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Excess all-cause mortality during COVID-19 outbreak: potential role of untreated cardiovascular disease

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Abstract

Background. Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) pandemic has rapidly spread globally. Due to different testing strategies, under-detection of positive subjects and COVID-19-related-deaths remains common. Aim of this analysis was to assess the real impact of COVID-19 through the analysis of 2020 Italian all-cause mortality data compared to historical series.

Methods. We performed a retrospective analysis of 2020 and 2015-2019 all-cause mortality data released by the Italian National Institute for Statistics (ISTAT) for the time period 'January 1 – March 21'. This preliminary sample included 1,084 Italian municipalities showing at least 10 deaths during the above-mentioned timeframe and an increase in mortality of more than 20% as compared to the previous five years (2015-2019), with a resulting coverage of 21% of Italian population. The difference between 2020 observed and expected deaths (mean of weekly deaths in 2015-2019) was computed, together with mortality rate ratio (MRR) for each of the four weeks following detection of the first autochthonous COVID-19 case in Italy (23 February, 2020 – 21 March, 2020), as well as for this entire timeframe. Subgroup analysis by age groups was also performed.

Results. Overall MRR was 1.79 [1.75-1.84], with an observed excess mortality of 8,750 individuals in the investigated sample, which in itself outweighs Italian Civil Protection report of only 4,825 COVID-19-related deaths across Italy, as of March 21. Subgroup analysis did not show any difference in mortality rate in '0-14 years' age group, while MRRs were significantly increased in older age groups, in particular in patients >75 years (MRR 1.84 [1.79-1.89]). In addition, week-by-week analysis showed a progressive increase in MRR during this period, peaking in the last week (15 March, 2020 – 21 March, 2020) with an estimated value of 2.65 [2.53-2.78].

Conclusions. The analysis of all-cause mortality data in Italy indicates that reported COVID-19-related deaths are an underestimate of the actual death toll. All-cause death should be seen as the epidemiological indicator of choice to assess the real mortality impact exerted by SARS-CoV-2, given that it also best reflects the toll on frail patient subsets (eg the elderly or those with cardiovascular disease).

Introduction

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has rapidly spread worldwide[1], forcing World Health Organization to declare a coronavirus disease 2019 (COVID-19) pandemic on March 11, 2020[2]. As of April 5, 2020, more than 1.2 million cases have been diagnosed in 183 countries, with more than 65,000 SARS-CoV-2-positive deaths[3]. Chinese data[4] suggest that the major risk factor for mortality, besides advanced age (case-fatality rate of 14.8% in patients older than 80 years), is an underlying cardiovascular disorder, with an estimated case-fatality of 10.5% in this subgroup of patients, followed by diabetes and hypertension (case-fatality rates of 7.3% and 6%, respectively). Similar data have been reported in Italy[5,6]. Several mechanisms have been hypothesized to explain the association between COVID-19 outcomes and cardiovascular disease[7]: for example, the strongest risk factor for cardiovascular disease is age, and the effect of aging on immune function may play a critical role in determining COVID-19 susceptibility and severity; in addition, it has been suggested that another traditional cardiovascular risk factor like diabetes may disregulate immune function, thus prevalent cardiovascular disease may also be a marker of accelerated immunologic aging; finally, higher expression of ACE2, the main cellular receptor used by the virus, in patients with hypertension and cardiovascular disease has been postulated to enhance susceptibility to SARS-CoV2, even though further studies are needed to shed light on this particular topic.

Mitigation and testing strategies differ between countries, resulting in varying estimates for infection, symptomatic disease and case-fatality. The latter is confounded by under-detection of both positive subjects and of COVID-19-related-deaths. Given these considerations, a more reliable way to assess the real impact of COVID-19 is to focus on all-cause mortality data, comparing them with historical series. Aim of this analysis was to assess the real impact of COVID-19 through the analysis of 2020 Italian all-cause mortality data compared to historical series (2015-2019) for a group of Italian municipalities.

