Prognostic factors for SARS-CoV-2 nasopharyngeal swab negativity: a multicentric study

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ABSTRACT

The diagnosis of coronavirus disease 2019 (COVID-19) is made by the detection of viral RNA by polymerase chain reaction on nasopharyngeal swabs. In some patients the test is falsely negative, while other biological samples are positive. The aim of the study is to identify characteristics and prognostic factors for swab negativity in COVID-19 patients with deep aspirate bronchus (BA)-confirmed disease. Multicentric retrospective case-control study of patients admitted for COVID-19 between March and November 2020 in two internal medicine units of the AOU Careggi and in the Internal Medicine of the Hospital of Varese. Were enrolled patients aged ≥18 years hospitalized for COVID-19 with viral RNA isolation on biological specimen, considering as cases the patients negative to swab but positive to BA. For each case, four controls with positive swab at admission were enrolled. The study included 95 patients, 19 cases and 76 controls. The mean time between symptoms onset and swab was 2.65±1.9 days in cases, with a statistically significant (P=0.003) difference compared to controls (5.53±3.0 days). Patients with negative swab had a longer mean length of stay and more frequent adverse outcome than controls. Swabbing within a short time of symptoms onset is a predictor for false negative. Patients with repeated negative swabs have a worse clinical picture with longer hospital stay, greater need for non-invasive ventilation and higher frequency of adverse outcome.

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Key words: SARS-CoV-2; nasopharyngeal swab; coronavirus.

Contributions: OP, conceptualization and methodology; CN, conceptualization and methodology; LC, writing original draft. All the other authors, resources. All the authors approved the final version to be published.

Conflict of interest: the authors declare no potential conflict of interest.

Ethical approval and consent to participate: all the procedures performed in this study were in ac-cordance with the ethical standards of the institutional or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. This is a retro-spective study that includes anonymized patients extracted from hospital database; data are presented aggregated and anonymously. No informed consent was taken.

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Received for publication: 21 November 2022.
Revision received: 3 December 2022.
Accepted for publication: 31 December 2022.

Licensee PAGEPress, Italy
Italian Journal of Medicine 2022; 16:1552
doi:10.4081/itjm.2022.1552

Introduction

Coronavirus disease 2019 (COVID-19), caused by severe acute respiratory syndrome-coronavirus 2 SARS-CoV-2, is rapidly expanding worldwide and it can turn into acute respiratory distress syndrome (ARDS) and death.[1] Diagnosis should be as timely and accurate as possible.

The research for SARS-CoV-2 genome with real time-polymerase chain reaction (RT-PCR) on a nasopharyngeal swab represents the standard method for the diagnosis of COVID-19.

The FIND Foundation has independently evaluated the molecular assays using clinically and laboratory-confirmed COVID-19 patient samples and reported 92-100% sensitivity and 100% specificity.[2] However, 40–80% sensitivity for the molecular assays have been reported in the real-world application, indicating high false negativity of these assays.[3]

A significant problem is inadequate testing could

result in unrecognized COVID-19 infected individuals, roaming freely in the population. Another important issue is the sensitivity of samples from different sites. Classically, the confirmation of diagnosis of COVID-19 depends on RT-PCR analysis to detect viral genetic material in either a nasal swab or bronchioalveolar lavage sample.[4] Wang *et al.* reported that bronchioalveolar lavage sample has the highest sensitivity in identifying COVID-19, followed by sputum and nasal swab with positive rates of 93%, 72% and 63%, respectively.[5]

However, in some patients this test is falsely negative even in repeated determinations.

The primary endpoint of our study was to identify clinical characteristics and factors related to the repeated negativity of the nasopharyngeal swab analyzed by RT-PCR in patients affected by COVID-19 in whom the disease has been confirmed by microbiological analysis on a sample of deep aspirate bronchus (BA) obtained by bronchoscopy.

The secondary objective was to evaluate the differences between the two study groups in terms of outcome, defined as in-hospital mortality and/or the need for transfer to a more intensive care setting and any prognostic factors related to the outcome.

