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

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Abstract

Background: aim of the present study is to describe characteristics of COVID-19 related deaths and to compare the clinical phenotype and course of COVID-19 related deaths occurring in adults (< 65 years) and older adults (≥ 65 years).

Methods: medical charts of 3,032 patients dying with COVID-19 in Italy (368 aged < 65 years and 2,664 aged ≥ 65 years) were revised to extract information on demographics, pre-existing comorbidities, and in-hospital complications leading to death.

Results: Older adults (≥ 65 years) presented with a higher number of comorbidities compared to those aged < 65 years (3.3 ± 1.9 vs. 2.5 ± 1.8, p<0.001). Prevalence of ischemic heart disease, atrial fibrillation, heart failure, stroke, hypertension, dementia, COPD, and chronic renal failure was higher in older patients (≥ 65 years), while obesity, chronic liver disease, and HIV infection were more common in younger adults (< 65 years); 10.9% of younger patients (< 65 years) had no comorbidities, compared to 3.2% of older patients (≥ 65 years). The younger adults had a higher rate of non-respiratory complications than older patients including acute renal failure (30.0% vs 20.6%), acute cardiac injury (13.5% vs 10.3%) and superinfections (30.9% vs. 9.8%).

Conclusions: individuals dying with COVID-19 present with high levels of comorbidities, irrespective of age group, but a small proportion of deaths occurs in healthy adults with no pre-existing conditions. Non-respiratory complications are common, suggesting that the treatment of respiratory conditions needs to be combined with strategies to prevent and mitigate the effects of non-respiratory complications.

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Introduction

The first case of COVID-19 was diagnosed in Italy on February 20, 2020 (1), with the first related death occurring on February 21, in a person aged 78 years suffering from pre-existing cardiovascular disease. As of May 21, 2020, Italy is one of the countries with the largest number of confirmed COVID-19 cases (n= 227,615) and related deaths (n=31,096) (2).

Since the beginning of the pandemic, older people had the highest fatality rate, but COVID-19 related deaths have also been reported in young and middle-aged adults (3-5). It has been shown that presence of comorbidities, including cardiovascular disease, diabetes and cancer, can influence prognosis in older individuals with COVID-19 (6-8) and it might be hypothesized that the coexistence of concomitant clinical conditions may increase the risk of COVID-19 related death in younger persons.

The aim of the present study is to describe the clinical features of COVID-19 related deaths occurring in Italy and compare the clinical characteristics and course of COVID-19 related deaths between younger (< 65 years) and older adults (≥ 65 years).

Methods

At the outset of the COVID-19 outbreak, the Italian National Institute of Health (Istituto Superiore di Sanità – ISS) launched an integrated national surveillance system to collect information on all individuals with COVID-19 throughout the country. Data on all confirmed COVID-19 cases were obtained from all 19 Italian Regions and the two autonomous provinces of Trento and Bozen (9).

All deaths occurring in patients with confirmed COVID-19 were tracked by the surveillance system. COVID-19 related deaths were defined as those occurring in patients who tested positive for SARS-CoV-2 through Reverse Transcription Polymerase Chain Reaction, independently from pre-existing diseases that may have caused or contributed to death. The system was unable to collect detailed clinical data. Thus, Regions and autonomous provinces were asked to send ISS the medical charts of COVID-19 patients who died in-hospital. These clinical charts were reviewed by a group of researchers of ISS to obtain more detailed information on demographics, COVID-19 related symptoms, pre-existing comorbidities, pharmacological treatments, and on complications leading to death.

Data on the following COVID-19 related symptoms were collected: fever, dyspnea, cough, diarrhea, and hemoptysis. Data on dates of hospitalization, SARS-CoV-2 testing, and death were extracted. Time of symptoms onset was calculated based on information in the clinical charts. Information on comorbidities diagnosed before hospital admission were collected based on anamnestic data reported in the chart.

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As of May 21 2020, 31,096 COVID-19 related deaths were reported in Italy (2) and 3,032 medical charts were examined by ISS (9.8% of COVID-19 related deaths). These charts were selected to be representative of the regional distribution of COVID-19 related deaths. 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.

