.
19. Rozzini R, Bianchetti A, Mazzeo F, et al. Delirium: clinical presentation and outcomes in older COVID-19 patients. *Front Psychiatry* 2020;11. <https://doi.org/10.3389/fpsy.2020.586686>.
 20. Annweiler C, Sacco G, Salles N, et al. National French Survey of coronavirus disease (COVID-19) symptoms in people aged 70 and over. *Clin Infect Dis* 2021; 72(3):490–4. <https://doi.org/10.1093/cid/ciaa792>.
 21. Ai JW, Zhang HC, Xu T, et al. Optimizing diagnostic strategy for novel coronavirus pneumonia, a multi-center study in Eastern China. *medRxiv* 2020. <https://doi.org/10.1101/2020.02.13.20022673>.
 22. Chen X, Tang Y, Mo Y, et al. A diagnostic model for coronavirus disease 2019 (COVID-19) based on radiological semantic and clinical features: a multi-center study. *Eur Radiol* 2020;30(9):4893–902. <https://doi.org/10.1007/s00330-020-06829-2>.
 23. Yang X, Yu Y, Xu J, et al. Clinical course and outcomes of critically ill patients with SARS-CoV-2 pneumonia in Wuhan, China: a single-centered, retrospective, observational study. *Lancet Respir Med* 2020;8(5):475–81. [https://doi.org/10.1016/S2213-2600\(20\)30079-5](https://doi.org/10.1016/S2213-2600(20)30079-5).
 24. Wu Z, McGoogan JM. Characteristics of and important lessons from the coronavirus disease 2019 (COVID-19) outbreak in China: summary of a report of 72314 cases from the Chinese Center for Disease Control and Prevention. *JAMA* 2020; 323(13):1239–42. <https://doi.org/10.1001/jama.2020.2648>.
 25. Malara A, Noale M, Abbatecola AM, et al. Clinical features of SARS-CoV-2 infection in Italian long-term care facilities: GeroCovid LTCFs observational study. *J Am Med Dir Assoc* 2022;23:15–8.
 26. Raparelli V, Palmieri L, Canevelli M, et al. Sex differences in clinical phenotype and transitions of care among individuals dying of COVID-19 in Italy. *Biol Sex Differences* 2020;11(1). <https://doi.org/10.1186/s13293-020-00334-3>.
 27. Zhou F, Yu T, Du R, et al. Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study. *Lancet* 2020;395(10229):1054–62. [https://doi.org/10.1016/S0140-6736\(20\)30566-3](https://doi.org/10.1016/S0140-6736(20)30566-3).
 28. Fried LP, Tangen CM, Walston J, et al. Frailty in older adults: evidence for a phenotype. vol. 56. 2001. Available at: <https://academic.oup.com/biomedgerontology/article/56/3/M146/545770>.
 29. Rockwood K, Song X, MacKnight C, et al. A global clinical measure of fitness and frailty in elderly people. *CMAJ* 2005;173(5):489–95. <https://doi.org/10.1503/cmaj.050051>.
 30. Guidet B, de Lange DW, Boumendil A, et al. The contribution of frailty, cognition, activity of daily life and comorbidities on outcome in acutely admitted patients over 80 years in European ICUs: the VIP2 study. *Intensive Care Med* 2020; 46(1):57–69. <https://doi.org/10.1007/s00134-019-05853-1>.
 31. Darvall JN, Bellomo R, Paul E, et al. Frailty in very old critically ill patients in Australia and New Zealand: a population-based cohort study. *Med J Aust* 2019;211(7):318–23. <https://doi.org/10.5694/mja2.50329>.
 32. Zeng A, Song X, Dong J, et al. Mortality in relation to frailty in patients admitted to a specialized geriatric intensive care unit. *Journals Gerontol - Ser A Biol Sci Med Sci* 2015;70(12):1586–94. <https://doi.org/10.1093/gerona/glv084>.