Materials and Methods

Study design

A retrospective case-control multicenter study was conducted on patients hospitalized for COVID-19 between March 1, 2020 and November 30, 2020 at two departments of Internal Medicine (Internal Medicine 1 and Internal Medicine 2) of Careggi University Hospital and at the Internal Medicine department of Circolo Hospital of Varese.

Patients ≥18 years of age admitted to COVID-19 during that period with viral RNA isolation from biological specimens were enrolled.

All study participants underwent the execution of nasopharyngeal swabs, carried out according to the procedures recommended by the National Institute of Health (ISS). The laboratory methods used in the microbiological analysis of nasopharyngeal and bronchus aspirate swabs were RT-PCR and transcription-mediated amplification (TMA).

We considered as cases the patients who tested negative for SARS-CoV-2 performed on nasopharyngeal swab, but positive at the same analysis carried out on BA samples taken by bronchoscopy. For each case four controls were selected, hospitalized in the same period, with positive results for SARS-CoV-2 on a nasal-oropharyngeal swab at the entrance. Using the electronic record system ArchiMed® medical software (version 8.33, by B. Dannaoui, Florence, Italy) and Whospital® (Varese, Italy), for each patient included in this study, the following data were collected: i) personal data (age, sex); ii) data on the time interval, expressed in days, between the appearance of symptoms and the execution of the nasal-oropharyngeal swab; iii) data on cardiovascular risk factors and chronic comorbidities: obesity, smoking, arterial hypertension, chronic obstructive pulmonary disease, asthma, diabetes mellitus, acute coronary syndromes, heart failure, atrial fibrillation, ischemic cerebrovascular disease, chronic renal failure, cirrhosis, dementia, solid and hematological tumors in the last five years, bed rest and the Charlson comorbidity index (CCI) was also calculated for each patient; iv) data relating to COVID-19 symptoms present at admission: fever, cough, dyspnea, tachypnea, diarrhea, nausea/vomiting, myalgia, asthenia, ageusia/anosmia; v) blood gas analytical data at admission: FiO_2, pH, pCO_2, pO_2, sO_2, lactates, bicarbonates, hemoglobin, P/F ratio and S/F ratio, collected on admission to the ward (or in the emergency room, where data upon entering the ward); vi) blood tests at entry: hemoglobin, white blood cell count, lymphocyte, neutrophil and platelet count, international normalized ratio, D-dimer, creatinine, lactate dehydrogenase, ferritin, interleukin-6, NT-proBNP, C-reactive protein (CRP), upon entering the ward (or in the emergency room, where data upon entering the ward is not available); vii) urinary antigens of *Legionella* and *Pneumococcus*; viii) instrumental examinations: bedside chest ultrasound, chest X-ray, possible chest CT scan; ix) information on oxygen therapy and respiratory support (need or CPAP/NIV); x) information on drugs taken chronically: corticosteroids, proton pump inhibitors, immunosuppressants and anticoagulants; xi) information on the outcome: length of stay, discharge, transfer to a higher intensity care setting/intubation, death.

Statistical analysis

Continuous variables were expressed as means ± standard deviation, while dichotomous variables were expressed as number and percentage of patients for each category. Student's test was used to compare normally distributed continuous variables, while Fisher's χ-square test was used to compare non-continuous variables. To analyze the independent contribution of the variables in predicting the chosen outcome, we performed the univariate and multivariate analysis. The results were considered statistically significant for P values <0.05 and 95% of the confidence interval. The statistically significant variables in the univariate analysis for differences between the 2 groups are shown in bold (P<0.05).

Results

Among COVID-19 patients admitted between March 1, 2020, and November 30, 2020 in the Internal Medicine wards 1 and 2 of the Careggi AOU and in the Internal Medicine department of the Circolo di Varese hospital, were included in the study 95 patients, 19 cases (20%) and 76 controls (80%).

