

Epidemiology of SARS-CoV-2: numbers matter!

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Abstract

The ongoing pandemic is the result of the spread of a recently identified Coronavirus, named SARS-CoV-2 (Severe Acute Respiratory Syndrome – Coronavirus – 2).

Since 31st December 2019, when the first cluster was reported in Wuhan (China), the global Novel CORonaVIRus Disease 2019 (COVID-19) cases significantly increased, and on 12th March 2020, the WHO Director declared the disease as pandemic.

As of April 28th 2020, 2,982,688 cases and 210,193 deaths were reported globally.

The aim of this article is the analysis of the main epidemiological characteristics of the current pandemic: transmission, basic reproduction number (R0), incubation period, global, European and Italian confirmed cases and deaths, focusing on the paediatric population.

Keywords

COVID-19, SARS-CoV-2, 2019-nCoV, Coronavirus, epidemiology, children, review.

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Introduction

On 31st December 2019, Chinese health authorities reported the outbreak of an atypical pneumonia of unknown etiology, allegedly viral, in the city of Wuhan, the capital of Hubei Province, central China [1].

On 9th January 2020, the Chinese National Institute of Viral Disease Control and Prevention (IVDC) isolated a new Coronavirus in bronchoalveolar lavage samples of a patient from Wuhan, recognizing it as the agent responsible for the outbreak of pneumonia. Phylogenetic analysis of the new virus, provisionally named as 2019-nCoV, allowed to classify it as belonging to the genus Betacoronavirus (Group 2B) of the subfamily Orthocoronavirinae [2].

Thereafter, Coronavirus Study Group (CSG) of the International Committee on Taxonomy of Viruses officially classified it as SARS-CoV-2 [3].

On 12th March 2020, the WHO Director, owing to 125,000 total cases over 2 weeks, the 118 countries involved, the rapid spread that over 2 weeks led to a 13-fold increase in the number of cases outside China, and to a 3-fold increase of the involved countries, declared the disease as pandemic [4].

Transmission

The significant increase in confirmed cases leads the scientific community to investigate Novel CORonaVIRUS Disease 2019 (COVID-19) ways of transmission. So, inter-human transmission was confirmed [5].

Up-to-now, SARS-CoV-2 was identified in samples from the respiratory system, blood, faeces [6] and urine [7].

The highest viral load was found in the posterior oropharyngeal secretions at an early stage of the disease, i.e. just before the appearance of symptoms or when they are still mild [8].

Viral load does not appear to vary between symptomatic and asymptomatic patients [9].

Recent studies highlighted that the serial interval is shorter than the incubation period, hence transmission from asymptomatic individuals plays an important role in the viral spread [9-11].

The viral identification in faecal samples [12] and the prolonged positivity compared to the negative nasopharyngeal swabs [13] led to hypothesize that faecal-oral transmission may play a crucial role [14].

The role of fomites (i.e. both porous and nonporous surfaces or objects that can become contaminated

with pathogenic microorganisms; in the past they proved to be associated particularly with hospital-acquired infections, since they are possible routes to pass pathogens between patients) in human-to-human transmission is not yet fully elucidated.

The virus survives 3 hours in the air, 4 hours on copper, 24 hours on paper, and up to 72 hours on plastic and stainless steel surfaces [15] and surface contamination was demonstrated also in hospitals [16].

Maternal-foetal transmission seems unlikely according to the studies carried out so far.

Viral search in maternal amniotic fluid, umbilical cord blood, placental tissue, breast milk, maternal vaginal swab and oropharyngeal swab of newborns were negative [17, 18].

As concerns breastfeeding, never SARS-CoV-2 was found in breast milk. Even admitting the theoretical risk of transmission from a mother to her child by airborne droplets, the Italian Society of Neonatology (*Società Italiana di Neonatologia*, SIN) pointed out the benefits of breastfeeding for newborns and mothers, in terms of health and relationship. According to the SIN, breastfeeding should be always promoted and infection prevented by increasing hygiene measures. The latter are the best way to prevent infections spread [19].

Incubation period

It usually ranges between 4 and 6 days [20, 21]. Although most of patients develop symptoms within 14 days, clinical onset may also be delayed, hence a personalized approach with a prolonged lockdown may be justified [21].

