

# Clinical characteristics of individuals under 40 years of age who died with COVID-19 in Italy

To the Editor,

Italy had a high death toll due to COVID-19 with 35,700 deaths and a case fatality rate (CFR) of 12% by September 21, 2020. Only 87 deaths were recorded in the age-group under 40 years old. We analyzed the clinical characteristics, comorbidities, and complications in this population, based on data coming from the epidemiological surveillance and 39 medical records.

The study population included COVID-19-related deaths <40 years, defined as those occurring in patients who tested positive for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) through Reverse Transcription Polymerase Chain Reaction, independently from pre-existing diseases that may have caused or contributed to death.<sup>1-3</sup>

The primary outcome of the study was to examine the clinical characteristics of young adults who died with COVID-19, including details of hospital admission, disease symptoms, pre-existing medical conditions, pharmacological treatments, and complications that occurred during hospitalization. All deaths occurring in patients with confirmed COVID-19 were tracked by the Italian case-based surveillance system coordinated by the National Institute of Health (Istituto Superiore di Sanità [ISS]). We analyzed the data of confirmed SARS-CoV-2 deaths from February 20 until September 21, 2020, collected from all 21 regions and autonomous provinces.<sup>4,5</sup> Additional data were obtained in a subset of hospitalized patients from medical records, as Regions were asked to send them to ISS. We included all medical records received to date, and as we had no control over this process, the sample was ultimately randomly collected and therefore representative. These clinical charts were reviewed by a group of researchers at ISS to obtain more detailed information on demographics, COVID-19-related symptoms, pre-existing comorbidities, pharmacological treatments, and complications leading to death.<sup>6</sup> The study was a part of public health and surveillance activities for the COVID-19 pandemic. On February 27, 2020, the Italian Presidency of the Council of Ministers authorized the collection and scientific dissemination of data related to COVID-19 by ISS.<sup>7</sup>

## DATA FROM THE SURVEILLANCE SYSTEM

In Italy, the total number of COVID-19 confirmed cases from the epidemiological surveillance by September 21, 2020 was 296,539, while the total number of deaths was 35,700, with a case fatality rate (CFR) of 12%. The number of COVID-19 cases among subjects under 40 was 69,854 with 87 deaths (CFR: 0.1%). The majority of these deaths involved males (65.5%) and the median age was 35 (Table 1);

78.2% were hospitalized (median length of stay: 15 days); 50% were admitted to the intensive care unit (ICU). The majority had more than one medical condition (35.6%), 34.5% had only one, and 29.9% had no pre-existing disease. The most common comorbidities were neurological or psychiatric disorders (45.9%), followed by cardiovascular diseases (31.1%), active cancer (27.9%), obesity, or other metabolic disorders including diabetes (21.7% each).

## DATA FROM MEDICAL RECORDS OF HOSPITALIZED PATIENTS

Of the 87 deaths, we retrieved medical records of 39 hospitalized patients (45%). The median age was 34 and the majority were males (61.5%) (Table 1). The most common symptoms on hospital admission were fever (69.2%), dyspnoea (53.8%), and cough (46.1%). Radiological evidence of pneumonia was found in 74.4% of the patients. 56.4% of the patients were admitted to ICU and 87.2% underwent respiratory assistance. 48.7% of the deaths occurred in patients with more than one pre-existing disease, the most common of which were neurological or psychiatric conditions (48.4%), cardiovascular diseases (35.5%), active cancer (29%), obesity (25.8%). Among the nine cases of active malignancy, the most represented was breast cancer (three cases). Moreover, 10 patients had pre-existing disabilities, including some living in a long-term care facility. Four children (age  $\leq 6$  years) who died with SARS-CoV-2 were all suffering either from rare genetic diseases or cancer. Overall, 84.6% of patients were treated with antibiotics, 74.4% with antivirals or hydroxychloroquine, 56.4% with steroids, and almost 17.9% with tocilizumab. The most frequent complications recorded during the hospitalization were acute respiratory distress syndrome (84.6%), shock (41.5%), superinfection (33.3%), acute renal failure (20.5%), acute cardiac injury (12.8%).