Methods

On March 31, 2020, the Italian National Institute for Statistics (ISTAT) officially released Italian all-cause mortality data for the ‘January 1, 2020 - March 21, 2020’ time period[8]. We used weekly data from this preliminary sample and we compared observed mortality trend in 2020 with the expected trend derived by data from the previous five years (2015-2019), with ‘week 1’ set as the first week (February 23, 2020 – February 29, 2020) after the first official autochthonous COVID-19 case in Codogno (Lombardia), as of February 20, 2020. In particular, considering the mean

of weekly deaths in 2015-2019 as the expected value, we calculated the difference between 2020 observed and expected deaths, together with mortality rate ratio (MRR, with corresponding 95% confidence interval [CI], based on an exact Poisson method), for each of the four weeks included in the time period '23 February, 2020–21 March, 2020', as well as for the entire timeframe. In addition, we also reported data stratified by four age groups: '0-14 years', '14-64 years', '65-74 years', '>75 years'. Statistical analysis were performed using STATA (StataCorp LLC, Texas, USA).

Results

This preliminary sample included 1,084 Italian municipalities[9] showing at least 10 deaths during the above-mentioned timeframe and an increase in mortality of more than 20%, with respect to the mean value of the previous five years (2015-2019). The resulting sample covers 21% of Italian population (12,673,821 out of 60,359,546 inhabitants), with broad heterogeneity in regional coverage, reflecting the differential impact of the disease across Italian regions (Figure 1). In particular, regional coverage ranged from 57% in Lombardia, the most affected region, to 2% in Calabria.

Figure 1 reports the graphical trends of weekly deaths in 2020 and in the previous five years (2015-2019). A rapid upsurge of weekly all-cause deaths is evident since March 2020, clearly departing from the anticipated trend.

Focusing on the timeframe 'February 23, 2020 – February 29, 2020', overall MRR was 1.79 [1.75-1.84], with an observed excess mortality of 8,750 individuals. Subgroup analysis did not show any difference in mortality rate in '0-14 years' age group, while MRRs were significantly increased in older age groups, in particular in patients >75 years (MRR 1.84 [1.79-1.89]). In addition, week-by-week analysis showed a progressive increase in MRR during this period, peaking in the last week (15 March, 2020 – 21 March, 2020) with an estimated value of 2.65 [2.53-2.78].

Discussion

Since Italian Civil Protection reported only 4,825 COVID-19-related deaths as of March 21, 2020[10], these data suggest that COVID-19 likely caused many more deaths than those officially reported. Indeed, compared to the previous five years, 8,750 additional deaths occurred between 23 February and 21 March, 2020, in a subsample representing the most affected Italian municipalities, which covers approximately 21% of Italian population. This finding is consistent with a previous report focused on a small municipality in Lombardy, Nembro[11]. The observed death excess occurred despite the dramatic reduction in traffic and work-related mortality caused by the national lockdown. This finding appears to be

due to the non-attribution to COVID-19-mortality of deaths occurred in patients being affected by the disease but not being tested for coronavirus. However, in addition to infection-related deaths, this figure is likely to include deaths not directly related to viral infection, but rather to collateral situations that arise, such as the reduced ability of the overwhelmed healthcare system to efficiently respond to other health needs or citizens' behavioural response to the pandemic.

