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TITLE

PREVALENCE OF DYSPHONIA IN NONHOSPITALIZED PATIENTS WITH COVID-19 IN LOMBARDY, THE ITALIAN EPICENTER OF THE PANDEMIC

RUNNING TITLE: Dysphonia in nonhospitalized COVID-19 patients

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ABSTRACT

Introduction: Dysphonia has been described in patients affected by coronavirus disease 2019 (COVID-19). The aim of this study was to evaluate the prevalence of dysphonia, and its severity and extent, of voice fatigue and of dysphagia in nonhospitalized patients affected by COVID-19 in Lombardy, the Italian region most hit by the first explosive outbreak of COVID-19 in Europe. **Methods:** Demographic and clinical data of 160 consecutive patients, with COVID-19 diagnosis confirmed by nasal swabs processed by reverse transcription polymerase chain reaction, were gathered by means of telephone interviews performed by physicians in charge of daily follow-up. General and specific symptoms concerning voice and swallowing impairment were investigated. Dysphonia grade and duration were graded on 4-point scales, while voice fatigue was graded on a 5-point scale. **Results:** Dysphonia was reported by 70 (43.7%) patients and was positively associated with voice fatigue (P<0.001), cough (P=0.005), rhinitis (P=0.01), and dyspnea (P=0.06); it was mild/moderate in 69 patients, but its duration was > 2 weeks in 33/70 (47.1%) patients and >1 month in 11/70 (15.7%). Grade and duration of dysphonia were positively associated with cough and rhinitis (all P-values <0.01). Voice fatigue was reported by 43/160 patients (26.8%) and its severity was correlated with dysphonia (P<0.0001), cough (P=0.02), rhinitis (P=0.02), dyspnea (P<0.001), and loss of appetite (P=0.01). Dysphagia was encountered in 27/160 patients (16.9%) and was associated with dysgeusia, cough, arthralgia, myalgia and loss of appetite but not with dysphonia. **Conclusions:** Dysphonia was a highly prevalent and long-lasting symptom in this series; it has been underestimated to date. Further studies might shed light on the pathophysiology of voice disorders in COVID-19 patients.

Keywords: Dysphonia; Coronavirus, COVID-19, SARS-CoV-2; Voice; Voice fatigue, Dysphagia; Symptoms; Infection; ENT

INTRODUCTION

The first outbreak of coronavirus disease 2019 (COVID-19), caused by a novel severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), emerged in Wuhan, China, in early December 2019 [1]. Italy was the first European country to be hard hit by the COVID-19 pandemic; on February 21, the first case was detected in the Italian region of Lombardy [2], which hence remained the region with the highest number of cases. Since January, severe cases of pneumonia unresponsive to medical treatment have been encountered by physicians in Lombardy. That unrecognized spreading, antecedent to the first case identified by specific diagnostic tests for COVID-19, might explain the explosive outbreak in the region. At the beginning of the pandemic, the patients diagnosed with COVID-19 were hospitalized, but then, when the virus quickly spread in a devastating way, the pressure on Italian hospitals abruptly increased, and consequently, all patients affected by less severe COVID-19 were home managed.

It is well known that COVID-19 may severely affect the lower respiratory system, causing bilateral pneumonia that can be the cause of acute respiratory distress [1]. Nevertheless, the upper airway can also be intensely affected by infection [3]. In particular, olfactory and taste dysfunctions have been extensively reported as typical and early symptoms of SARS-CoV-2 infection, and they can be considered warning signs and might reveal the diagnosis in pauci-symptomatic patients [4, 5]. Anosmia and dysgeusia have also been reported in patients without other typical signs of upper respiratory tract infection. The pathogenesis of olfactory and gustatory dysfunctions has not yet been clarified. Possible mechanisms include the neuroinvasive potential of SARS-CoV-2. SARS-CoV-2 invades cells through the angiotensin-converting enzyme 2 (ACE2) receptor [6], and olfactory and gustatory dysfunctions could be related to viral neuroinvasion and not necessarily to an inflammatory reaction of the upper airway mucosa to viral infection [5, 7]. Nevertheless, patients affected by COVID-19 may frequently exhibit the typical and nonspecific symptoms of upper

airway infection, such as rhinorrhea, nasal obstruction, and pharyngitis, and symptoms related to laryngeal involvement in the inflammatory process [3]. Dysphonia was previously described in 26.8% of patients affected by mild-to-moderate COVID-19 [8].

The main aim of this study was to evaluate the prevalence of dysphonia and voice fatigue in nonhospitalized Italian patients in Lombardy affected by mild-to-moderate COVID-19 and to ascertain its duration and the perceived degree of severity. A secondary aim was to evaluate the prevalence of dysphagia in the same cohort of patients.

METHODS

Patients and Clinical Data

The study was approved by the Ethical Committee of the University of Milan.