It is worth acknowledging that recent estimates from the Italian serosurvey show that 1,482,000 people were infected by SARS-CoV-2, five times more than the number of cases recorded by ISS, lowering the CFR to 2.4%.<sup>8</sup> Moreover, in Italy, COVID-19 had no impact on excess mortality in the population under the age of 50, even in the most affected areas, with only 1% of the deaths involving this age-group.<sup>9</sup>

As highlighted in a previous Italian study, the characteristics of younger patients who died with COVID-19 were different from the ones observed in the elderly.<sup>6</sup> Subjects over 65 years showed on average a higher number of underlying conditions compared with our population (3.3 vs. 1.2) and presented no comorbidities in only 3.2%

**TABLE 1** Clinical characteristics of patients <40 years with COVID-19 who died in Italy, February 20–September 21, 2020

	Surveillance		Medical records	
	<i>n</i> or median	% or IQR	<i>n</i> or median	% or IQR
Total cases	87		39	
Males	57	65.5	24	61.5
Females	30	34.5	15	38.5
Age (years) (median, IQR)	35	30–38	34	29–38
Hospitalization	68	78.2	39	100.0
Length of stay (median, IQR)	15	5–24	16	9–23
Intensive care unit	34	50.0	22	56.4
Respiratory assistance	n.a.	n.a.	34	87.2
Radiological finding of pneumonia	n.a.	n.a.	29	74.4
Temperature, maximum (median, IQR)	n.a.	n.a.	39	38–39
C reactive protein (mg/L) (median, IQR) (normal range <5 mg/L)	n.a.	n.a.	35	22–179
Pre-existing underlying medical conditions				
0	26	29.9	8	20.5
1	30	34.5	12	30.8
>1	31	35.6	19	48.7
Underling conditions	61	70.1	31	79.5
Neurological/psychiatric diseases	28	45.9	15	48.4
Cardiovascular diseases	19	31.1	11	35.5
Active cancer	17	27.9	9	29.0
Obesity	13	21.3	8	25.8
Metabolic disorders/diabetes	13	21.3	2	6.5
Respiratory disease	5	8.2	3	9.7
Chronic renal failure	5	8.2	4	12.9
Immune system disorders	3	4.9	3	9.7
Chronic liver disease	1	1.6	1	3.2
Hematological disease	1	1.6	1	3.2
COVID-19 symptoms at hospitalization	n.a.			
Fever	–	–	27	69.2
Dyspnea	–	–	21	53.8
Cough	–	–	18	46.1
Diarrhea	–	–	3	7.7
Hemoptysis	–	–	1	2.6
Oxygen saturation (%) (median, IQR)	–	–	93	88–97
Heart rate (beats/min) (median, IQR)	–	–	101	90–112
Respiratory rate (beats/min) (median, IQR)	–	–	20	18–30
Treatments during hospitalization	n.a.			
Antivirals	–	–	29	74.4
Antibiotics	–	–	33	84.6
Steroids	–	–	22	56.4
Tocilizumab	–	–	7	17.9
Complications during hospitalization	n.a.			
Acute respiratory distress syndrome	–	–	33	84.6
Shock	–	–	16	41.5
Superinfection	–	–	13	33.3
Acute renal failure	–	–	8	20.5
Acute cardiac injury	–	–	5	12.8

(Continues)

TABLE 1 (Continued)

	Surveillance		Medical records	
	n or median	% or IQR	n or median	% or IQR
Days from symptoms onset to diagnosis (median, IQR)	6	2–7	5	3–8
Days from symptoms onset to hospitalization (median, IQR)	4	1–8	6	3–7
Days from onset symptoms to death (median, IQR)	17	8–28	23	11–28
Days from hospitalization to death (median, IQR)	15	5–24	16	9–23

Abbreviations: IQR, interquartile range; n.a., not available.

versus 29.9% of cases, and three or more in 61.7% versus 13.8%.<sup>6</sup> Our population also seemed to develop and frequently die of serious nonrespiratory complications that occurred during hospitalization, such as shock, superinfection, acute renal failure, and acute cardiac injury. Patients below 40 years also had a rather long time from symptoms onset to hospitalization (6 days), and this may be interpreted as delayed hospital referral, potentially also explaining the higher risk of complications. Overall, younger patients were likely to receive more intensive treatment, including pharmacological therapy, such as antivirals, steroids, and antibiotics; this may be explained by their long life expectancy. The widespread use of antibiotics in younger patients may be related to the high prevalence of superinfections, but probably also to the ongoing process of research and learning on the most effective drug regimens, with various drugs used empirically or off-label, (e.g., azithromycin<sup>10</sup>). Nevertheless, the compassionate and empirical use of drugs during the first phase of the pandemic allowed testing different combinations of therapies and gave way to structured clinical trials to evaluate effective treatments for COVID-19.

