Features of Mild-to-Moderate COVID-19 Patients With Dysphonia

*,§Jerome R. Lechien, *,‖Carlos M. Chiesa-Estomba, *,¶Pierre Cabaraux, *,#Quentin Mat, *,**Kathy Huet, *,**Bernard Harmegnies, *,§Mihaela Horoi, *,§Serge D. Le Bon, *,§Alexandra Rodriguez, *,§Didier Dequanter, *,‡Stéphane Hans, *,‡Lise Crevier-Buchman, *,‡Baptiste Hochet, *,‡Lea Distinguin, *,‡Younes Chekkoury-Idrissi, *,‡Marta Circiu, *,‡Fahd El Afia, *,††Maria Rosaria Barillari, *,‡‡Giovanni Cammaroto, *,§§Nicolas Fakhry, *,§§Justin Michel, *,§§Thomas Radulesco, ‖,‖‖‖Delphine Martiny, *,¶¶Philippe Lavigne, *,##Lionel Jouffe, *,†Géraldine Descamps, *,†Fabrice Journe, *,***Eleonora M.C. Trecca, *,†††Julien Hsieh, *,‡‡‡Irene Lopez Delgado, *,§§§Christian Calvo-Henriquez, *,‖‖‖Sebastien Vergez, *,¶¶¶Mohamad Khalife, *,###Gabriele Molteni, *,****Giuditta Mannelli, ††††Giovanna Cantarella, *,‡‡‡‡Manuel Tucciarone, §§§§Christel Souchay, §§§§Pierre Leich, *,¶¶,aTareck Ayad, and †,§,¶¶,aSven Saussez, *, †§§§§‖ ‖ ‖ ‖Mons, §‖ ‖Brussels, ¶#Charleroi, **, and ¶¶Baudour, Belgium, ‡Paris, §§Marseille, ##Changé, and ‖ ‖ ‖Toulouse, France, ‖San Sebastian, ‡‡§§§, and ‡‡‡‡Jerez, Spain, ††Naples, ‡‡Forli, ***Foggia, ###Verona, ****, and ††††Milan, Italy, ¶¶Montreal, Canada, and †††Geneva, Switzerland

Summary: Introduction. To explore the prevalence of dysphonia in European patients with mild-to-moderate COVID-19 and the clinical features of dysphonic patients.

Methods. The clinical and epidemiological data of 702 patients with mild-to-moderate COVID-19 were collected from 19 European Hospitals. The following data were extracted: age, sex, ethnicity, tobacco consumption, comorbidities, general, and otolaryngological symptoms. Dysphonia and otolaryngological symptoms were self-assessed through a 4-point scale. The prevalence of dysphonia, as part of the COVID-19 symptoms, was assessed. The outcomes were compared between dysphonic and nondysphonic patients. The association between dysphonia severity and outcomes was studied through Bayesian analysis.

Results. A total of 188 patients were dysphonic, accounting for 26.8% of cases. Females developed more frequently dysphonia than males ($P = 0.022$). The proportion of smokers was significantly higher in the dysphonic group ($P = 0.042$). The prevalence of the following symptoms was higher in dysphonic patients compared with nondysphonic patients: cough, chest pain, sticky sputum, arthralgia, diarrhea, headache, fatigue, nausea, and vomiting. The severity of dyspnea, dysphagia, ear pain, face pain, throat pain, and nasal obstruction was higher in dysphonic group compared with nondysphonic group. There were significant associations between the severity of dysphonia, dysphagia, and cough.

Conclusion. Dysphonia may be encountered in a quarter of patients with mild-to-moderate COVID-19 and should be considered as a symptom list of the infection. Dysphonic COVID-19 patients are more symptomatic than nondysphonic individuals. Future studies are needed to investigate the relevance of dysphonia in the COVID-19 clinical presentation.

Key Words: Dysphonia−Covid-19−Coronavirus−Voice−Symptoms−Clinical−Findings−ENT.

INTRODUCTION

Since the first reported cases from Wuhan, the coronavirus disease 2019 (COVID-19) has spread rapidly worldwide.[1] As of April 25, a total of 2,719,897 individuals have been diagnosed through laboratory testing, with 187,705 corresponding deaths.[2] According to Asian studies, the clinical presentation of COVID-19 mainly includes fever, fatigue, cough, and anorexia.[3,4] However, recent European epidemiological studies suggested that European mild-to-moderate COVID-19 patients could present a different clinical picture than Asian.[5] In Europe, the most prevalent symptoms are headache, total loss of smell, nasal obstruction and cough.[5,6] Thus, the otolaryngological symptoms are more prevalent than previously presumed in Asia. Throughout a recent epidemiological study,[7] we observed the occurrence of dysphonia in some COVID-19 patients, with a minority reporting aphonia over the clinical course of the disease.

