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

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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 classes.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.
during SARS-CoV-2 infection.\textsuperscript{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.\textsuperscript{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.\textsuperscript{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.\textsuperscript{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.\textsuperscript{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.\textsuperscript{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.\textsuperscript{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.\textsuperscript{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,
vomiting, and diarrhea), hyporexia, delirium, and falls. 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.

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. 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. 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). Consistently, several studies highlighted the presence of opposite trends in the frequency of typical and atypical symptoms across age classes: 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 colleagues 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. Like other infections, 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%). 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, whereas no atypical signs were reported in other works involving adult individuals. Of note, because of the young age of both samples (37 and 46.7 years old, respectively), no associated comorbidities were described.

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. In a mentioned study conducted on older patients with COVID-19, 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.

Moreover, a widespread hypothesis supported by the scientific community is that the presence of typical geriatric syndromes (eg, multimorbidity, disability) can
| Author/Year         | Cohort (Country) | Study Design        | 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, 2020      | China            | Prospective (3 wk)  | 53 individuals with suspected SARS-CoV-2 pneumonia | COVID-19 patients: median 37.0 (IQR 33.75–50.5) | 50.9%   | 37.7% N/A           | Fever (80%) Cough (55%) Diarrhea (15%) and headache (15%) | N/A                      | N/A | Symptoms were not specific for the diagnosis of COVID-19, because similar to other viral pneumonia |
| Andrés-Esteban et al, 2021 | Spain          | Retrospective (2 wk) | 254 individuals \(\geq 65\) y with SARS-CoV-2 infection | Robust patients: median 69.5 (IQR 55.0–79.0) | 37.8%   | 100%                | Hypertension (35.5%) Diabetes (17.5%) Cardiomyopathy (17.2%) | Cough (56.2%) Fever (53.6%) Dypnea (34.5%) | N/A | Frailty was associated with adverse outcomes, as death, in older people with COVID-19 |
| Annweiler et al, 2020 | France          | Cross-sectional     | 103 individuals \(\geq 70\) 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%) | 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 |
| Study                  | Location          | Study Design       | Participants | Median Age (IQR or SD) | COVID-19 Symptoms | Non-COVID-19 Symptoms | Complications | Mortality Risk |
|------------------------|-------------------|--------------------|--------------|------------------------|--------------------|-----------------------|---------------|----------------|
| Bavaro et al., 2020    | Italy             | Retrospective (4 mo) | 206 individuals ≥ 65 y with SARS-CoV-2 infection | Median 80.0 (IQR 72.0–86.0) | Dyspnea (61.0%) | Fever (55.0%) | Cough (40.0%) |
| Chen et al., 2020      | China             | Retrospective (5 wk) | 136 individuals with suspected SARS-CoV-2 infection | COVID-19 patients: mean 42.9 (SD ± 13.3) | Cough (88.6%) | Fatigue (31.4%) | Sore throat (12.9%) |
| Chen et al., 2020      | China             | Retrospective (6 wk) | 203 individuals ≥ 18 y with SARS-CoV-2 infection | Median 54.0 (IQR 20.0–91.0) | Fever (89.2%) | Cough (60.1%) | Chest distress (35.5%) |
| Galván-Barón et al., 2021 | Spain          | Ambispective (8 wk) | 103 individuals ≥ 80 y with SARS-CoV-2 infection | Mean 86.8 (SD ± 4.7) | Fever (68.9%) | Dyspnea (60.2%) | Cough (99.8%) |
| Gómez-Belda et al., 2020 | Spain             | Retrospective (6 wk) | 340 individuals ≥ 18 y with SARS-CoV-2 infection | Mean 65.5 (SD ± 15.0) | Fever (83.2%) | Confusion (17.4%) | Hypoxemia (15.3%) |
| Guo et al., 2020       | China             | Retrospective (4 wk) | 107 individuals ≥ 60 y with SARS-CoV-2 infection | Median 67.0 (IQR 64.0–74.0) | Fever (66.7%) | Hypoxemia (8.6%) | Nausea/vomiting (5.7%) |

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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, 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, 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, 2020 | China | Retrospective (4 wk) | 788 individuals with SARS-CoV-2 infection | Patients <60 y: mean 41.2 (SD ± 11.4) | 48.4% | 100% | Patients <60 y: Hypertension (11.2%) | Diabetes (5.0%) | CVD (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, 2021 | Italy | Prospective (10 mo) | 586 individuals ≥60 y with suspected SARS-CoV-2 infection | COVID-19 patients: mean 85.5 (SD ± 8.1) | 35.7% | COVID-19 patients: Nervous system disorders (68.2%) | COVID-19 patients: Fever (74.9%) | Delirium (41.2%) | Sudden worsening of health status (35.0%) | Delirium (41.2%) | Hypoxia (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., 2020

- **Country**: Italy
- **Study Type**: Retrospective
- **Duration**: 5 weeks
- **Participants**: 165 individuals
- **Age**: ≥65 y with SARS-CoV-2 infection
- **Mean Age**: 69.3 (SD ± 14.5)
- **Main Findings**:
  - 39.4% of participants had hypertension
  - 100% of participants had fever
  - 42.4% of participants had dyspnea

