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A STRUCTURAL EQUATION MODEL TO EXAMINE THE CLINICAL FEATURES OF MILD-TO-MODERATE COVID-19: A MULTICENTER ITALIAN STUDY

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Compliance with Ethical Standards

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Ethics approval: Approval for the National study was obtained from the ethics committee of "Luigi Vanvitelli" University Hospital, Naples, Italy. The procedures used in this study adhere to the tenets of the Declaration of Helsinki.

Informed consent: Informed consent was obtained from all individual participants included in the study

Abstract:

Purpose: To evaluate the clinical features of mild-to-moderate COVID-19 in a sample of Italian patients and to investigate the occurrence of smell and taste disorders.

Methods: Infected individuals with suspected (clinical diagnosis) or laboratory-confirmed COVID-19 infection were recruited. Patients completed a survey-based questionnaire with the aim of assessing their epidemiological and clinical characteristics, general otorhinolaryngological symptoms and smell and taste disorders.

Results: A total of 294 mild-to-moderate COVID19 patients completed the survey (147 females). The most prevalent general symptoms included fever, myalgia, cough and headache. A total of 70.4% and 59.2% of patients reported smell and taste disorders, respectively. A significant association between the two above-mentioned disorders was found (*rs*: 0.412; $p<0.001$). Smell disorders occurred prior to the other symptoms in 11.6% of patients and was not significantly associated with nasal obstruction or rhinorrhea. Interestingly, our statistical analysis did not show any significant difference, either for general symptoms or otorhinolaryngological features, between the clinical diagnosis group and the laboratory confirmed diagnosis (PCR) group. The structural equation model confirmed significant standardized paths ($p<0.05$) between general symptoms, comorbidities and general otorhinolaryngological complaints in the absence of a significant correlation between these elements and smell and taste alterations.

Conclusion: The prevalence of smell and taste disorders in mild-to-moderate Italian COVID-19 patients is significant both in suspected and laboratory confirmed cases and reveals a strong correlation between these clinical signs regardless of the presence of general or otorhinolaryngological symptoms, such as nasal obstruction or rhinorrhea.

Key words: coronavirus; COVID-19; SARS-CoV-2; ENT; anosmia; smell and taste; structural equation model

Running title: Structural equation model and clinical features of COVID-19

1. Introduction:

Coronavirus Disease 2019 (COVID-19) has become a serious threat to global public health. On March 11, 2020, the World Health Organization (WHO) declared the novel coronavirus outbreak a global pandemic, which has resulted in approximately 4,000,000 cases in 215 different countries worldwide; more than 220,000 affected people and 31,000 deaths had

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been confirmed in Italy through May 17th 2020, with a higher prevalence in the northern regions [1].

This condition, caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), consists of fever, dry cough, dyspnea and fatigue associated with typical laboratory findings and lung abnormalities on computed tomography scan, especially bilateral pneumonia with multiple ground-glass opacities, according to clinical studies from Asia [2]. The incubation period of COVID-19 is thought to be about 3-9 days, with a range between 0-24 days [3]; human-to-human transmission through respiratory droplets among close contacts is considered the primary mechanism of contagion [4].

The literature has highlighted significant differences between Asian and European COVID-19 patients, both among hospitalized and non-hospitalized ones, regarding not only the spread rate and mortality of the disease [5], but also the clinical presentation, with a major prevalence of headache, myalgia and smell and taste disorders in the European population [6,7].

According to European data, there is increasing evidence that patients with COVID-19 may present with a heterogeneous spectrum of ear-nose-throat (ENT) symptoms and many subjects affected by mild-to-moderate forms exhibited ENT manifestations even without fever, cough or other systemic abnormalities [6,7]. Severe smell and taste disorders as the initial or main clinical manifestation of COVID-19, even in the absence of rhinorrhea or nasal obstruction, have also been reported [7,8] and, in a small percentage of mildly symptomatic patients, anosmia is the only symptom [9].

At the beginning of the pandemic, these paucisymptomatic subjects were not suspected to be infected by SARS-CoV-2 and they did not undergo rhino-pharyngeal swabs or other specific objective tests to confirm the diagnosis. These patients, not initially identified as infected, could have represented a potential way to spread the infection among the population; therefore, physicians, should be aware of this possible association.

On the basis of the previous reports published by the COVID-19 Task Force of the Young-Otolaryngologists of the International Federation of Oto-rhino-laryngological Societies (YO-IFOS) from all over Europe [6,7,10] the aim of this study is to investigate the epidemiological characteristics and the occurrence of general and ENT symptoms, including olfactory dysfunction (OD) and gustatory dysfunction (GD), in a sample of Italian patients with suspected or laboratory-confirmed COVID-19 infection.

2. Materials and methods

This observational multicenter study was started by the YO- IFOS COVID-19 Task Force in March 2020 and the original study protocol was approved by four ethics committees

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(HAP2020-011; CHUSP20032020; EpiCURA-2020-2303; CHU-Charleroi: B32522020). In addition to these European approvals, the national study protocol was approved by the local ethics committee of the "Luigi Vanvitelli" University Hospital (Naples, Italy). The Italian members of the YO-IFOS collected data in collaboration with internal medicine physicians, pneumologists and infectiologists of their respective hospitals and with the help of General Practitioners (GPs).

Patients were invited to participate and informed consent was electronically obtained in light of the urgent need to collect data. In addition, some infected physicians and nurses have been voluntarily enrolled in the study.

2.1 Subjects and setting

Clinical data were collected from medical departments of seven different Italian university hospitals (Naples, Milan, Forlì, Verona, Florence, Foggia and Catania) and from medical offices of the GPs of the respective cities. Infected physicians and nurses of the same hospitals and cities have been voluntarily enrolled in the study.

The following inclusion criteria were considered: adult (>18 years of age); laboratory-confirmed COVID-19 infection (real-time reverse-transcriptase–polymerase-chain-reaction: RT-PCR); "suspected" COVID-19 patients defined as subjects who were clinically diagnosed as infected based on a consultation with a physician or GP, even in the absence of a laboratory-confirmed diagnosis; patients with mild-to-moderate infection, defined as an infection that did not require intensive care; patients clinically able to fulfill the questionnaire.