Basic reproduction number (R0)

The basic reproduction number (R0) is between 2.0 and 3.0 [20]. This number is affected by many factors, including place of infection, number of subjects faced by the infected, preventive measures put in place, data collection and so on.

Worldwide and European cases

As of 28th April 2020, a peak of 2,982,688 of COVID-19 cases were confirmed in 213 countries [22].

Of these, 36.4% (1,087,272) were diagnosed in Europe [23].

The US reported the largest number of confirmed cases (988,451), followed by Spain, Italy, United Kingdom, and Germany (**Tab. 1**) [22].

Table 1. Confirmed cases per 100,000 residents of the first 5 countries in the world for total confirmed cases. Table created with data from ECDC [22], ECDC European Surveillance System (TESSy) [23], and Italian Civil Protection agency [28].

Country	Total confirmed cases	Confirmed cases per 100,000 residents
United States	988,451	6.9
Spain	209,465	2.8
Italy	201,505	2.9
United Kingdom	157,149	6.5
Germany	156,337	1.4

As to age distribution, disease affects the elderly the most. The analysis of data reported by the Chinese Center for Disease Control and Prevention (CCDC), the European Centre for Disease Prevention and Control (ECDC) and the US Centers for Disease Control and Prevention (CDC) showed that most of infected patients were older than 49 years (CCDC, ECDC) or older than 45 years (CDC) (**Fig. 1**) [23-25].

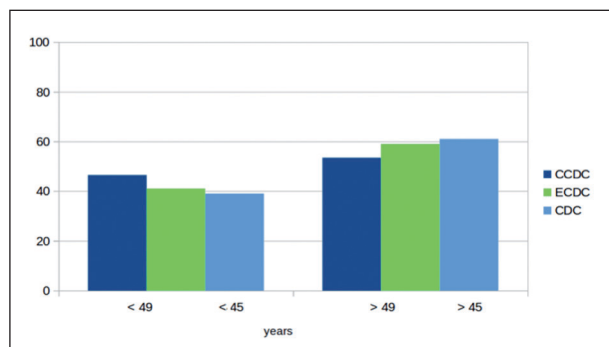


Figure 1. Age distribution of COVID-19 cases reported by CCDC (n = 44,672), ECDC (n = 427,981), and CDC (n = 723,584).

Graph created with data from CCDC Novel Coronavirus Pneumonia Emergency Response Epidemiology Team [24], ECDC European Surveillance System (TESSy) [23], and CDC [25].

In relation to the sex distribution, the number of male patients is greater than that of female patients in the series published by the CCDC and CDC (the difference was 2.8% and 6%, respectively). Conversely, opposite findings came from the ECDC (the difference was 4%) (**Fig. 2**) [23, 24, 26].

The data collected by the CDC and ECDC revealed that the percentages of patients who required general hospital care or were admitted to Intensive Care Units (ICU) were similar (**Tab. 2**) [23, 26].

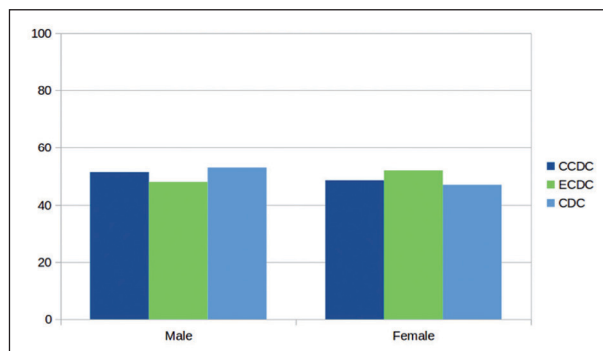


Figure 2. Sex distribution of COVID-19 cases reported by CCDC (n = 44,672), ECDC (n = 427,981), and CDC (n = 143,414).

Graph created with data from CCDC Novel Coronavirus Pneumonia Emergency Response Epidemiology Team [24], ECDC European Surveillance System (TESSy) [23], and CDC COVID-19 Response Team [26].

