Ann Ig 2021 Nov-Dic; 33(6): 533-542. doi: 10.7416/ai.2021.2435. Epub 2021 Feb 11.

SHORT PAPER

Public health and clinical approach to proactive Prevalence of symptoms-based diagnosis of mild SARS-CoV-2 infection in southern Tuscany

M. Scalese[1], G. Trivellini[1], B. Sposato[2]

Key words: COVID-19, SARS-CoV-2 infection, study, epidemiology, pharyngeal swab, prevalence, incidence

Parole chiave: COVID-19, SARS-CoV-2, infezione, studio, epidemiologia, tampone faringeo, prevalenza, incidenza

Abstract

Background. *To date, it is unknown how many Italians have had or have a mild* **SARS-CoV-2** *infection, because of the lack of epidemiological studies involving the general population.*

Study design. Aim of this study was to investigate the prevalence/incidence of a symptoms-based mild **SARS-CoV-2** *infection in southern Tuscany, by using an online survey.*

Methods. *An anonymous random middle-aged sample of 3,460 individuals completed the survey. A symptom-score ≥5, calculated on 195 patients with RT-PCR COVID-19 disease (sensitivity/specificity of 0.815/0.780 respectively) was used for the diagnosis.*

Results. *This cut-off highlighted that 12.3% of all the population might have had a* **SARS-CoV-2** *infection, while 3.9% of them might have it at the time of the survey. Female sex (OR=1.334 [1.029-1.728]; p=0.030), obesity status (OR=1.961 [1.304-2.949]; p=0.001), asthma (OR=2.035 [1.433-2.890]; p=0.0001), autoimmune diseases (OR=2.103 [1.381-3.201]; p=0.001), were all risk factors for showing mild* **SARS-CoV-2** *infection. Instead, the elderly had a low probability to develop mild forms of the disease (OR=0.984 [0.975-0.994]; p=0.001).*

Conclusion: *A remarkable number of subjects in Southern Tuscany may have already had a mild SARS-CoV-2 infection. Symptoms scores might be used to screen subjects with a suspected infection. Female sex, obesity, asthma, autoimmune diseases may be factors linked with mild forms of COVID-19 disease.*

[1] *Institute of Clinical Physiology, National Research Council, Pisa, Italy*

[2] *Pneumology Department, "Misericordia" Hospital, Grosseto, Ital*

Annali di Igiene : Medicina Preventiva e di Comunità (Ann Ig)
ISSN 1120-9135 https://www.annali-igiene.it

Introduction

By April 7 2020 the estimated Italian **SARS-CoV-2** infection prevalence (based on the disease mortality data and assumptive fatality case-rate) varied from 0.35% in Sicily to 13.3% in Lombardy (1). In the period of March-April, a general Italian non-hospitalized population of 171,310 individuals underwent a survey that analyzed self-reported symptoms compatible with COVID-19 that highlighted that 4.4% of the participants had typical symptoms of such disease. A further percentage of 7.7% of respondents reported symptoms compatible with a possible SARS-CoV-2 infection. These results, applied to the totality of the Italian adult population, made it possible to estimate at 2.2 million the number of people with typical manifestations of the disease in the March-April period of the survey who had had limited access to throat swabs (2). However, without an epidemiological study assessing the real prevalence/incidence of the disease in the general population, we do not know exactly how many patients can have mild/moderate COVID-19 symptoms (not requiring hospitalization) or how many may be asymptomatic. We only know the number of asymptomatic or poorly symptomatic subjects who did an RT-PCR pharyngeal swab test. In Italy, the number of pauci-asymptomatic patients has been variable, resulting between 40 and 75%, a value depending on the period, number of swabs performed and lockdown restrictions (according to the data of the Istituto Superiore della Sanità (National Institute of Health). As already said, little is known about COVD-19 mild forms. However, according to a recent article, mild COVID-19 patients differ from individuals affected by severe forms for the presence of a small number of comorbidities, such as diabetes, arterial hypertension, and cardiovascular disease (3). Furthermore, it appears that mild forms may have the same symptoms as severe types of the COVID-19 infections, except for dry cough (more frequent) and dyspnoea, anorexia, abdominal pain, fatigue and dizziness (less frequent) (3). Many individuals with mild COVID-19 infections may remain beyond the control of Health Authorities, thus representing an important source of further spread of the infection. Therefore, it becomes important to identify mild or asymptomatic COVID-19 subjects. Identifying asymptomatic individuals or the ones with poor symptoms would permit more targeted disease containment measures and facilitate political choices.