The laboratory diagnosis of COVID-19 infection was based on WHO interim guidance and consisted of a positive result on high-throughput sequencing or RT-PCR assay of nasal and pharyngeal swab specimens [11]. Home- managed patients, who were monitored daily for COVID-19 symptoms by a physician or their GP were included in the study as well as moderately symptomatic hospitalized patients who needed to be monitored in a non-intensive care unit because of risk factors or comorbidities.

Patients who were in the intensive or subintensive care unit at the time of the study were not included owing to their health status.

2.2 Data Collection

Clinical and epidemiological outcome data were obtained using an online (electronic)

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standardized questionnaire. The implemented survey is 'one-shot'; one specific user is associated to a unique token (random numerical value) to access the platform so, in this way, it was possible to obtain the answer only once by each participant. The electronic survey was chosen to centralize the data from all the centers, and to facilitate automatic data extraction for the analysis, simplifying the generation of statistical matrices. It was created with Professional Survey Monkey (San Mateo, California, USA) and it was open for respondents for a period of eight consecutive weeks.

The questionnaire could be easily completed by the patients through their own mobile devices in a hospital room (hospitalized patients with moderate symptoms) or at home (house-bound patients or self-isolating infected health professionals), through a specific link sent directly to their phones or e-mail addresses by the physician or GP.

The following outcomes were analyzed: age, sex, comorbidities, general symptoms and ENT symptoms (4-point scale from 0=no symptom to 4=severe symptoms), including smell and taste disorders.

The olfactory and gustatory questions were based on the smell and taste component of the National Health and Nutrition Examination Survey [12]. In cases of self-reported hyposmia/anosmia, patients were also invited to complete the part of the survey that included the short version of the Questionnaire of Olfactory Disorders-Negative Statements (sQOD-NS) to better assess the impact of olfactory dysfunction on their quality of life (QoL) [13].

2.3 Study Outcomes

The selection of relevant epidemiological and clinical features composing the questionnaire was carried out by the COVID-19 Task Force members. The outcomes recorded included in the survey and taken into consideration for statistical analysis were: demographic data, comorbidities, general symptoms, and ENT symptoms/smell and taste disorders. The disease onset was defined as the first day of symptoms appearances. The length of symptoms was defined as the number of days during which the patients had >1 general or otolaryngological symptoms associated with the COVID-19 infection.

2.4 Statistical Methods

All statistical analyses were performed using Stata/SE 13.1 and SPSS Version 24.

Categorical variables are expressed as percentages, while continuous variables are expressed as the means and standard deviations (SDs).

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Principal Component Factors (PCF) analysis was used to examine the assumed construct validity and unidimensionality of the twelve general symptoms most related to the infection (fever, cough, chest pain, loss of appetite, sticky mucus, arthralgia, myalgia, diarrhea, abdominal pain, nausea and/or vomiting, headache, fatigue). The number of dimensions and the item loading structure of PCF with orthogonal rotation (*varimax method*) were conducted on the abovementioned twelve general symptoms.

Two classical criteria from PCF were used: the eigenvalue rule (number of factors with eigenvalue >1) and the factor loading rule (item-factor correlations >0.32). *Cronbach's alpha* was used to assess internal consistency, with values above 0.7 indicating desirable levels.

The scores related to General Symptoms (GS score), comorbidities, ENT disorders (ENT score) and smell and taste disorders (S-T score) are calculated and expressed as the means and SDs. Nonparametric statistical analysis for independent samples was performed to compare each score between males and females, and *Spearman's rho* was calculated to evaluate the correlation between each score and age.

Univariate and multiple regression models were performed to evaluate the relationship between the general symptoms (as dependent variables) and age, sex, comorbidities, ENT symptoms and smell and taste dysfunction (as independent variables). Before the multiple regression model analysis, covariates were individually tested with a univariate linear regression model and only significant covariates were included. A *Structural Equation Model* (SEM) was generated to explore the relationship between the symptoms, factorial structure highlighted by the PCF analysis and the other latent variables.

Confirmatory factor analysis (CFA) was used to test an overall measurement model that included correlated latent variables [14]. The CFA process determines whether the hypothesized structure provides a good fit to the data or whether a relationship between the observed variables and their underlying latent (or unobserved) constructs exists.

Overall model fit was assessed using different statistics. First, a *chi-square* analysis was used. The other indices were the *Root Mean Square Error of Approximation* (RMSEA) (values between 0.05 and 0.10 indicate an acceptable fit, and values < 0.05 indicate a good fit) and *Standardized Root Mean Square Residual* (SRMR) (values < 0.10 indicate a good fit). Comparative Fit Index (CFI) and Tucker-Lewis Index (TLI) were also calculated (values > 0.90 indicate a good fit). The level of significance was set at $p < 0.05$.

Regarding the sample size estimation, we referred to the frequently promoted N: t rule of thumb, which concerns the minimum recommended ratio of sample size (N) to the specific

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number of items (t) cited in the questionnaire and considered in order to build the SEM model. Using a typical 8:1 ratio (t=34), we estimated a sample size of N=272.[15]

3. Results

A total of 294 patients completed the survey. A laboratory diagnosis of COVID-19 infection through RT- PCR was obtained for 179 patients (60.9%: PCR group) while the remaining 115 subjects (39.1%: no PCR/clinical group) were home-managed patients considered COVID-19 infected on the basis of clinical symptoms, even without RT-PCR positivity; among the overall sample, only 48 patients (16.3%) required hospitalization.

3.1General characteristics and general symptoms

The mean age of the patients was 42.1 ± 12.3 years (range 18-72).

Males and females were represented equally (147 females); 49 patients (16,7%) were habitual smokers.

The mean time between the onset of the infection and the evaluation was 11.6 ± 7.4 days.

Among all patients, 111 (37.7%) completed the survey during the acute phase of the disease whereas the rest of the patients did not complain of any general symptoms.

The basic demographic characteristics and general symptoms are reported in Table 1.

