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BRIEF REPORT

Severe Acute Respiratory Syndrome Coronavirus 2 Lethality Did not Change Over Time in Two Italian Provinces

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This retrospective cohort study included all the subjects diagnosed with severe acute respiratory syndrome coronavirus 2 infection (n = 2493) in 2 Italian provinces. Two hundred fifty-eight persons died, after a median of 14.0 ± 11.0 days. Adjusting for age, gender, and main comorbidities, the ≥28-day case-fatality rate did not decrease from March to April 2020 (adjusted hazard ratio, 0.93; $P = .6$).

Keywords. case-fatality rate; COVID-19; lethality; SARS-CoV-2; trend over time.

As of mid-July 2020, the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) pandemic has caused more than 500 000 deaths worldwide [1], with largely discrepant case-fatality rates across countries (from <1% to 16%) [2], likely due to differences in population age structure [3, 4], variations in testing policies and case recording [5], and/or preparedness of the healthcare system, which in turn is affected by the intensity of the spread [4, 5].

Since the start of the pandemic, Italy has been among the countries with the highest death toll, with approximately 35 000 recorded deaths [1], and an estimated case-fatality rate of 14% [2], which peaked at 20% among the citizens aged ≥80 years [6].

In the last months, it has been suggested that SARS-CoV-2 lethality may have decreased, mostly as a consequence of more tailored therapeutic approaches [7–11]. Although the claims were made by physicians actively engaged in the care of infected patients, the available evidence is anecdotal or based upon case studies.

In this study, we analyzed the data of all infected cases in 2 Italian provinces to evaluate whether the SARS-CoV-2 case-fatality rate decreased with time, adjusting for main potential confounders.

METHODS

This retrospective cohort study included all subjects with a diagnosed SARS-CoV-2 infection in the Provinces of Ferrara and Pescara, between March 3 (the onset date of the first cases) and May 3, 2020. All participants were followed up to May 31, 2020. All infections were diagnosed by the central laboratories of Ferrara University Hospital or Pescara Hospital through reverse-transcription polymerase chain reaction (RT-PCR) test on nasopharyngeal swabs and were confirmed by the Italian National Institute of Health. Information on age, gender, and comorbidities were collected from local registries, clinical charts (for hospitalized patients), and through data-linkage with hospital discharge abstracts. To gather further information on prior clinical history of the included subjects, the above records were further linked (through anonymized unique patient identifiers) with drug prescription datasets, which include all medicines prescribed by the Italian Health Service and dispensed by both community and hospital pharmacies (known as "Ministry Records D and F").

Electronic databases were queried from the day of the diagnosis until January 1, 2015. All data have been revised manually by 2 physicians (L.M. and M.E.F.), and the following conditions have been included in the analyses: hypertension, type II diabetes, major cardiovascular diseases (heart failure, myocardial infarction, and stroke—cardiovascular disease [CVD]), chronic obstructive pulmonary diseases ([COPD], bronchitis, pneumonia, asthma, and emphysema), cancers, and renal disease. No additional data were collected.

Patient Consent Statement

The study complies with the Declaration of Helsinki; the research protocol was approved by the Ethics Committee of the Emilia-Romagna Region (code 287, approved on March 24, 2020), and the requirement for informed consent was waived because of the retrospective and pseudo-anonymized nature of the data.

Data Analysis

We compared the case-fatality rate (fatal/confirmed cases) during the first 29 days after index day (from March 3 to

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March 31, 2020) with that of the second half of the period (days 30–63; from April 1 to May 3, 2020). For the sake of simplicity, the second period, composed by April and a few days of May, will be defined as "April." The differences between the 2 periods were initially evaluated using *t* test for continuous variables and χ^2 test for categorical ones. The potential independent predictors of death were then evaluated using Cox proportional hazards analysis (censoring at May 31, 2020 to include ≥28 days of follow up). The hazard ratio (HR) predicting the risk of death in April versus March was computed twice, either without or with an incorporated frailty term, to account for cluster-specific random effects potentially arising from the inclusion of cases diagnosed in 2 different provinces. All covariates were included a priori in the model in their original form, with the exception of age, which was treated as either continuous or ordinal, to explore several age classes. Schoenfeld's test was used to assess the validity of proportional hazards assumption, and Nelson-Aalen cumulative hazard estimates was used to check the validity of constant incidence ratios during follow up [12]. Censoring at 28 days of follow-up, a random-effect logistic regression was also fit, with province as the cluster unit. The same above criteria were used to build the final model. Missing data were <5% in all primary analyses; therefore, no missing imputation technique was adopted. Statistical significance was defined as a 2-sided $P < .05$, and all analyses were carried out using Stata, version 13.1 (2014; StataCorp, College Station, TX). The same analytical approach was adopted to assess a previous dataset [13], which was based upon samples collected up to April 25, 2020 using a shorter, 10-day follow-up period.