We investigated, through a survey, the presence of symptoms suggestive of COVID-19 infection in the general population resident in southern Tuscany, to predict the disease prevalence/incidence of a mild form of COVID-19 that did not require hospitalization. We also assessed which factors might be associated with mild infections.

Materials and Methods

An anonymous non-probabilistic sample of 3,460 individuals from the Italian general population, mostly concentrated in southern Tuscany, completed a survey (provided via smartphone/tablet/PC) including questions about place of residence, socio-demographic aspects, lifestyle behaviors, presence of comorbidities, pharyngeal swab execution, type of exposure, allergies and, above all, symptoms related to **SARS-CoV-2** infection. In particular, the questionnaire investigated whether they had had those symptoms since March 1, 2020. The main question was: *Have you had one or more of the following symptoms since March 1, 2020?* This date was chosen to exclude winter influenza symptoms. In fact, the epidemic curves of the flu syndrome show that the incidence of new flu cases in March 2020 was extremely low. People had to choose from a list of

possible COVID-19-related symptoms (table 1). They were also asked whether they had these symptoms at the time of the test. The question was: *Do you currently have one or more of these symptoms?* In addition, it was investigated whether they had undergone a pharyngeal swab test and whether it had been negative/positive. Furthermore, they were also asked if they had been hospitalized. The survey was conducted between 12/04/20 and 17/04/20. It listed 16 typical COVID-19 infection symptoms. According to the Italian Ministry of Health (4), the most common symptoms are represented by: fever, dry cough, difficult breathing, pneumonia, loss of taste and smell and weariness. When analyzing the answers to the survey, we calculated the sum of all the symptoms indicated by people by giving double weight to the most important of the above listed symptoms. Scores given could range from 0 to 22. At this point, we considered the group of subjects who had undergone the RT-PCR test and knew the result (195 individuals) to calculate the ideal score necessary to obtain an almost certain COVID-19 diagnosis by using ROC analysis. The best relationship between sensitivity and specificity was chosen as optimum cut-off point used as a score to discriminate diseased from non-diseased patients. Such score was applied to the southern Tuscany population to find how many people could have most likely had an infection. It was applied also to subjects showing symptoms while responding to the survey's questions to detect the incidence of the disease. Participants were recruited through snowball sampling. This method has the advantage of reducing costs, increasing the sample size and was used because the lockdown measures severely limited the mobility of researchers. A link to the questionnaire was sent to potential participants via email and social media. Snowball sampling involves primary data sources nominating other potential data origins that will be able to participate in the research studies. Therefore, it is purely based on referrals and is also called the chain-referral sampling method. For each symptom**,** the area under the curve (AUC), sensitivity, specificity, positive and negative predictive values were calculated. Confirmatory Factor Analysis (CFA) via Structural Equation Modelling (SEM) was assessed as internal consistency. Standardized Root Mean Square Residual (SRMR) and Root Mean Square Error of Approximation (RMSEA) not higher than 0.10 were used as goodness-of-fit criteria.

Subjects with presumed COVID-19 infection were then compared with non-COVID-19 individuals, using a univariate analysis, to understand if they had different characteristics that could favor a mild infection. Significant variables obtained at univariate analysis were tested in a multivariate logistic regression model by using a stepwise method. Patients who did not acceptably complete the questionnaire were excluded from the analysis. Also those who needed hospitalization were not considered. Participants completed an anonymous and voluntary online survey, after reading the written consent form and explicitly agreeing to participate in the survey.

Results

Interviews were evaluated on the basis of COVID-19 symptoms. Table 1 shows the main characteristics and symptoms declared by interviewed individuals. 1,771 subjects had had at least one symptom, whereas 382 reported having symptoms (at least one) at the time of responding to the survey's answers. The most frequent symptoms were rhinitis, sore throat, headache, asthenia and muscular pain (table 1).

ROC analysis performed on 195 subjects that knew the RT-PCR test result, showed that a symptom score ≥5 allowed us to carry out

Table 1 - Characteristics and symptoms reported by 3,460 subjects (divided into those with past and those with current symptomatology) who responded to the survey.