Table 2. Percentages* of hospitalizations and ICU admissions reported by CDC (35,806 cases aged between 0 and 64 years whose informations about hospitalization status were available) and ECDC (156,091 and 121,013 cases whose informations about hospitalization status and ICU admission were available, respectively).

Table created with data from CDC COVID-19 Response Team [26] and ECDC European Surveillance System (TESSy) [23].

	Hospitalization (%)	ICU (%)
CDC	10-33%	1.4-4.5%
ECDC	10-29%	1-3.5%

ICU: Intensive Care Units.

*The denominator for determining the range lower limit included cases with both known and unknown hospitalization or ICU status; the denominator for the upper limit included only cases with known hospitalization or ICU status.

Regarding the paediatric population, the analysis of epidemiological characteristics highlighted a prevalence of the disease in older males [26, 27].

This distribution was confirmed when comparing the data published by CDC, Dong et al., and ECDC (**Figures 3-5**) [23].

The report published by CDC [26] on 2,572 paediatric confirmed cases included an analysis of hospitalizations and comorbidities (data were available for 745 and 345 of the enrolled patients, respectively).

As regards the hospitalizations, the CDC released its findings as a range. More specifically, the denominator for determining the lower limit included cases with both known and unknown hospitalization or ICU status, and the upper limit included only cases with known hospitalization or ICU status. These percentages are low: 5.7-20% and 0.58-2%, respectively, for hospitalization and admission to ICU.

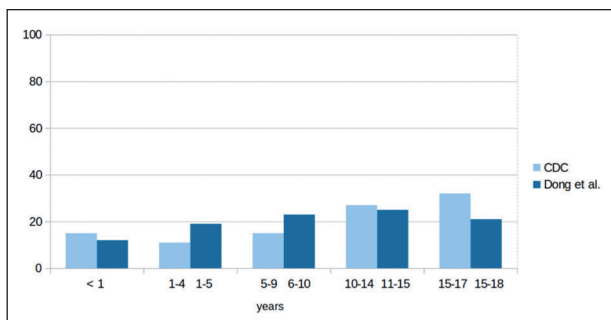


Figure 3. Age distribution of COVID-19 paediatric cases reported by CDC (n = 2,572) and Dong et al. (n = 731). Graph created with data from CDC COVID-19 Response Team [26] and Dong et al. [27].

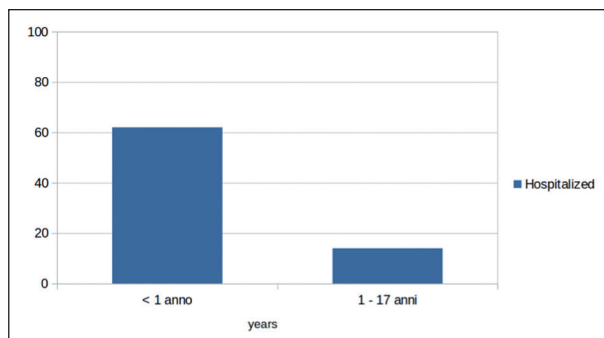


Figure 6. Age distribution of children hospitalised for COVID-19 in the United States (n = 745). Graph created with data from CDC COVID-19 Response Team [26].

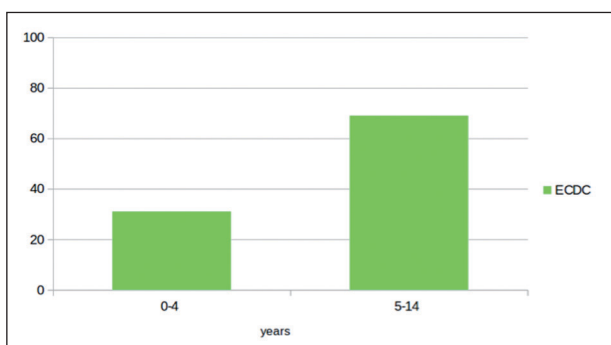


Figure 4. Age distribution of COVID-19 paediatric cases reported by ECDC (n = 8,939). Graph created with data from ECDC European Surveillance System (TESSy) [23].