RESULTS

The sample consisted of 2493 subjects (mean age 58.6 ± 21.1 years; 47.7% males); 33.0% of them were hypertensive, 13.0% were diabetics, and 15.5% had CVD; a total of 914 subjects (36.7%) required hospital assistance. Some of the characteristics of the sample significantly varied from March to April 2020. Infected subjects were older by 3.1 years, and the proportion of females, diabetics, subjects with CVD, cancer, and renal diseases significantly increased (Table 1).

Overall, 258 persons died (247 during hospitalization), after a median of 14.0 ± 11.0 days of follow up: 157 (149 in-hospital) of the 1658 subjects diagnosed in March 2020 (9.5%), and 101 (98 in-hospital) of the 835 subjects diagnosed from April 1 to May 3, 2020 (12.1%). The mean age of those who died substantially increased: it was 78.1 ± 11.0 for those diagnosed in March 2020, and 84.3 ± 10.2 for those detected in April 2020 ($P < .001$). In March 2020, 33 of those deceased were younger than 70 years, and 10 were younger than 60 years. In April 2020, 6 deaths occurred in subjects younger than 70 years (2 among those younger than 60 years).

As shown in Table 2, in the overall sample, the crude SARS-CoV-2 lethality significantly increased from March to April 2020 (from 9.5% to 12.1%; $P = .042$). The increase was significant among the males (from 9.9% to 15.8%; $P = .005$) and those

Table 1. Characteristics of the Sample, Overall and by Time of SARS-CoV-2 Infection Diagnosis After the First Case (March 3, 2020)

Characteristics	Total Sample	March 2020[a]	April 1–May 3, 2020[b]	*P*[c]
	(n = 2493)	(n = 1658)	(n = 835)	
Mean age (SD), years	58.6 (21.1)	57.6 (19.5)	60.7 (24.0)	<.001
Age-Class in Years, %				
<18	3.6	3.1	4.4	.10
18–39.9	15.1	14.2	16.9	.074
40–49.9	14.5	16.1	11.3	.001
50–59.9	17.6	18.8	15.3	.034
60–69.9	16.1	19.0	10.4	<.001
70–79.9	13.2	14.2	11.1	.031
≥80	19.9	14.6	30.5	<.001
Male gender, %	47.7	51.8	39.5	<.001
Hypertension, %	33.0	33.5	32.1	.5
Diabetes, %	13.0	11.3	16.2	.001
Major cardiovascular diseases, %	15.5	14.1	18.4	.004
COPD, %	5.1	5.4	4.7	.5
Cancer, %	7.1	8.0	5.4	.016
Renal diseases, %	5.3	4.3	7.4	.001
Hospital admission, %	36.7	37.8	34.4	.09

Abbreviations: COPD, chronic obstructive pulmonary disease; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; SD, standard deviation.

[a]From March 3 to March 31, 2020.

[b]From April 1 to May 3, 2020.

[c]χ^2 test for categorical variables, *t* test for continuous ones.

Table 2. Proportion of Deaths, Overall and by Time of SARS-CoV-2 Infection Diagnosis After the First Case (March 3, 2020), and Hazard Ratios Predicting the Risk of Death of Patients Diagnosed in April vs March 2020