The aim of this study was to investigate the occurrence of dysphonia in mild-to-moderate COVID-19 patients.

METHODS

Five European Ethics Committees approved the study protocol (HAP2020-011; CHUSP20032020; EpiCURA-2020-2303, CHUC,P20/30-24/03-B325-2020; J.Bordet Institute: CE3137). The patient informed consent was obtained electronically.

Setting & patients

From March 22 to April 24, 2020, the data of hospitalized or home-managed COVID-19 patients were collected by otolaryngologists and nonotolaryngologist physicians from 19 European Hospitals (Paris, Marseille, Milan, Verona, Naples, Genova, Florence, Foggia, Forli, Sevilla, Santiago de Compostela, San Sebastian, Mons, Brussels, Charleroi, and Saint-Ghislain).

The diagnosis of Covid-19 infection was based on the WHO interim guidance.[8] Precisely, nasal or throat swabs were collected in suspected patients and the virus was identified through reverse transcription polymerase chain reaction (RT-PCR) analysis. The details of the viral RNA extraction and analyses are available in a previous paper.[7]

The mild-to-moderate COVID-19 patients were identified through different ways. First, the database of the laboratories of the hospitals provided a list of hospitalized or home-managed patients. Second, many patients were referred by the family physician or specialists from hospital departments (eg, Emergency, Internal Medicine, or Otolaryngology Departments). A public call of University of Mons allowed an increase in the recruitment of patients. Third, many infected health care workers were included.

Patients who were hospitalized in intensive care units were not included due to their health status and the inability to answer to the questions. Patients who reported dysphonia prior to the infection were not included in the present analysis. Patients with a history of head & neck trauma, (chemo) radiotherapy, benign or malignant laryngeal lesions, or head and neck cancer surgery were identified through the epidemiological questionnaire and carefully excluded.

Regarding the inclusion and exclusion criteria, the patients included in the present study were defined as mild-to-moderate COVID-19 patients.

Epidemiological & clinical outcomes

Due to the sanitary situation, the data were collected through an electronic patient-reported outcome questionnaire. Home-managed patients were contacted over the phone. Physicians completed the questionnaire in the patient's room for hospitalized patients through an electronic device. For these patients, physicians had access to the patient medical records to complete some data. The professional Survey Monkey (San Mateo, California, USA) was used for the patient reported outcome questionnaire.

The following epidemiological and clinical data were considered: age, sex, ethnicity, tobacco consumption, comorbidities, general, and otolaryngological symptoms. The general symptoms included headache, asthenia, myalgia, arthralgia, cough, loss of appetite, dyspnea, fever, diarrhea, nausea/vomiting, abdominal pain, and chest pain. The otolaryngological symptoms included nasal obstruction, rhinorrhea, postnasal drip, sore throat, face pain, dysphonia, ear pain, dysphagia, and sticky throat mucus. Otolaryngological symptoms were assessed through a 4-point scale, ranging from 0 (=no symptom) to 4 (=very severe symptom). The prevalence rates of total or partial loss of smell and dysgeusia were evaluated through questions from the smell and taste component of the National Health and Nutrition Examination Survey (NHNES).[8] NHNES is a population survey that monitors the health of U.S. citizens through a nationally representative sample of 5,000 persons on a yearly basis.[8]

Statistical methods

The statistical analysis was realized through Bayesian networks. The details about the qualitative and quantitative models of the network analysis were reported in a previous study.[7] The outcomes were compared between dysphonic and nondysphonic patients. The relationships between dysphonia, epidemiological data and general and otolaryngological symptoms were studied. A P - value <0.05 was considered as significant.

