

Correlation between relative age-standardized mortality rates and COVID-19 mortality over time in Italy

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Abstract. *Background and aim:* This study was planned to estimate the contribution of coronavirus disease 2019 (COVID-19) related mortality on excess deaths recorded in Italy since the beginning of the pandemic. *Methods:* Official data on weekly number of COVID-19 related deaths in Italy were retrieved from the website of the Italian Ministry of Health, whilst information on weekly relative age-standardised mortality rates (rASMRs) in Italy during the COVID-19 pandemic was downloaded from the UK Office for National Statistics website. Univariate and multivariate correlation was conducted to explore the association between these two variables throughout the pandemic. *Results:* Significant univariate correlation was found between rASMR and number of official COVID-19 related deaths throughout the pandemic period. Such correlation was especially high during predominance of pre-Alpha and Alpha variants, remained significant during Delta variant predominance, but become no longer significant during Omicron variant predominance. In multivariable analysis, we estimated that COVID-19 may have contributed to 72% of the excess mortality recorded in Italy throughout the pandemic. The impact was higher during pre-Alpha and Alpha periods (i.e., 78% and 89%, respectively), decreased to 41% during Delta variant predominance, and became no longer significant after emergence of the Omicron variant. *Conclusions:* These results would suggest that COVID-19 may have largely contributed to excess mortality in Italy until the recent emergence of the Omicron variant, by which time previous loss of vulnerable people and radical changes in delivering healthcare may have paradoxically contributed to improve the cumulative death rate in the country. (www.actabiomedica.it)

Key words: SARS-CoV-2; COVID-19; mortality, excess deaths

Introduction

More than one hundred years after the Spanish flu pandemic, the world is facing a new global challenge represented by a new pandemic disease sustained by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) (1). It is now undeniable that coronavirus disease 2019 (COVID-19) has triggered a kind of worldwide “permacrisis” (2), which has been associated with paramount clinical consequences, disrupting the integrity of society, economy and healthcare (3). Although it is particularly

challenging to collectively estimate the clinical burden that COVID-19 had caused since its origin in 2019 (4), several lines of evidence now attest that million people may have died from the direct and indirect consequences of the virus (5), thus unquestionably causing an excess number of deaths (often underestimated or largely uncounted and unreported) all around the world (6,7), including Italy (8). Yet, the straightforward translation of COVID-19 related deaths into excess mortality (and vice versa) is essentially inappropriate and potentially misleading, since these two terms cannot be used as synonymous due to

the fact that many other factors, not directly related to the biological effects of SARS-CoV-2 infection (i.e., diagnostic and therapeutic delays during period of more problematic care access, increase prevalence of chronic diseases and frailty due to social isolation and so forth), may have played a role in boosting the number of deaths throughout the ongoing COVID-19 pandemic (9). Thus, this study was planned for attempting to estimate the potential cumulative contribution of COVID-19 related mortality on the volume of excess deaths that was recorded in Italy throughout the ongoing COVID-19 pandemic.

Materials and methods

We accessed official data of the Italian Ministry of Health (10) for retrieving the official (weekly) number of COVID-19 related deaths in Italy throughout the pandemic. Although inherently biased and perhaps even partially inaccurate, the Italian Ministry of health uses for “COVID-19 related death” the World Health Organization (WHO) definition, thus encompassing four criteria, as follows: (i) death occurred in a patient classified as confirmed case of COVID-19; (ii) presence of a clinical picture suggestive of COVID-19, or a clinical diagnosis that certifies the presence of symptoms attributable to SARS-CoV-2 infection; (iii) absence of

a clear cause of death other than COVID-19 (i.e., not directly attributable to SARS-CoV-2 infection); and (iv) incomplete clinical recovery between COVID-19 illness and subsequent death (10). The information on weekly relative age-standardised mortality rates (rASMRs) in Italy throughout the COVID-19 pandemic, expressed as percentage change per week from the average age-standardised mortality rate recorded during the recent pre-COVID-19 period (i.e., between years 2015-2019), was downloaded from the website of the UK Office for National Statistics (11). The information herein available concerns rASMRs stratified for each European country from the beginning of the pandemic (i.e., from February 28, 2020), up to the last available date used for its calculation (i.e., July 1, 2022).