Both populations presented advanced age (70.11±11.88 for cases, 68.43±16.10 for controls), without a significant difference between the two groups. Both in the group of subjects who tested negative for nasopharyngeal swab and in the control group, male patients were more interested than female, reaching respectively 73.7% (14 of 19 patients) and 53.9% (41 out of 76 patients). The mean length of hospital stay was longer in patients with negative nasopharyngeal swab than in those with positive swab, 22.53±19.38 days and 14.16±11.32 days, respectively. The mean time between symptom onset and nasopharyngeal swab was 2.65±1.9 days in the case group, with a statistically significant difference (P=0.003) compared to patients in the control group, with time interval of 5.53±3.75 days.

The most common comorbidity was hypertension, present in 13 out of 19 patients (68.4%) in the case group and in 44 out of 76 patients (57.9%) in the control group.

About half of the patients included in the study had more than two comorbidities: 57.9% of the case group (11 out of 19) and 43.4% in the control group (33 out of 76). The mean of the CCI was 3.83±2.53, with no significant differences between cases and controls, being 4.33±2.85 and 3.71±2.45, respectively.

An adverse outcome was observed more in cases (52.6%) than in controls (30.3%). In particular, death occurred in 23 patients, 8 among the cases (42.1%) and 15 among the controls (19.7%). The demographic characteristics of the study population are shown in Table 1.

Table 1. Demographic characteristics and comorbidities.

Demographic characteristics	Overall population N=95 (%)	Cases N=19 (%)	Controls N=76 (%)	P value
Mean age±SD	68.77±15.31	70.11±11.88	68.43±16.10	0.615
Gender, N (%) Males Females	 55 (57.9) 40 (42,1)	 14 (73.7) 5 (26,3)	 41 (53.9) 35 (46.1)	0.193
Time between onset of symptoms and swab, mean±SD	(N=81) 4.8±3.76	(N=17) 2.65±1.90	(N=64) 5.53±3.75	0.003
Length of hospital stay, mean±SD	15.83±13.62	22.53±19.38	14.16±11.32	0.016
Adverse outcome	33 (34.7)	10 (52.6)	23 (30.3)	0.104
Deaths	23 (24.2)	8 (42.1)	15 (19.7)	0.069
Obesity	18 (18.9)	2 (10.5)	16 (21.1)	0.513
Current or past smoking	37 (38.9)	9 (47.4)	28 (36.9)	0.438
Hypertension	57 (60)	13 (68.4)	44 (57.9)	0.445
COPD	12 (12.6)	4 (21.1)	8 (10.5)	0.250
Asthma	7 (7.4)	3 (15.8)	4 (5.3)	0.140
Diabetes mellitus	22 (23.2)	3 (15.8)	19 (25)	0.548
Acute coronary syndromes	13 (13.7)	3 (15.8)	10 (13.2)	0.719
Heart failure	8 (8.4)	3 (15.8)	5 (6.6)	0.196
Atrial fibrillation	12 (12.6)	0 (0)	12 (15.8)	0.116
Stroke	5 (5.3)	1 (5.3)	4 (5.3)	1
Chronic renal failure	17 (17.9)	4 (21.1)	13 (17.1)	0.740
Cirrhosis	1 (1.1)	1 (5.3)	0 (0)	0.200
Dementia	9 (9.5%)	0 (0)	9 (11.8)	0.197
Solid tumor in the last 5 years	16 (16.8)	3 (15.8)	13 (17.1)	1
Hematologic cancer in the last 5 years	7 (7.4)	3 (15.8)	4 (5.3)	0.140
Bedridden	10 (10.5)	2 (10.5)	8 (10.5)	1
Presence of >2 comorbidities	44 (46.3)	11 (57.9)	33 (43.4)	0.309
Charlson comorbidity index, mean±SD	3.83±2.53	4.33±2.85	3.71±2.45	0.401

SD, standard deviation; COPD, chronic obstructive pulmonary disease.

The most frequently occurring signs/symptoms were fever and dyspnea in the case group (both found in 57.9% of these patients) and fever and tachypnea in controls (detected in 71.1% and 73.7% of patients, respectively of this group). The use of respiratory support as CPAP or NIV was instead necessary in 47.1% of cases and in 26.3% of controls. Results for clinical signs and symptoms are listed in Table 2.

