

Determinants of SARS-CoV-2 Infection in the Older Adult Population: Data From the LOST in Lombardia Study

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Abstract

Most COVID-19-related fatalities occurred among older adults, however to date, evidence on determinants of SARS-CoV-2 infection in this population is limited and mostly based on case series without a comparison group. A telephone-based cross-sectional study was conducted in November 2020 on a representative sample of 4,400 Italians aged ≥ 65 years residing in the Lombardy region. We determined the prevalence of a history of SARS-CoV-2 infection in the period between the beginning of the pandemic and the time of the interview. Thorough unconditional multiple logistic regression models, we estimated odds ratios (OR) of SARS-CoV-2 infection and the corresponding 95% confidence intervals (CI). We also evaluated if the infection was a determinant of a worsening in mental health wellbeing. Overall, 4.9% of participants reported a history of SARS-CoV-2 infection. No significant relationship between sex and SARS-CoV-2 infection was observed. SARS-CoV-2 infection was less frequently reported in subjects aged ≥ 70 (OR=0.55; 95% 0.41-0.74) compared to 65-69 years. No trend was observed after 70 years of age. Those with at least one chronic condition reported a lower infection rate compared to healthy subjects (OR=0.68 95% CI: 0.49-0.93). Separated/divorced participants less frequently reported infection than married/cohabiting ones (OR=2.33 95% CI: 1.29-4.20). Self-reported history of SARS-CoV-2 infection resulted being a determinant of an increase in depressive symptoms (OR=1.57; 95% CI: 1.17-2.10). This first large representative study of people aged 65 years or over suggests that in Italy the oldest subjects and those having chronic conditions less frequently expose themselves to SARS-CoV-2 infection during the pandemic.

Introduction

During the first wave of COVID-19 contagion, Italy's Lombardy region, among the first hit in western countries, experienced high levels of hospitals congestion and a relevant COVID-19 case fatality rate¹⁻³. By the end of 2020, this region had registered the highest number of infections in the country, as well as one of the highest cumulative incidence rates of infection^{1,4}

According to the national-level COVID-19 surveillance system, the cumulative incidence of SARS-CoV-2 infection in Italy in 2020 (before vaccines were available) showed an increasing trend with increasing age, and by the end of the same year, 96% and 86% of COVID-19-related fatalities had occurred among people aged 60 and 70 years and over, respectively⁴. It is well documented in the literature how advanced age, being male and the presence of chronic diseases are risk factors for adverse outcomes in COVID-19 patients^{5,6}.

To date, knowledge about potential determinants of SARS-CoV-2 infection is mostly based on case series (inappropriate to investigate the issue not having a comparison group), or surveys enrolling convenience samples (providing findings not extensible to the general population)⁷. The few representative cross-sectional studies were online surveys which are unsuitable for examining those populations, like the elderly, that often do not have internet access or have a low level of computer skills⁸.

To the best of our knowledge, this is the first study that evaluates the prevalence of individuals self-reporting a history of SARS-CoV-2 infection and investigates its possible determinants in a representative sample of Italian home-dwelling people aged 65 years or older.

Results

In November 2020, out of 4,400 participants, 213 (4.9%) reported to have been infected by SARS-CoV-2. In particular, 98 participants (2.2%) received a diagnosis through a positive rhino pharyngeal swab test, 46 (1.1%) through positive serological test and 70 (1.6%) had experienced signs or symptoms without a confirmed diagnosis (**Figure 1**).

Table 1 shows the ORs of subjects reporting SARS-CoV-2 infection by selected characteristics. No relationship was observed between sex and infection (compared to women, OR for men was 1.02; 95% CI: 0.77-1.36). Subjects aged 70 years and older reported SARS-CoV-2 infection less frequently than those aged 65-69 years (OR=0.55; 95% CI: 0.41-0.74). When considering participants aged 70 years or more no trend of infection was observed with increasing age (p for trend=0.447). Compared to participants from Milan (Lombardy region's capital city), participants from Bergamo and Brescia more frequently reported SARS-CoV-2 infection (OR=2.11; 95% CI: 1.46-3.06). Divorced and separated subjects reported to have been infected more frequently compared to married ones or those living with a partner (OR=2.33; 95% CI: 1.29-4.20).

Table 1

Distribution of 4,400 Italian subjects aged 65 years or more according to SARS-CoV-2 infection, overall and by selected characteristics. Corresponding odds ratios[^] (OR) and 95% confidence intervals (CI). Lombardy region, Italy 2020.

