Short Communication

# Condition-specific mortality risk can explain differences in COVID-19 case fatality ratios around the globe

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ABSTRACT

Objectives: With COVID-19 infections resulting in death according to a hierarchy of risks, with age and pre-existing health conditions enhancing disease severity, the objective of this study is to estimate the condition-specific case fatality ratio (CFR) for different subpopulations in Italy.
Study design: The design of the study was to estimate the 'pre-existing comorbidity'-conditional CFR to eventually explain the mortality risk variability reported around in different countries.
Methods: We use the available information on pre-existing health conditions identified for deceased patients 'positive with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2)' in Italy. We (i) estimated the total number of deaths for different pre-existing health conditions categories and (ii) calculated a conditional CFR based upon the number of comorbidities before SARS-CoV-2 infection.
Results: Our results show a 0.6% conditional CFR for a population with zero pre-existing pathology, increasing to 13.9% for a population diagnosed with one and more pre-existing health conditions.
Conclusions: Condition-specific mortality risks are important to be evaluated during the COVID-19 pandemic, with potential elements to explain the CFR variability around the globe. A careful postmortem examination of deceased cases to differentiate death 'caused by COVID-19' from death 'positive with SARS-CoV-2' is therefore urgently needed and will likely improve our understanding of the COVID-19 mortality risk and virus pathogenicity.

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In December 2019, a severe respiratory syndrome (COVID-19) caused by a new severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) was identified in China[1] and spread rapidly around the globe. COVID-19 was declared a pandemic by the World Health Organization (WHO) in March, 2020. As of the date of preparation of this manuscript, more than 8 million cases were confirmed with about 450 thousand deaths and a global case fatality ratio (CFR) of approximately 5.5%.[2] The CFR is the proportion of deceased cases over the total number of persons diagnosed with a disease during the course of the outbreak. The CFR is often used as a disease severity indicator. Many viral diseases affecting humans have a well-established CFR such as seasonal influenza (<0.1%)[3] and un-vaccinated measles (1–3%),[4] Severe acute respiratory syndrome - SARS (15%)[5] and Middle Eastern Respiratory Syndrome - MERS (34.4%),[6] for example, with a pandemic potential without effective

control measuers in place. As testing capacities have increased, symptomatic cases of lower severity have been detected producing a slow decline in global COVID-19 CFR. Yet, the national CFR varies around the world. As of this writing, Qatar has a CFR less than 1%, South Korea around 2.5%, and Germany 4.7%, compared with 14.5% in Italy and the United Kingdom and approximately 19% in France.[2] And why do these reported CFR differ? Do differences relate to differences in population susceptibility to SARS-CoV-2 infection? Because COVID-19 is a new virus, it is likely that overall population susceptibility to infection might be similar while susceptibility to disease expression might differ. Infection rates may be controlled by social distancing and crowding, while the force of infection may be controlled by many factors. Assumptions concerning these variables are used in most modeling approaches used to guide public health authorities during the COVID-19 pandemic.

Many other fundamental questions could be raised such as the capacity of the health systems to cope with a new infectious disease or even the overall health condition of a population, but to

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understand the CFR reported in different countries, the first question to be answered is how are the COVID-19 deceased cases reported around the globe? Is it done in a standard format, via a postmortem examination[7] to differentiate death 'caused by COVID-19', defined for surveillance purposes as a death resulting from a clinically compatible illness, from death 'positive with SARS-CoV-2', a conditional effect of high viral transmissibility?

Starting on May 13, 2020, the 'Coronavirus disease situation reports' from the WHO highlight the importance of defining COVID-19 death following the international guidelines for certification and its classification of COVID-19 as cause of death by confirmed laboratory testing or clinical or epidemiological diagnosis.[2] However, the CFR is still reported without considering differences in subpopulations.

Italy, the first hard-hit country in Europe, reported on June 11, 2020, a population CFR of 14.5% after reaching 34,167 deaths among 236,142 confirmed cases 'positive with SARS-CoV-2'.[8] Approximately 85% of reported deaths occurred in individuals older than 70 years, but the CFR changes when evaluated in subpopulations. The average age-group stratified CFR (number of deaths in the age group divided by the number of confirmed cases in the same age group) is approximately 33%.[9] However, the cumulative number of death from inpatients aged 70 years and older tested 'positive with SARS-CoV-2' over the infection level of the whole population (quantified by the cumulative notified incidences in Italy up to June 11, 2020) leads to a much lower conditional CFR of 12% for individuals aged 70 years and older .

Data about the pre-existing health conditions of all infected individuals in Italy are not available to measure the specific CFR for each comorbidity group; however, a detailed report characterizing the deceased patients which were tested positive with SARS-CoV-2 is published, once a week, by the Istituto Superiore di Sanità in Italy. The studied population is divided into groups with '0 pre-existing pathology', '1 pre-existing pathology', '2 pre-existing pathologies', and '3 or more pre-existing pathologies' diagnosed before the patient became infected with SARS-CoV-2.[10] We note that this report[10] does not show the correlation between pre-existing pathologies and age but states that 1.1% of the deceased individuals positive with SARS-CoV-2 were younger than 50 years. Among those, 83 deceased patients were younger than 40 years, which are expected to be in the category with a low risk of death 'caused by COVID-19'. However, for this group, approximately 75% ($N = 62$) of individuals were suffering from severe pre-existing health conditions against 17% ($N = 14$) who did not have any important underlying health condition. Medical records were not available for the remaining patients.