	Total Sample	March 2020[a]	April 1–May 3, 2020[b]	*P*[c]	April vs March HR (95% CI)	*P*[d]
Overall	10.3	9.5	12.1	.042	0.93* (0.71–1.21)	.6
					0.93** (0.71–1.21)	.6
Age-Class in Years, %						
<18	0.0	0.0	0.0	–	–	–
18–39.9	0.3	0.0	0.7	.2	–	–
40–49.9	0.6	0.8	0.0	.4	–	–
50–59.9	2.1	2.6	0.8	.2	0.22 (0.02–2.05)	.2
60–69.9	6.7	7.3	4.6	.4	0.66 (0.22–1.99)	.5
70–79.9	18.8	19.1	18.3	.9	0.92 (0.52–1.63)	.8
≥80	31.6	32.6	30.6	.6	0.94 (0.67–1.30)	.7
Gender, %						
Females	9.3	9.0	9.7	.7	0.65 (0.44–0.95)	.027
Males	11.5	9.9	15.8	.005	1.12 (0.77–1.61)	.6
Hypertension, %						
No	5.2	4.4	6.7	.040	0.92 (0.58–1.45)	.7
Yes	20.9	19.6	23.5	.2	0.85 (0.61–1.19)	.3
Diabetes, %						
No	8.3	7.4	10.7	.005	1.03 (0.75–1.42)	.8
Yes	24.2	27.7	19.3	.08	0.57 (0.34–0.94)	.028
Major Cardiovascular Diseases, %						
No	7.1	6.7	7.9	.3	0.81 (0.57–1.16)	.2
Yes	27.9	26.2	30.5	.4	0.98 (0.65–1.48)	.9
COPD, %						
No	9.3	8.5	11.1	.04	0.87 (0.65–1.16)	.3
Yes	28.9	27.0	33.3	.5	0.78 (0.37–1.63)	.5
Cancer, %						
No	9.6	8.7	11.3	.050	0.84 (0.63–1.12)	.2
Yes	20.2	18.1	26.7	.2	0.89 (0.43–1.86)	.8
Renal diseases, %						
No	9.3	8.6	10.9	.07	0.93 (0.70–1.24)	.6
Yes	28.6	29.6	27.4	.8	0.56 (0.27–1.15)	.11
Presence of comorbidities, %[e]						
No	3.2	2.7	4.4	.078	1.23 (0.67–2.28)	.5
Yes	19.7	18.4	22.3	.14	0.93 (0.70–1.24)	.3

Abbreviations: CI, confidence interval; COPD, chronic obstructive pulmonary disease; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.

The hazard ratios predicting the risk of death in April vs March was computed twice, adopting 2 separate models: in the first (*), a Cox proportional hazard analysis was performed; in the second (**), a frailty term was incorporated to the Cox model, to include cluster-specific random effects potentially arising from the presence of patients diagnosed in 2 different provinces.

[a]From March 3 to March 31, 2020.

[b]From April 1 to May 3, 2020.

[c]χ^2 test for categorical variables.

[d]Cox proportional hazard model, adjusted for age, gender, hypertension, diabetes, major cardiovascular diseases, COPD, cancer, and renal disease. Some models could not be fit due to the scarce number of deaths.

[e]Including patients with ≥1 chronic condition among hypertension, diabetes, major cardiovascular diseases, COPD, cancer, or renal diseases.

without hypertension (from 4.4% to 6.7%; $P = .040$), diabetes (from 7.4% to 10.7%; $P = .005$), COPD (from 8.5% to 11.1%; $P = .040$), and cancer (from 8.7% to 11.3%; $P = .050$). No significant change were observed among the other categories of subjects.

Multivariate Cox analysis did not confirm univariate results: adjusting for age, gender, hypertension, diabetes, CVD, COPD, cancer, and renal disease, the HR of death of those diagnosed in April 2020, compared with March 2020, was no more significant: 0.93 (95% confidence interval [CI], 0.71–1.21) (Table 2), and it did not change either including or excluding from the analyses the province of diagnosis. From March to April 2020, the risk of death did not significantly change in any subset of the sample, with the only exceptions of the females (adjusted HR, 0.65; 95% CI, 0.44–0.95) and diabetics (adjusted HR, 0.57; 95% CI, 0.34–0.94), whose risk significantly decreased (Table 2). The results of the random-effect logistic regression did not vary: overall, the adjusted odds ratio of death at 28 days was 0.77 (95% CI, 0.55–1.07; $P = .12$) for those diagnosed in April 2020, compared with the subjects detected in March 2020.

DISCUSSION

In this sample from 2 Italian provinces, after adjusting for several potential confounders, the SARS-CoV-2 case-fatality rate did not significantly decrease from March to April 2020, overall and in any age-class. The mortality trend throughout time was stable across all categories of risk, with the only exceptions of females and diabetics, both showing a significantly lower death rate in April 2020, compared with March 2020.