	Question: Have you had one or more of the following symptoms since March 1, 2020?		**Question**: Do you currently have one or more of these symptoms?
	No symptoms	At least one symptom	At least one symptom
Number of subjects	1513 (45.8%)	1793 (54.2%)	378 (21.1%)
Male/females	600/887 (40.3/59.7%)	608/1150 (34.6/65.4%)	122/250 (32.8/67.2%)
Age	50±13	49±13	50±14
Smokers/ex-smokers	614 (43.1%)	795 (47.7%)	184 (52.1%)
Subjects with Flu vaccination	264 (17.5%)	320 (17.9%)	87 (23%)
At least one comorbidity	427 (33.2%)	622 (41.2%)	155 (48.3%)
Obesity	55 (4.3%)	120 (7.9%)	30 (9.3%)
Inhalant allergies (at least one)	368 (27.1%)	498 (31.8%)	99 (29.9%)
Food allergies	60 (4.4%)	83 (5.3%)	25 (7.6%)
Health operators (doctors, nurses, others)	234 (16.4%)	330 (19.8%)	78 (22%)
Workers at risk (shop assistants, drivers, public employees)	456 (31.9%)	585 (35%)	134 (37.9%)
Contact with COVID_19 positive people	110 (7.3%)	192 (10.7%)	51 (13.5%)
Pharyngeal swab done	61 (4%)	149 (8.3%)	43 (11.4%)
Pharyngeal swab positive	1 (1.7%)	53 (35.6%)	21 (48.8%)
Symptoms			
Fever	-	303 (16.9%)	75 (19.8%)
Pneumonia	-	14 (0.8%)	5 (1.3%)
Rhinitis	-	604 (33.7%)	163 (43.1%)
Cough	-	348 (19.4%)	108 (28.6%)
Sputum	-	329 (18.3%)	114 (30.2%)
Sore throat	-	623 (34.7%)	152 (40.2%)
Dyspnea	-	111 (6.2%)	51 (13.5%)
Diarrhea	-	383 (21.4%)	83 (22%)
Nausea/vomit	-	100 (5.6%)	27 (7.1%)
Abdominal pain	-	156 (8.7%)	49 (13%)
Lack of appetite	-	96 (5.4%)	31 (8.2%)
Headache	-	512 (28.6%)	118 (31.2%)
Conjunctivitis	-	182 (10.2%)	56 (14.8%)
Asthenia	-	434 (24.2%)	129 (34.1%)
Muscular pain	-	409 (22.8%)	135 (35.7%)
Loss of taste and smell	-	81 (4.5%)	30 (7.9%)

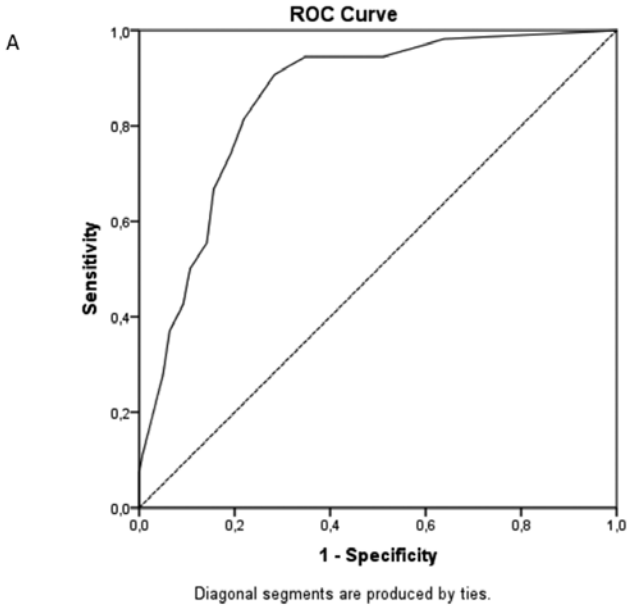

Figure 1A - ROC analysis performed on 195 individuals who had undergone the pharyngeal swab test and whose outcome was known.
* sensitivity and specificity value correspond to the score equal to 5

a diagnosis of COVID-19 with a sensitivity and specificity of 0.815 and 0.780 (AUC: 0.855 [0.800-0.911]) respectively (figure 1A). Fever and asthenia had the highest sensitivity (64.8%); instead, the highest specificity was linked to nausea (97.9%), pneumonia (97.2%) and loss of taste and smell (97.2%). The best PPV performances (Positive Predictive Value) were obtained with loss of taste and smell (87.5%), nausea (75.0%) and lack of appetite (72.0%).