	PCR		**No PRC**			**Total**	
	Mean ± (SD)	**(Range)**	**Mean ± (SD)**	**(Range)**	**P-value**	**Mean ± (SD)**	**(Range)**
Age	41.0 ± (11.9)	18-66	44.0 ± (12.6)	22-72	0.090	42,1 ± (12,3)	18-72
Gender	**n°**	**%**	**n°**	**%**		**n°**	**%**
Male	90	50.3	57	49.6	0.950	147	50
Female	89	49.7	58	50.4		147	50
Habitual Smokers	26	14.5	23	20.0	0.219	49	16.7

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General Symptoms							
Fever (> 38°C°) and chills	110	61.4	66	57.4	0.488	176	59.9
Cough	74	41.3	60	52.2	0.080	134	45.6
Chest pain	29	16.2	26	22.6	0.169	55	18.7
Loss of appetite	50	27.9	34	29.6	0.762	84	28.6
Sticky mucus / phlegm	11	6.1	7	6.1	0.984	18	6.1
Arthralgia	62	34.6	49	42.6	0.170	111	37.8
Myalgia	84	46.9	58	50.4	0.557	142	48.3
Diarrhea	45	25.1	36	31.3	0.248	81	27.6
Abdominal pain	20	11.2	17	14.8	0.363	37	12.6
Nausea and/or vomiting	22	12.3	20	17.4	0.223	42	14.3
Headache	73	40.8	63	54.8	0.020	136	46.3
Fatigue	69	38.5	59	51.3	0.031	128	43.5

Table 1. Demographic characteristics and general symptoms of COVID-19 patients. SD: standard deviation.

The mean general symptoms score (GS score) was 3.90 ± 2.59 (SD); it was the sum of the twelve items inserted in the survey to investigate the presence of general symptoms in COVID-19 patients (fever, cough, chest pain, loss of appetite, sticky mucus, arthralgia, myalgia, diarrhea, abdominal pain, nausea and/or vomiting, headache, fatigue). A significant difference in the GS score was observed between males (3.56 ± 2.45) and females (4.22 ± 2.70).

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The general symptoms most related to the infection were fever (59.9%), myalgia (48.3%), headache (46.3%), cough (45.6%) and fatigue (43.5%), while less represented were nausea/vomiting (14.3%), abdominal pain (12.6%) and sticky mucus (6.1%).

Compared to men, women more frequently reported diarrhea (female 34.0%; male 21.1%), nausea and vomiting (female 21.2%; male 7.5%), headache (female 55.1%; male 37.4%) and fatigue (female 50.3%; male 36.7%), while men more frequently reported fever and chills (female 51.7%; male 68.0%). A low positive correlation between GS score and age was found (*rs*: 0.138;<0.018).

The GS score was not different between the PCR group (3.6 ± 2.5) and the clinical diagnosis group (4.2 ± 2.6).

3.2 Comorbidities

Regarding comorbidities, the most prevalent were high blood pressure (13.3%), allergy (13.9%), allergic rhinitis (11.9%), GERD (8.2%) and hypothyroidism (6.8%), as shown in Table 2.

Comorbidities	**n°**	**%**
Chronic rhinosinusitis	18	6.1
Allergic rhinitis	35	11.9
High blood pressure	39	13.3
Hypothyroidism	20	6.8
Gastroesophageal reflux disease (GERD)	24	8.2
Chronic pulmonary disease (COPD)	1	0.3
Asthma	18	6.1

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Allergy		41	13.9
Other	Diabetes	5	1.7
	Heart problems	4	1.4
	Neurological diseases	1	0.3
	Depression	3	1.0
	Autoimmune diseases	8	2.7
	Tumors	3	1.0

Table 2. Comorbidities of COVID-19 patients.

Males (17.7%) were more affected by hypertension than females (8.8%); on the other hand females showed higher prevalence of hypothyroidism (10.2%) than males (1.4%). No gender differences were found for other investigated diseases; a low positive correlation between comorbidities and age was present (*rs*: 0.285; p<0.001).

3.3 Ear-Nose-Throat disorders

ENT complaints associated with COVID-19 infection are summarized in Table 3.

		Not related	**Somewhat related**	**Highly related**
		0-1	**2-3**	**4**
Nasal obstruction	n°	191	93	7
	%	65.6	32.0	2.4

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Rhinorrhea	n°	231	52	1
	%	81.3	18.3	0.4
Postnasal drip	n°	232	49	3
	%	81.7	17.3	1.1
Sore throat	n°	220	66	3
	%	76.1	22.8	1.0
Face pain/heaviness	n°	245	36	3
	%	86.3	12.7	1.1
Ear pain	n°	270	14	1
	%	94.8	4.9	0.4
Dysphagia	n°	267	16	1
	%	94.0	5.6	0.4
Dyspnea	n°	218	69	2
	%	75.4	23.9	0.7
Hoarseness	n°	212	16	1
	%	92.6	7.0	0.4

Table 3**.** Otolaryngological complaints associated with COVID-19 infection. Four point scale. Patients had to rate each of the symptoms in terms of their relationship with COVID-19 infection (scale 0-4, where 0= not related, 4= highly related).

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The mean ENT- related symptoms score (ENT score) was 5.13 ± 4.49 (SD); it was the sum of the nine ENT items (Nasal obstruction, Rhinorrhea, Postnasal drip, Sore throat, Face pain/heaviness, Ear pain, Dysphagia, Dyspnea, Hoarseness) inserted in the survey to investigate the presence of these complaints in COVID-19 patients. No significant difference was observed between males and females (males 4.61%; females 5.56%). Nasal obstruction, dyspnea and sore throat were the most frequent general ENT manifestations (Table 3). Our results showed only a major prevalence of postnasal drip in females (47.2%) than in males (36.4%).No gender difference was found for the other ENT symptoms while a low negative correlation between ENT score and age was present (*rs*: -0.117; p <0.046).