Characteristics	N	SARS-CoV-2 infection based on confirmed diagnosis or symptoms		SARS-CoV-2 infection based on confirmed diagnosis only*	
		%	OR (95% CI)	%	OR (95% CI)
Total	4400	4.9		3.3	
Sex					
Women	2498	4.7	1.00°	3.1	1.00°
Men	1902	5.0	1.02 (0.77-1.36)	3.6	1.11 (0.79-1.56)
Age group (years)					
65-69	1289	7.3	1.00°	5.6	1.00°
70-74	838	3.2	0.45 (0.29-0.70)	2.3	0.41 (0.24-0.70)
75-79	1188	4.3	0.62 (0.43-0.88)	2.8	0.52 (0.33-0.80)
80+	1085	3.8	0.57 (0.38-0.86)	2.1	0.41 (0.25-0.69)
P for trend			0.006		<0.001
Level of education					
Low	788	3.7	1.00°	2.5	1.00°
Intermediate	3168	5.2	1.20 (0.78-1.84)	3.5	1.04 (0.62-1.74)
High	444	4.3	0.92 (0.50-1.71)	3.1	0.81 (0.39-1.67)
P for trend			0.914		0.592
Province					
MI	1424	3.5	1.00°	2.4	1.00°
CO+LC+MB+VA+SO	1262	4.8	1.34 (0.91-1.97)	3.2	1.24 (0.77-1.98)
BG+BS	1038	7.2	2.11 (1.46-3.06)	4.6	1.87 (1.19-2.95)
CR+LO+MN+PV	677	4.1	1.11 (0.69-1.79)	3.5	1.35 (0.79-2.31)

[^] Estimated by unconditional multiple logistic regression models after adjustment for sex, age, education level, province and number of chronic conditions; estimates in bold are those statistically significant at 0.05 level.

* 70 subjects reporting COVID-19 symptoms but no diagnosis were excluded from the analyses.

° Reference category

Characteristics	N	SARS-CoV-2 infection based on confirmed diagnosis or symptoms		SARS-CoV-2 infection based on confirmed diagnosis only*	
		%	OR (95% CI)	%	OR (95% CI)
Marital status					
Married\Living with a partner	3113	4.7	1.00 [°]	3.3	1.00 [°]
Divorced/separated	140	10.0	2.33 (1.29-4.20)	5.4	1.66 (0.75-3.67)
Widowed	871	4.3	1.16 (0.77-1.73)	2.7	1.19 (0.73-1.95)
Never married	276	5.5	1.06 (0.61-1.84)	4.1	1.10 (0.58-2.08)
^ Estimated by unconditional multiple logistic regression models after adjustment for sex, age, education level, province and number of chronic conditions; estimates in bold are those statistically significant at 0.05 level.					
* 70 subjects reporting COVID-19 symptoms but no diagnosis were excluded from the analyses.					
° Reference category					

Compared to those with no diseases, subjects with one or more chronic conditions less frequently reported SARS-CoV-2 infection (OR= 0.68; 95% CI: 0.49-0.93). No trend was observed with increasing number of chronic diseases (p for trend=0.112). People with diabetes less frequently reported SARS-CoV-2 infection, compared to subjects without that disease (OR=0.64; 95% CI: 0.42-0.99), whereas people with migraine more frequently reported SARS-CoV-2 infection, compared to those without that condition (OR=2.01; 95% CI: 1.21-3.34; Table 2).

Table 2

Distribution of 4,400 Italian subjects aged 65 years or more according to SARS-CoV-2 infection, overall and by chronic conditions. Corresponding odds ratios[^] (OR) and 95% confidence intervals (CI). Lombardy region, Italy 2020.

