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March 23, 2020

Case-Fatality Rate and Characteristics of Patients Dying in Relation to COVID-19 in Italy



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Graziano Onder, MD, PhD¹; Giovanni Rezza, MD²; Silvio Brusaferrò, MD³

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COVID-19 Resource Center

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Only 3 cases of coronavirus disease 2019 (COVID-19) were identified in Italy in the first half of February 2020 and all involved people who had recently traveled to China. On February 20, 2020, a severe case of pneumonia due to SARS-CoV-2 (severe acute respiratory syndrome coronavirus 2) was diagnosed in northern Italy's Lombardy region in a man in his 30s who had no history of possible exposure abroad. Within 14 days, many other cases of COVID-19 in the surrounding area were diagnosed, including a substantial number of critically ill patients.¹ On the basis of the number of cases and of the advanced stage of the disease it was hypothesized that the virus had been circulating within the population since January.

Another cluster of patients with COVID-19 was simultaneously identified in Veneto, which borders Lombardy. Since then, the number of cases identified in Italy has rapidly increased, mainly in northern Italy, but all regions of the country have reported having patients with COVID-19. After China, Italy now has the second largest number of COVID-19 cases² and also has a very high case-fatality rate.³ This Viewpoint reviews the Italian experience with COVID-19 with an emphasis on fatalities.

Surveillance System and Overall Fatality Rate

At the outset of the COVID-19 outbreak, the Italian National Institute of Health (Istituto Superiore di Sanità [ISS]) launched a surveillance system to collect information on all people with COVID-19 throughout the country. Data on all COVID-19 cases were obtained from all 19 Italian regions and the 2 autonomous provinces of Trento and Bozen. COVID-19 cases were identified by reverse transcriptase-polymerase chain reaction (RT-PCR) testing for the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). The fatality rate was defined as number of deaths in persons who tested positive for SARS-CoV-2 divided by number of SARS-CoV-2

cases. The overall fatality rate of persons with confirmed COVID-19 in the Italian population, based on data up to March 17, was 7.2% (1625 deaths/22 512 cases).³ This rate is higher than that observed in other countries² and may be related to 3 factors.

Fatality Rate and Population Age

The demographic characteristics of the Italian population differ from other countries. In 2019, approximately 23% of the Italian population was aged 65 years or older. COVID-19 is more lethal in older patients, so the older age distribution in Italy may explain, in part, Italy's higher case-fatality rate compared with that of other countries. The **Table** shows the age-specific fatality rate in Italy compared with that of China.⁴



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Table. Case-Fatality Rate by Age Group in Italy and China^a

Table. Case-Fatality Rate by Age Group in Italy and China^a

	Italy as of March 17, 2020		China as of February 11, 2020	
	No. of deaths (% of total)	Case-fatality rate, % ^b	No. of deaths (% of total)	Case-fatality rate, % ^b
All	1625 (100)	7.2	1023 (100)	2.3
Age groups, y				
0-9	0	0	0	0
10-19	0	0	1 (0.1)	0.2
20-29	0	0	7 (0.7)	0.2
30-39	4 (0.3)	0.3	18 (1.8)	0.2
40-49	10 (0.6)	0.4	38 (3.7)	0.4
50-59	43 (2.7)	1.0	130 (12.7)	1.3
60-69	139 (8.6)	3.5	309 (30.2)	3.6
70-79	578 (35.6)	12.8	312 (30.5)	8.0
≥80	850 (52.3)	20.2	208 (20.3)	14.8

^a Data from China are from Chinese Center for Disease Control and Prevention.⁴ Age was not available for 1 patient.

^b Case-fatality rate calculated as number of deaths/number of cases.