The ENT score symptoms score was not different between the PCR group (1.25±1.56) and the clinical diagnosis group (1.67 ± 1.71) (p=0.078), except for two symptoms: dyspnea (PCR: 21.0%; no PCR: 30.9%, Chi-Square Tests p-value =0.035) and nasal obstruction (PCR: 29.8%; no PCR: 41.8%, chi-square tests p-value =0.022). (Figure 1).

3.4 Smell and taste disorders

In the overall sample, a total of 207 patients (70.4%) had smell disorders related to the infection, with a higher prevalence in females than in males; among them 140 (67.6%) were anosmic and 67 (32.4%) were hyposmic. A total of 174 patients (59.2%) reported taste disorders, which were characterized by impairment of the following four taste modalities: salty, sweet, bitter and sour; the prevalence was higher in females. (Figure 2)

OD appeared before (11.6%), after (57.1%) or at the same time (31.3%) as the onset of other symptoms and it persisted after the resolution of the other general symptoms in 65 patients (31.4%). A total of 79 patients (38.1%) completed the survey while the OD was still present; for the other hyposmic/anosmic patients we found the following recovery times for the sense of smell: 1-4 days (22.2%), 5-8 days (15.4%) and 9-15 days (24.3%). A total of 61.9 % of the

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patients completely recovered from olfactory dysfunction. OD and GD were constant over time in the majority (78%) of patients and presented an acute onset (90%).

In the overall sample, a total of 13 patients (4%) reported smell and taste disorders as the only symptoms of the infection and, in 10 (77%) of them, a confirmed laboratory diagnosis of COVID-19 was obtained. Selective smell alteration was present in 4 patients (1.3%) while combined OD and GD as selected symptoms of the infection was present in 9 subjects (3%).

OD was not significantly associated with ENT-complaints (*Spearman's rho*: .210; p=0.127), especially in terms of rhinorrhea (*Spearman's rho*: .121; p=0.098) and nasal obstruction (*Spearman's rho*: .144; p=0.118); however, the association between OD and GD (*Spearman's rho*: .412; p< 0.0001) was significant.

A significant negative correlation was observed between anosmic patients and the sQOS-NS (*Spearman's rho*: -.223; p<0.0001), especially regarding anxiety and eating questions.

The mean general Smell-and-Taste score (S-T score) was 2.39 ± 1.61 (SD); it was the sum of the five items (Parosmia, Hyposmia, Anosmia, Phantosmia and Gustatory dysfunction) inserted in the survey to investigate the presence of smell and taste disorders in COVID-19 patients. A significant difference was observed between males (2.18 ± 1.61) and females (2.59 ± 1.59). Women, in fact, were proportionally more affected by smell and taste disorders compared than men and more frequently reported hyposmia (females 62.8%; males 50.1%), taste impairment for salty, sweet, bitter or sour (females 56.0%; males 41.9%) and taste impairment in perceiving aromas (females 69.5%; males 57.6%). The S-T score was not different between the PCR group (2.2 ± 1.5) and the clinical diagnosis group (2.5 ± 1.6) (Figure 3), with the following percentages: PCR/taste score: 54.2%; no PCR/taste score: 55.6%, *chi-square tests p-value* =0.705. PCR/Smell score 65.9%; no PCR/smell score 63.4%, *chi-square tests p-value* =0.835. No significant correlation between the S-T score and age was found (*Spearman's rho*: -.0.24; p= 0.681)

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3.5 *Principal Component Factors* (PCF) *analysis and Structural Equation Model (SEM)*

Regarding general symptoms, PCF analysis identified two principal components (PCs) with an eigenvalue >1 (first eigenvalue = 4.312; second eigenvalue = 1.191), which explained 72.10 % (First eigenvalue 56.47% + second eigenvalue 15.61%) of the total observed variance. The Scree plot identified two PCs; thus, rotation was performed and the dimensionality of the twelve general symptoms was explored. The values reported in table 4 represent the factor loading extracted by the PCF analysis.

General Symptoms	**Two -factors solution**	
	Symptoms 2	Symptoms 1
1) Fever (>38 °) and chills		0.251
2) Cough		0.762
3) Chest pain		0.683
4) Loss of appetite	0.596	
5) Sticky mucus	0.169	
6) Arthralgia	0.656	
7) Myalgia	0.433	
8) Diarrhea	0.555	
9) Abdominal pain	0.619	
10) Nausea and / or vomiting	0.681	
11) Headache	0.536	

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12) Fatigue	0.671

Table 4. General symptoms of COVID 19 infection and the related factor loading extracted by the PCF analysis. The first factor or "influenza-like syndrome" or "symptoms 1" is influenced by: fever and chills; cough; chest pain and fatigue. The second factor or "gastrointestinal and osteoarticular-like syndrome" or "symptoms 2" is influenced by: loss of appetite; sticky mucus; arthralgia; myalgia; diarrhea; abdominal pain; nausea and / or vomiting and headache.

In particular, when the obtained value (factor loading) is > 0.25 we can assume that the item rule is acceptable and can be maintained for the construction of the latent variable [16,17].Furthermore, a high value means that the considered item contributes or weighs a lot in the construction of the latent variable, while a low value means that the considered item contributes less in the construction of the latent variable.

Each factor loading higher than 0.25 indicates the importance of the corresponding item to Symptoms 1 or Symptoms 2 latent variable. In this case, nausea and / or vomiting (0.681), arthralgia (0.656) and abdominal pain (0.619) are the most important observed variables within the Symptoms 2 latent variable, whereas cough (0.762) and chest pain (0.683) are the most important variables within the Symptoms 1 latent variable.

In summary the first factor, labeled "influenza-like syndrome" or "Symptoms 1" was influenced by: fever and chills, cough, chest pain and fatigue.

The second factor, labeled "gastrointestinal and osteoarticular symptoms" or "Symptoms 2" was influenced by: loss of appetite, sticky mucus, arthralgia, myalgia, diarrhea, abdominal pain, nausea and / or vomiting, headache. *Cronbach's alpha* for the « two components" was 0.732 ($p<0.001$) (95% CI; 0.665–0.761).

In the univariable analysis, the general symptoms score showed a significant positive association with age, gender (F>M), ENT score, GERD and high blood pressure; no significant association was found between the general symptoms and S-T score.