For example, a decrease in hospital admissions for acute coronary syndromes has been documented in several countries: in Italy, a recent study highlighted a reduction in daily acute coronary syndrome admissions across 15 hospitals in northern Italy in the period February 20, 2020 – March 31, 2020, with a 36% and 40% drop if compared to the first part of the year and to the same period in 2019, respectively[12]; in particular, this drop was even greater if focusing only on the time period following Italian national lockdown (March 8, 2020); similarly, a study involving 9 high-volume centres in United States demonstrated a 38% reduction in ST-elevation myocardial infarction (STEMI) activations for March 2020, if compared to data of the previous 14 months[13]; finally, Spanish data are in line with Italian and American trends, with an estimated 40% drop in STEMI hospital admissions during the outbreak[14]. Altogether, it is implausible to attribute these findings to a COVID-19-related decrease in acute coronary syndrome incidence, since it is well known that acute respiratory infections may trigger cardiovascular events such as myocardial infarction[15], since the infection-related inflammation may promote a pro-thrombotic state, which favours plaque instability and rupture. Thus, this reduction seems sustained by behavioural changes induced after lockdown initiation, with less patients seeking medical care complaining of acute chest pain due to the fear of being infected. The implication of such behaviour may be dramatic, since untreated acute myocardial infarction may lead to life-threatening conditions such as sudden cardiac death and cardiac rupture, as well as more subtle conditions such as chronic heart failure. Therefore, it is possible that a significant part of the observed excess indirect mortality seen in the present study is related to untreated acute myocardial infarction. In this regard, a recent report strongly support this hypothesis, indicating a significant increase in STEMI case-fatality rate (relative risk 3.3, 95% confidence interval 1.7-6.6), sided by a parallel increase in complication rate, in Italy during a 1-week window after the national lockdown (12 March, 2020 – 19 March, 2020). In addition, this hypothesis may also be reinforced by the results of a recent Italian study, based on data from Lombardia Cardiac Arrest Registry (CARe)[16]: the authors highlighted a 58% increase in out-of-hospital cardiac arrest in 2020, with cumulative incidence strongly associated with COVID-19 outbreak; strikingly, COVID-19 confirmed or suspected cases accounted for 77.4% of the excess in cases of out-of-hospital cardiac arrest if compared to 2019 data. Since the most prevalent cause of out-of-hospital cardiac arrest is myocardial infarction, it can be speculated that these epidemiological findings may be the consequence of several untreated myocardial infarctions.

Altogether, these considerations suggest that acute cardiovascular conditions such as myocardial infarction may significantly contribute to the observed excess mortality during COVID-19 outbreak, most likely due to citizens' behavioural response to the lockdown.[17] This prompts urgent considerations in order to prepare for a likely upcoming surge of both short and long-term sequealae of untreated myocardial infarction, such as ventricular aneurysms, ventricular arrhythmias and heart failure.

Finally, shifting the focus on a global scale, recent epidemiological data about the observed excess mortality during the pandemic with respect to the previous year, which were gathered by Financial Times based on various national sources[18], consistently reproduced the findings of the present study. In fact, if we compared the observed excess mortality in several countries with the officially reported number of COVID-19-related deaths[19] (Figure 3), it is evident that for most of the investigated countries the observed excess deaths greatly outweighs the reported COVID-19 mortality. In particular, the countries with the highest percentage difference between observed excess deaths and COVID-19 reported deaths are Latin America countries, such as Peru (+328%) and Brazil (+116%). Conversely, Belgium and France do not show significant differences (-13% and -3%, respectively). These data strongly emphasize the importance of an epidemiological monitoring of excess deaths during COVID-19 pandemic, which will also be useful in the near future to rapidly detect eventual outbreak recrudescences.[20-21]

Limitations of this work are several. In particular, this preliminary Italian sample included only the highest-risk Italian municipalities, thus it is not possible to infer conclusion regarding the whole Italian population. In addition, it was not possible to differentiate between infection-related deaths and indirect deaths. Furthermore, the impact of important cardiovascular or clinical risk factors, either impacting individually (eg smoking) or collectively (eg climate or pollution), was not systematically appraised or analyzed.[22-25] Similarly, analysis of the role of ancillary medical therapy (eg use of dexamethasone) or invasive mechanical support (eg ventricular assist devices or extracorporeal membrane oxygenation), which could prove in many cases lifesaving, was beyond our scope.[26-27] Finally, ecological fallacy, regression to the mean and other typical biases impacting on aggregate analyses should not be disregarded.[28-30]

Conclusion

The analysis of all-cause mortality data in Italy indicates that reported COVID-19-related deaths are underestimated. Accordingly, all-cause death should evidently be seen as the most poignant epidemiological indicator and parameter of choice to assess the real mortality impact exerted by SARS-CoV-2 and the effectiveness of the adopted mitigation measurements to limit viral diffusion[7,19,20]. In addition, part of the excess observed mortality may be indirectly related to COVID-19, as in the case of untreated myocardial infarctions due to citizens' behavioural response to the outbreak.