From this perspective, the 'pre-existing comorbidity'-conditional CFR, which is defined here as the number of deceased cases with one or more pre-existing health conditions before SARS-CoV-2 infection divided by the total number of detected infected cases in the population, is a relevant and important measure to understand the current differences between the CFR reported around the globe.

Up to June 11, 2020, 3438 medical records for deceased cases tested positive with SARS-CoV-2 were analyzed, with 4.1% of the deceased cases classified with zero pre-existing pathologies versus approximately 60% of the deceased patients suffering with 3 or more pre-existing pathologies prior SARS-CoV-2 infection. By assuming that the deceased case characterization in Italy is performed randomly as the deaths are reported, we use the stratified data for individuals with zero, one, two, three, or more pre-existing conditions to estimate the total number of deaths expected in each category in the population. The 'pre-existing comorbidity'-conditional CFR was obtained by dividing the total estimated number of deaths from each category by the overall confirmed cases in the population.

Our results have shown that mortality risk varies significantly between the number of pre-existing pathology groups, with CFR = 0.6% for individuals with 0 pre-existing pathology, CFR = 2.1% for individuals with 1 pre-existing pathology, CFR = 3.1% for individuals with 2 pre-existing pathologies, and CFR = 8.6% for individuals with 3 or more pre-existing pathologies (refer upper part of Table 1). By using the aggregated data, the higher CFR estimations were obtained for the group of individuals diagnosed with two or more pre-existing health conditions (CFR = 11.7%) and the group of individuals with at least one pre-existing health conditions (CFR = 13.9%), refer lower part of Table 1, which are closer to the currently reported CFR in Italy and comparable with the current CFR reported in the United Kingdom,[2] for example, where patient postmortem examination is not used as tool of investigation before death notification.[7] However, for the group of individuals diagnosed with zero and one pre-existing health conditions prior SARS-CoV-2 infection (at most one), the CFR is low (CFR = 2.7%) and comparable with the current CFR reported in Norway[2] and the Republic of Korea.[2,12]

**Table 1**
Estimation of conditional COVID-19 CFR in Italy, by June 11, 2020. Addressing the number of pre-existing health conditions and disease mortality risks, conditional CFR is estimated using stratified (upper part) and aggregated (lower part) information for population subgroups.

| Italy by June 11, 2020 — current CFR = 14,5% | | | | |
| --- | --- | --- | --- | --- |
| **Stratified information by June 11, 2020** | | | | |
| Pre-existing pathologies diagnosed before the patient became infected with SARS-CoV-2 (N = 3438 of 32938 deceased)[11] | Number of patients classified per number of pre-existing pathology[11] | Percentage of deceased patients positive for SARS-CoV-2 infection by the number of pre-existing health conditions category[11] | Estimated cumulative number of death in Italy for each pre-existing health condition category (with 34167 notified deceased cases in the whole population of Italy on June 11, 2020[11]) | Estimated current conditional CRF (with 236142 confirmed cases in the whole population of Italy on June 11, 2020[11]) |
| 0 pathology | 144 | 4.19% | 1431 | **0.61%** |
| 1 pathology | 505 | 14.69% | 5019 | **2.13%** |
| 2 pathologies | 738 | 21.47% | 7334 | **3.11%** |
| 3 or more pathologies | 2051 | 59.66% | 20383 | **8.63%** |
| **Aggregated information by June 11, 2020** | | | | |
| **At most 1 pathology** (zero and 1 pre-existing condition prior SARS-COV-2 infection) | 649 | 18.88% | 6450 | **2.73%** |
| **Two or more pathologies** (two, three, or more pre-existing conditions prior SARS-COV-2 infection) | 2789 | 81.12% | 27717 | **11.74%** |
| **At least 1 pathology** (one, two, and three or more pre-existing conditions prior SARS-COV-2 infection) | 3294 | 95.81% | 32736 | **13.86%** |

CFR, case fatality ratio.

In Italy, the most common reported underlying health conditions in deceased cases are hypertension (60%) and diabetes (30%).[10] Knowing that middle-age patients have high risk to have been already diagnosed with at least one of those chronic, but treatable, diseases,[13] our results suggest that the biological COVID-19 CFR, that is, the disease-induced death by SARS-CoV-2 infection, could be much lower than the currently reported value. CRF measurement reported as a unique number for the whole population, without considering differences in subpopulations, will overestimate the biological disease-induced mortality rate.

Condition-specific mortality risks are important to be evaluated during this pandemic, with potential elements to explain the CFR variance in different countries. A careful postmortem examination of deceased cases to differentiate death 'caused by COVID-19' from death 'positive with SARS-CoV-2' is therefore urgently needed and will likely improve our understanding of the SARS-CoV-2 pathogenicity. As those estimations are not final until the characterization of the deceased cases is finished and data on all medical records for all infected individuals in the populations would become available, this exercise has the objective to discuss the urgent need of using a more standardized method for deceased notification across many nations during the COVID-19 pandemic.

## Author statements

### Author contributions

MA has collected the data. MA and NS conceived the study, analyzed the data and drafted the paper. All authors read and approved the final manuscript.

### Ethical approval

None sought.

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### Competing interest

The authors declare that they have no conflicting interests.

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