RESULTS

The data of 702 patients were collected. Among them, 188 reported dysphonia (26.8%) as a COVID-19 symptom while 514 patients did not report dysphonia during the clinical course of the disease. Seven dysphonic patients reported

TABLE 1.
Epidemiological Characteristics of Dysphonic and Nondysphonic Patients

Characteristic	Patients (n = 702)	Dysphonic (n = 188)	Nondysphonic (n = 514)
Age			
Median (SD) - yo	40.3 ± 11.8	42.0 ± 11.9	39.6 ± 11.7
Gender (n - %)			
Male	206 (29.2)	44 (23.4)	162 (31.5)
Female	496 (70.8)	144 (76.6)	352 (68.5)
Ethnicity (n - %)			
European	640 (91.2)	172 (91.5)	469 (91.2)
Asian	11 (1.6)	2 (1.1)	9 (1.8)
Black African	14 (2.0)	1 (0.5)	13 (2.5)
North African	26 (3.7)	10 (5.3)	16 (3.1)
North American	1 (0.1)	0 (0)	1 (0.2)
South American	5 (0.1)	2 (1.1)	3 (0.6)
Oceanian	0 (0)	0 (0)	0 (0)
Mixing	4 (0.6)	1 (0.5)	3 (0.6)
Addictions (n - %)			
Nonsmoker	597 (85.0)	148 (78.2)	450 (87.5)
Mild smoker (1−10 cigarettes daily)	83 (11.8)	19 (10.1)	64 (12.5)
Moderate smoker (11−20 cigarettes daily)	18 (2.6)	9 (4.8)	9 (1.8)
Heavy smoker (>20 cigarettes daily)	4 (0.6)	2 (1.1)	2 (0.4)
Allergic patients	126 (17.9)	37 (19.7)	89 (17.3)
Comorbidities			
Allergic rhinitis	75 (10.7)	23 (12.2)	52 (10.1)
High blood pressure	60 (8.5)	15 (8.0)	45 (8.8)
GERD	53 (7.5)	15 (8.0)	38 (7.4)
Asthma	42 (6.0)	13 (6.9)	29 (5.6)
Hypothyroidism (treated)	42 (6.0)	12 (6.4)	30 (5.8)
Depression	23 (3.3)	9 (4.8)	14 (2.7)
CRS with or without polyps	11 (1.6)	5 (2.7)	6 (1.2)
Heart problems	8 (1.1)	2 (1.1)	6 (1.2)
Diabetes (insulin-dependent)	8 (1.1)	4 (2.1)	4 (0.8)
Autoimmune diseases	3 (0.4)	1 (0.5)	2 (0.4)
Respiratory insufficiency	3 (0.4)	2 (1.1)	1 (0.2)
Hypothyroidism (untreated)	2 (0.3)	0 (0)	2 (0.4)
Renal failure	0 (0)	0 (0)	0 (0)
Hepatic insufficiency	0 (0)	0 (0)	0 (0)
Neurological diseases	0 (0)	0 (0)	0 (0)

The percentages are in brackets. Abbreviations: CRS, chronic rhinosinusitis; GERD, gastroesophageal reflux disease; SD, standard deviation.

aphonia throughout the clinical course of the disease (3.7%). The characteristics of patient groups are described in Table 1. There were 70.8% of females, the proportion of females reaching 76.6% in the dysphonic group. The female proportion was significantly higher in the dysphonic group compared to the nondysphonic group ($P = 0.022$). The majority of patients were Caucasian. The percentage of smokers was significantly higher in dysphonic group compared with nondysphonic group ($P = 0.042$). The proportion of allergic patients was similar in both groups. The most prevalent comorbidities were allergic rhinitis, hypertension, and gastroesophageal reflux disease.

The prevalence of general symptoms in both groups is available in Table 2. Patients with dysphonia had a higher proportion of systemic symptoms compared with nondysphonic patients, including cough, chest pain, sticky sputum, arthralgia, diarrhea, headache, fatigue, nausea, and vomiting (Figure 1).

Symptoms are described in Table 3. According to NHNES questions, the total and partial losses of smell concerned 128 (68.1%) and 20 (10.6%) dysphonic patients, respectively. In the group of nondysphonic patients, there were 369 (71.8%) and 66 (12.8%) individuals with total and partial losses of smell, respectively. As reported in Table 3, dysphonic patients had higher proportions of dyspnea, dysphagia, ear pain, face pain, throat pain, and nasal obstruction compared with nondysphonic individuals. The severity of dysphonia was significantly associated with the severity