The association between rASMR and official COVID-19 deaths throughout the study period and within different periods characterized by predominance of specific SARS-CoV-2 variants (Table 1) (12) was analyzed with univariate (Pearson’s test) and multivariate (multiple linear regression analysis), using Analyse-it (Analyse-it Software Ltd, Leeds, UK). The study was performed in accordance with the Declaration of Helsinki, under the terms of relevant local legislations, using publicly available repositories, such that no informed consent or Ethical Committee approvals were necessary.

Table 1. Values and correlation between weekly relative age-standardised mortality rates a(rASMR) and coronavirus disease 2019 (COVID-19) mortality throughout the pandemic in Italy.

Period	Variant	rASMR	COVID-19 related deaths	Correlation (r)	Contribution to rASMR	p
February 28, 2020 to July 1, 2022	All	-	-	0.69 (95%CI, 0.59 to 0.78)	72%	<0.001
February 28, 2020 to January 31, 2021	Pre-Alpha	12±21	1793±1828	0.74 (95%CI, 0.59 to 0.85)	78%	<0.001
February 01, 2021 to June 27, 2021	Alpha (B.1.1.7)	4±8	1884±942	0.56 (95%CI, 0.18 to 0.80)	89%	0.001
June 28, 2021 to January 2, 2021	Delta (B.1.167.2)	1±4	370±232	0.47 (95%CI, 0.11 to 0.72)	41%	0.013
January 3, 2022 to July 1, 2022	Omicron (B.1.1.529)	-3±4	1193±698	0.20 (95%CI, -0.20 to 0.55)	-	0.322

Results

The timeline variation of COVID-19 related deaths and rASMR throughout the pandemic in Italy is shown in figure 1. As summarized in table 1 and figure 2, a significant univariate correlation could be found between rASMR and number of official COVID-19 related deaths throughout the pandemic period in Italy. Such correlation was especially high during predominance of the pre-Alpha and Alpha variants, remained statistically significant during the Delta variant predominance, but was found to be no longer significant after emergence of the Omicron variant (Table 1, Figure 2). In multivariable analysis, including rASMR as the dependent variable and the official COVID-19 related deaths and time (i.e., week) as

independent variables, we estimated that COVID-19 may have contributed to 72% of the excess mortality recorded in Italy throughout the pandemic. Such impact was remarkably high during the pre-Alpha and Alpha period (i.e., 78% and 89%, respectively, both $p < 0.001$), whilst it decreased to 41% ($p = 0.044$) during predominance of Delta variant, and with loss of significance after emergence of the Omicron variant ($p = 0.439$) (Table 1).

Discussion

It can be inferred from our analysis that COVID-19 has contributed to boost – to a very high extent (i.e., between 78–89%) – excess mortality during