Ethical issues

On February 27th, 2020, the Italian Presidency of the Council of Ministers authorized the collection and scientific dissemination of data related to COVID-19 by the ISS and other public health institutions (10).

Results

As of May 21, 2020 at a national level, 2,644 COVID-19 related deaths occurred in persons aged < 65 years (8.5% of total COVID-19 related deaths) and 28,452 in persons aged ≥ 65 years (91.5%). The present report is based on a sample of this population which includes 368 cases of COVID-19 related deaths occurring in individuals aged < 65 years (12.1% of study sample, age range 5-64 years) and 2,664 in individuals aged ≥ 65 years (87.9%, age range 65-105 years). The proportion of women who died was 33.4% in the study sample and 40.6% in the national COVID-19 population.

Table 1 summarizes the most common comorbidities diagnosed before COVID-19 infection by age group. Patients had a high number of comorbidities (mean number 3.2 ± 1.9). Hypertension, diabetes, and ischemic heart disease were the most common pre-existing 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 (≥ 65 years) than younger adults (< 65 years), while obesity, chronic liver disease, and HIV infection, were significantly more frequent in the younger patients. Older patients (≥ 65 years) had on average a higher number of pre-existing comorbidities compared to younger adults (< 65 years) (3.3 ± 1.9 vs. 2.5 ± 1.8, p<0.001). Overall, 10.9% of younger patients (< 65 years) had no comorbidities compared to 3.2% of older patients (≥ 65 years).

The most commonly observed COVID-19 related symptoms were fever and dyspnea, regardless of age; diarrhea resulted significantly more frequent in younger patients (< 65 years) than in older ones (≥ 65 years). Acute Respiratory Distress Syndrome was diagnosed in the majority of patients, independently from age group, while non-respiratory complications (i.e. acute renal failure and superinfections) were more commonly observed in the younger adults. Pharmacological

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treatment varied across age groups, with younger patients (<65 years) receiving significantly more antivirals and steroids.

Table 2 presents median times and interquartile ranges (IQR), in days, from the onset of symptoms to death (11 days, IQR 7-16), SARS-CoV-2 testing (5 days, IQR 3-9) and hospitalization (5 days, IQR 2-7), as well as time from hospitalization to death (6 days, IQR 3-10). Younger patients (< 65 years) had a longer median time from symptoms onset to death (16 vs 10 days, p<0.001), from symptoms onset to SARS-CoV-2 testing (6 vs 5 days, p=0.011), from symptoms onset to hospitalization (5 vs 4 days, p=0.001) and from hospitalization to death (9 vs 5 days, p<0.001).

Discussion

The present study provides clinical data on a large sample of individuals dying with COVID-19 in Italy. Less than 9% of patients dying with COVID-19 were younger than 65 years. The majority of patients suffered from relevant pre-existing comorbidities, including cardiovascular disease, diabetes, cancer, dementia, and respiratory diseases. This finding is in line with previous studies suggesting that presence of comorbidities is associated with a higher risk of mortality and negative outcomes in COVID-19 patients (6-8). Further, most pre-existing co-morbidities were more common in older patients, with the exception of obesity, HIV infection, and chronic liver disease, which were higher in younger patients.

The high prevalence of pre-existing conditions in patients dying with COVID-19 led to a debate in the Italian media regarding the main causes of death in COVID-19 patients (11). In presence of a high level of comorbidities (i.e. advanced cancer, dementia, heart failure), COVID-19 might represent the final event leading to death, but not necessarily the main cause of death. For this reason, the attribution of causes of deaths in persons with very severe comorbidities to COVID-19 is difficult to establish. In Italy, all deaths occurring in patients with SARS-CoV-2 infection were identified as related to COVID-19, independently from presence of pre-existing comorbidities and this decision may have led to a higher COVID-19 case fatality rate than has been reported in other countries (7). Therefore, it is pivotal to establish internationally agreed criteria to classify deaths as attributable to COVID-19 infection, in order to make comparisons between COVID-19 case-fatality and mortality rates across countries and regions and to better assess the impact of interventions on COVID-19 related deaths. Recently, World Health Organization provided international guidelines for certificating and coding SARS-CoV-2 infection as cause of death, which will help to standardize and compare mortality results across countries (12).