As regards the blood tests performed at admission higher values of CRP, platelets, leukocytes and neutrophils were recorded in patients with negative swab compared to the control group. No patient was found to be positive for the Legionella urinary antigen, while in 6 patients of the control group pneumococcal urinary antigen was detected.

The results of the laboratory tests are summarized in Table 3.

The blood gas analytical parameters at admission, showed in Table 4, did not show substantial differences between the two groups.

Chest ultrasound data are available for 23 patients and show the presence of bilateral or diffuse B lines in 47.8% of study participants. Chest X-ray, not available for only five patients who directly performed a CT scan

Table 2. Signs and symptoms.

Symptoms/signs	Overall population N=95 (%)	Cases N=19 (%)	Controls N=76 (%)	P value
Cough	40 (42.1)	7 (36.8)	33 (43.4)	0.796
Fever	65 (68.4)	11 (57.9)	54 (71.1)	0.282
Maximum body temperature mean ±SD	(N=46) 38.42±0.64	(N=9) 38.57±0.56	(N=37) 38.39±0.66	0.418
Dyspnea	54 (56.8)	11 (57.9)	43 (56.6)	1
Tachypnea	63 (66.3)	7 (36.8)	56 (73.7)	0.005
Diarrhea	13 (13.7)	4 (21.1)	9 (11.8)	0.285
Nausea/vomiting	5 (5.3)	1 (5.3)	4 (5.3)	1
Myalgias	3 (3.2)	0 (0)	3 (3.9)	1
Asthenia	14 (11.1)	5 (26.3)	9 (11.8)	0.146
Ageusia/anosmia	4 (4.2)	1 (5.3)	3 (3.9)	1
Need for CPAP/NIV	(N=93) 28 (30.1)	(N=17) 8 (47.1)	(N=76) 20 (26.3)	0.141

Table 3. Blood tests at admission.

Blood tests at admission, mean±SD	Overall population N=94	Cases N=19	Controls N=75	P value
Hemoglobin	12.51±2.35	11.95±1.86	12.65±2.45	0.179
Leukocytes	7.48±3.53	8.45±4.09	7.23±3.36	0.240
Neutrophils	(N=88) 6.13±3.41	(N=15) 8.14±3.28	(N=73) 5.72±3.31	0.017
Lymphocytes	(N=88) 1.20±1.11	(N=15) 1.64±2.30	(N=73) 1.11±0.64	0.093
Platelets	202±81	227±109	196±72	0.146
D-dimer	(N=90) 2163±7514	(N=17) 1738±1984	(N=73) 2262± 8299	0.630
Creatinine	1.54±1.76	1.62±0.90	1.52±1.92	0.731
LDH	(N=91) 327±132	(N=18) 325±124	(N=73) 328±135	0.942
Ferritin	(N=85) 920±1010	(N=15) 812±625	(N=70) 943±1077	0.529
IL-6	(N=59) 19.64±23,05	(N=6) 16.17±13.31	(N=53) 20.03±23.96	0.557
CRP	(N=92) 97±99	(N=19) 113±151	(N=73) 93±81	0.577
NT-proBNP	(N=75) 2581±5930	(N=6) 4684±4638	(N=69) 2398± 6021	0.299

LDH, lactate dehydrogenase; IL, interleukin; CRP, C-reactive protein.

of the chest, showed an interstitial disease and bilateral thickening for more than half of the subjects, with a percentage of 58.9% in negative swab patients and 60.2% in patients with positive swab.

On chest CT, available for 31 patients, the most represented pattern is interstitial disease and bilateral thickening, with similar percentages between the two study groups. A normal radiological picture was described in a single chest CT scan.

Imaging patterns (chest ultrasound, chest X-ray, and chest CT, where performed) are shown in Table 5.

Chronic therapies with four types of drugs were evaluated: corticosteroids, immunosuppressants, proton pump inhibitors (PPIs) and anticoagulants. Among

Table 4. Hemogasanalysis.