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The multiple regression analysis (Table 5) included all the variables that were significant according to the univariable linear regression. Age (β = .188; p = .002) and ENT score (β = .342; p < 0.0001) were the independent variables more significantly related with the general symptoms score, followed by GERD (β = .123; p = .027) and, mildly, high blood pressure (β = .116; p = .055). Gender was not significantly related (β = .098; p = .077) to general symptoms.

Dependent variable	**Independent variable**	**β*s***	**p-value**
General Symptoms	**Age**	.188	**.002**
	Gender	.098	**.077**
	ENT Score	.342	**.000**
	High Blood Pressure	.116	**.055**
	GERD	.123	**.027**

Table 5. Multivariable model exploring the associations between the general symptoms score (as the dependent variables) and age, gender, comorbidities and ENT score (as independent variables).

As described in Table 6, we recognized six latent variables that provided an acceptable explanation for their associated observed variables (coefficients above 0.200), except for 3 comorbidities (chronic rhinosinusitis, pulmonary disease and allergy) that showed a coefficient < 0.200 with a p-value >0.05.

The standardized paths of all six latent variables and their respective observed variables are specified in Table 6.

Latent Variables	**Observed variables**	**Standardized regression coefficient**	**Standard Error**	**P > |z|**	**Standardized regression coefficient [95% Conf.**

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					Interval]
Symptoms 1	**Fever (> 38° C) and chills**	.378	.094	0.000	.192 - .564
	Cough	.321	.100	0.001	.124 - .553
	Chest pain	.489	.091	0.000	.309 - .662
	Fatigue	.579	.084	0.000	.414 - .746
Symptoms 2	**Loss of appetite**	.519	.078	0.000	.366 - .675
	Stcky mucus / phlegm	.265	.094	0.005	.080 - .454
	Arthralgia	.390	.086	0.009	.220 - .567
	Myalgia	.297	.093	0.001	.113 - .411
	Diarrhea	.511	.078	0.011	.357 - .664
	Abdominal pain	.477	.081	0.000	.318 - .636
	Nausea and/or vomiting	.384	.089	0.000	.208 - .564
	Headache	.463	.079	0.000	.307 - .622
ENT	**Nasal obstruction**	.674	.060	0.000	.555 - .791
	Rhinorrhea	.504	.074	0.000	.358 - .655
	Postnasal drip	.603	.064	0.000	.475 - .732

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	Sore throat	.556	.070	0.000	.418 - .695
	Face pain/heaviness	.428	.077	0.000	.277 - .583
	Ear pain	.408	.078	0.000	.254- .661
	Dysphagia	.468	.078	0.000	.313 - .625
	Dyspnea	.498	.073	0.000	.354 - .646
	Hoarseness	.543	.070	0.000	.404 - .681
Smell	**Parosmia**	.854	.052	0.000	.750 - .955
	Hyposmia/Anosmia	.767	.055	0.000	.659 - .870
	Phantosmia	.262	.089	0.003	.087 - .435
Taste	**Gustatory dysfunction for salty, sweet, bitter and sour**	.894	.043	0.000	.809 - .945
	Gustatory dysfunction in the perception of aromas	.852	.044	0.000	.765 - .939
Comorbidities	**Tobacco use**	.243	.135	0.075	-.024 - .512
	Chronic rhinosinusitis	.050	.123	0.683	-.191 - .293
	Hypothyroidism	.247	.125	0.048	.122 - .445
	GERD	338	.125	0.014	.147 - .511
	Chronic pulmonary disease	.136	.141	0.333	-.139 - .413

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Allergy	.078	0.123	0.524	-.319 - .167
High blood pressure	.152	0.118	0.201	-.080 - .385

Table 6 Standardized regression coefficient for the Structural Equation Model.

The *Structural Model Fit indices* indicated that the proposed model fit the data (RMSEA = .058; SRMR = .082; CFI = .910; TLI =.948).

As presented in our Structural Equation Model (Fig.4), the significant standardized paths (*p value* < 0.05) were between the latent variables Symptoms 1 and Symptoms 2 (β = .757, SE = .115, *p* < 0.001), both positively related to ENT general symptoms (Symptoms 1: β = .493, SE = .115, *p* < 0.001; Symptoms 2: β = .315, SE = .109, *p* = 0.004).

A strong relationship was also observed between Symptoms 2 and Comorbidities (β = .918, SE = .219, *p* = 0.000) and a strong correlation was observed between the latent variables of Taste and Smell (β = .687, SE = .060, *p* < 0.001). In contrast, there was no significant correlation between Smell or Taste and ENT symptoms, Comorbidities and Symptoms 1 and 2. (Symptoms 1 vs Smell: β = .012, SE = .131, p = .924 and Symptoms 1 vs Taste: β = -.126, SE = .123, p = .306; Symptoms 2 vs Smell: β = .097, SE = .113, p = .393 and Symptoms 2 vs Taste: β = .031, SE = -.110, p = .775).

4. Discussion

The clinical presentation of COVID-19 in European patients appears different from that reported in Asian patients, for whom it is mainly associated with fever, cough and dyspnea [18,19]. Regarding ENT manifestations, Asian studies have reported sore throat as a prevalent ENT complaint, followed by rhinorrhea and nasal congestion, although in small percentages (1-6%). [20-21]

Surprisingly, only one Asian study described OD and GD in hospitalized patients with COVID-19, accounting for 5.1% and 5.8% of patients, respectively [22].

From the end of March, an increasing number of studies [7,23-25] have begun reporting a high prevalence of sudden anosmia or hyposmia in patients who tested positive for SARS-CoV-2, proposing to add smell and taste disorders as a clinical screening tools for COVID-19 patients.

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Our previous results obtained from a European sample of 417 patients with mild or moderate COVID-19 [7], showed that 86% had smell disorder and 88% had taste disorder; we further observed in a clinical series of 1420 patients with mild to moderate COVID-19 [6,7] that 88% of patients reported OD and approximately 70% of them reported GD, even without nasal obstruction or rhinorrhea. Subsequently, a larger sample of 2013 European subjects presenting with a high prevalence of new onset OD during the COVID-19 pandemic has been reported [10]. Our preliminary data showed that the prevalence of symptoms significantly varied according to age and sex, with younger patients more frequently affected by ear, nose and throat complaints than elderly individuals [6,7].

