
**Title:** Clinical Characteristics of Hospitalized Individuals Dying with COVID-19 by Age Group in Italy

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**1st Reviewer:** Eileen Partridge

**2nd Reviewer:** Nathaniel Chin

### 1. Purpose of the Study

<table>
<thead>
<tr>
<th>a. Describe the purpose of the study in your own words.</th>
<th>To describe the clinical features of patients who died of COVID-19 in Italy and compare those features between adults younger than age 65 and adults age 65+</th>
</tr>
</thead>
<tbody>
<tr>
<td>b. What was the gap in knowledge that researchers wanted to address with this study?</td>
<td>Not clear</td>
</tr>
</tbody>
</table>

### 2. Study Design

<table>
<thead>
<tr>
<th>a. What is the overall study design (RCT, case-control, observational, prospective cohort study, etc.)?</th>
<th>Retrospective cohort</th>
</tr>
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</table>

### 3. Sample description

<table>
<thead>
<tr>
<th>a. What is the sample size?</th>
<th>3,032 cases of COVID-19-related deaths: 368 cases in people &lt;65 years 2,664 in individuals aged ≥65 years</th>
</tr>
</thead>
<tbody>
<tr>
<td>b. What are the samples’ characteristics (demographics)?</td>
<td>&lt;65 group: age range 5–64 year 65+ group: age range 65–105 years</td>
</tr>
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</table>
c. **What were the eligibility and/or exclusion criteria?**

Patients who died of COVID-19 in the hospital as reported to the Italian national COVID surveillance system, sample was “…selected to be representative of the regional distribution of COVID-19-related deaths”

d. **What was the attrition rate? What was the majority of attrition attributed to?**

N/A

### 4. Methods & Outcomes

b. **What main outcomes were researchers looking for, and how were they measured? (e.g. prevalence of depression, measured using PHQ-9)**

COVID-19-related symptoms: “…fever, dyspnea, cough, diarrhea, and hemoptysis.”

Times of Sx onset; Dates of hospitalization, SARS-CoV-2 testing, and death.

Comorbidities diagnosed before hospital admission

c. **How did the researchers analyze the data? What tests did they use?**

“To compare characteristics of patients according to age group, we used t tests for normally distributed variables, non-parametric Mann–Whitney U-test for skewed variables, and Fisher’s Exact Test for categorical variables.”

### 5. Results

a. **What were the results for the main outcomes?**

**COVID-19-related deaths by age group**

*In sample: Age <65: 12.1%; Age ≥65: 87.9%*

*National population: Age <65: 8.5%; Age ≥65: 91.5%*

**# of pre-hospitalization comorbidities:** Older adults had more preexisting comorbidities compared to younger adults (3.3 ± 1.9 vs 2.5 ± 1.8, p < .001).

“10.9% of younger patients (<65 years) had no comorbidities compared to 3.2% of older patients (≥65 years).”

**Types of comorbidities**- “Hypertension, diabetes, and ischemic heart disease were the most common preexisting comorbidities. The prevalence of ischemic heart disease, atrial fibrillation, heart failure, stroke, hypertension, dementia, COPD, and chronic renal failure was significantly higher in older patients … while obesity, chronic liver disease, and HIV infection, were significantly more frequent in the younger patients.”
Symptoms: Most common COVID-19 Sx were fever and dyspnea, independent of age. Diarrhea more common in younger group.

Complications “Acute Respiratory Distress Syndrome was diagnosed in the majority of patients, independently from age group, while non-respiratory complications (ie, acute renal failure and superinfections) were more commonly observed in the younger adults.”

Median times of Sx onset to death/testing/hospitalization: “Younger patients ... had a longer median time from symptoms onset to death (16 vs 10 days, p < .001), from symptoms onset to SARS-CoV-2 testing (6 vs 5 days, p = .011), from symptoms onset to hospitalization (5 vs 4 days, p = .001) and from hospitalization to death (9 vs 5 days, p < .001)”

Were there any other findings? “The proportion of women who died was 33.4% in the study sample and 40.6% in the national COVID-19 population.” Younger patients received significantly more antivirals and steroids.

6. Limitations & Interpretation

a. What were the authors’ major conclusions? Please use quotation marks and page number if using exact wording. Results align with other studies finding an association between comorbidities & mortality. However, healthy people without comorbidities can also develop serious complications/death.

In Italy, all patients who died and were COVID+ were considered a COVID death, which may confound the cause of death (versus co-morbidities as cause of death).

Suggest younger adults more likely to die from complications, and older adults more related to pre-existing co-morbidities.