Hemogasanalysis at admission, mean±SD	Overall population	Cases	Controls
FiO_2	(N=85) 32.75±23.74	(N=17) 22.35±5.58	(N=68) 35.35±25.78
pH	(N=85) 7.45±0.08	(N=18) 7.42±0.11	(N=67) 7.45±0.06
pCO_2	(N=84) 34.52±6.47	(N=17) 34.76±7.16	(N=67) 34.46±6.34
pO_2	(N=86) 76.64±39.41	(N=18) 68.51±27.74	(N=68) 78.79±41.87
sO_2	(N=79) 92.26±10.28	(N=14) 92.17±4.85	(N=65) 92.28±11.14
Lactates	(N=69) 4.10±6.57	(N=12) 2.49±2.13	(N=57) 4.44±7.13
HCO_{3-}	(N=75) 24.77±3.33	(N=12) 23.81±2.41	(N=63) 24.96±3.46
P/F	(N=84) 284±99	(N=16) 285±66	(N=68) 284±106
S/F	(N=77) 376±134	(N=13) 418±65	(N=64) 368±143

P/F, partial oxygen pressure/fractional inspired oxygen; S/F, oxygen saturation/fractional inspired oxygen.

Table 5. Chest imaging.

Lung ultrasound	**Overall population N=23 (%)**	**Cases N=3 (%)**	**Controls N=20 (%)**
Negative	6 (26.1)	2 (66.7)	4 (20)
Monolateral B lines	6 (26.1)	0 (0)	6 (30)
Bilateral B lines	5 (21.7)	1 (33.3)	4 (20)
Diffuse B lines	6 (26.1)	0 (0)	6 (30)
Chest RX	**Overall population N=90 (%)**	**Cases N=17 (%)**	**Controls N=73 (%)**
Negative	15 (16.7)	3 (17.6)	12 (16.5)
Monolateral interstitial disease	7 (7.8)	1 (5.9)	6 (8.2)
Bilateral interstitial disease	14 (15.5)	3 (17.6)	11 (15.1)
Interstitial disease+infiltrate	54 (60)	10 (58.9)	44 (60.2)
Chest CT	**Overall population N=31 (%)**	**Cases N=12 (%)**	**Controls N=19 (%)**
Negative	1 (3.2)	0 (0)	1 (5.3)
Monolateral interstitial disease	0 (0)	0 (0)	0 (0)
Bilateral interstitial disease	3 (9.7)	1 (8.3)	2 (10.5)
Interstitial disease+infiltrate	27 (87.1)	11 (91.7)	16 (84.2)

these drugs pump inhibitors were the most frequently taken, both in the group of cases (57.9%) and in the control group (26.3%).

The drugs taken chronically by patients enrolled in the study are summarized in Table 6.

Discussion

Data analysis regarding the average time interval between symptoms onset and nose-pharyngeal swab execution, which were available for 81 patients (17 cases and 64 controls), showed a statistically significant difference (P=0.003) between these two groups: patients with an instant positive nose-pharyngeal swab underwent to the molecular investigation after 3 days average, as compared to patients with a negative one.

As a matter of fact, for the case group the average time interval from the appearance of COVID-19 symptoms and the execution of the swab was 2.65±1.90 days, whereas for the control group was 5.53±3.75 days. The precocious execution of the swab is one of the main causes of a falsely negative result and implicates a high rate of false negative results especially during the first days of the infection, as demonstrated in a study conducted by John Hopkins University in Baltimora.[6] However, it should be emphasized that patients with a negative swab, even if executed after a brief period from symptoms onset, were in clinical conditions that required hospitalization already. Signs/symptoms more frequently complained were fever and dyspnea, followed by cough and tachypnea.

Data regarding the average length of in-hospital stay showed a statistically significant difference (P=0.016) between the two groups: patients with a negative swab at admission had a longer length of stay on average, as compared to patients with a positive swab.

Patients with a negative swab had a more severe disease, requiring respiratory support with non-invasive ventilation (CPAP/NIV) and a worse outcome, meaning in-hospital death or transfer in Intensive Care Unit.