The overall case-fatality rate in Italy (7.2%) is substantially higher than in China (2.3%). When data were stratified by age group, the case-fatality rate in Italy and China appear very similar for age groups 0 to 69 years, but rates are higher in Italy

among individuals aged 70 years or older, and in particular among those aged 80 years or older. This difference is difficult to explain. The distribution of cases is very different in the 2 countries: individuals aged 70 years or older represent 37.6% of cases in Italy and only 11.9% in China. In addition, a relevant number of cases in Italy are in people aged 90 years or older (n=687), and this age group has a very high fatality rate (22.7%); data on cases in those aged 90 years or older were not reported in China. In addition, the report from the WHO-China Joint Mission on Coronavirus Disease 2019 Mortality, which presents data on 2114 COVID-19 related deaths among 55 924 laboratory-confirmed cases in China, reported a fatality rate among patients aged 80 years or older that was similar to the rate in the Italian sample (21.9% in China vs 20.2% in Italy).⁵

Thus, the overall older age distribution in Italy relative to that in China may explain, in part, the higher average case-fatality rate in Italy.

Definition of COVID-19–Related Deaths

A second possible explanation for the high Italian case-fatality rate may be how COVID-19–related deaths are identified in Italy. Case-fatality statistics in Italy are based on defining COVID-19–related deaths as those occurring in patients who test positive for SARS-CoV-2 via RT-PCR, independently from preexisting diseases that may have caused death. This method was selected because clear criteria for the definition of COVID-19–related deaths is not available.

Electing to define death from COVID-19 in this way may have resulted in an overestimation of the case-fatality rate. A subsample of 355 patients with COVID-19 who died in Italy underwent detailed chart review. Among these patients, the mean age was 79.5 years (SD, 8.1) and 106 (30.0%) were women. In this sample, 117 patients (30%) had ischemic heart disease, 126 (35.5%) had diabetes, 72 (20.3%) had active cancer, 87 (24.5%) had atrial fibrillation, 24 (6.8%) had dementia, and 34 (9.6%) had a history of stroke. The mean number of preexisting diseases was 2.7 (SD, 1.6). Overall, only 3 patients (0.8%) had no diseases, 89

(25.1%) had a single disease, 91 (25.6%) had 2 diseases, and 172 (48.5%) had 3 or more underlying diseases. The presence of these comorbidities might have increased the risk of mortality independent of COVID-19 infection.

COVID-19-related deaths are not clearly defined in the international reports available so far, and differences in definitions of what is or is not a COVID-19-related death might explain variation in case-fatality rates among different countries. To better understand the actual causes of death, the ISS is now reviewing the complete medical records of all patients with positive RT-PCR results who have died in Italy.

Testing Strategies

A third possible explanation for variation in country-specific case-fatality rates are the differing strategies used for SARS-CoV-2 RT-PCR testing. After an initial, extensive testing strategy of both symptomatic and asymptomatic contacts of infected patients in a very early phase of the epidemic, on February 25, the Italian Ministry of Health issued more stringent testing policies. This recommendation prioritized testing for patients with more severe clinical symptoms who were suspected of having COVID-19 and required hospitalization. Testing was limited for asymptomatic people or those who had limited, mild symptoms. This testing strategy resulted in a high proportion of positive results, ie, 19.3% (positive cases, 21 157 of 109 170 tested as of March 14, 2020), and an apparent increase in the case-fatality rate because patients who presented with less severe clinical disease (and therefore with lower fatality rate) were no longer tested (case-fatality rate changed from 3.1% on February 24 to 7.2% on March 17). These more mild cases, with low fatality rate, were thus no longer counted in the denominator.

Other countries have different testing strategies. For example, the Republic of Korea has adopted a strategy of widely testing for SARS-CoV-2. This may have led to the identification of a large number of individuals who had mild or limited symptoms, but a much lower case-fatality rate compared with Italy (1.0% vs 7.2%) be-

cause many patients with mild disease who would not be tested in Italy were included in the denominator in Korea.²

Conclusions

In conclusion, the current data illustrate that Italy has a high proportion of older patients with confirmed COVID-19 infection and that the older population in Italy may partly explain differences in cases and case-fatality rates among countries. Within Italy, COVID-19 deaths are mainly observed among older, male patients who also have multiple comorbidities. However, these data are limited and were derived from the first month of documented COVID-19 cases in Italy. In addition, some patients who are currently infected may die in the near future, which may change the mortality pattern.