In the majority of our cases (79.5%), the patients who died with COVID-19 were suffering from underlying diseases, sometimes severe; in these patients SARS-CoV-2 contributed to the fatal outcome, further compromising the clinical conditions. However, it is worth acknowledging that some patients were healthy before SARS-CoV-2 infection. This might be due to the unawareness of previous conditions; however, COVID-19 only should be considered responsible for these deaths. Similarly, a recently published report<sup>11</sup> based on the analysis of the Italian death records identifies COVID-19 as the direct cause of death in 89% of the patients who tested positive for SARS-CoV-2, including when superimposed on other pre-existing diseases. In the remaining cases, death can be considered due to another disease, and COVID-19 may have contributed to the death by accelerating or aggravating the outcome of pre-existing diseases or limiting the possibility of treatment.

Several studies showed similar findings compared with ours. In a large British study<sup>12</sup> comorbidities mainly contributed in increasing the risk of death for COVID-19, including diabetes, severe asthma,

respiratory disease, chronic heart disease, liver disease, stroke/dementia, other neurological diseases, reduced kidney function, autoimmune diseases, and other immunosuppressive conditions; increasing risk was observed with increasing obesity. Overall being male, over 65 years and with one or more underlying conditions increased the risk of developing severe disease or death.<sup>13</sup> Moreover, a modeling study<sup>14</sup> shows that one in five individuals worldwide has an underlying condition that could increase their risk of severe COVID-19 if infected, ranging from less than 5% of those younger than 20 years to more than 66% of those aged 70 years.

It is still unclear what individual characteristics determine the disease severity in each subject. HLA and ABO alleles have been involved to explain the individual susceptibility to COVID-19. However, a recently published genome association study involving 1980 patients with COVID-19 and severe disease at seven Italian and Spanish hospitals showed no significant allele associations of the classical human leukocyte antigen loci with either COVID-19 or disease severity.<sup>15</sup> This study also confirms that blood group O is associated with a lower risk of acquiring COVID-19, whereas blood group A was associated with a higher risk than non-A blood groups.

In our view, it is also crucial to reflect on the high proportion (26%) of patients in our sample with either physical or mental disability or suffering from a rare disease, that is, Marfan and Williams syndromes, rare cancers, congenital heart diseases, for whom taking precautions and using personal protective equipment may be difficult. We should protect these vulnerable patients through the implementation of infection control measures to prevent COVID-19 spread in long-term care facilities or hospitals.

This study has some limitations; first, the generalizability of our findings may be limited by the small sample size, however, the analysis covers more than 40% of all deaths in patients younger than 40 years in the country to date; moreover, our analysis is focused on patients dying in the hospital only, however, the patients in our sample were all hospitalized.

Overall, our data indicate that a low number of young persons die with COVID-19. Although the majority of the patients aged below 40 who died with COVID-19 suffered from previous and often severe

pre-existing conditions, a small proportion did not suffer from any chronic disease, suggesting that COVID-19 can lead to death in young healthy subjects.

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#### CONFLICT OF INTERESTS

The authors declare that there are no conflict of interests.

#### AUTHOR CONTRIBUTIONS

Ornella Punzo conceptualized and designed the manuscript, collected and interpreted the clinical data, drafted the manuscript and revised it; Stefania Bellino analyzed the data and critically reviewed the manuscript; Luigi Palmieri carried out the final medical records database; Cinzia Lo Noce was responsible for the supervision of data collection and data management; Marina Giuliano and Paola Meli contributed to clinical data collection and revised the manuscript; Stefania Bellino contributed to the surveillance data collection; Flavia Riccardo contributed to the coordination of the COVID-19 national surveillance; Antonino Bella coordinated and supervised the surveillance data collection; Patrizio Pezzotti is the Head of the Italian COVID-19 surveillance system and revised the manuscript; Graziano Onder contributed to conceptualize the manuscript, critically reviewed the manuscript and is the Head of the COVID-19 ISS group on Mortality Causes; COVID-19 mortality and surveillance groups data collection and revision of the draft. All authors approved the final manuscript as submitted and agree to be accountable for all aspects of the work.

#### DATA AVAILABILITY STATEMENT

The data that supports the findings of this study are available in the supplementary (table) of this article.

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