Interestingly, anosmia was reported to be the first symptom of the disease in 12% of the cases and, in a small percentage of subjects (< 4%), it was found to be the only symptom of the infection.

The underlying mechanisms for OD are still unclear but transient impairment of olfaction may be caused by two different types of processes: inflammation in the olfactory epithelium or damage to olfactory receptor neurons; the last hypothesis seems to be more related to smell disorders caused by SARS-CoV-2.

The brain has been reported to express angiotensin-converting enzyme 2 (ACE2) receptors, which have been detected in glial cells and neurons [26]; it is known that SARS-CoV-2 invades human cells via the obligatory receptor ACE2 and that viral uptake is further facilitated by a priming protease, TMPRSS2 [27]. *Bilinska et al* [28] showed in a mouse model that the cell surface protein ACE2 and the protease TMPRSS2 are well expressed in sustentacular cells of the olfactory epithelium but not, or much less frequently, in most olfactory receptor neurons. These data suggest that sustentacular cells are involved in SARS-CoV-2 virus entry and impairment of the sense of smell in COVID-19 patients, because these cells play key roles in supporting olfactory neuron metabolism and odor sensing [29]. Cells with high ACE2 and TMPRSS2 expression have strong virus binding capacity and are particularly susceptible to infection.

Therefore, as European patients present a greater ACE2 expression in the nasal mucosa, the higher prevalence of OD and GD in the European population could be related to SARS-CoV-2 neuroinvasive potential [30].

Regarding the present Italian study, the general symptoms most related to the infection were loss of the sense of smell (70%), fever (59.9%), taste disorders (59%), myalgia (48.3%) and headache (46.3%), followed by cough (45.6%) and fatigue (43.5%), with differences between genders.

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General ENT complaints were mainly characterized by nasal obstruction, dyspnea and sore throat; no gender differences were found but a negative correlation between ENT score and age was present, confirming a higher prevalence of these disorders in younger patients.

Smell and taste disorders were well represented in our Italian sample, with a prevalence of 70.4% and 59.2%, respectively; in the majority of patients (>90%) the onset of OD and GD was acute and, in line with previous study findings [6,7,31-34], our statistical analysis did not show a significant correlation between self-reported OD/GD and other ENT-complaints, such as rhinorrhea or nasal obstruction (that can explain, for example, anosmia/hyposmia in relation to the seasonal flu), indicating an acute sensorineural smell and taste loss.

Moreover, recent data reported by *Lechien et al.*[35] confirmed the absence of a significant relationship between symptoms of nasal inflammation and objective olfactory dysfunction, in contrast with what generally occurs in the common cold.

Interestingly, olfactory dysfunction appeared before the onset of other symptoms in 11.6% of patients in our sample, indicating that the symptom is important for early detection of the disease.

The structural equation model (Figure 4) demonstrated a significant correlation among the latent variables "Symptoms 1" and "Symptoms 2", "Symptoms 1" and "ENT complaints" and between "Symptoms 2" and "ENT complaints". The latent variables "Comorbidities" and"Symptoms 2" were also strictly related, especially the observed variables GERD and hypothyroidism. According to the literature [30, 32,34,36] OD and GD are strongly correlated and clustered separately from other general and ENT symptoms.

A recent Italian paper stated that a persistence of chemosensitivity dysfunction longer than 7days, possibly linked to long lasting viral multiplication in the upper aerodigestive tract, might be associated with a more severe clinical course [36]. The same authors considered that anamnestic and interview studies may underestimate the frequency of smell and taste disorders as the objective analysis performed in their patients who did not report taste and smell disturbances, showed mild hyposmia in 30 % of patients.

In the present study, the majority of patients recovered the sense of smell and taste within 9-15 days (24.3%). The statistical correlation with the sQOD-NS score, highlighted a negative impact of smell dysfunction on daily quality of life, especially regarding anxiety and eating items (*rs*: -.223; $p<0.001$).

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Boscolo Rizzo et al [37] observed that many household contacts not-tested for SARS-CoV-2 complained symptoms compatible with COVID-19 and a substantial proportion reported an altered sense of smell or taste which was by far lower in subjects negative to SARS-CoV-2 than in to nontested cases [9].

In our study the mean score of the smell and test disorders was not different between confirmed COVID-19 patients and suspected/clinical COVID-19 patients; our results emphasize that patients who self-report smell and taste disorders, even in the absence of other ENT or general typical symptoms (cough and fever), may be highly suspicious for COVID-19 infection and that OD/GD might represent an important clinical tool for monitoring all paucisymptomatic patients who may not be objectively tested for SARS-CoV-2.

Recently, *Paderno et al* [34] observed that OD and GD are more prevalent in home-quarantined subjects than in hospitalized subjects and they further confirmed that OD is strongly correlated to GD but not with other symptoms suggestive of upper airway infection.

Interestingly, our statistical analysis did not show any significant difference between the PCR group and the clinical diagnosis group in terms of OD/GD, underling the crucial role of these symptoms in the early clinical diagnosis of COVID-19.

We strongly believe that anosmia plays a crucial role in the timely identification of COVID-19 patients who may be unwittingly transmitting the virus; anosmia and taste dysfunction must imperatively be added to the list of specific symptoms of COVID-19 infection [38-39], emphasizing the role of otolaryngologists as first-line physicians in the diagnosis of mildly symptomatic COVID-19 patients.

It is recommended that every patient with mild to moderate ENT-symptoms and unknown COVID-19 status should be examined by otolaryngologists and full personal protective equipment (FFP3/N95 mask, glasses, fluid resistant gloves and gown) [40,41] must be strictly mandatory while examining suspected COVID 19 patients.

Our study has several limitations. First, all data were self-reported and based on ad hoc questions. Regarding ENT-complaints, subjects did not benefit from specific and objective examinations for OD/GD; in this case the prevalence of OD related to COVID-19 patients could be over or underestimated.