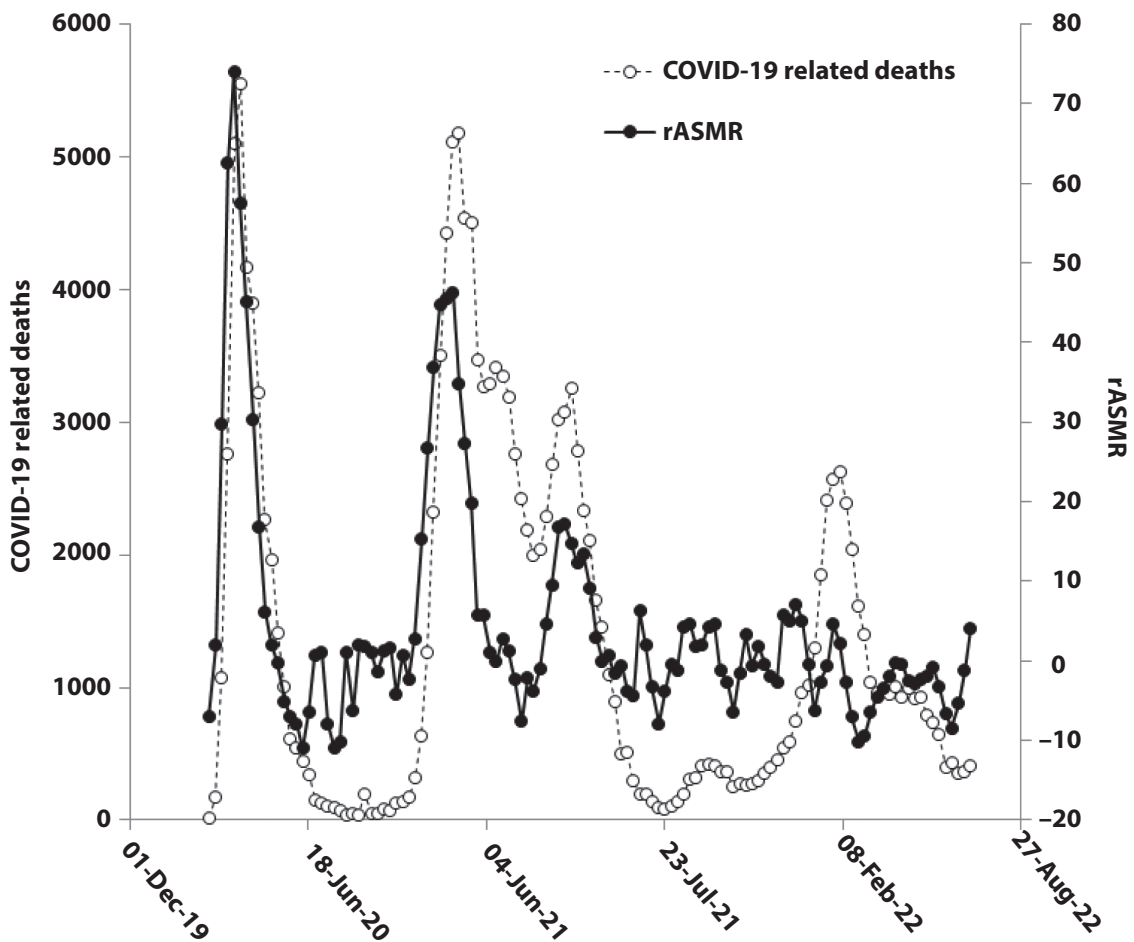


Figure 1. Timeline variation of relative age-standardised mortality rates (rASMR) and coronavirus disease 2019 (COVID-19) mortality in Italy (rASMRs: relative age-standardised mortality rates).