Finally, the highest NPVs were related to fever (85.7%), asthenia (85.2%), muscular pain (84.1%) and loss of taste and smell (84.0%) (Table 2). The significance of each factor loading ($p<0.001$) indicates the importance of the corresponding item to the score. For example, asthenia and fever were the most important variables with values equal to 0.60 and 0.55. The other variables with good specific validity index were muscular pain (0.50), cough (0.43), lack of appetite (0.42), loss of taste and smell (0.42), diarrhea (0.40), sore throat (0.39), nausea/vomit (0.38), headache (0.37), dyspnea (0.37) and rhinitis (0.36). The lowest values were observed for abdominal pain (0.30), sputum (0.30), pneumonia (0.21) and conjunctivitis (0.20). The score efficacy was acceptable because RMSEA and SRMR indexes were lower than 0.10 (0.051 and 0.039 respectively).

By applying the symptom score ≥5 to southern Tuscany survey responders, we found that 257 subjects (12.3% of the total sample, 95% CI 10.9-13.8%) might have had a COVID-19 infection, while 81 individuals (3.9%, 95% CI 3.1-4.8%) might have it at the time of completing the survey (figure 1B).

About the same percentages can be estimated in southern Tuscany population, even if a non-probability sampling technique was used and our estimates might be distorted.

When we compared subjects with a symptom score ≥5 with individuals having

Table 2 - Diagnostic characteristics of symptoms reported by 195 subjects who had undergone the RT-PCR test and knew the result

Symptoms	N (%)	Sensitivity	Specificity	Positive Predictive Value	Negative Predictive Value	AUC
Fever	62 (31.8)	64.8	80.9	56.5	85.7	0.728
Pneumonia	11 (5.6)	13.0	97.2	63.6	74.5	0.551
Rhinitis	57 (29.2)	46.3	77.3	43.9	79.0	0.618
Cough	57 (29.2)	51.9	79.4	49.1	81.2	0.656
Sputum	24 (12.3)	16.7	89.4	37.5	73.7	0.530
Sore throat	58 (29.7)	40.7	74.5	37.9	76.6	0.576
Dyspnea	19 (9.7)	16.7	92.9	47.4	74.4	0.548
Diarrhea	46 (23.6)	38.9	82.3	45.7	77.9	0.606
Nausea/vomit	12 (6.2)	16.7	97.9	75.0	75.4	0.573
Abdominal pain	18 (9.2)	18.5	94.3	55.6	75.1	0.564
Lack of appetite	25 (12.8)	33.3	95.0	72.0	78.8	0.642
Headache	57 (29.2)	51.9	79.4	49.1	81.2	0.656
Conjunctivitis	16 (8.2)	16.7	95.0	56.3	74.9	0.559
Asthenia	67 (34.4)	64.8	77.3	52.2	85.2	0.711
Muscular pain	57 (29.2)	59.3	82.3	56.1	84.1	0.708
Loss of taste and smell	32 (16.4)	51.9	97.2	87.5	84.0	0.745

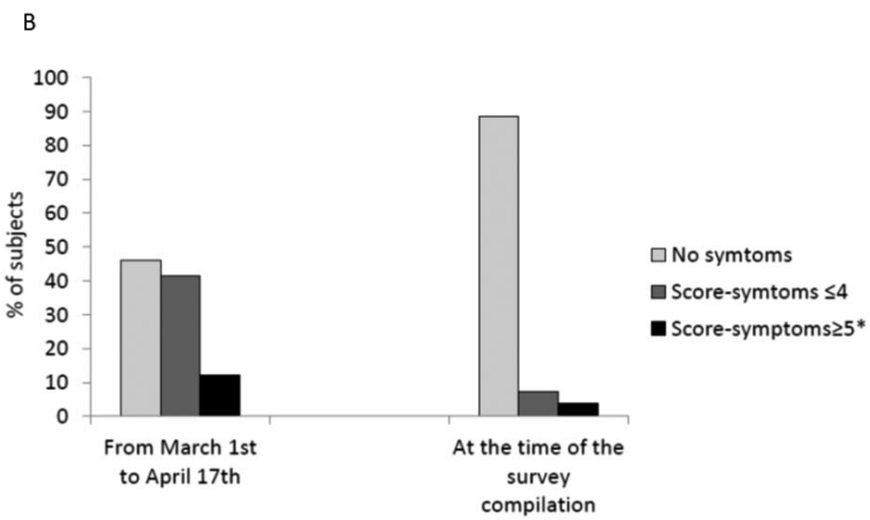

Figure 1B - Percentage of subjects with or without a COVID-19 infection diagnosis based on symptom scores and percentage of individuals that had the disease at the moment of the survey compilation.
* symptom score≥5 was the cut-off used to confirm a COVID-19 infection