Data were collected from March 25 to May 30, 2020, by telephone interviews performed by physicians who were in charge of verifying the clinical conditions of home-managed patients affected by mild-to-moderate COVID-19.

This study included consecutive patients who had been examined in the emergency room in the main hospitals in Milan; COVID-19 diagnosis was confirmed by nasal swabs processed by reverse transcription polymerase chain reaction (RT-PCR). The patients were typically discharged home after 1-3 days of observation in the emergency room if they were in stable condition, and then they were followed-up by means of daily phone calls. Physicians used a questionnaire to gather patient demographic and clinical data, such as age, sex, body mass index, and smoking status, and information about the symptoms of fever, asthenia, anosmia, dysgeusia, cough, rhinitis, dyspnea, arthralgias, myalgias, a loss of appetite, dysphonia, voice fatigue and dysphagia. Information were gathered within three days from discharge.

Dysphonia grade and duration were assessed by means of 4-point scales (grade: 0=none; 1= mild; 2= moderate; 3=severe) (duration: 1= < 1 week; 2 = >1 week; 3= > 2 weeks; 4= >1 month). Voice fatigue was assessed on a 5-point scale ranging from 0= none to 4= severe.

Dysphagia was defined as difficulty swallowing food.

The exclusion criteria for this study were dysphonia present prior to SARS-CoV-2 infection, a history of head and neck cancer treated in any way, and swallowing impairment antecedent to COVID-19.

Statistical analysis

The comparison of age between male and female patients was evaluated with the Mann-Whitney test. Categorical variables were analyzed using the chi-squared test. The variables fever and asthenia were not considered because almost all (96%) patients reported these symptoms. To analyze the association of selected variables with the ordinal variables grade and duration of dysphonia and voice fatigue, we calculated P-values from Spearman's rank correlation analysis. Statistical analysis was performed with Stata 16 software (StataCorp, 2019).

RESULTS

The study included 160 consecutive patients (110 females and 50 males). Females patients were younger (mean age 49 years, range: 16-90) than male patients (mean age 55.0 years, range 20-87) (P=0.055). Body mass index (BMI) was higher in males than in females (P= 0.02). The majority of patients (117; 73.1%) were defined as "moderate" COVID-19 cases as they had clinical or radiographic evidence of pneumonia with a blood oxygen saturation ≥94%, while the remaining 43 (26.9%) were mild cases, affected by mild symptoms and no dyspnea [9].

Overall, seventy patients (43.7%) reported dysphonia; no difference was detected between sexes and between mild and moderate cases. Sixty-four patients (40.0%) were former or current smokers. Being dysphonic during SARS-CoV-2 infection was not related to smoking status or to BMI (Table

I). Dysphonia was positively correlated to the following symptoms: voice fatigue (P<0.001), cough (P=0.005), rhinitis (P=0.01), and dyspnea (P=0.06) (Table II).

Dysphagia was ascertained in 27 (16.9%) patients (Table II). It was positively associated with cough (P=0.009), arthralgia (P=0.002), dysgeusia (0.005), myalgia (P=0.05), and a loss of appetite (P=0.002).

Dysphonia grade was mild/moderate in 69 patients and severe (aphonia) in a single patient. The duration of dysphonia was longer than 2 weeks in 33 of the 70 dysphonic patients (44.1%), including 11 subjects who exhibited dysphonia for more than a month (Table III). Dysphonia grade and duration did not vary according to sex, age, smoking status, or BMI. The grade of dysphonia was more severe in subjects with cough (P=0.003) and rhinitis (P=0.004). Similarly, the duration of dysphonia was longer in patients with cough (P=0.002) and rhinitis (P=0.005).

Voice fatigue (any grade) was reported by 43/160 patients (26.9%) and was more frequent among dysphonic patients (33/70=47.1%) than in non-dysphonic patients (10/90=11.1%) (Table IV). Although there were some patients with mild (9/90) or moderate (1/90) voice fatigue among non-dysphonic subjects, grade of self-perceived voice fatigue was definitely higher in patients with dysphonia (P<0.0001), with 14/70 (20.0%) reporting moderate to severe fatigue. Voice fatigue grade was also positively correlated with cough (P=0.02), rhinitis (P=0.02), dyspnea (P<0.0001), and loss of appetite (P=0.01).

DISCUSSION

This study highlighted a high prevalence (>40%) of self-evaluated dysphonia among nonhospitalized COVID-19 patients, although the severity of voice impairment was considered mild/moderate by all except one patient. Voice impairment might be overlooked in COVID-19 patients for two main reasons. First, the percentage of dysphonic patients might be even higher if we consider that in hospitalized patients, the severity of pneumonia dominates the clinical picture,

and voice impairment might not be taken into consideration, remaining underdiagnosed; then, if the patient underwent invasive or noninvasive ventilation, possible subsequent dysphonia would be possibly ascribed to the damage consequent to ventilation with or without intubation.