 33. Hewitt J, Carter B, Vilches-Moraga A, et al. The effect of frailty on survival in patients with COVID-19 (COPE): a multicentre, European, observational cohort

- study. *Lancet Public Health* 2020;5(8):e444–51. [https://doi.org/10.1016/S2468-2667\(20\)30146-8](https://doi.org/10.1016/S2468-2667(20)30146-8).
34. Miles A, Webb TE, Mcloughlin BC, et al. Outcomes from COVID-19 across the range of frailty: excess mortality in fitter older people. *Eur Geriatr Med* 2020; 11(5):851–5. <https://doi.org/10.1007/s41999-020-00354-7>.
 35. Marengoni A, Zucchelli A, Vetrano DL, et al. Beyond chronological age: frailty and multimorbidity predict in-hospital mortality in patients with coronavirus disease 2019. *Journals Gerontol - Ser A Biol Sci Med Sci* 2021;76(3):E38–45. <https://doi.org/10.1093/gerona/glaa291>.
 36. Owen RK, Conroy SP, Taub N, et al. Comparing associations between frailty and mortality in hospitalised older adults with or without COVID-19 infection: a retrospective observational study using electronic health records. *Age and Ageing* 2021;50(2):307–16. <https://doi.org/10.1093/ageing/afaa167>.
 37. Andrés-Esteban EM, Quintana-Díaz M, Ramírez-Cervantes KL, et al. Outcomes of hospitalized patients with COVID-19 according to level of frailty. *PeerJ* 2021;9. <https://doi.org/10.7717/peerj.11260>.
 38. Rockwood K, Theou O. Using the clinical frailty scale in allocating scarce health care resources. *Can Geriatr J* 2020;23(3):254–9. <https://doi.org/10.5770/CGJ.23.463>.
 39. Bavaro DF, Diella L, Fabrizio C, et al. Peculiar clinical presentation of COVID-19 and predictors of mortality in the elderly: a multicentre retrospective cohort study. *Int J Infect Dis* 2021;105:709–15. <https://doi.org/10.1016/j.ijid.2021.03.021>.
 40. Zazzara MB, Penfold RS, Roberts AL, et al. Probable delirium is a presenting symptom of COVID-19 in frail, older adults: a cohort study of 322 hospitalised and 535 community-based older adults. *Age and Ageing* 2021;50(1):40–8. <https://doi.org/10.1093/ageing/afaa223>.
 41. Bianchetti A, Bellelli G, Guerini F, et al. Improving the care of older patients during the COVID-19 pandemic. *Aging Clin Exp Res* 2020;32(9):1883–8. <https://doi.org/10.1007/s40520-020-01641-w>.
 42. Sudre CH, Lee KA, Ni Lochlainn M, et al. Symptom clusters COVID-19: a potential clin prediction tool COVID symptom study App. Vol 7.; 2021.
 43. Chen TL, Dai Z, Mo P, et al. Clinical characteristics and outcomes of older patients with coronavirus disease 2019 (COVID-19) in Wuhan, China: a single-centered, retrospective study. *Journals Gerontol - Ser A Biol Sci Med Sci* 2020; 75(9):1788–95. <https://doi.org/10.1093/gerona/glaa089>.
 44. Zhou J, Huang L, Chen J, et al. Clinical features predicting mortality risk in older patients with COVID-19. *Curr Med Res Opin* 2020. <https://doi.org/10.1080/03007995.2020.1825365>.
 45. Karlsson LK, Jakobsen LH, Hollensberg L, et al. Clinical presentation and mortality in hospitalized patients aged 80+ years with COVID-19—a retrospective cohort study. *Arch Gerontol Geriatr* 2021;94. <https://doi.org/10.1016/j.archger.2020.104335>.
 46. Gómez-Belda AB, Fernández-Garcés M, Mateo-Sanchis E, et al. COVID-19 in older adults: what are the differences with younger patients? *Geriatr Gerontol Int* 2021;21(1):60–5. <https://doi.org/10.1111/ggi.14102>.