Table 3 - Factors associated with Sars-Cov-2 infection diagnosed using a symptom score≥5

	Adjusted OR [95% CI]	p
Age	0.984 [0.975-0.994]	0.001
Females	1.334 [1.029-1.728]	0.030
Obesity	1.961 [1.304-2.949]	0.001
Asthma	2.035 [1.433-2.890]	<0.001
Autoimmune disease	2.103 [1.381-3.201]	0.001
Children at home	1.311 [1.013-1.697]	0.039
Contacts with COVID-19 infected subjects	*Yes* 2.693 [1.915-3.788]	<0.001
	Probably 2.161 [1.645-2.838]	<0.001

* Only significant ORs are reported in the table. Infected individuals were compared to uninfected subjects (symptom score ≤4) using a logistic regression model (stepwise procedure) adjusted for age, sex, place of residence, smoking, comorbidities (cardiovascular disease, hypertension, diabetes, COPD, asthma, kidney failure, autoimmune disease, oncological disease, obesity, other chronic disease), types of allergies (pollen, dust mite, animal hair, drugs, other), dog, cat and children at home, pharyngeal swab, type of exposure (health operators , workers at risk, contacts with COVID-19 infected subjects), flu vaccination.

a lower score, by using a multivariate analysis**,** we found that the elderly had a low probability of developing mild COVID-19 infection (OR=0.984 [0.975-0.994]; p=0.001). Instead, female sex (OR=1.334 [1.029-1.728]; p=0.030), obesity status (OR=1.961 [1.304-2.949]; p=0.001), asthma (OR=2.035 [1.433-2.890]; p<0.001), autoimmune diseases (OR=2.103 [1.381-3.201]; p=0.001), having children in the house (OR=1.311 [1.013-1.697]; p=0.039) and contacts with infected subjects (OR=2.693 [1.915-3.788]; p<0.001) were all risk factors for showing mild COVID-19 disease (table 3).

Discussion

Our study showed that 12.3% of southern Tuscany individuals (average age 50 years) had strongly suggestive COVID-19 infection symptoms between March 1st and April 17th. The high sensitivity/specificity of symptom score ≥5 suggest a very likely mild infection (even if the gold standard diagnosis for SARS-CoV-2 would be RT-PCR).

A fair percentage of these individuals might have been infected between early March and mid April. Such datum might be underestimated because a few young and old subjects missed the survey. Besides, we did not investigate the period prior to March 1. Had we known the number of asymptomatic subjects unidentified by the survey, the prevalence of already infected individuals might have been even higher. This datum is perfectly in line with what other authors observed in the same period in Italy (2). This study also identified subjects (3.9% of the population) with ongoing mild COVID-19 infection (based on the symptom-score). Therefore, a score based on a questionnaire symptoms may contribute to identify subjects to be tested with the RT-PCR test for a COVID-19 diagnosis which may be valuable also when testing materials are limited, as Dutch healthcare workers have already experienced (5). According to our study, the symptoms that made it possible to predict COVID-19 with greater sensitivity/specificity were fever, rhinitis, cough, headache, muscular pain, and loss of taste and smell, in line with what was observed by other authors (2, 3).

This study highlighted some differences

between subjects with a mild infection and those not infected. Increasing age leads to a low risk to develop a mild infection. In fact, the elderly are much more likely to develop more severe forms of COVID-19 (6).

Several studies suggest gender differences in SARS-CoV-2 disease, with women being less severely affected than men (7). We found a greater association between females (compared to males) and mild infections. In fact IgG antibody concentration in mild, general and recovering patients were similar in males and females (8). On the contrary, in severe status there were more women with relatively high concentrations of serum SARS-CoV-2 IgG antibodies (8). This discrepancy in SARS-CoV-2 IgG antibody levels in the two sexes may justify different outcomes of COVID-19 in men and women (8).