TABLE 2.
Prevalence of General Symptoms in Dysphonic and Nondysphonic Patients

Symptoms	Patients (n = 702)	Dysphonic (n = 188)	Nondysphonic (n = 514)
Fever	287 (40.9)	89 (47.3)	198 (38.5)
Cough	351 (50.0)	119 (63.3)	232 (45.1)
Chest pain	179 (25.5)	64 (34.0)	115 (22.4)
Loss of appetite	263 (37.5)	92 (48.9)	171 (333)
Sticky Sputum	47 (6.7)	22 (11.7)	25 (4.9)
Arthralgia	181 (25.8)	71 (37.8)	110 (21.4)
Myalgia	371 (52.9)	108 (57.5)	263 (51.2)
Diarrhea	213 (30.3)	71 (37.8)	142 (27.6)
Abdominal pain	113 (16.1)	40 (21.3)	73 (14.2)
Nausea/vomiting	108 (15.4)	39 (20.7)	69 (13.4)
Headache	447 (63.7)	143 (76.1)	304 (59.1)
Asthenia	519 (73.9)	161 (85.6)	358 (69.6)

The percentages are in brackets.
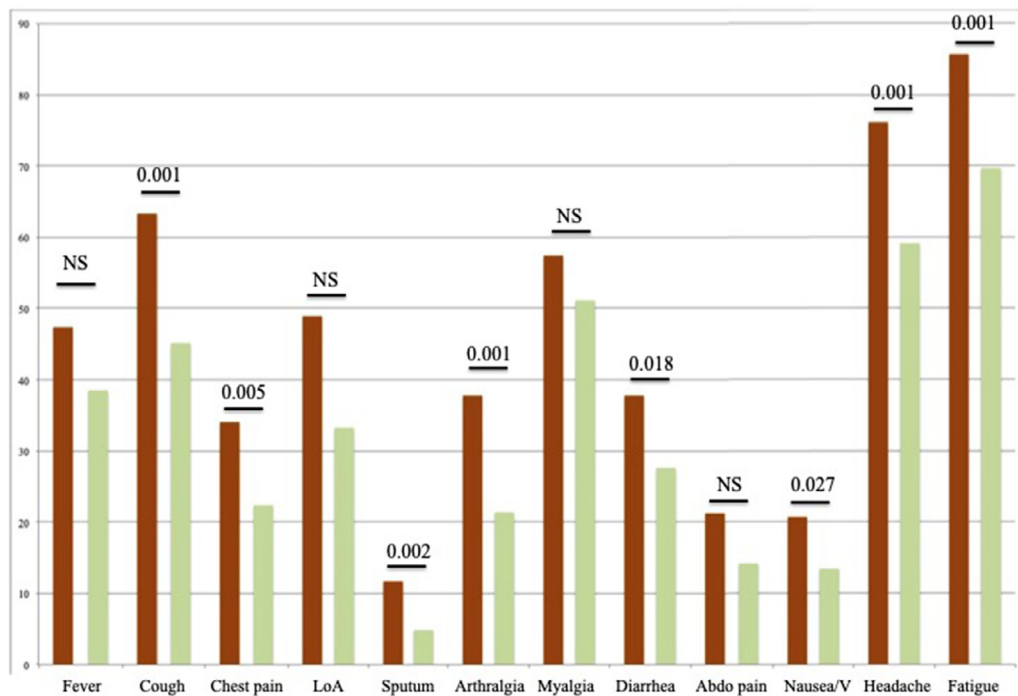
FIGURE 1. The Proportions of general symptoms in dysphonic and nondysphonic patients.
The ordinate axis consists of the prevalence of symptoms (percentages). Dysphonic Patients are represented in orange, nondysphonic are in green. Abbreviations: Abdo pain, Abdominal pain; LoA, loss of appetite; V, vomiting.

of dysphagia. A significant positive association was found between dysphonia and cough.

DISCUSSION

The spread of COVID-19 in Europe led to the emergence of an otolaryngological clinical picture of the infection, which is mainly associated with loss of smell and taste. However, many other otolaryngological symptoms could be prevalent in COVID-19. The self-reported dysphonia could concern a quarter of COVID-19 patients.

Dysphonia is encountered in less than 20% of common viral infections such as common cold or flu.[9,10] Naturally, the prevalence of dysphonia in COVID-19 remains lower