The longer in-hospital stay, and the worse outcome could suggest a more severe disease progression in this particular group of subjects. One of the possible explanations, as supposed in a study published in *Journal of Clinical Microbiology*, could be a precocious and more relevant involvement of the inferior respiratory tract; such an element could also explain the false negativity of the nose-pharyngeal swab.[7]

Regarding comorbidities, there were not statistically significant differences between the two groups. Having two or more comorbidities was a very recurrent condition in both groups, in agreement both with the population that more frequently develops symptomatic forms of COVID-19 and with the typical population of Internal Medicine wards, composed of complex and frail patients. CCI, a score that predicts one-year mortality risk, was 3.83±2.53, without significant differences between the two groups.

Regarding blood tests at admission, the mean value of neutrophils was significantly higher in the case group (P=0.017). In many studies neutrophilia is considered a risk factor predicting a negative outcome in patients with SARS-CoV-2 infection.[8,9] This element could be an additional confirmation of a worse disease severity in patients with a negative swab.

Instrumental exams considered in our study were thoracic ultrasound, radiography and CT scan. Using ultrasound, the most frequently observed pattern was bilateral or diffused B lines (47.8% of the population in study); nevertheless, the retrospective nature of the study does not allow to collect sufficient data in order to conduct a proper statistical analysis.

In our study there were not significant differences among identified instrumental findings, which therefore were useless in differentiating the two groups of patients. Radiologic exams could pose a high suspicion of COVID-19, indeed there are various scores like CO-RADS or RSNA Classification System which predict the risk of having COVID-19 relying on CT patterns.[10] However, we can make a definitive diagnosis only through the isolation of SARS-CoV-2 viral RNA. For this reason, it is not surprising how the two groups' radiologic images are significantly superimposable, since they are all affected from COVID-19 bilateral interstitial pneumonia with certainty (given the isolation of the viral genome through broncho aspiration in patients with a negative swab).

Concerning the pharmacologic therapy of our patients, PPI's chronic use was significantly more common (P=0.013) in the case group. Several studies pinpointed how PPI's pre-hospital chronic use could be associated with an unfavorable outcome in patients with

Table 6. Drugs.

Drugs	Overall population N=95 (%)	Cases N=19 (%)	Controls N=76 (%)	P value
Corticosteroids	8 (8.4)	2 (10.5)	6 (7.9)	0.661
Proton pump inhibitors	31 (32.6)	11 (57.9)	20 (26.3)	0.013
Anticoagulants	13 (13.7)	0 (0)	13 (17.1)	0.064
Immunosuppressants	1 (1.1)	1 (5.3)	0 (0)	0.200

COVID-19. Hypochlorhydria induced by these medications reduces the gastric acids' inhibiting effect on SARS-CoV-2 and modifies the gastrointestinal microbiome, thus facilitating secondary infections that increase the risk of ARDS and negative outcome.[11,12] For this reason, the worst clinical scenario of our cases could be at least in part attributable to a more widespread use of proton pump inhibitors in this group.

The main limits of our study are related to the restricted clinical records availability and to its retrospective nature, with some data that remain unavailable.

A possible bias is also the inter-operator variability in performing the nose-pharyngeal swab, which is significantly reduced to this time since the standardization of the procedure through the Italian National Institute of Health's guidelines.

Conclusions

In our observational multicentric study, patients with a nose-pharyngeal swab repeatedly negative for SARS-CoV-2 but affected by COVID-19, as confirmed by the virus isolation through bronchoaspiration, had a longer length of stay on average, a more severe respiratory involvement with requirement of ventilatory support through CPAP/NIV and, more frequently, an adverse outcome. A brief time interval between symptoms onset and the execution of the nose-pharyngeal swab, neutrophilia and PPI therapy were risk factors predictive of a false negative result in the research of SARS-CoV-2 through RT-PCR conducted on nose-pharyngeal swabs.

It will be interesting to carry out further studies aimed to identifying clinical characteristics and factors tied to the nose-pharyngeal swabs false negativity, in order to optimize the precocious diagnosis and the proper management of patients at risk to develop more severe forms of disease.

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