Tables

Table 1. Weekly and overall all-cause deaths in the included Italian municipalities in 2020 and in the previous five years (2015-2019), with the corresponding mortality rate ratio (overall and age-stratified), for the investigated time period (February 23, 2020 – March 21, 2020). Data source: ISTAT (Italian National Institute for Statistics).

Week/Time Period	2020	2015-2019*	Observed - expected	Mortality rate-ratio	LCI	UCI	p-value
23 Feb - 29 Feb	**2869**	**2491**	**378**	**1.02**	**0.97**	**1.08**	**0.467**
0-14 years	2	7	-5	0.25	0.03	1.33	0.076
15-64 years	237	228	9	0.92	0.76	1.11	0.373
65-74 years	378	320	58	1.05	0.90	1.22	0.552
> 75 years	2252	1937	315	1.03	0.97	1.09	0.344
1 Mar - 7 Mar	**3839**	**2692**	**1147**	**1.43**	**1.36**	**1.50**	**<0.001**
0-14 years	5	6	-1	0.83	0.20	3.28	0.774
15-64 years	320	249	71	1.29	1.09	1.52	0.002
65-74 years	491	353	138	1.39	1.21	1.60	<0.001
> 75 years	3023	2084	939	1.45	1.37	1.53	<0.001
8 Mar - 14 Mar	**5624**	**2606**	**3018**	**2.16**	**2.06**	**2.26**	**<0.001**
0-14 years	7	7	0	1.00	0.30	3.34	1
15-64 years	391	237	154	1.65	1.40	1.95	<0.001
65-74 years	727	337	390	2.16	1.89	2.46	<0.001
> 75 years	4499	2025	2474	2.22	2.11	2.34	<0.001
15 Mar -21 Mar	**6753**	**2546**	**4207**	**2.65**	**2.53**	**2.78**	**<0.001**
0-14 years	5	6	-1	0.83	0.20	3.28	0.774
15-64 years	433	239	194	1.81	1.54	2.13	<0.001
65-74 years	901	335	566	2.69	2.37	3.06	<0.001
> 75 years	5414	1966	3448	2.75	2.61	2.90	<0.001
Total (23 Feb - 21 Mar)	**19085**	**10335**	**8750**	**1.79**	**1.75**	**1.84**	**<0.001**
0-14 years	19	27	-8	0.68	0.36	1.28	0.21
15-64 years	1381	952	429	1.41	1.30	1.53	<0.001
65-74 years	2497	1344	1153	1.80	1.69	1.93	<0.001
> 75 years	15188	8011	7177	1.84	1.79	1.89	<0.001

*****Mean count; LCI: lower confidence interval; UCI: upper confidence interval.

Figure Legends

Figure 1. Italian map reporting the percentage of regional coverage in the included sample. Data source: ISTAT (Italian National Institute for Statistics).

Figure 2. Weekly all-cause deaths in the included Italian municipalities in 2020 and in the previous five years (2015-2019)*. Time origin (week 0) was set at 23 February 2020. Data source: ISTAT (Italian National Institute for Statistics).

*Mean value ± 1.96 x standard deviation

Figure 3. Difference between observed excess mortality (with respect to the previous five years) and the official number of reported COVID-19-related deaths. Countries with highest percentage difference between observed excess deaths and COVID-19 reported deaths are Peru (+328%) and Brazil (+116%), while Belgium (-13%) and France (-3%) do not show significant differences. Data source: Financial Times[18] and World Health Organization[19].

Authors' contribution

AS and GBZ conceived the analysis. AS performed the analysis on Italian mortality data. All the authors actively participated in data interpretation and wrote the manuscript. All the authors read and approved the final version of the manuscript.

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