TABLE 3.
Severity of Ear, Nose, and Throat Symptoms in Patients With or Without Dysphonia

| Ear, nose & throat Symptoms	0 = No Problem		1 = Very Mild Problem		2 = Mild/Slight Problem		3 = Moderate Problem		4 = Severe Problem		P-value
	Dysphonic	Nondysphonic	Dysphonic	Nondysphonic	Dysphonic	Nondysphonic	Dysphonic	Nondysphonic	Dysphonic	Nondysphonic	
Nasal obstruction	48 (25.5)	205 (39.9)	50 (26.6)	146 (28.4)	51 (27.1)	87 (16.9)	26 (13.8)	57 (11.1)	13 (6.9)	19 (3.7)	0.008
Rhinorrhea	74 (39.4)	240 (46.7)	68 (36.2)	179 (34.8)	28 (14.9)	67 (13.0)	15 (8.0)	27 (5.3)	3 (1.6)	1 (0.2)	NS
Postnasal drip	95 (50.5)	309 (60.1)	50 (27.6)	112 (21.8)	23 (12.2)	67 (13.0)	18 (9.6)	24 (4.7)	2 (1.1)	2 (0.4)	NS
Throat pain	76 (40.4)	301 (58.6)	53 (28.2)	141 (27.4)	39 (20.7)	47 (9.1)	12 (6.4)	22 (4.3)	8 (4.3)	3 (0.6)	<0.001
Facial pain	98 (52.1)	343 (66.7)	28 (14.9)	75 (14.6)	22 (11.7)	47 (9.1)	31 (16.5)	39 (7.6)	9 (4.8)	10 (2.0)	<0.001
Ear pain	114 (60.6)	409 (79.6)	47 (25.0)	74 (14.4)	15 (8.0)	20 (3.9)	9 (4.8)	11 (2.1)	3 (1.6)	0 (0)	<0.001
Dysphagia	131 (69.7)	453 (88.1)	35 (18.6)	43 (8.4)	13 (6.9)	13 (2.5)	8 (4.3)	5 (1.0)	1 (0.5)	0 (0)	<0.001
Dyspnea	76 (40.4)	306 (59.5)	52 (27.7)	124 (24.1)	29 (15.4)	55 (10.7)	21 (11.2)	19 (3.7)	10 (5.3)	10 (2.0)	<0.001

The patients assessed their symptom severity through a 5-point scale (0 to 4).

compared with other common symptoms, such as total loss of smell and taste. However, the place of dysphonia in the diagnosis of the disease and, regarding our results, as part of a more severe clinical presentation of the disease have to be investigated in future studies. The realization of multidimensional investigation of voice in COVID-19 is still challenging regarding the risk of contamination related to the videolaryngostroboscopic examination. Physicians have to keep in mind that COVID-19 patients may develop dysphonia throughout the clinical course of disease as in common viral infection of the upper aerodigestive tract mucosa.

Dysphonia could be likely related to laryngeal involvement by the airway inflammatory process and may be caused by vocal fold edema or inflammation. However, the etiology of dysphonia in COVID-19 patients needs to be investigated. An ongoing study conducted in the Anatomy Department of University of Mons observed that vocal folds were associated with a high expression of angiotensin-converting enzyme 2 (ACE2), which is the COVID-19 receptor (Figure 2) (No published data). These preliminary data could strengthen the corditis etiology of dysphonia related to COVID-19; ACE2 being present in epithelia of the lung, small intestine, vascular endothelium, and oral cavity.[11,12] Studies about the expression of ACE2 receptor by laryngeal cells would provide interesting findings to clarify the pathogenesis of dysphonia in patients affected by COVID-19. Moreover, regarding the ACE2 expression in lung, abdominal, and chest muscles,[13] it could be conceivable that muscle or lung virus-related impairments may lead to dysphonia. As for the ACE2 expression in laryngeal tissue, this hypothesis has to be investigated in future studies.

Another issue that could be studied concerns the impact of gender in the voice-related presentation of COVID-19. Indeed, female could be most at risk of dysphonia in COVID-19, which could involve gender-related difference in the inflammatory process.[14] The future studies have to be conducted in the context of potential hormonal and gender differences in the expression of ACE2, in the inflammatory process and, therefore, the clinical presentation of the disease.[7,15]