Characteristics	N	SARS-CoV-2 infection with confirmed diagnosis or symptoms		SARS-CoV-2 infection with confirmed diagnosis only*	
		%	OR (95% CI)	%	OR (95% CI)
Total	4400	4.9		3.3	
Chronic diseases [†]					
No	890	6.9	1.00	5.1	1.00 [°]
Yes	3510	4.3	0.68 (0.49-0.93)	2.9	0.63 (0.43-0.92)
1	1264	4.6	0.70 (0.48-1.01)	3.4	0.70 (0.45-1.08)
2	1375	3.8	0.61 (0.41-0.90)	2.4	0.53 (0.33-0.85)
3+	870	4.6	0.76 (0.50-1.17)	2.9	0.68 (0.40-1.14)
P for trend			0.112		0.043
Diabetes [†]	936	3.2	0.64 (0.42-0.99)	2.2	0.71 (0.42-1.21)
Hypertension [†]	2443	4.2	0.92 (0.63-1.35)	2.8	1.00 (0.63-1.59)
Osteoarthritis or arthritis [†]	1485	4.6	1.18 (0.82-1.71)	3.1	1.39 (0.88-2.19)
Asthma [†]	148	6.2	1.47 (0.73-2.97)	5.0	1.80 (0.81-3.98)
Cancer [†]	170	5.8	1.50 (0.76-2.96)	1.9	0.70 (0.22-2.25)
Heart disease [†]	539	4.3	1.07 (0.66-1.72)	2.6	1.05 (0.57-1.91)
Osteoporosis [†]	652	4.6	1.10 (0.70-1.74)	2.8	1.05 (0.59-1.87)
Kidney failure [†]	95	6.0	1.53 (0.63-3.75)	2.2	0.86 (0.20-3.65)
Bronchitis [†]	188	4.4	0.96 (0.46-2.01)	2.9	0.96 (0.39-2.39)
[^] Estimated by unconditional multiple logistic regression models after adjustment for sex, age, education level, province and number of chronic conditions; estimates in bold are those statistically significant at 0.05 level.					
* 70 subjects reporting COVID-19 symptoms but no diagnosis were excluded from the analyses.					
[°] Reference category					
[†] Diagnosed prior to the COVID-19 pandemic breakout.					

Characteristics	N	SARS-CoV-2 infection with confirmed diagnosis or symptoms		SARS-CoV-2 infection with confirmed diagnosis only*	
		%	OR (95% CI)	%	OR (95% CI)
Migraine [†]	252	8.5	2.01 (1.21-3.34)	4.6	1.52 (0.78-2.98)
[^] Estimated by unconditional multiple logistic regression models after adjustment for sex, age, education level, province and number of chronic conditions; estimates in bold are those statistically significant at 0.05 level.					
[*] 70 subjects reporting COVID-19 symptoms but no diagnosis were excluded from the analyses.					
[°] Reference category					
[†] Diagnosed prior to the COVID-19 pandemic breakout.					

Table 3 shows the OR of a worsening in anxiety and depressive symptoms during COVID-19 pandemic, according to SARS-CoV-2 infection. No relationship was observed between infection and an increase in anxiety symptoms, whereas an increase in depressive symptoms was more frequently reported in individuals who contracted the SARS-CoV-2 infection (OR=1.57; 95% CI: 1.17-2.10). The sensitivity analysis produced comparable results.

Table 3

Distribution of 4,400 Italian subjects aged 65 years or more according to a worsening in anxiety and depressive symptoms, by to SARS-CoV-2 infection. Corresponding odds ratios[^] (OR) and 95% confidence intervals (CI). Lombardy region, Italy 2020.

Characteristics	N	Increased anxiety symptoms during COVID-19 pandemic		Increased depressive symptoms during COVID-19 pandemic	
		%	OR (95% CI)	%	OR (95% CI)
SARS-CoV-2 infection with confirmed diagnosis or symptoms vs. no infection	213	39.9	1.13 (0.85-1.51)	37.8	1.57 (1.17-2.10)
SARS-CoV-2 infection with confirmed diagnosis only* vs. no infection or infection but no diagnosis	144	44.3	1.36 (0.97-1.90)	39.5	1.68 (1.19-2.38)
[^] Estimated by unconditional multiple logistic regression models after adjustment for sex, age, education level, province and number of chronic conditions; estimates in bold are those statistically significant at 0.05 level.					
[*] 70 subjects reporting COVID-19 symptoms but no diagnosis were excluded from the analyses.					

Discussion

In November 2020, almost 5% of older people from Lombardy region reported having had signs or symptoms compatible with COVID-19 or having been tested positive for SARS-CoV-2 infection based on a nasopharyngeal swab or a serological test. No relationship between sex or level of education and SARS-

CoV-2 infection was observed. Subjects aged 65-69 years more frequently reported to have been infected compared to older subjects. Having one or more chronic diseases were related to a lower rate of infection. SARS-CoV-2 infection resulted being a determinant of a worsening in depressive symptoms.

