



Centenarians born before 1919 are resistant to COVID-19

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Abstract

Although mortality from COVID-19 progressively increases with age, there are controversial data in the literature on the probability of centenarians dying from COVID-19. Moreover, it has been claimed that men in their 90s and 100s are more resilient than women. To gain insight into this matter, we analysed, according to gender, mortality data during the first year of pandemic of Sicilian nonagenarians and centenarians. We used mortality data from the 2019 as a control. The crude excess mortality between the two years was calculated. Data on deaths of Sicilian 90+ years show that, in line with what is known about the different response to infections between the two genders, oldest females are more resilient to COVID-19 than males. Moreover, centenarians born before 1919, but not “younger centenarians”, are resilient to COVID-19. This latter datum should be related to the 1918 Spanish flu epidemic, although the mechanisms involved are not clear.

Keywords Centenarians · COVID-19 · Gender · Immune responses · Spanish Flu

Introduction

Coronavirus disease 2019 (COVID-19), induced by SARS-CoV-2, may arise as a variety of clinical manifestations, ranging from an asymptomatic condition to a life-threatening disease associated with cytokine storm, multiorgan and respiratory failure [1]. Although mortality from COVID-19 progressively increases with age, there are controversial data in the literature on the probability of centenarians dying from this disease [2–6]. Anecdotal data suggest the resilience to COVID-19 of either centenarians, regardless of gender, or only male centenarians [2, 3]. A study conducted in Lombardy showed that excess mortality increased steadily up until very old age, and at the same time males older than 90 years were relatively more resilient than age-matched females [4]. On the other hand, another study suggested that centenarians, regardless of gender, were not particularly resistant to COVID-19 compared to younger patients [5]. A more recent study, conducted in Belgium, examined the mortality of centenarians during the COVID-19 pandemic. The centenarians, of both genders, born before

August 1, 1918, showed a lower risk of excess mortality in 2020 in comparison to the mortality of previous years, when compared to centenarians born after August 1, 1918. The Authors pointed out that this date corresponds to the time when the first victims of the “Spanish flu” H1N1 pandemic in Belgium were reported [6].

In this context, the following questions arise: (1) Did centenarians die more than usual during the COVID-19 pandemic? (2) Are men in their 90 s and 100 s more resilient than women? (3) Are the centenarians exposed to the “Spanish flu” H1N1 pandemic (i.e., born before 1919 and therefore aged 102 or older in 2020) more resistant to the SARS-CoV-2 compared to younger centenarians (i.e., aged either 100 or 101 years)? To gain insight into this matter, we looked in mortality data during the first year of pandemic of Sicilian nonagenarians and centenarians analysed according to gender.

Materials and methods

We obtained, anonymously, from the Ninth Unit of the Department for Health Activities and Epidemiological Observatory of the Sicily Region [7], the mortality data of the 91+ years old, divided by sex and date of birth. We analysed deaths occurred in the period from 10 March 2020 (official start date of the pandemic in Italy) to December 31

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of the same year (after this date the vaccines changed the epidemiology of the disease and made interpretation of the data more difficult). We used mortality data from the same period in 2019 as a control. To get the crude excess mortality between the two years, data were calculated as ratio between the deaths of oldest (90+) Sicilians observed in 2020 and those observed in 2019.

Results and discussion

As previously stated, older patients are at higher risk of getting severe COVID-19, including death. Accordingly, as of March 31, 2021, at the beginning of mass vaccination of the older people, almost 86% of SARS-CoV-2 positive Italian patients that died were patients over 70 years old, with a median of 82 years (range 0–109), more than 30 years higher than that registered in infected people (median age 47) [8]. Disease severity in older patients is thought to be mainly due to the presence of comorbidities in older people. However, the ageing of the immune system, *i.e.*, immunosenescence, closely associated with a low-grade inflammatory status called "inflamm-ageing," also plays a key role. The age-related remodelling of both innate and adaptive immune response makes older people particularly vulnerable to new infectious agents never encountered before as SARS-CoV-2, while inflamm-ageing enhances the pro-inflammatory effects of the infection [8, 9].

Coming back to Sicilian data, according to National Institute of Statistics (ISTAT, [10]), the excess mortality of the Sicilian population as a whole was not as striking as in Northern Italy, since the total excess mortality was 6% (55,583 deaths compared to 52,405; ratio 1.06). This is probably due to the early lockdown that limited the circulation of the virus in the southern regions, including Sicily (the first to be affected were Lombardy and the other regions of northern Italy).

Table 1 shows the mortality data for 2020 and 2019 for the various age groups. If we look at oldest people as a whole (91+ years), the excess mortality, as expected, was greater than that reported above for the general population, being 11%. In fact, in 2020, there were 8140 deaths vs. 7352 deaths that occurred in 2019 (ratio 1.11). Mortality excess was greater in men than in women (13% vs. 10%). This datum is confirmed by examining centenarians (100+) where the excess mortality rises to 28% (ratio 1.28; 476 deaths vs. 371), and, again, is greater in men than in women (33% vs. 27%) of same age. It is noteworthy that the excess mortality observed in people aged 91–99 years was lower of that observed in centenarians, being 10% (ratio 1.10; 7664 deaths vs. 6981), always greater in men than in women (12% vs. 10%).