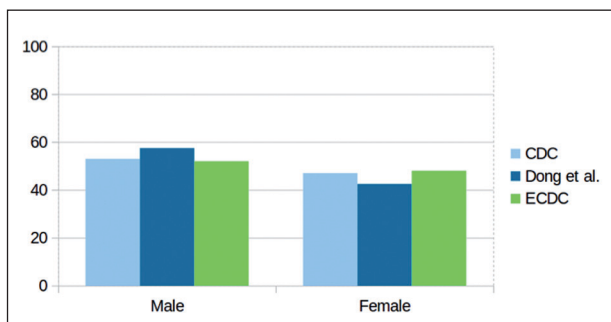


Figure 5. Sex distribution of COVID-19 paediatric cases reported by CDC (n = 2,490), Dong et al. (n = 731), and ECDC (n = 8,878). Graph created with data from CDC COVID-19 Response Team [26], Dong et al. [27], and ECDC European Surveillance System (TESSy) [23].

The greatest number of hospitalisations was among children under the age of 1 (**Fig. 6**).

Regarding comorbidities, on the basis of the available data, 23% had at least one comorbidity. Among these, the most common were chronic respiratory diseases and asthma (50%), cardiovascular diseases (31%) and immunosuppression (12.5%).

Of the 295 paediatric cases with available information on both hospitalisation and diagnosis of pre-existing conditions, 77% of the hospitalised patients (37) had at least 1 previous condition. Conversely, among the remaining 258 patients who did not need hospital care, 12% had at least 1 previous illness.

Italian cases

As of 28th April 2020, with 201,505 registered cases, Italy was the second European country as for confirmed cases of COVID-19 [28].

According to the Italian National Institute of Health (*Istituto Superiore di Sanità*, ISS), Italian data were similar to global ones concerning age distribution and most of patients were older than 49 years (**Fig. 7**) [29].

The median age was 62 years and the most affected age group was that between 50 and 59 years (**Fig. 8**) [29].

Regarding sex distribution, 51.4% of the patients whose information about sex was available were female. In all age groups except for those aged 0-9, 60-69, and 70-79 years the female sex was predominant [29].

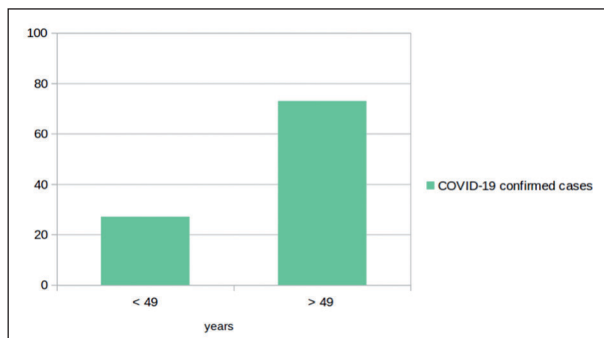


Figure 7. Age distribution of Italian confirmed cases (n = 177,025). Graph created with data from ISS [29].

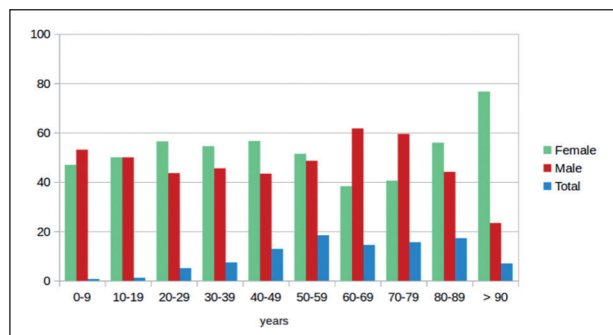


Figure 8. Age and sex distribution of Italian confirmed cases (n = 177,143). Graph created with data from ISS [29].

By examining the data of the last bulletin released by the Italian Civil Protection agency (*Dipartimento della Protezione Civile*) on 28th April 2020, the patients admitted to ICU were 1.8% (1,863), while those admitted to other wards were 18.7% (19,723) among the positive cases (105,205) [28], in line with global percentages.

The paediatric subpopulation (< 18 years) accounted for about 1.6% of the cases, i.e. 2,846 cases out of 177,143.

Similarly to the global findings, the analysis of Italian data highlighted a prevalence of the disease in older males (**Fig. 9**) [29].