Based on our data, after almost one year from the beginning of the COVID-19 pandemic, 2.2% of adults aged 65 and older from the Lombardy region reported having had a positive nasopharyngeal swab. In November 2020, corresponding official data from the Italian National Health Institute showed that the cumulative incidence was around 3.5% in Italian adults aged 60 or more and around 3.8% in the Lombardy general population⁹. The lower prevalence of people who tested positive on a swab detected within our survey might be explained by the exclusion from our sample of the individuals residing in nursing homes, and subjects who died within the 2020 due to the infection.

However, it is interesting to note that the percentage of participants who have been infected rose by 50% (reaching 3.3%) when adding those who declared having tested positive for the serological test, and potentially more than doubled (up to 4.9%) when adding those who experienced signs or symptoms compatible with COVID-19 without any test confirmation. These results might be explained by the fact that, in Italy, in the early stages of the pandemic, the performance of nasopharyngeal swabs was almost exclusively addressed to patients in severe conditions, thus excluding a large number of individuals with none or mild signs or symptoms¹⁰. Accordingly, the Italian Ministry of Health conducted a seroprevalence study between May 25, 2020, and July 15, 2020, which revealed that 7.5% (95% CI: 6.8 – 8.3) of the Lombardy general population had SARS-CoV-2 antibodies¹¹, confirming the fact that the real cumulative incidence is underestimated when considering only nasopharyngeal swab data.

With regard to the determinants of infection, an important clarification must be made.

Since COVID-19 is characterized by non-specific signs and symptoms¹² some of which can be very common in the elderly population^{13,14}, as a sensitivity analysis, we excluded subjects reporting only signs or symptoms without a confirmed diagnosis.

We did not observe any significant relationship between sex and SARS-CoV-2 infection, although our data seem to suggest a marginally higher prevalence of infection in males. This is partly in line with a recent systematic review¹⁵, that found men having a slightly higher frequency of infection^{16,17}.

We found a lower frequency of infection in participants aged 70 years or older than in participants aged 65-69 years. This result could be explained by the fact that the latter group included a higher proportion of working subjects, likely more exposed to SARS-CoV-2 infection because of more frequent social interactions. In addition, since social isolation increases with age¹⁸, it is conceivable that subjects aged 70 years or more, having had fewer interactions, were better able to protect themselves from possible opportunities for infection. It is also likely that older people, aware of the higher risks to which they were exposed, were more careful to comply with preventive measures¹⁹. Our finding is in line with a large systematic review and meta-analysis including 241 seroprevalence studies showing that the proportion

of individuals aged 65 years or older with SARS-CoV-2 antibodies tended to decrease with age¹⁶. Also, data from an Italian Ministry of Health survey show a decrease in seroprevalence in the over-70 age group compared to the 60-69 age group¹¹. Since our survey did not allow for the inclusion of those who died of COVID-19, we recalculated the prevalence in every age group considering the number of expected cases, which is obtained by adding the proportion of deaths per age group based on the case fatality rate provided by the National Health Institute referring to November 2020⁹. The cases distribution by age remained substantially unchanged.

Participants residing in the neighboring provinces of Bergamo and Brescia showed a higher infection rate than participants from the Milan province. These results reflect data from seroprevalence studies in Lombardy^{17,20}. In line with other studies^{21,22}, compared to married or cohabiting subjects, divorced and separated ones more frequently reported SARS-CoV-2 infection. However, the reasons for this finding are unclear.

The absence of chronic diseases was associated with a higher frequency of infection. This can be explained by a less cautious attitude of this sub-group compared to individuals with at least one chronic condition who were probably aware of the increased risks they were facing. In fact, the presence of specific chronic diseases leads to a depression of the immune system²³ and an increased risk of COVID-19 resulting in adverse outcomes⁵. This has been shown particularly among patients with diabetes. By contrast, patients reporting having been diagnosed with some forms of chronic migraine before the COVID-19 pandemic showed a higher infection rate.

Both COVID-19 and Post COVID-19 Syndrome can occur with migraine^{24,25}, however our results seems to suggest that this condition could also result in an increased risk of infection. Further studies are needed to clarify this relationship.

A higher frequency of infection was observed in subjects reporting a worsening of depressive symptoms during the pandemic. Evidence from the literature shows that people who suffered from COVID-19 frequently experienced a deterioration of their mental health²⁵⁻²⁸. Furthermore, people who reported being infected most likely had other cases in their family²⁹ and may have lost relatives as a result of COVID-19. The likelihood of reporting signs and symptoms referable to COVID-19 may be related to the presence of depression and/or anxiety: studies comparing the prevalence of anxiety and depression among subjects who tested positive and subjects who tested negative to SARS-CoV-2 infection found different results^{30,31}, so further research is needed to understand the nature of this relationship.