From a research perspective, the comparisons discussed highlight the need for transparency in reporting testing policies, with clear reporting of the denominators used to calculate case-fatality rates and the age, sex, and clinical comorbid status of affected persons when comparing COVID-19 case and mortality rates between different countries and regions. Finally, because the outbreak is new, continued surveillance, with transparent and accurate reporting of patient characteristics and testing policies, is needed from multiple countries to better understand the global epidemiology of COVID-19.

Article Information

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Correction: This article was corrected on April 16, 2020, to correct a data error reported in the eighth paragraph (number of women in the subsample was 106).

Conflict of Interest Disclosures: None reported.

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18 Comments for this article

EXPAND ALL

March 24, 2020

Why are Healthy Patients Dying of COVID-19?

David Carter, MD | Broome Pediatrics, SUNY Upstate Medical University

If the primary cause of death in COVID-19 is ARDS with significant pulmonary inflammation resulting in massive cytokine release causing V/Q mismatch manifesting as patchy infiltrates and ground-glass opacities, why then aren't patients being given high dose inhaled steroids? This has been studied in pediatric asthma, and is considered safe and effective. Why are we looking for novel or investigational antivirals when corticosteroids are cheap, safe and known effective reducers of cytokine release?

CONFLICT OF INTEREST: None Reported

March 23, 2020

Immune Status

Mona Sheikh |

Nicely written article, very informative, and I agree with the writer that countries

need to be transparent in reporting cases. For example, the number of cases in Japan and India is low, given that they are very close to China and compared to Western countries which have more cases and higher mortality.

I wished you would have analyzed the immune system status of patients who died from the virus.



CONFLICT OF INTEREST: None Reported

March 23, 2020

The Italian Anomaly

Edoardo Cervoni, M.D. | LD4U Ltd.

There are significant challenges in interpreting the overall case fatality rate (CFR) in Italy as it is substantially higher than in China and many other countries. It is also clear that the CFR has increased further since this document was presented, perhaps reflecting a health system overwhelmed by the pandemic. In fact, the picture is irregular throughout the Italian territory as is the presence of positive subjects. However, it emerges that age cannot absolutely justify the differences. For example, the CFR in Japan is substantially lower than in Italy, although the population is even older. A thorough analysis seems extremely ...

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March 24, 2020

COVID 19: IS COMPARISON WITH CHINA SO IMPORTANT?

Giuliano Ramadori, Professor of Medicine | University clinic ,Internal Medicine,Göttingen,Germany

The Italian patient number one (38 year old) has just been released from the hospital San Matteo. His pregnant wife, who was also infected, was already at home-

.The patient`s father, however, unfortunately died of COVID-19. We are informed by very transparent Italian journalism. This makes comparison of numbers coming from other countries around the world very difficult.

On the other hand it is important to focus on Italian numbers which mostly come from Lombardy. In some of the areas of Lombardy, the number of deaths are five times higher compared with those of the same period ...

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March 25, 2020

Percent with active cancer

T Christopher Bond, PhD | Bristol Myers Squibb

What should we make of the percentage with active cancer? How much of this is prostate cancer in elderly men?



CONFLICT OF INTEREST: I am an employee of Bristol Myers Squibb

March 25, 2020

High Mortality Due to Not Testing Enough Patients with Mild Symptoms

Hunasikatti Mahadevappa, MD FCCP | INOVA Fairfax Hospital, Fairfax, VA and INOVA Alexandria Hospital, VA

HIGH MORTALITY: The authors state that "The overall case-fatality rate in Italy (7.2%) is substantially higher than in China (2.3%). When data were stratified by age group, the case-fatality rate in Italy and China appear very similar for age groups 0 to 69 years, but rates are higher in Italy among individuals aged 70 years or older, and in particular among those aged 80 years or older". However, this may be due to not testing many asymptomatic or patients with mild symptoms. Testing should be widely available to get an accurate assessment of Case Fatality Ratio. It

is irrational to ...