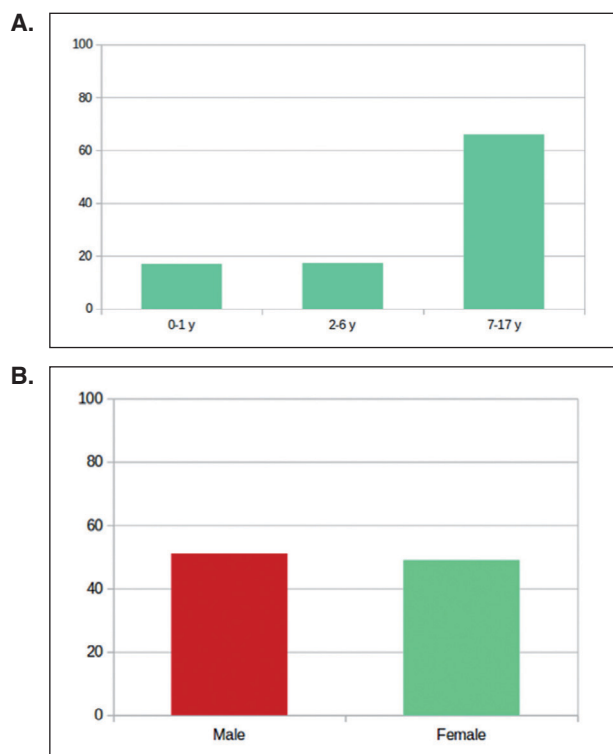


Figure 9. Age (A) and sex (B) distribution of Italian paediatric cases (n = 2,846). Graph created with data from ISS [29].

It is noteworthy to specify that in just 75.1% (2,138) of the 2,846 paediatric patients it was known whether they needed hospitalisation or not. In this respect, 4.1% of infected children (119 out of 2,138) was admitted to hospital. The age group with the highest percentage of hospitalization was that between 0 and 1 year (9.1%) (**Fig. 10**) [29].

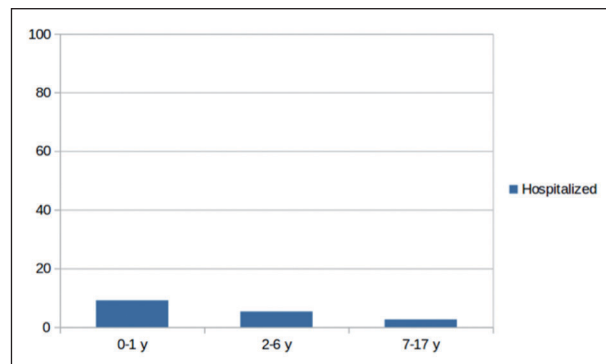


Figure 10. Age distribution of Italian children hospitalised for COVID-19 (n = 119). Graph created with data from ISS [29].

Worldwide and European deaths

The 28th April 2020 update reported 210,193 deaths due to COVID-19 [22].

In Europe (EU, EEA, UK), a total of 120,144 deaths in patients infected with COVID-19 were reported. They corresponded to 57% of the worldwide deaths [22].

The United States were the first country in terms of number of deceased (56,245), followed by Italy, France, Spain, and the United Kingdom. In these countries were declared 70% of the global deaths (**Tab. 3**) [22].

Death toll and case fatality rate (CFR) analysis requires some preliminary considerations.

Firstly, CFR, i.e. the ratio between the number of deceased patients and that of patients diagnosed with a specific pathology, is strongly affected by time.

Table 3. First 5 countries in the world for COVID-19 deaths. Table created with data from ECDC [22] and Italian Civil Protection agency [28].

Country	Total deaths	% deaths
United States	56,245	26.8
Italy	27,359	13
France	23,293	11
Spain	23,190	11
United Kingdom	21,092	10

This is very important when examining an ongoing pandemic, such as that caused by SARS-CoV-2, since this index is strongly dependent on the reported cases so far, which are likely to be less than those real.

Secondly, it can vary a lot as well, due to the variable interpretation of deaths themselves (i.e., deaths attributed to COVID-19 or to comorbidities), thus leading to its overestimation or underestimation.

The underestimation may be the result of the clinical instability of patients and the uncertainty of their outcomes at the time of the “snapshot”. This implies that confirmed cases may become deaths in the future.