Second, the sample was relatively small and only subjects >18 years and affected with mild-to-moderate COVID19 were enrolled in the study. Given that patients in the subintensive/intensive care units were excluded in this study, the prevalence of some symptoms, such as fever and respiratory failure, may be higher.

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Third, the lack of consistent follow-up of our patients limits us from investigating the recovery time of olfactory and gustatory functions, and, therefore, from defining the rate of permanent anosmia or taste loss.

Fourth, 39% of our sample was not laboratory tested for SARS-CoV-2 because of limitations in testing availability but, similar to other studies [42], these patients were included in our analysis as they met current Italian guidelines for a likely diagnosis of COVID-19 infection and social isolation.

Finally our data seem to be in line with previous articles, showing that some classic ENT symptoms, such as rhinorrhea or nasal obstruction, are less frequently associated with smell and taste disorders in COVID-19 patients. OD and GD represent two of the most prevalent symptoms and, therefore, new onsets of these complaints during the COVID-19 pandemic should be considered a manifestation of SARS-CoV-2 infection until proven otherwise [37], especially in those regions where a lack of resources may not allow objective testing of suspected patients. Future epidemiological studies associated with objective tests are needed to elucidate this statement.

5. Conclusions

The clinical presentation of mild-to-moderate COVID-19 infection is substantially different from that of more severe patterns, and clinical features may be different according to gender and age; moreover, it appears that infected patients may present with only OD and GD even without other significant complaints.

Patients and the scientific community need to know that sudden anosmia or ageusia could be an important symptom of COVID-19 infection, especially in paucisymptomatic forms. An early recognition of mild clinical symptoms is crucial and may help to obtain a full control of SARS-CoV-2 diffusion, preventing further spread of the infection.

Anosmia must imperatively be added to the list of specific symptoms of COVID-19 infection especially in “suspected” and not tested patients.

Data Availability Statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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Fig 1 Prevalence of ENT symptoms in PCR group and no PCR (clinic) group. No significant differences were found between groups, except for dyspnea (p value * =0.035) and nasal obstruction (p-value* =0.022).