“Younger patients also have a slightly longer time from symptoms onset to hospitalization than the older patients, suggesting that delayed hospital referral can indeed be related to suboptimal care and higher risk of complications development.”

“Younger patients are more likely to receive pharmacological treatments ... indicating a more intensive treatment in this sample presenting with fewer preexisting disease and longer life expectancy.”

Obesity was more common in the younger group, aligns with other research finding obesity is risk factor in adults <60.
b. Do the authors’ conclusions make sense to you? If no, why not?

Yes in the context of other studies with similar findings, but this study did not look at clinical characteristics of those that survived or were not hospitalized. Authors cannot definitely conclude whether comorbidities are associated with higher mortality, or even hospitalization.

c. What limitations did the authors discuss?

“First, they focused only on patients dying in hospital, while deaths occurring at home or in long-term care facilities were not included.”

“Second, there may be an underreporting of some preexisting conditions.”

“...data on patients surviving to the disease were not collected. This limits the possibility of identifying factors associated with increased COVID-19-related mortality (ie, preexisting conditions) and defines the incidence of non-respiratory complications in the young and older population.”

Generalizability- Italian data only

d. What are the contributions of the article as described by the authors?

None explicitly stated.

7. Analysis

a. What do you think are the article/study’s strengths?

Supports existing studies, & helpful in lending understanding to the role of comorbidities & age. Clinical information included in the sample was collected from medical charts- so I think the data is high quality.

b. What do you think are the article/study’s weaknesses?

Only looking at deaths occurring in the hospital; excluding survivors.

The proportion of deaths in each age group, and the proportion of women, did not match the larger population. Authors did not report if sample was statistically significant from population or why this may have occurred.

Authors did not discuss age as a possible independent risk factor or discuss whether the lower rates of pharm Tx among older adults contribute to the higher proportion of deaths.

c. What do you think are the most meaningful takeaways for clinical practice or research?

Young people more likely than older adults to develop non-respiratory complications- so clinicians should carefully monitor for those. Younger adults also have a longer time from Sx onset to hospitalization, consider whether earlier intervention is needed to prevent complication/death.
Awareness that the comorbidities seen more often in patients with poor outcomes are diabetes and vascular conditions; obesity seems to be a risk factor for younger adults.

For researchers - importance of a standardized definition of COVID-related death.

Summary paragraph:

This study compared the clinical characteristics and course of COVID-19-related deaths in adults over the age of 65 to adults under the age of 65. The study sample was extracted from COVID-19 related deaths occurring in hospitals as reported to the Italian National Institute of Health. Investigators collected data from medical charts for 3,032 cases: 368 cases in people less than 65 years of age, and 2,664 cases of individuals aged 65 and older. Pre-existing co-morbidities, number of co-morbidities, some COVID-19 related symptoms, and time course of the disease were compared between the two age groups. Investigators found that older adults (aged 65 and older) comprised approximately 88% of the deaths in the sample and had more pre-existing co-morbidities than the younger group. These results support other studies associating chronic illnesses with mortality; but adults without co-morbidities can develop serious complications and death. The most prevalent co-morbidities were diabetes and cardiovascular diseases independent of age. However, cardiovascular diseases, dementia, COPD and chronic renal failure were more common in older adults while obesity, chronic liver disease and HIV were more prevalent in the younger group. Younger adults were also more likely to develop non-respiratory complications; receive pharmacotherapeutics; and have a longer lapse of time from symptom onset to COVID testing, hospitalization and death than the older group. Investigators are unable to conclude which factors or comorbidities are associated with increased mortality due to the exclusion of patients who survived and those who died outside the hospital setting. The authors highlight that in Italy, fatalities were defined as any death occurring in people with COVID-19 regardless of comorbidities; and therefore, the case fatality rate may be higher than other countries. Age was not discussed as an independent risk factor, and investigators report that higher rates of pharmacological treatment in younger adults reflect more intensive treatment of patients with fewer comorbidities and longer life expectancy. Investigators did not discuss whether less aggressive treatment was due to rationing of medications, frailty of older adults, or whether it was a factor in the greater proportion of deaths occurring in older adults.

THE TAKEWAY: Similar to other studies exploring factors associated with COVID-19 mortality, this study cannot on its own cannot confirm which comorbidities increase mortality risk. Adults under the age of 65 tend to have a longer time from symptom onset to diagnosis and hospitalization; delay of hospitalization or treatment could impact the patient’s outcome. Additional risk factors to consider in adults under 65 are a higher prevalence of obesity and non-respiratory COVID-19 complications.