The CFR may also be overestimated, because the identification of total cases (both symptomatic and asymptomatic) is complicated and depends on the number of performed tests, so even on the measures implemented by each country.

As of 28th April 2020, worldwide case fatality rate was 7%, though as told this value is matter of concerns (**Tab. 4**).

The analysis of CFR variation among the population groups is crucial to identify the ones at higher risk.

The CCDC [24] reported a case fatality rate of 2.3% on a sample of 44,672 cases and 1,023 deaths. This index varied quite a lot depending on age and sex, being higher in those over 80 years (14.8%) and lower (about 0%) in those aged 0-9. Furthermore, it was higher in males than in females.

In addition, the CCDC study examined the pre-existing pathological conditions. The CFR was higher in those with a previous a cardiovascular

Table 4. Total confirmed cases, total deaths and case fatality rate (CFR) of the first 9 countries for COVID-19 deaths in the world.

Table created with data from ECDC [22] and Italian Civil Protection agency [28].

Country	Total confirmed cases	Total deaths	CFR
United States	988,451	56,245	5.6%
Italy	201,505	27,359	13.6%
France	128,339	23,293	18%
Spain	209,465	23,190	11%
United Kingdom	157,149	21,092	13.4%
Belgium	46,687	7,207	15.4%
Germany	156,337	5,913	3.7%
Iran	91,472	5,806	6.3%
China	83,938	4,637	5.5%
World	2,982,688	210,193	7%

CFR: case fatality rate.

disease (10.5%), followed by those who had a diagnosis of diabetes (7.3%), chronic lung disease (6.3%), hypertension (6%), or neoplasia (5.6%). Lethality rate dropped to 0.9% in patients without a previous comorbidity (**Tab. 5**).

As of 28th April 2020, the paediatric deaths were 25, namely: 2 in China (a 10-month-old boy and a 14-years-old boy) [27, 30], 6 in the US (a 6-weeks-old child, a 17-years-old boy with not specified comorbidities and whose case is still under review by the CDC, a child younger than 1 year of age, a 17-years-old boy, a 5-years-old child with not

Table 5. Total confirmed cases, total deaths and case fatality rate (CFR) in China, analysed by age, sex and comorbidities.

Modified from CCDC Novel Coronavirus Pneumonia Emergency Response Epidemiology Team [24].

Categories	Total confirmed cases (%)	Total deaths (%)	CFR	
Age (years)	0-9	416 (0.9%)	-	-
	10-19	549 (1.2%)	1 (0.1%)	0.2%
	20-29	3,619 (8.1%)	7 (0.7%)	0.2%
	30-39	7,600 (17%)	18 (1.8%)	0.2%
	40-49	8,571 (19.2%)	38 (3.7%)	0.4%
	50-59	10,008 (22.4%)	130 (12.7%)	1.3%
	60-69	8,583 (19.2%)	309 (30.2%)	3.6%
	70-79	3,918 (8.8%)	312 (30.5%)	8%
	> 80	1,408 (3.2%)	208 (20.3%)	14.8%
Sex	Male	22,981 (51.4%)	653 (63.8%)	2.8%
	Female	21,691 (48.6%)	370 (36.2%)	1.7%
Comorbidities	Hypertension	2,683 (12.8%)	161 (39.7%)	6%
	Diabetes	1,102 (5.3%)	80 (19.7%)	7.3%
	Cardiovascular disease	873 (4.2%)	92 (22.7%)	10.5%
	Chronic respiratory disease	511 (2.4%)	32 (7.9%)	6.3%
	Cancer	107 (0.5%)	6 (1.5%)	5.6%
	None	15,536 (74%)	133 (32.8%)	0.9%
	Unknown	23,690 (53%)	617 (60.3%)	2.6%

CFR: case fatality rate.

specified comorbidities, a 5-years-old girl) [31-36], 1 in Panama (a 13-years-old girl) [37], 2 in France (a 16-years-old girl without comorbidities and a child younger than 10 years with significant pre-existing comorbidities) [38, 39], 3 in the United Kingdom (3 children aged 13, 5, and 11 years, respectively) [40-42], 1 in Belgium (a 12-years-old girl) [43], 2 in Brazil (2 boys aged 12 and 15 years, respectively) [44, 45], 1 in El Salvador (a 4-years-old child) [46], 1 in Mexico (a 4-months-old child) [47], 1 in Portugal (a 14-years-old boy) [48], 1 in Colombia (a 3-years-old child with comorbidities) [49], 1 in Jamaica (4-years-old) [50], 1 in India (45-days-old) [51], 2 in Italy (a 5-years-old girl with unspecified comorbidities and a child younger than 9 years of age) [52].