### Martin-Sánchez et al., 2020

- **Country**: Spain
- **Study Type**: Retrospective
- **Duration**: 4 weeks
- **Participants**: 1379 individuals
- **Age**: ≥18 y with SARS-CoV-2 infection
- **Median Age**: 63.0 (IQR 48.0–77.0)
- **Main Findings**:
  - 46.4% of participants had hypertension
  - 42.4% of participants had dyspnea

### Miles et al., 2020

- **Country**: United Kingdom
- **Study Type**: Retrospective
- **Duration**: 4 weeks
- **Participants**: 377 individuals
- **Age**: ≥70 y with or without SARS-CoV-2 infection
- **Mean Age**: 80.0 (SD ± 6.8)
- **Main Findings**:
  - 57.6% of patients had fever
  - 30.8% of patients had cough

### Niu et al., 2020

- **Country**: China
- **Study Type**: Retrospective
- **Duration**: 5 weeks
- **Participants**: 141 individuals
- **Age**: ≥50 y with SARS-CoV-2 infection
- **Mean Age**: 57.5% 50–64 y: 57.5% 65–79 y: 31.2% 80 y: 11.3%
- **Main Findings**:
  - 50.4% of patients had fever
  - 45.7% of patients had cough

### Rozzini et al., 2020

- **Country**: Italy
- **Study Type**: Prospective
- **Duration**: N/A
- **Participants**: 14 individuals
- **Age**: ≥70 y with SARS-CoV-2 infection developing delirium
- **Mean Age**: 78.2 (SD N/A)
- **Main Findings**:
  - 21.4% of patients had hypertension
  - 100% of patients had dyspnea

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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,** 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,** 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. 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)

| Symptom                  | Survivors | Nonsurvivors |
|--------------------------|-----------|--------------|
| Hypertension             | 60.2%     | 100%         |
| Diabetes                 | 59.3%     | 25.0%        |
| CHD                      | 21.3%     |              |
| Fever                    | 75.9%     | 75.0%        |
| Cough                    | 75.0%     |              |
| Polypnea                 | 64.8%     |              |
| Vomiting or hyporexia    | 37.2%     | 35.2%        |
| Dizziness                | 13.9%     |              |
| Diarrhea                 | 4.6%      |              |
| Disturbance of consciousness | 4.6%     |              |

#### 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) and were more likely to develop a severe form of the disease. In the study of Lian and colleagues, 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, that reported a higher prevalence of severe COVID-19 disease in older patients and higher mortality among people \( \geq 80 \) 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. 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).

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 Fried or Rockwood criteria, is strongly correlated with adverse outcomes. 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. 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. In an observational study on 165 individuals with COVID-19 admitted in a Geriatrics Unit, Marengoni and colleagues demonstrated that patients who were more likely to die during the hospitalization were already frail before COVID-19 onset (37.5% vs 4.1%). In addition, every unit increment on the Clinical Frailty Scale (CFS) was associated with a 30% increased risk of death, regardless of age. Despite some contrasting results, 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.](image-url)
than a twofold risk in the case of a CFS of 7 to 9, regardless of age. 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.

Concerning clinical presentation, Bavaro and colleagues 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. Considering that the presence of dementia is strictly connected with frailty, Annweiler and colleagues 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, 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). Dixon and colleagues 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 colleagues 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, 2021 United States | Prospective (3 mo) | 8.214 individuals | 55.6% | 5 | SARS-CoV-2 positivity | 
| | | <40 y: | 29.0% | | | 
| | | ≥12 y | 40–59 y: | 37.0% | | | 
| | | screened for SARS-CoV-2 infection | ≥60 y: | 34.1% | | | 
| | | SARS-CoV-2 positivity 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. |
| Study                          | Country                | Design       | Sample Size | Mean (±SD) | C.1: 70.6% | C.2: 73.7% | C.3: 80.1% | C.4: 83.2% | C.5: 72.3% | C.6: 71.9% | Need for respiratory support | Specific symptom clusters predicted the necessity of respiratory support in COVID-19 patients |
|-------------------------------|------------------------|--------------|-------------|------------|------------|------------|------------|------------|------------|------------|-------------------------------|----------------------------------------------------------------------------------|
| Sudre et al, 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) | 100% 6 | C.4 (flulike symptoms), C.5 (combined respiratory symptoms), and C.6 (nonspecific symptoms) were associated with the necessity of respiratory support |
| Trevisan et al, 2021          | Italy                  | Cross-sectional | 6,688 individuals ≥18 y screened for SARS-CoV-2 infection | Mean (±SD) | 47.9 (SD ± 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, 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 colleagues: 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. 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. These findings are consistent with those described by previous geriatric literature, 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. In addition to these symptoms, Gómez-Belda and colleagues 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 \( \geq 70 \) 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. This work was conducted by Sudre and colleagues 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 heterogeneous 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 hypoxemia) 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, hypoxemia, 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.

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