Table 1 Ratio between the deaths of oldest (91+ years) Sicilians observed in 2020 and those observed in 2019

	No. deaths 2020	No. deaths 2019	
91+ years			
All people	8140	7352	1.11
Men	2723	2411	1.13
Women	5417	4941	1.10
91–99 years			
All people	7664	6981	1.10
Men	2611	2327	1.12
Women	5103	4654	1.10
100+ years			
All people	476	371	1.28
Men	112	84	1.33
Women	364	287	1.27
100 and 101 years			
All people	313	194	1.61
Men	79	49	1.61
Women	234	145	1.61
102+ years			
All people	163	177	0.92
Men	33	35	0.94
Women	130	142	0.91

The deaths of centenarians born before 1919 were put together due to the small number of male deaths

The year of birth 1918 was, then, taken to separately analyse centenarians who died in 2020 [6], by dividing them in those dead at the age of 100 and 101 years, and in those dead at age of 102+ years. Both male and female 100–101 years old were extremely vulnerable to COVID-19. In 2020, 313 subjects of 100 and 101 years died while in 2019 were dead 194 subjects of 100 and 101 years (ratio 1.61), so the excess of mortality was 61%, without sex differences. The subjects of 102 and older than 102 (102+) who died in 2020 were 163, 14 fewer than in 2019. So, the centenarians of both sexes aged 102+ years did not show an increase in mortality related to the pandemic.

Concerning the three questions arisen in the Introduction, our data allow us to exclude that men over ninety are more resilient to the virus than women as suggested by anecdotal findings [2], and by the study conducted in Lombardy. On the other hand, this study is not entirely comparable to our one, as, in the study carried out in Lombardy, the deaths were analysed at the peak of the epidemic, and Lombardy was the Italian region most affected by COVID-19 [4]. However, the Sicilian data on the better resilience of old women than old men are in line with what is known about the different response to infections between the two genders. It has been demonstrated a slower rate of decline in several immunological parameters in women [9, 11], and in almost

all infections, indeed, mortality is greater for men than for women [9]. Moreover, older men have higher genomic activity for monocytes and inflammation whereas older females have higher genomic activity for cells of the acquired arm of immune response. So, men have higher pro-inflammatory activity and lower acquired activity than observed in women [9, 12]. These differences, that contribute to health- and life-span disparities between genders, fit very well with pathophysiological mechanisms of COVID-19 [8].

Concerning the question whether centenarians die more than usual during the COVID-19 pandemic, the centenarians analysed all together (100+) show an excess of mortality. This datum is not surprising since it is well known that most centenarians are very frail individuals [13, 14]. This high mortality cannot be influenced by their specific living conditions, because in Sicily most centenarians live in family [15]. However, we observe that the younger centenarians display a strong excess of deaths while the older centenarians, born before 1919 (102+) display the opposite, a deficit of deaths. The observation of this difference between younger and older centenarians is in agreement with data of Poulain et al. [6].

According to the Belgian paper [6], there would be a link between exposure to the 1918 H1N1 pandemic influenza and resistance to SARS-Cov-2 in 2020. The Authors hypothesize that the persistence throughout life of cross-reactive immune mechanisms has allowed the centenarians exposed to the Spanish flu to overcome the threat of COVID-19 a century later [6], although, to best of our knowledge, it has never been proven the existence of this cross-reaction between influenza myxoviruses and coronaviruses, such as SARS-Cov-2. This does not rule out the role of Spanish flu in the reduced COVID-19 mortality of "older" centenarians. We can speculate that the Spanish flu acted as a selective event for infants/children with a more robust immune system.

Like other studies [4, 6], total mortality was analysed, not COVID-19 related deaths. This is both a limitation and a strength. As discussed by [4], due to the strong pressure imposed on the Health Service, an increase in general mortality due to failure to respond to other clinical problems cannot be excluded. However, it is difficult to understand why this problem would have spared the older centenarians. Theoretically, analysing only confirmed deaths from COVID-19 would be more specific, but it should be considered that in 90+ people only a small part of deaths due to the infection was reported as infected. Furthermore, in the absence of clear typical manifestations, some of the mortality from COVID-19 could be erroneously attributed to other causes, even after a more careful reanalysis, since the swabs were only partially available.

In conclusion, data on deaths of Sicilian 90+ years show that oldest females are more resilient to COVID-19 and that a subset of centenarians, those born before 1919, are

resilient to COVID-19. The latter figure should be related to the 1918 Spanish flu epidemic, although the mechanisms involved are not clear. However, as regards the data on the deaths of centenarians, a caution note should be added for the small numbers observed.

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Declarations

Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval The Institutional Ethics Committee ("Paolo Giaccone", University Hospital) approved the DESIGN study protocol (No. 032017), that was conducted in accordance with the Declaration of Helsinki and its amendments.

Statement of human and animal rights This article does not contain any studies with human participants or animals performed by any of the authors.

Informed consent Not applicable.

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