Our findings should be interpreted in light of some limitations. The first one to mention is that data on diagnostic tests and COVID-19-like signs and symptoms were self-reported, this exposes to potential recall bias. Furthermore, it must be considered that testing capacity in Italy changed during 2020 and that some participants may have passed through an asymptomatic SARS-CoV-2 infection without ever being tested. Moreover, as this is a cross-sectional study, we could not establish any causal relationship, although all efforts have been considered to give a longitudinal context to the analyses. However, to the

best of our knowledge, this is the first study that investigates the role of possible determinants of SARS-CoV-2 infection in older people. We also believe that this study provides useful elements to obtain a more reliable estimate of the magnitude of the cumulative incidence of COVID-19 in this population than data on nasopharyngeal swabs alone. Furthermore, we used a large representative sample of the population aged 65 or more from the Lombardy Region, and data were collected through a telephone-based interview, which can be considered the most suitable solution for the older population in a pandemic context. In fact, during the pandemic, online surveys proved to be an effective tool for overcoming social distancing measures³², but they carry the risk of selection bias since they exclude those who, like many seniors, have poor digital literacy and internet access³³.

In conclusion, our results suggest that the oldest old subjects and those having chronic conditions limited their exposure to SARS-CoV-2 infection. Although the COVID-19 case fatality rate increases dramatically after the age of 70³⁴, our study seems to indicate that those between the ages of 65 and 69 are more susceptible to SARS-CoV-2 infection and should be targeted by preventive strategies to better contain the spread of contagion.

Methods

A telephone-based cross-sectional survey was performed by Doxa, the Italian division of the Worldwide Independent Network/Gallup International Association, and coordinated by Mario Negri Institute and other Italian universities and research institutions³⁵. The LOckdown and lifeSTyles in Lombardia (LOST in Lombardia) study has been conducted between November 17th and 30th 2020, on a representative sample of 4,400 older adults (aged 65 and over) from Lombardy region (Northern Italy)³⁶.

Participants were randomly selected within a list of approximately 30,000 families, representative, by province and size of municipality, of the families from Lombardy region. A quota method was applied to ensure the representativeness of the sample in terms of sex, age, and province of residence.

The study protocol was approved by the ethics committee (EC) of the coordinating group (EC of Fondazione IRCCS Istituto Neurologico Carlo Besta, File number 76, October 2020). All participants provided their informed consent to participate to the study. All methods were performed in accordance with the relevant guidelines and regulations of Scientific Reports and of Nature Research journals.

Participants provided information on socio-demographic characteristics (such as sex, age, level of education, province of residence), marital status, and the presence of selected chronic conditions before the pandemic onset (reference time: November 2019).

Anxiety and depressive symptoms were assessed using the two-item Generalized anxiety disorder scale (GAD-2)³⁷ and the two-item patient health questionnaire (PHQ-2)³⁸, respectively. In order to evaluate any potential changes in psychological wellbeing, the presence of anxiety and depressive symptoms was asked twice, referring to the time of the interview (November 2020) and one year before (November 2019).

Respondents reported if they had been infected by SARS-CoV-2 and the type of diagnosis they received: a positive rhino pharyngeal swab test, a positive serological test or if they thought they had experienced signs or symptoms attributable to COVID-19 without a confirmed diagnosis. We defined this measure as history of SARS-CoV-2 infection.

Statistical Analysis

To investigate the determinants of SARS-CoV-2 infection, we estimated odds ratios (OR) and their corresponding 95% confidence intervals (CI) through unconditional multiple logistic models. As a sensitivity analysis, we re-run all the models excluding subjects reporting only signs or symptoms but who had not received a diagnosis. We defined a worsening in anxiety and depressive symptoms as any increase in the corresponding scales. All the models were adjusted for sex, age, level of education, province and number of comorbidities. A statistical weight was applied to all the analyses to guarantee the representativeness of the sample in terms of sex, age and province of residence.

All statistical analyses were performed using SAS 9.4 (Cary, North Carolina, USA).

Declarations

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Author contributions statements

GM, CS, SG, and AO conceptualized and designed the study. CS analysed the data under the supervision of SG. GM wrote the first draft of the manuscript in collaboration with CS, and SG. All other authors provided important contributions for the interpretation of findings. AO, and SG provided supervision and important intellectual support in various steps of the study. All authors have read and approved the last version of the manuscript.