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March 24, 2020

Over 70s Reverse Triage

Fraser Magee, MBChB | Royal Melbourne Hospital

Is the difference in mortality rates between Italy and China in the over 70 year old age group not at least partially explained by ICU admission restrictions in the elderly Italian population?

There have been widespread reports of "not for mechanical ventilation" decisions being made in the over 80 and over 70 age groups when bed pressures became intense in Lombardy and Emilio-Romano.



CONFLICT OF INTEREST: None Reported

March 24, 2020

Calculating Case Fatality Rate at the Beginning of Pandemics

ANDRE R FREITAS, PhD, MD | Faculdade São Leopoldo Mandic, Department of Epidemiology , Campinas, Sao Paulo, Brazil

This paper uses the number of deaths divided by the total number of cases to calculate the case fatality rate. This method of calculation, when used at the beginning of a pandemic, which is still exponentially increasing underestimates the case fatality rate. This is because a large part of the patients are still evolving and we do not know the final outcome of healing or death. At the present time, a simple and adequate way to calculate the case fatality rate would be to divide the number of deaths by the sum of the deaths plus those recovered, as proposed ...

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March 25, 2020

Underestimation of the Role of the Italian Regional Healthcare System on Critical Patients' Care

Federico Gheza, MD | University of Brescia, Brescia, Italy

The mortality rate among ICU patients is relatively low in northern Italy compared to other European Countries. In our large community hospital in Brescia we admitted about 2000 positive patients in the last 30 days and 850 are currently under treatment here. Our ICU mortality rate is extremely low and comparable with WHO data for Germany or South Korea. The vast majority of deaths occur outside the ICU, in-hospital or at home. Intensive care units in Bergamo, Milan, and Brescia are renowned centers of excellence. An obvious selection bias is lowering the ICU death rate due to admissions of younger ...

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March 25, 2020

Even Worse Case-fatality Rates in Italy?

Caterina Zanetti, Dr. | University Hospital of Padua, Italy

As a possible explanation for Italy's high case-fatality rates the authors mention the more stringent testing policies in place since February, 25, so that more mild cases, with low fatality rate, were thus no longer counted in the denominator.

I'm concerned that the worst cases, too, are no longer counted in the numerator, as they die before getting tested, seeing as the health care system is overwhelmed (1).

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March 25, 2020

Complete Anamnesis?

Hedley Quintana, PhD | Gorgas Memorial Institute for Health Studies, Panama

When I was an intern, I was obliged to write down a complete anamnesis (history) of every patient.

I don't understand why descriptive papers after been peer-reviewed lack information regarding medical background and physical examination. Smoking and medications are almost universally lacking!

Regarding treatments, I strongly discourage pharmacological interventions without being tested with an RCT.

Regarding support treatment, I am surprised how little is mentioned regard invasive cardiovascular monitoring. Deceased patients in this paper clearly point out how relevant it is to closely assess the fluid balance, and to address the causes of septic shock, ...

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March 25, 2020

Spreading of Disease in Early Stages

Richard Levicki, BSc MSc | Gaiadoc

In the UK at present there are political issues such as the Government mixing the construction profession and health professionals on the London Underground, an area where we have a high concentration of current deaths. The health workers do not have adequate protection and even face masks being needed and therefore it seems that we may be spreading the disease ourselves in the early onset period. At the same time the political decisions are it seems taken on economic grounds

whilst the Government has used contradictory arguments to take martial law powers. These factors mean that the UK Government cannot ...