Younger adults who died with COVID-19 presented with a lower number of pre-existing conditions, compared with older patients, but almost half of them still suffered from 3 or more pre-

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existing diseases. The prevalence of comorbidities in the general adult population in Italy is much lower than is observed in the study sample: in the adult population in Italy (age range 35-64 years), hypertension, obesity and diabetes have a prevalence of 38.4%, 23.1% and 7.1%, respectively (13). This observation suggests that that the burden of comorbidities may play a role in increasing mortality risk in adults with COVID-19.

Overall, 4.1% of the study sample appeared to be healthy before the SARS-CoV-2 infection. Such low prevalence could be related to an underreporting of pre-existing conditions. However, if extrapolated to the total number of deaths so far in Italy, in actual numbers about 1300 COVID-19 deaths could have occurred in patients with no underlying medical issues. This finding is a matter of concern, suggesting that also healthy individuals can develop clinical important respiratory and non-respiratory complications from COVID-19, potentially leading to death. Specifically, non-respiratory complications, including acute renal failure, acute cardiac injury and superinfection were common in the study population. This mirrors reports from China suggesting that cardiac injury is a common condition among hospitalized patients with COVID-19 and is associated with higher risk of in-hospital mortality (14). These observations underline the need of implementing strategies to prevent these complications regardless of the patient's age, with the ultimate goal of reducing COVID-19 fatality. In addition, ISS is also analyzing data from death certificates of patients dying with COVID-19. These data will provide further evidence on cascade of events leading to death in this population.

Some relevant differences were noted in the clinical aspects of COVID-19 in younger adults. They suffered from less pre-existing conditions as compared with older adults but were more likely to die with non respiratory complications. This finding suggests that while in older adults mortality is closely related to a pre-existing vulnerability due to presence of chronic conditions, COVID-19 related death in adults aged < 65 years is often due to the development of complications. 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, including antivirals, steroids and antibiotics, indicating a more intensive treatment in this sample presenting with fewer pre-existing disease and longer life expectancy. Also, the high use of antibiotics in the adult sample might be related to the common occurrence of superinfections.

Although most of the examined comorbidities were more prevalent in older adults, obesity was more common in the younger group. This finding is in line with a recent study suggesting that obesity is a risk factor for hospital admission and need for critical care in patients aged < 60 years with COVID-19, but not in those aged 60 years or older (15). In older persons with acute infections

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an obesity paradox has been described, where higher BMI is associated with better outcomes when acute conditions occur (16).

Our findings should be interpreted in light of potential limitations. First, they focused only on patients dying in hospital, while deaths occurring at home or in long-term care facilities were not included. However, the data are still informative for providing the clinical history and disease progression among the subset of hospitalized patients whose medical charts were carefully reviewed. Second, there may be an underreporting of some pre-existing conditions. Third, we reviewed charts of patients dying with COVID-19 and data on patients surviving to the disease were not collected. This limits the possibility of identifying factors associated with increased COVID-19 related mortality (i.e. pre-existing conditions) and to define the incidence of non-respiratory complications in the young and older population. Finally, the generalizability of our findings might be limited as we provide data only on Italian patients.

In conclusion, hospitalized individuals dying with COVID-19 in Italy have a high number of comorbidities, regardless of age. However, a small proportion of deaths occurred in younger adult patients with no pre-existing conditions, indicating that COVID-19 might have negative consequences also in healthy individuals. The younger age group had fewer pre-existing conditions, which are known risk factors for COVID-19-related complications, but individuals in this group are more likely to die with non-respiratory complications. This finding suggests that, in order to reduce COVID-19 case-fatality, the treatment of respiratory conditions needs to be combined with an appropriate management of pre-existing conditions and with strategies to prevent and mitigate the effects of non-respiratory complications.

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Contributors: GO designed the study, had full access to all data in the study, and takes responsibility for the integrity and accuracy of the data analysis. NV, MC, VR, DT, OP, LV, PP, FL, AB, MF and EC contributed to data acquisition and data interpretation. LP and GO were responsible for literature search, manuscript writing and data analysis. CD and CLN were responsible for supervision of data collection and data management. All authors reviewed and approved the final version of the manuscript. The corresponding author attests that all listed authors meet authorship criteria and that no others meeting the criteria have been omitted. GO is the guarantor.