Furthermore, our study showed that obesity was also a risk factor for mild COVID-19 infection. Actually, we know that obesity is also associated with severe forms (9). Obesity and SARS-CoV-2 share common elements of the inflammatory process (and possibly also metabolic disturbances), exacerbating SARS-CoV-2 infection in obese subjects.

Asthma/COPD did not appear to be among the major comorbidities linked with severe COVID-19 forms (10). Our study highlighted that asthma was a risk factor for mild infection. This may be due to a favorable asthma-induced immunomodulation or to a protective effect of inhaled corticosteroids reducing the risk for severe forms. This protective effect may have also been increased because people adhered more strictly to the use of controller medications during pandemic (11).

Our observation also highlighted a significant relationship between autoimmune disease and mild infections. Patients with systemic autoimmune diseases do not show an increased risk for severe SARS-CoV-2 disease as compared to the general population, probably because of immunosuppressive treatments, particularly hydroxychloroquine, colchicine and tocilizumab (12). We hypothesized that SARS-CoV-2 may only induce less severe forms of the disease in subjects affected by autoimmune diseases.

It is not clear why the presence of children in the home is a risk for mild COVID-19 infection. They seem to be a protective factor for severe illness. We know that Coronaviruses, like 229E, NL63, HKU1, OC43 can infected humans, causing respiratory infections during winter, especially in children/adolescents (the diffusion being favored by the around-school environment). These infections may induce a cross-immunity also against SARS-CoV-2. Adults with CoVs contact, induced by living or working with children, may either be protected against COVID-19 or develop less severe symptoms (13). However, this result is an aspect that deserves further investigation with specific studies.

Possible limitations of this paper are related to the small number of subjects who had undergone the RT-PCR test with which the score was created. Furthermore, the questionnaire was self-referential and there was a possible recall bias for the presence of symptoms. The external validation was not carried out due to the lack of a second sample to test the score. In addition, as already mentioned, younger and older subjects were underrepresented.

Conclusions

A remarkable number of subjects in Southern Tuscany may have already had a mild/moderate COVID-19 infection or was having one at the time of the survey. This method, based on symptoms score, might be used to screen possibly infected individuals who should subsequently undergo more specific tests. Female sex, obesity, asthma, autoimmune diseases may be all factors

linked with mild forms of SARS–CoV-2 disease. On the contrary, the elderly could be prone for severe infections.

Conflict of interest: None
Authors' contributions: MS conceived the analysis plan and wrote the manuscript; BS conceived the study and wrote the manuscript; GT helped in data management.

Riassunto

Prevalenza della diagnosi dell'infezione lieve da SARS-CoV-2 *basata sui sintomi nella Toscana meridionale*

Premessa. Ad oggi non è noto quanti italiani abbiano avuto o abbiano una infezione lieve da **SARS-CoV-2** a causa della mancanza di uno studio epidemiologico che coinvolga la popolazione generale.

Disegno dello studio. Lo scopo di questo studio è stato di indagare la prevalenza/incidenza dell'infezione da **SARS-CoV-2** in forma lieve nella Toscana meridionale nel periodo Marzo/Aprile del 2020. La diagnosi veniva eseguita basandosi sui sintomi tipici della malattia, utilizzando un sondaggio online.

Metodi. Un campione casuale anonimo di mezza età di 3,460 individui completava il sondaggio. Un punteggio dei sintomi ≥5 veniva utilizzato come cut-off diagnostico, calcolato su 195 pazienti con malattia RT-PCR COVID-19 (sensibilità/specificità di 0,815 / 0,780 rispettivamente).

Risultati. Questo cut-off evidenziava come il 12,3% di tutta la popolazione poteva aver avuto un'infezione da **SARS-CoV-2,** mentre il 3,9% di loro poteva averlo al momento del sondaggio. Il sesso femminile (OR = 1.334 [1.029-1.728]; p = 0.030), l'obesità (OR = 1.961 [1.304-2.949]; p = 0.001), l'asma (OR = 2.035 [1.433-2.890]; p = 0.0001), le malattie autoimmuni (OR = 2.103 [1.381-3.201]; p = 0.001) erano tutti fattori di rischio per una infezione da **SARS-CoV-2** in forma lieve. Invece, gli anziani avevano una bassa probabilità di sviluppare forme lievi della malattia (OR = 0,984 [0,975-0,994]; p = 0,001).