Italian deaths

As of 28th April 2020, the number of deceased in Italy was 27,359 [28].

Case fatality rate was 13.6%. It increased with age and it was higher in males (**Tab. 6**) [29].

The ISS had set up a working group to analyze the deaths of patients who were tested positive for SARS-CoV-2. The last update was published on 23rd April 2020 and analysed data on 23,188 patients who died in Italy for COVID-19 [52].

Their median age at death was 81 years. When comparing the median ages at diagnosis (62 years) and death (81 years), a difference of 19 years was detected. The most affected age group was that between 80 and 89 years and the number of deceased men was higher than women (63.3% vs 36.7%).

This was evident in all age groups, apart from in those above 90 years and in those less than 9 years of age (**Tab. 7**).

The median age of deceased women was higher than that of men (84 versus 79).

Data on pre-existing comorbidities were available on 2,041 patients (8.8%).

In this respect, the deceased patients had an average of 3.3 previously diagnosed diseases (median 3, standard deviation 1.9).

Again, 3.6% of the deceased had no pre-existing pathologies, 14.4% just 1, 21.1% 2 pathologies, and 60.9% 3 or more comorbidities. Patients with 3 or more previously diagnosed diseases were more than 50% of the enrolled and 96.4% of the study sample had at least 1 pre-existing disease. Prior to hospital admission, 24% of COVID-19 patients were under treatment with ACE-inhibitor and 16% with ARB. It should be pointed out that data on drugs taken

Table 6. Total confirmed cases, total deaths and case fatality rate (CFR) in Italy, analysed by age and sex. Modified from ISS [29].

Categories		Total confirmed cases (%)	Total deaths (%)	CFR
Age (years)	0-9	1,304 (0.7%)	2 (0.0%)	0.2%
	10-19	2,146 (1.2%)	0 (0.0%)	0.0%
	20-29	8,963 (5.1%)	7 (0.0%)	0.1%
	30-39	13,173 (7.4%)	48 (0.2%)	0.4%
	40-49	22,767 (12.9%)	203 (0.9%)	0.9%
	50-59	32,524 (18.4%)	861 (3.7%)	2.6%
	60-69	25,707 (14.5%)	2,576 (11.1%)	10%
	70-79	27,615 (15.6%)	6,882 (29.7%)	24.9%
	80-89	30,534 (17.2%)	9,396 (40.5%)	30.8%
> 90	12,328 (7%)	3,213 (13.9%)	26.1%	
Sex	Male	85,821 (48.6%)	14,668 (63.3%)	17.1%
	Female	90,895 (51.4%)	8,496 (36.7%)	9.3%

CFR: case fatality rate.

Table 7. Age and sex distribution of the Italian COVID-19 deaths (n = 23,188).

Table created with data from ISS [52].

Age	Female	Male	Total deaths
0-9	1	1	2
10-19	0	0	0
20-29	2	5	7
30-39	18	30	48
40-49	49	154	203
50-59	180	681	861
60-69	579	1,997	2,576
70-79	1,924	4,958	6,882
80-89	3,746	5,650	9,396
> 90	2,001	1,212	3,213

by patients prior to admission may have been underestimated due to incomplete data collection.

The most common concomitant pathologies were hypertension (69.1%), type 2 diabetes (31.7%), and coronary artery disease (27.5%) (**Tab. 8**).

Regarding symptoms, the most common was fever (75%); 72% of the patients reported dyspnea,

Table 8. Comorbidities in Italian COVID-19 deceased patients.

Table created with data from ISS [52].