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Table 1. Comorbidities, symptoms, complications, and treatments in COVID-19 patients who die, according to age group

	All (n=3,032)		**Younger adults < 65 years (n=368)**	**Older adults ≥ 65 years (n=2,664)**	***p-value****
	n (%)		**n (%)**	**n (%)**	
Comorbidities					
Ischemic heart disease	856 (28.2)		42 (11.4)	814 (30.6)	*<0.001*
Atrial fibrillation	681 (22.5)		18 (4.9)	663 (24.9)	*<0.001*
Heart failure	490 (16.2)		31 (8.1)	459 (16.9)	*<0.001*
Stroke	310 (10.2)		16 (4.3)	294 (11.0)	*<0.001*
Hypertension	2071 (68.3)		188 (51.1)	1883 (70.7)	*<0.001*
Type 2 diabetes	914 (30.1)		106 (28.8)	808 (30.3)	*0.586*
Dementia	480 (15.8)		12 (3.3)	468 (17.6)	*<0.001*
COPD	498 (16.4)		41 (11.1)	457 (17.2)	*0.003*
Active cancer	480 (15.8)		56 (15.2)	424 (15.9)	*0.761*
Chronic liver disease	120 (4.0)		24 (6.5)	96 (3.6)	*0.010*
Chronic renal failure	618 (20.4)		42 (11.4)	576 (21.6)	*<0.001*
Dialysis	55 (1.8)		9 (2.4)	46 (1.7)	*0.301*
HIV	6 (0.2)		4 (1.1)	2 (0.1)	*0.003*
Autoimmune diseases	115 (3.8)		15 (4.1)	100 (3.8)	*0.770*
Obesity	335 (11.0)		108 (29.3)	227 (8.5)	*<0.001*
N of comorbidities					
0	124 (4.1)		40 (10.9)	84 (3.2)	*<0.001*
1	454 (15.0)		85 (23.1)	369 (13.9)	
2	648 (21.4)		82 (22.3)	566 (21.2)	
3 or more	1806 (59.6)		161 (43.8)	1645 (61.7)	
COVID-19 Symptoms					
Fever	2292 (76.4)		283 (77.3)	2009 (76.3)	*0.694*
Dyspnea	2211 (73.7)		270 (73.8)	1941 (73.7)	*1.000*
Cough	1162 (38.7)		146 (39.9)	1016 (38.6)	*0.647*
Diarrhea	175 (5.8)		34 (9.3)	141 (5.4)	*0.004*
Hemoptysis	17 (0.6)		3 (0.8)	14 (0.5)	*0.453*
Complications during hospitalization					
Acute Respiratory Distress Syndrome	2856 (96.9)		353 (97.2)	2503 (96.9)	*0.871*
Acute renal failure	641 (21.8)		109 (30.0)	532 (20.6)	*<0.001*
Acute cardiac injury	314 (10.7)		49 (13.5)	265 (10.3)	*0.069*

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Superinfection	364 (12.4)		112 (30.9)	252 (9.8)	*<0.001*
Treatments					
Antibiotics	2390 (85.4)		338 (90.6)	2216 (84.9)	*0.003*
Antivirals	1760 (59.0)		268 (71.8)	1492 (57.2)	*<0.001*
Steroids	1115 (37.4)		178 (47.7)	937 (35.9)	*<0.001*

* p value for difference between younger and older adults.

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Table 2. Median times related to onset of symptoms, testing, hospitalization and death

	All (n=3,032)		**Younger adults < 65 years (n=368)**		**Older adults ≥ 65 years (n=2,664)**		***p-value****
	Median	**IQR**	**Median**	**IQR**	**Median**	**IQR**	
From symptoms onset to death	11	7-16	16	11-22.5	10	7-22	*<0.001*
From symptoms onset to SARS-CoV-2 testing	5	3-9	6	3-10	5	3-8	*0.011*
From symptoms onset to hospitalization	5	2-7	5	3-9	4	2-7	*0.001*
From hospitalization to death	6	3-10	9	5-17	5	3-9	*<0.001*

* p value for difference between younger and older adults.

IQR=Inter-Quartile Range

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