A previous study by *Lechien et al*. [8] on a wider number of European cases was the first to reveal dysphonia as a relevant symptom in mild-to-moderate COVID-19 patients, demonstrating a prevalence of 26.8% [8]. In our study the prevalence was higher, being 43.7%. This difference might be partially related to a dissimilar study protocol, since data were self-reported in the former study [8], while in the present research, data were collected by physicians via telephone interviews, with detailed questions about severity and duration. Therefore, the present data might be more accurate.

It should also be considered that the present study was conducted entirely on Italian patients from the Lombardy region, where the first outbreak of the COVID-19 pandemic occurred and which remained the epicenter of the Italian COVID-19 pandemic, being the area with the highest number of diagnosed and severe cases. The rapid spread of the virus did not permit the hospitalization of all patients; only the most critically ill had access to the inpatient wards. Mild-to-moderate COVID-19 patients were secluded in the hospital emergency room for 1-3 days and then discharged to quarantine at home with daily telephone follow-up calls from the service physicians. This peculiar situation might explain the higher prevalence of symptoms related to severe upper airway inflammation among nonhospitalized patients in this series, who were considered as mild-to-moderate cases, but might be more severe than those included in previous studies [8]. One more reason explaining the high prevalence of voice impairment in this series could be the high number of female patients, who constituted 69% of the whole sample; it is known that females are more likely to develop voice disorders than males [10]. However, our study found no difference in the prevalence of dysphonia between females and males. The predominance of female patients is an unexplained finding of this study.

Interestingly, despite a mild-to-moderate grade of dysphonia in the described patients, the duration of voice impairment was over 15 days in 31.4% of cases and in 15% exceeded a month. This long-term impairment is indicative of more severe and longer-lasting disturbance in voice production than is usually seen in viral laryngitis.

Since the SARS-CoV-2 virus affects both upper and lower respiratory tracts one should expect that there would be multiple possible causes for the dysphonia with this viral infection. .It has been recently demonstrated that ACE2 is expressed in the epithelial cells of the vocal folds [11], and that ACE2 is the receptor utilized by SARS-CoV-2 to penetrate human cells [6,11]. Therefore dysphonia might be caused by direct entry of SARS-CoV-2 into the glottic epithelium with consequent infection and damage. It is also known that ACE2 receptors are present in epithelia of the nose and lung and in abdominal and chest muscles [12-14]; thus, the larynx might also be indirectly affected in the inflammatory process of the nasal airway. At the same time the efficiency of voice production might be hindered by respiratory impairment due to lung infection and muscle fatigue.

The significant association between dysphonia and voice fatigue, rhinitis, cough and dyspnea is not surprising. Laryngeal irritation related to cough and to the abundance of mucus in the airway due to rhinitis with postnasal drip can explain this correlation. Voice fatigue can be due to the effort required to produce the vibration of inflamed vocal folds, or the negative impact of dyspnea on voice production through decreased expiratory airflow.

The positive association of voice fatigue with cough, rhinitis and dyspnea and the association between the grade and duration of dysphonia with cough and rhinitis may be explained on the same basis. Voice fatigue was a common finding detected in more than one-fourth of patients and was not necessarily associated with perceivable dysphonia. This finding supports a role of muscular and respiratory impairment in the genesis of voice fatigue in some patients.

Dysphagia was reported by 16.9% of patients; the neuroinvasive potential of SARS-CoV-2 might explain dysphagia and its association with taste dysfunction, while a loss of appetite might be a consequence of swallowing impairment. Myalgias and arthralgias associated with dysphagia could also be due to viral neurological injury or the consequence of the inflammatory process.

This report is the first to highlight dysphonia as a long-lasting symptom in patients affected by mild-to-moderate COVID-19. There are emerging reports about prolonged persistence of symptoms such as exercise intolerance and autonomic dysfunctions in patients who recovered from a mild form of SARS-CoV-2 infection; this condition has been defined as "long COVID" or "long-haul COVID" [15]. Future studies might clarify whether dysphonia might be part of the long-lasting symptoms after recovery from mild acute COVID-19, which are similar to those of chronic fatigue syndrome [15].

This study has several limitations, the main one being that it relied on information gathered by phone calls and that patients reporting dysphonia or dysphagia did not undergo an objective evaluation. Performing video laryngoscopy, stroboscopy or a functional endoscopic swallowing study in those patients was not feasible since the study was performed in the most critical period of the COVID-19 outbreak in Lombardy, in which all routine outpatient activities were halted and all clinical resources were reserved for the care of critically ill patients.