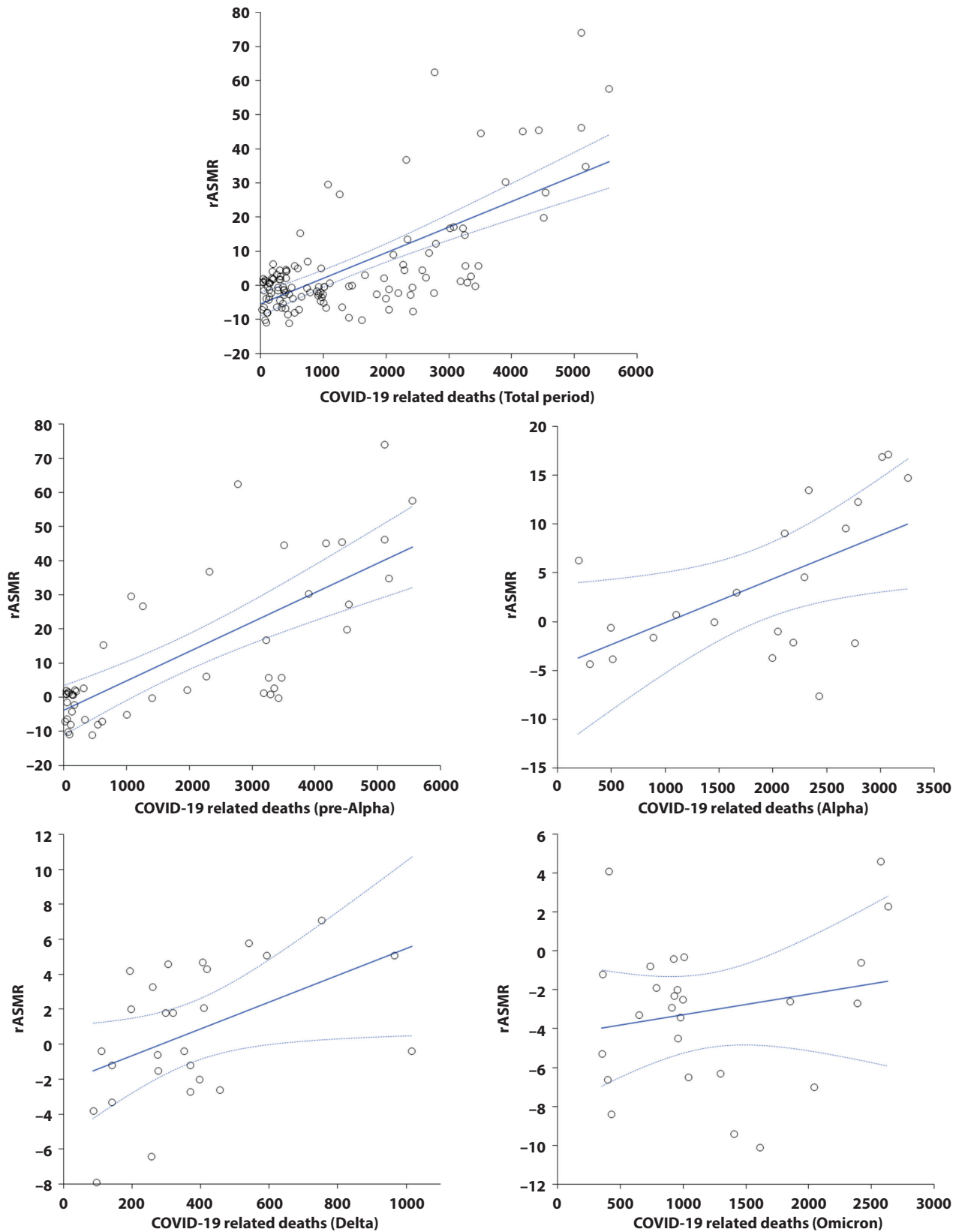


Figure 2. Correlation between relative age-standardised mortality rates (rASMR) and coronavirus disease 2019 (COVID-19) mortality over time, stratified for the different variants in Italy. (rASMRs: relative age-standardised mortality rates).

the early phases of the pandemic in Italy, i.e., especially when the pre-Alpha and Alpha variants were prevalent. In the following period, characterized by predominance of Delta variant and beneficial effects of a recently initiated (i.e., December 2020) nationwide COVID-19 vaccination campaign, the strength of such association decreased and the relative contribution of COVID-19 related deaths to excess mortality fell to around 40%. During the period of Omicron prevalence, two main aspects emerged. First, in such period the weekly rASMR has become substantially negative (i.e., -3 ± 4), whilst the number of weekly COVID-19 related deaths has remained considerably high, (i.e., 1193 ± 698), but compounded by a death rate that was over 10-fold lower compared to the pre-Alpha period (i.e., 0.2% vs 3.5%) (13). This is mostly due to the fact that the infectivity of the Omicron sublineages have caused an unprecedented surge of contagions (SARS-CoV-2 infections grew by several orders of magnitude), while the lethality rate gradually decreased as a consequence of natural or vaccination-elicited immunity, better clinical management and attenuation of viral pathogenicity (14). Moreover, the two parameters (weekly rASMR and COVID-19 related deaths) were no longer significantly correlated after emergence and surge of the Omicron sublineages. This implies that while people were still dying from COVID-19, the mortality for other causes may have unexpectedly decreased during that period. It is not really easy to identify the many causes underlying this unprecedented trend, though we can speculate that the radically mutated organization of the Italian national healthcare system after the lessons learnt from the pandemic, encompassing enrolment of many thousands of new healthcare professionals, modernisation, development and use of innovative therapies and drug repurposing strategies, introduction of accurate and fast diagnostic technologies, as well as provision of more efficient and updated services to the citizens may have ultimately contributed to reducing the lethal burden of other common pathologies (15,16). The loss of a huge number of older people during the first two years of the pandemic (i.e., 2020-2021) is another possible explanation for our findings (i.e., over 90% of people who died for COVID-19 were aged 50 years or older, 80% were ≥ 65 years) (17), in that the relative prevalence

of fragile and vulnerable subjects within the general population may have dramatically decreased by 2022, thus explaining the more recent reduction seen in the rASMR.

In conclusion, the results of our analysis would suggest that COVID-19 may have largely contributed to the excess mortality in Italy, at least until the recent emergence of the Omicron variant, by which time previous loss of vulnerable people and radical changes in delivering healthcare to face the pandemic challenge may have paradoxically contributed to improve the cumulative death rate in the country.

Authors' Contributions: CM and GL designed the study; GL was responsible for the statistical analysis. GF prepared a preliminary draft of the manuscript, which was critically reviewed by CM and BMH. All authors have read and approved the final manuscript.

Conflicts of Interest: Each author declares that he or she has no commercial associations (e.g. consultancies, stock ownership, equity interest, patent/licensing arrangement, etc.) that might pose a conflict of interest in connection with the submitted article

Data availability Statement: The complete dataset will be provided upon reasonable request to the corresponding author.

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