Comorbidities	Deaths
Hypertension	69.1%
Type 2 diabetes	31.7%
Coronary artery disease	27.5%
Atrial fibrillation	22%
Chronic kidney disease	21.1%
Chronic obstructive pulmonary disease	17.1%
Active cancer in the last 5 years	16.1%
Heart failure	16.1%
Dementia	15%
Obesity	12.2%
Stroke	11.2%
Respiratory failure	5.4%
Chronic liver disease	4%
Immune system disorders	3.7%
Chronic kidney disease requiring dialysis	2.1%
HIV	0.2%

38% cough, 6% diarrhoea, 1% haemoptysis, while 6.1% were asymptomatic.

At the time of hospital admission, 92.3% of the patients reported signs (pneumonia, respiratory failure) and/or symptoms (fever, dyspnea, cough) suggestive for COVID-19.

The ISS quantified that the average time between the onset of symptoms and hospitalization was 5 days, between the onset of symptoms and death was 10 days, and between hospitalization and death was 5 days. As to the latter, there is a 4 days difference depending on having been moved to ICU or not (8 vs. 4 days, respectively).

The most frequent complication in COVID-19 deceased patients was respiratory failure (96.8%), followed by acute kidney injury (22.8%), bacterial superinfection (12.8%) and acute myocardial injury (9.9%).

Concerning the administered medication to deceased patients, antibiotic therapy was the most frequently used (85%), followed by antiviral therapy (57%), and steroids (36%).

Antibiotics were prescribed because of a bacterial superinfection or as an empirical therapy for treating pneumonia, when the results of laboratory investigation for COVID-19 were still pending.

All the above stated, 3 therapies were administered together in 20.8% of the patients.

In addition, 4.4% of the deceased patients were taking tocilizumab during hospitalization.

In Italy there were 2 deaths in the pediatric age group, so that the lethality was 0.1% in the group between 0 and 9 years and 0% in that between 10 and 19 years [52].

Conclusions

The epidemiological study of an ongoing pandemic is affected by the need to steadily update data, which are often incomplete, owing to the emergency-induced mess. That is the reason why our conclusions cannot be considered definitive or comprehensive, but are referred to a specific period, which extends from December 31st 2019 to April 28th 2020 (i.e. the first 4 months since the appearance of the disease).

On the basis of the available data, the current pandemic is due to a new Coronavirus, named SARS-CoV-2.

Its transmission is mainly human-to-human through airborne droplets or direct contact. Symptomatic and asymptomatic patients are the carriers, with a basic reproduction number between 2 and 3.

The virus has also been identified in blood, urine and faeces and a faecal-oral transmission is supposed.

SARS-CoV-2 is able to survive on a number of different surfaces, especially those made up of plastic and stainless steel, but whether fomites play a crucial role in its transmission is still under debate.

All studies carried out so far failed to prove maternal-foetal transmission, the virus not being found in amniotic fluid, cord blood, placental tissue, vaginal swab, and breast milk. It is therefore recommended to promote breastfeeding each time is possible. Hygiene is the best way to prevent the infection from spreading.

The average period of incubation is 4-6 days.

As of 28th April 2020, the total confirmed cases were 2,982,688 worldwide, 1,087,272 in Europe, and 201,505 in Italy.

The cited documents in this article showed that the disease affects the elderly the most. Conversely, data on sex distribution are discordant.

The paediatric population appeared to be less affected than adults, with a prevalence of the disease in older males.

Even though the real prevalence of the infection in the paediatric population may be underestimated, since symptoms are often very mild or absent, as a general rule children have a good prognosis and less need to be admitted to hospital.

The global number of deaths confirmed as of 28th April 2020 was 210,193 (120,144 in Europe and 27,359 in Italy).

The estimation of COVID-19 case fatality rate is affected by many factors, including time, the number of tests performed, asymptomatic subjects, eventually subdividing deaths due to COVID-19 from those attributed to a concomitant pathology, and prompt provision of data from each of the involved countries. That is the origin of the reported fluctuations.

On 28th April 2020, the global CFR was 7% and 13.6% in Italy.

It decreased with age and the number of deceased males outweighed deceased females.

In relation to the paediatric population, 25 deaths were reported globally, and 2 in Italy.

Declaration of interest

The Authors declare that there is no conflict of interest.

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