CONCLUSIONS

Dysphonia was a highly prevalent and long-lasting symptom in this series; it has been underestimated to date. Further research is needed to shed light on the pathophysiology of voice disorders in COVID-19 patients.

Future studies might confirm the relevance of voice impairment as a frequent symptom in mild-to-moderate COVID-19 patents and might clarify whether persistent dysphonia may play a prognostic role concerning disease severity and duration of general symptoms.

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Table I Characteristics and frequency of dysphonia in nonhospitalized patients with mild-to-moderate COVID-19

Variable	Patients	Dysphonia	P-value
	N	N (%)	
Sex			
Female	110	49 (44.6)	0.76
Male	50	21 (42.0)	
Age (years)			
<50	82	35 (42.7)	0.96
50-64	42	19 (45.2)	
65+	36	16 (44.4)	
Smoking			
Never	96	46 (47.9)	0.40
Former	38	15 (39.5)	
Current	26	9 (34.6)	
BMI (kg/m^2)			
<18.5	13	5 (38.5)	0.73
18.5-24.9	79	32 (40.5)	
25.0-29.9	49	23 (46.9)	
> 30	19	10 (52.6)	

Table II Prevalence of dysphonia and dysphagia according to selected symptoms in nonhospitalized patients with mild-to-moderate COVID-19

Variable	Patients	Dysphonia	P*	Dysphagia	P*
	N	N (%)		N (%)	
Dysgeusia					
Yes	42	23 (54.8)	0.09	13 (31.0)	0.005
No	118	47 (39.8)		14 (11.9)	
Anosmia					
Yes	39	19 (48.7)	0.47	10 (25.6)	0.09
No	121	51 (42.1)		17 (14.0)	
Cough					
Yes	76	42 (55.3)	0.005	19 (25.0)	0.009
No	84	28 (33.3)		8 (9.5)	
Rhinitis					
Yes	46	27 (58.7)	0.01	11 (23.9)	0.13
No	114	43 (37.7)		16 (14.0)	
Dyspnea					
Yes	47	26 (55.3)	0.06	11 (23.4)	0.16
No	113	44 (38.9)		16 (14.2)	
Arthralgia					
Yes	44	23 (52.3)	0.18	14 (31.8)	0.002
No	116	47 (40.5)		13 (11.2)	
Myalgia					
Yes	57	29 (50.9)	0.18	14 (24.6)	0.05
No	103	41 (39.8)		13 (12.6)	
Loss of appetite					
Yes	54	28 (51.9)	0.14	16 (29.6)	0.002
No	106	42 (39.6)		11 (10.4)	
Diarrhea					
Yes	27	14 (51.9)	0.35	6 (22.2)	0.42
No	133	56 (42.1)		21 (15.8)	
Dysphagia					
Yes	27	11 (40.8)	0.28	/	
No	133	59 (44.4)		/	

*P-values from chi-squared test

Table III Correlation of cough and rhinitis with grade and duration of dysphonia in nonhospitalized mild-to-moderate COVID-19 patients

	Grade of dysphonia					Duration of dysphonia (weeks)					
	None (%)	**Mild (%)**	**Moderate (%)**	**Severe (%)**		**0**	**<1 (%)**	**>=1 (%)**	**>=2 (%)**	**>=4 (%)**	**Total (%)**
Cough Yes	34 (44.7)	19 (25.0)	23 (30.3)	0 (0.0)		34 (44.7)	10 (13.2)	10 (13.2)	14 (18.4)	8 (10.5)	76 (100)
Cough No	56 (66.7)	17 (20.2)	10 (11.9)	1 (1.2)		56 (66.7)	11 (13.1)	6 (7.1)	8 (9.5)	3 (3.6)	84 (100)
	P=0.003*					P=0.002*					
Rhinitis Yes	19 (41.3)	10 (21.7)	17 (37.0)	0 (0.0)		19 (41.3)	6 (13.0)	6 (13.0)	9 (19.6)	6 (13.0)	76 (100)
Rhinitis No	71 (62.3)	26 (22.8)	16 (14.0)	1 (0.9)		71 (62.3)	15 (13.2)	10 (8.8)	13 (11.4)	5 (4.4)	84 (100)
	P=0.004*					P=0.005*					

* P-values from Spearman's rank correlation analysis

Table IV Correlation of dysphonia with self-perceived voice fatigue in nonhospitalized mild-to-moderate COVID-19 patients

	Perceived voice fatigue				
	None (%)	**Mild (%)**	**Moderate (%)**	**Severe (%)**	**Total (%)**
Dysphonic	37 (52.9)	19 (27.1)	10 (14.3)	4 (5.7)	**70 (100)**
Nondysphonic	80 (88.9)	9 (10.0)	1 (1.1)	0 (0.0)	**90 (100)**
	P<0.0001*				

*P-value from Spearman's rank correlation analysis