This study is a preliminary epidemiological study investigating potential association between COVID-19 and the development of dysphonia. Many limitations have to be addressed. First, the lack of video-laryngostroboscopical examination of dysphonic patients limits us in the characterization of the dysphonia. Due to the sanitary situation, it is however discouraged to perform such examinations in COVID-19 patients. Second, many confounding factors might have occurred such as the occurrence of co-infection by COVID-19 and other virus (influenza), potentiating the risk to develop inflammation in the upper aerodigestive tract mucosa and dysphonia, the stress of patients and the stress-related risk to develop laryngopharyngeal reflux, and the occurrence of seasonal allergies with laryngopharyngeal symptoms.
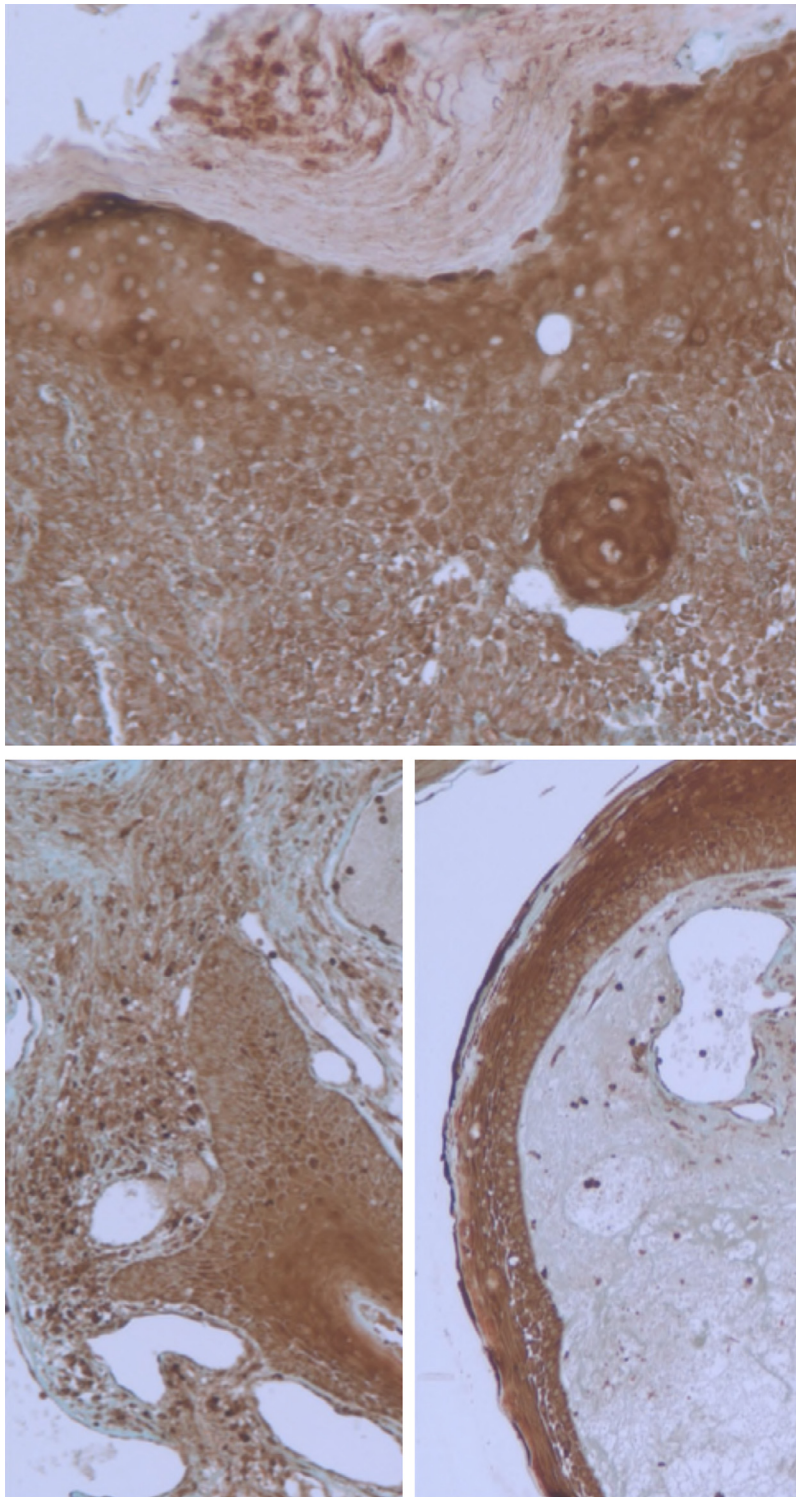
FIGURE 2. Angiotensin converting enzyme-2 (ACE2) expression in vocal folds.
The immunohistochemistry analysis found a high expression of ACE2 in vocal fold tissues of healthy human (ongoing study - unpublished data). Ampliation: 1/100.

CONCLUSION

Dysphonia was encountered in 26.8% of patients with mild-to-moderate COVID-19 and could be added to the symptom list of COVID-19. Dysphonia may appear in patients with a more severe clinical COVID-19 presentation. Only 3.7% of patients reported severe dysphonia characterized by aphonia. Future studies are needed to investigate the relevance of dysphonia in the COVID-19 clinical presentation.

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