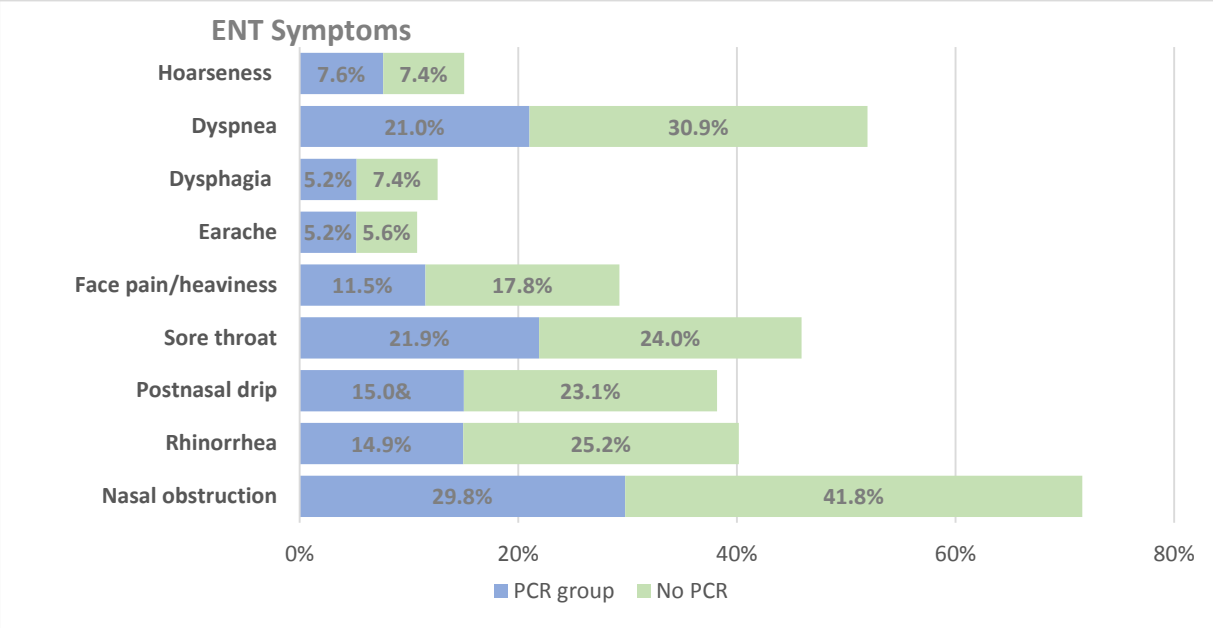

Fig 2. Prevalence of smell and taste disorders in COVID-19 patients**.**

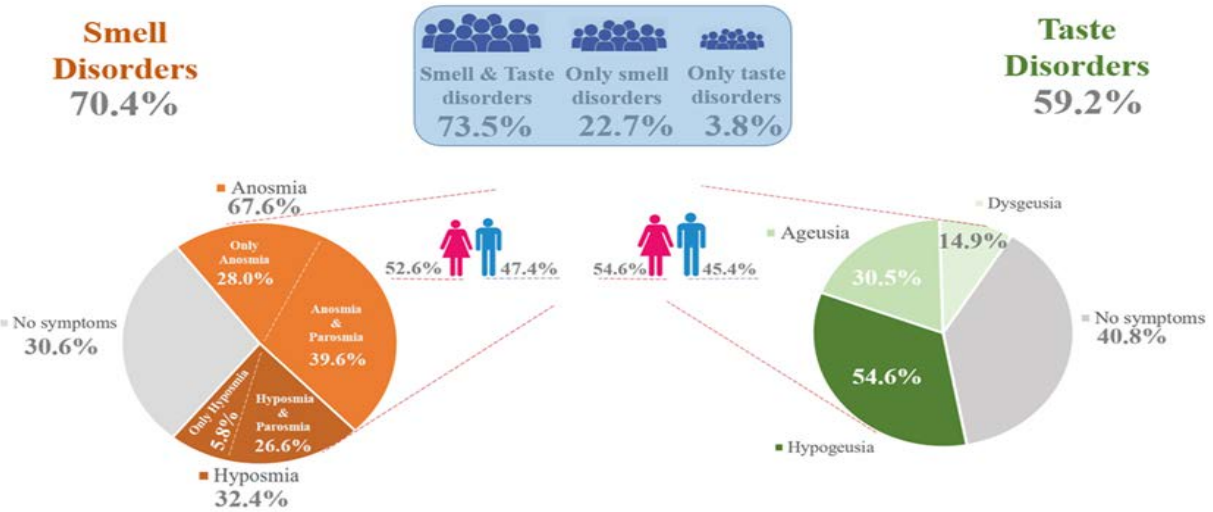

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Fig 3. Prevalence of smell and taste disorders in PCR group and no PCR group. No significant difference in smell and taste loss was found between groups (*p value* smell = 0.835; *p value* taste = 0.705).

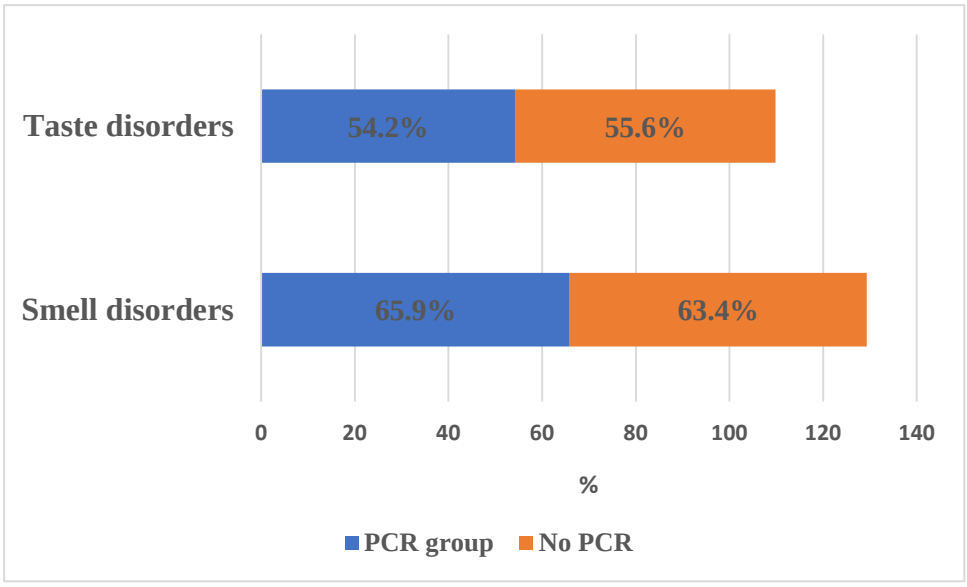
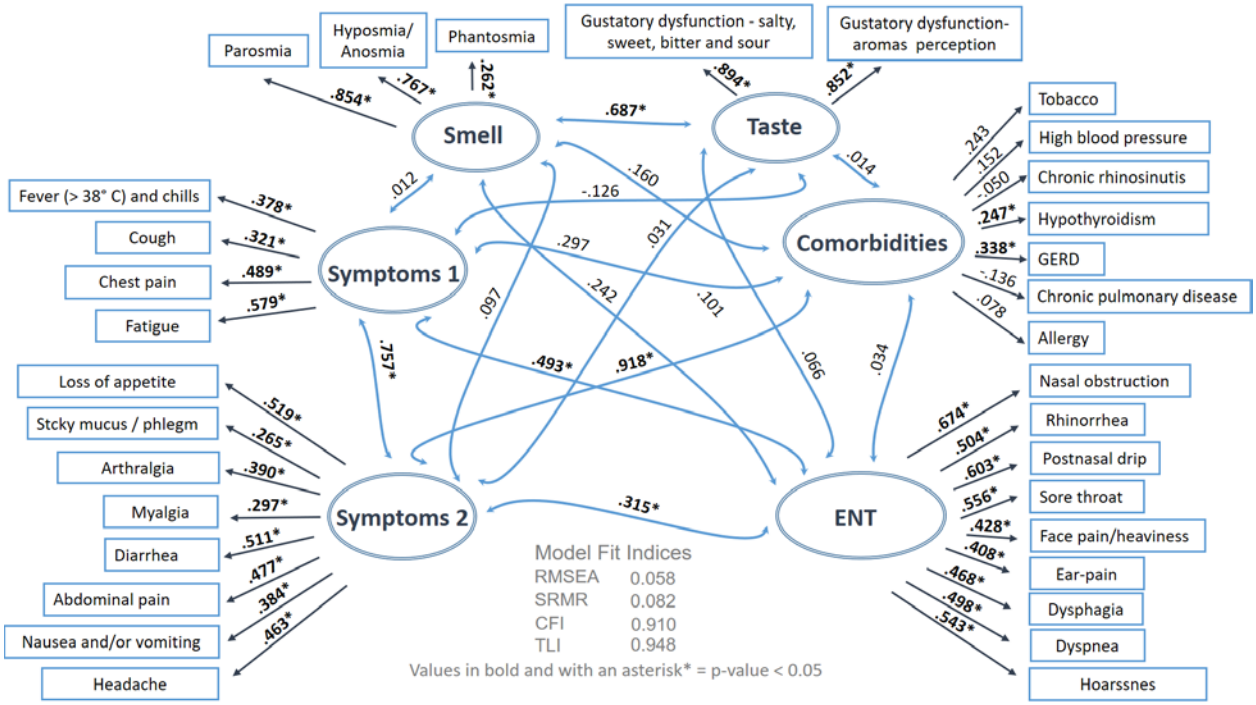


Fig 4. The Structural Equation Model (SEM). SRMR: Standardized Root Mean Square Residual. RMSEA: Root Mean Square Error of Approximation. CFI: Comparative Fit Index. TLI: Tucker-Lewis Index. *p values < 0.05: significant correlation between variables.



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