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March 27, 2020

CFR Italy vs Germany

Rajat Dhameja, MD, MHA | Hospital Administration Executive

The information and research in the publication bridges gaps and helps in understanding the data made available from Italy. Several media sources point to Germany's low fatality rate despite high rates of infection. Parallels can be drawn between the high testing rate of Germany and South Korea. Germany and Italy also seem to contrast in how each are reporting fatalities where it concerns comorbidities. Together with demographic variances, this paper further clarifies how data is collected and interpreted for the general public.

CONFLICT OF INTEREST: None Reported

March 30, 2020

Managing COVID-19 at Home (and by Phone)

Paolo Mazzeo, MD | and Giovanni Pietro Corsini, MD, Genoa, Italy

Dr Carter wonders whether COVID-19 patients could give high dose inhaled steroids. In two mild to moderate COVID-19 suspected cases, patients reported bronchostenosis together with upper airway allergy symptoms. We prescribed by phone a standard dose of inhaled steroids together with montelukast 10 mg once a day (1). In COVID-19, inflammatory cytokines and chemokines levels are high. Montelukast is a leukotriene receptor antagonist; leukotrienes induce both the production of inflammatory cytokines and that of chemokines. In practice, in lungs, montelukast decreases inflammation and relaxes smooth muscle. In our

cases, one should use it only for a short time and without ...

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March 31, 2020

Air Pollution and Tobacco use

Jose Ramiro Cruz, DSc Virology/Immunology | Independent Consultant

The EEA Air Quality in Europe - 2019 Report indicates that Italy has one of the highest indicators of air pollution by particulate matter, ozone, and nitrogen dioxide and other substances (Map 9.1, page 64). Within the country, Lombardi shows the most contaminated air. Additionally, the World Population Review summarizes tobacco smoking by country and shows that, in 2015, 24% of Italians (28.30% of males, 19.70% of females) were smokers. The accumulated exposure to both air pollutants and tobacco smoke produces important morbidity and mortality by itself. These factors should be taken into consideration when examining case fatality rates associated ...

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April 1, 2020

CFR in Italy Explained By Age Structure of Positive Cases

Simona Bignami, PhD | Université de Montréal

The crude CFR is an inaccurate measure of the disease severity since the pandemic is still unfolding. With the goal to improve its comparability over time and across countries at this stage, we have developed a demographic adjustment of the CFR that addresses the bias arising from differential case ascertainment by age (1). When applied to publicly released data for Italy, we show that until March 16 our adjusted CFR was similar to that of Wuhan. This indicates that our adjusted CFR improves its comparability over time, making an important tool to chart the course of the COVID-19 pandemic across ...

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April 2, 2020

Sporting Event in Lombardy and COVID-19 Viral Transmission

Giuliano Ramadori, Professor of Medicine | University Clinic, Internal Medicine, Göttingen, Germany

The soccer fight Atalanta Bergamo against Valencia which took place in Milan on February 19 may become a milestone in the history of epidemiological studies. About one third of the population of Bergamo attended the match. One can only imagine what happened in Bergamo when the fans went back to Bergamo from Milan after their team had won the match.

On March 16th the news paper La Repubblica published an article :Spagna, Valencia: " il 35% di noi positivi dopo aver giocato a Milano" ("35% of us are positive after playing in Milan).

Two days after the match the ...

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April 3, 2020

Really surprising outcomes?

Alessandro Capone, MD | Statistics for Health Economic Evaluation Group (external collaborator), Department of Statistical Science, University College London, London, UK

When Onder et al. published their paper, Italian epidemiological data on COVID-19 were just preliminary and often not fully integrated. Epidemiology is a dynamic science and parameters such as case-fatality rate (CFR) or RO may vary as function of time, and hence be subject to biases early in an epidemic by definition. Nonetheless, explanations provided by authors concerning the supposed higher CFR value compared to China (especially in elderly and/or in patients affected by several comorbidities) are solid and rational. Indeed, Italy was not as ready to manage a so-rapid and dramatic pandemic, as many other countries were, actually. The ...

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