Therefore, our data do not support the hypothesis of a decline in SARS-CoV-2 lethality, which has been first suggested by some clinicians [7–11], after a reduction in the number of severe cases requiring hospitalization or intensive care unit support [14]. The above hypothesis has been recently propelled by the results of a study showing a reduced viral load during the latest phases of the pandemic in the nasopharingeal swabs collected from hospitalized patients in Northern Italy [15]. However, the available data were based on a limited number of subjects, and the correlation between viral load and clinical outcome of coronavirus disease 2019 (COVID-19) was almost entirely speculative [15].

Our data are in agreement with the officially available Italian data, showing a substantially stable raw case-fatality rate—approaching 13% during March and April 2020 [16]. A study from a single Italian province found no significant change in COVID-19 lethality in the last considered week (March 23 to 29, 2020), compared with the previous one (March 16 to 22, 2020), although the lethality was lower than that of the very initial epidemic period (February 27 to March 15, 2020) [17]. However, it is notable that the follow up of the last considered week ended on April 3, 2020, thus lasting less than 14 days for a substantial proportion of participants.

It is worth considering that none of the potential explanations to support a decline in virus lethality have been demonstrated so far [18]: less virulent virus strains have not been reported [9]; none of the treatments that have been gradually administered to the study participants during the course of the pandemic (including antivirals, low molecular weight heparin, and monoclonal antibodies against inflammatory cytokines) has been proven effective to date [19, 20]; and finally, the healthcare system in the 2 provinces under study has never been overcrowded during the pandemic [21].

The present data are updating a previous, preliminary analysis [13], significantly expanding the sample and length of follow up. Nonetheless, they require confirmation from larger datasets across multiple countries, comparing more distant time frames (because 1 month might be too short to detect substantial changes in healthcare system preparedness and medical treatments) and accounting for additional potential confounders (such as body mass index—that we initially did not include among the variables to collect, but which later emerged as a significant predictor of death from COVID-19 [22, 23]—or data regarding acute physiology, organ damage, or vital signs observed among hospitalized subjects [24]) during time periods with a stable diagnostic capacity. In fact, in both of the selected regions, the number of RT-PCR tests increased substantially from March to April 2020 (from a total of ≈500/daily to almost 6000/daily) [25, 26], and it cannot be excluded that the proportions of undetected infections or unrecognized COVID-19 deaths were unbalanced over time. It should be noted, however, that in the regions under examination, the positivity rate slightly declined throughout the time frame [26], which may likely reflect a consistent increase in the diagnostic capacity, in spite of the rise in the number of positive cases.

Another limitation of the present study is the lack of specific information on the treatments against COVID-19 administered in hospital or prescribed at home. It is possible, or even likely, that the medical approach varied between March and April 2020, potentially impacting lethality. However, there is still scarce evidence of effectiveness for most of the treatments that were used in the selected periods (lopinavir/ritonavir, hydroxychloroquine, and tocilizumab) [19, 20]. In addition, and more importantly, the evaluation of the potential motivations of the observed trend over time (including the impact of each risk factor or adopted treatment) was beyond the scope of the study, whose main aim was to describe whether a change in SARS-CoV-2 lethality occurred over time, regardless of any treatment, patient characteristic, of healthcare services change.

Male gender and some comorbidities were more frequent among the subjects infected in April 2020, which may have increased the observed lethality. However, the case-fatality rates remained similar between March and April 2020 even when the sample was stratified for the presence of comorbidity, and these results were confirmed in multivariate analyses. It is worth noting that we relied on routinely collected hospitalization data to define comorbidities for nonhospitalized subjects (63.3% of the sample). Although this source of information may underestimate the prevalence of those comorbidities that rarely lead to hospitalization (such as mild COPD, hypertension or diabetes), we integrated these data (retrospectively collected up to 8 years before) with drugs prescriptions, which typically limit the inadequacy of disease burden estimates [17]. Indeed, collecting information on the clinical history registered before the epidemic onset may increase the accuracy of the data, because the experience with the early days of the pandemic suggests that the reliability of clinical history was limited, mainly due to critical patient conditions, common distance of relatives who could not confirm prior conditions, or lack of time to spend on clinical history taking due to the overwhelming number of observed cases [17].

CONCLUSIONS

Acknowledging these caveats, our data provide the most comprehensive evidence of a lack of a significant decrease of SARS-CoV-2 case-fatality rate between March and April 2020, on a prospective sample, adjusting for several potential predictors of death. We trust that some of the many ongoing trials testing new therapies [27, 28]—starting from those reporting promising results on dexamethasone [29]—will determine a breakthrough in the clinical course of the pandemic.

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