Data availability statement

Data that support findings of this study and materials are available from the corresponding author, AO, upon reasonable request.

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Declaration of Conflicts of Interest

None.

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Figures

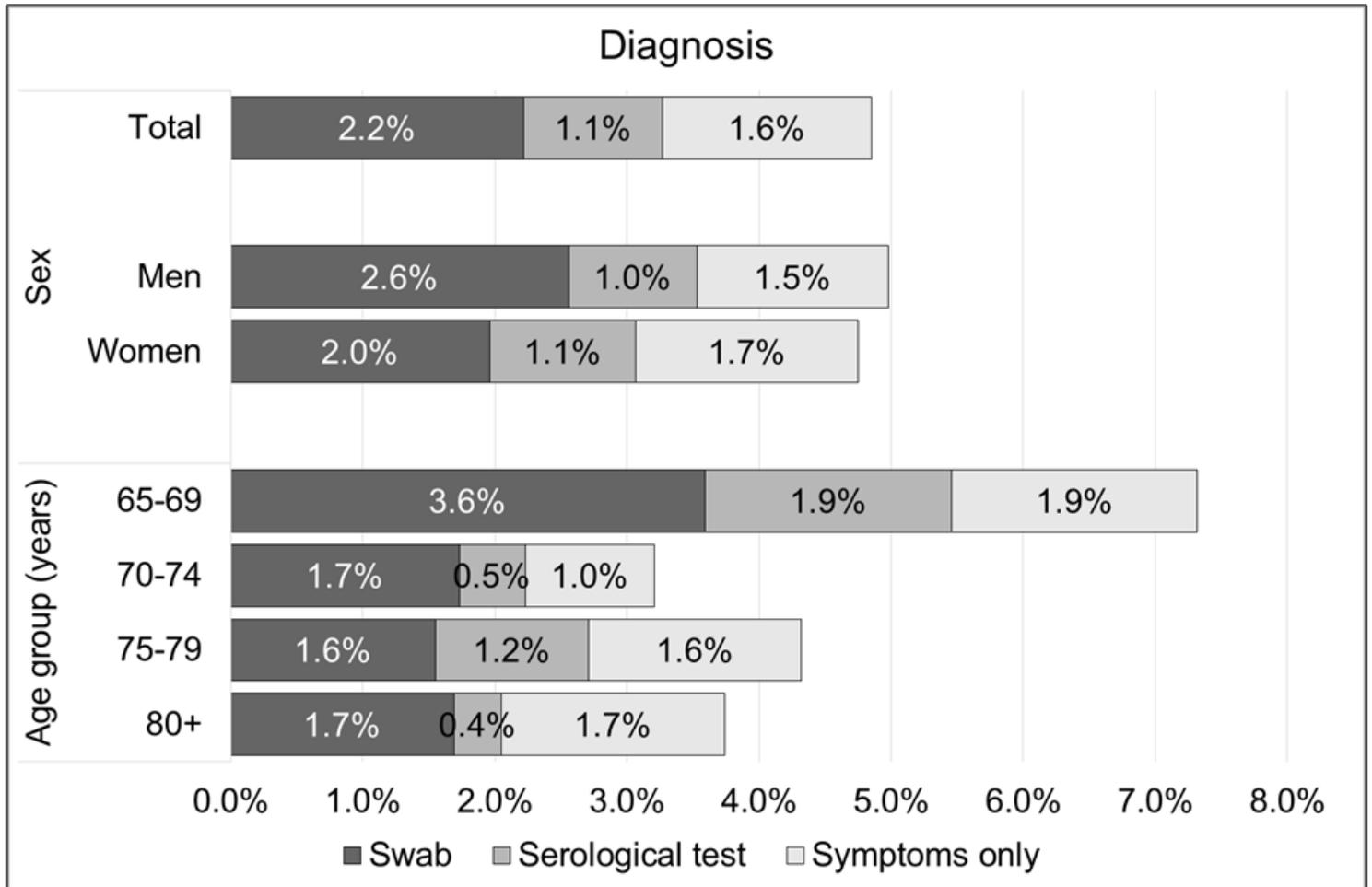


Figure 1

Distribution of 4400 Italian subjects aged 65 years or more according to COVID-19 infection and type of diagnosis, overall and by sex and age group. Lombardy region, Italy 2020.

Supplementary Files

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