Conclusione. Un numero notevole di soggetti nella Toscana meridionale poteva aver già avuto una lieve infezione da **SARS-CoV-2**. Lo score dei sintomi potrebbe essere utilizzato per lo screening di soggetti con sospetta infezione. Il sesso femminile, l'obesità, l'asma, le malattie autoimmuni possono essere fattori correlati a forme lievi di malattia COVID-19.

References

1. Signorelli C, Scognamiglio T, Odone A. COVID-19 in Italy: impact of containment measures and prevalence estimates of infection in the general population. Acta Biomed 2020; **91**(3-S): 175-9. doi: 10.23750/abm.v91i3-S.9511.
2. Adorni F, Prinelli F, Bianchi F, et al. Self-Reported Symptoms of SARS-CoV-2 Infection in a Nonhospitalized Population in Italy: Cross-Sectional Study of the EPICOVID19 Web-Based Survey. JMIR Public Health Surveill 2020 Sep 18; **6**(3): e21866. doi: 10.2196/21866.
3. Mudatsir M, Fajar JK, Wulandari L, et al. Predictors of COVID-19 severity: a systematic review and meta-analysis [version 2; peer review: 2 approved]. F1000Res 2021; **9**: 1107. https://doi.org/10.12688/f1000research.26186.2.
4. http://www.salute.gov.it/portale/nuovocoronavirus/dettaglioContenutiNuovoCoronavirus.jsp?lingua=italiano&id=5337&area=nuovoCoronavirus&menu=vuoto [Last accessed: 2020, Sep 22].
5. Tostmann A, Bradley J, Bousema T, et al. Strong associations and moderate predictive value of early symptoms for SARS-CoV-2 test positivity among healthcare workers, the Netherlands, March 2020. Euro Surveill 2020; **25**(16). doi: 10.2807/1560-7917.ES.2020.25.16.2000508.
6. Garg S, Kim L, Whitaker M, O'Halloran A, et al. Hospitalization Rates and Characteristics of Patients Hospitalized with Laboratory-Confirmed Coronavirus Disease 2019 - COVID-NET, 14 States, March 1-30, 2020. MMWR Morb Mortal Wkly Rep 2020; **69**(15): 458-64. doi: 10.15585/mmwr.mm6915e3.
7. Conti P, Younes A. Coronavirus COV-19/SARS-CoV-2 affects women less than men: clinical response to viral infection. J Biol Regul Homeost Agents 2020; **34**(2): 339-43. doi: 10.23812/Editorial-Conti-3.
8. Zeng F, Dai C, Caiet al. A comparison study of SARS-CoV-2 IgG antibody between male and female COVID-19 patients: a possible reason underlying different outcome between sex. J Med Virol 2020; **92**(10): 2054-4. doi: 10.1002/jmv.25989. Epub 2020 May 8.
9. Caussy C, Wallet F, Laville M, Disse E. Obesity is associated with severe forms of COVID-19. Obesity (Silver Spring). 2020; **28**(7): doi: 10.1002/oby.22842. Epub 2020 Apr 21.

10. The Lancet Respiratory Medicine. Reflecting on World Asthma Day in the era of COVID-19. Lancet Respir Med 2020; **8**(5): 423. doi: 10.1016/S2213-2600(20)30184-3. Epub 2020 Apr 23.
11. Kaye L, Theye B, Smeenk I, Gondalia R, Barrett MA, Stempel DA. Changes in medication adherence among patients with asthma and COPD during the COVID-19 pandemic. J Allergy Clin Immunol Pract 2020; **8**(7) 2384-5. doi: 10.1016/j.jaip.2020.04.053. Epub 2020 May 1.
12. Emmi G, Bettiol A, Mattioli I, et al. SARS-CoV-2 infection among patients with systemic autoimmune diseases. Autoimmun Rev 2020; 19(7)102575. doi: 10.1016/j.autrev.2020.102575. Epub 2020 May 5.
13. Sposato B, Scalese M. Why do children seem to be more protected against COVID-19? A hypothesis. Med Hypotheses 2020; **143**: 110151. doi: 10.1016/j.mehy.2020.110151.

Corresponding Author: Marco Scalese, Institute of Clinical Physiology, National Research Council, Via Moruzzi 1, 56124 Pisa, Italy
e-mail: scalese@ifc.cnr.it