

Persistent Dysphonia in Hospitalized COVID-19 Patients

*Carlos Leis-Cofiño, *Paula Arriero-Sánchez, †Ramón González-Herranz, †Óscar Arenas-Brítez, †Estefanía Hernández-García, and †Guillermo Plaza, *†‡Fuenlabrada, Spain

Summary: Introduction. The main objective of this study is to estimate the prevalence of persistent dysphonia in hospitalised COVID-19 patients.

Methods. Data were collected from those COVID-19 patients who, during the months of March to April 2020, were hospitalised in ward or intensive care unit at the University Hospital of Fuenlabrada. Patients with dysphonia prior to SARS-CoV-2 were excluded. Informed consent was obtained orally by a telephone call, as well as clinical and epidemiological data. Patients who reported persistent dysphonia were assessed using the Voice Handicap Index 10, the maximum phonation time, the s/z ratio and a fibrolaryngoscope examination. Patients who reported persistent dysphagia were assessed with the Eating Assessment Tool 10.

Results. A total of 79 patients were included in the study (48 men and 31 women). 10 ICU patients (25%) and 4 ward patients (10,3%) had dysphonia at least 3 months after hospital discharge, but no association was found between ICU admission and the presence of persistent dysphonia ($P = 0.139$). Persistent dysphonia in patients admitted to the ICU is associated with persistent dysphagia ($P = 0.002$), also the age of patients with persistent dysphonia is significantly higher than the age of non-dysphonic patients ($P = 0.046$). The most frequent exploratory finding was vocal cord paresis/paralysis (60.4%).

Conclusion. This is one of the first studies to show that persistence of dysphonia may be a consequence of COVID-19, so further studies are needed to assess the evolution and prognosis of these patients and the possible association of dysphonia with the severity of the disease.

Key Words: Dysphonia—COVID-19—Voice—ENT—Coronavirus—Dysphagia.

INTRODUCTION

COVID-19 is a disease with a broad clinical spectrum, ranging from asymptomatic forms to severe forms leading to severe acute respiratory syndrome. It is estimated that prevalence of asymptomatic forms is 40–45% and they are capable of transmitting the disease.¹ Most symptomatic cases are mild to moderate.^{2,3} One of the most frequent otorhinolaryngological complications of COVID-19 according to Özçelik Korkmaz et al⁴ is dysphonia with a frequency of 19.8%. Dysphonia in relation to COVID-19 has been associated with mechanical ventilation and cough, and a significant association between the severity of dysphonia and dysphagia has been observed.⁵

The main objective of this study is to estimate the prevalence of persistent dysphonia in hospitalised COVID-19 patients. The secondary objectives are to describe the exploratory findings found in patients with persistent dysphonia and to assess the association between the presence of dysphonia and dysphagia.

METHODS

This study was approved in November 2020 by the Ethical Committee of the University Hospital of Fuenlabrada. Data were collected from those COVID-19 patients who, during the months of March to April 2020, were hospitalised in ward or intensive care unit (ICU) at the University Hospital of Fuenlabrada. The following inclusion criteria were used: patient ≥ 18 years of age, PCR-confirmed diagnosis of SARS-CoV-2, ≥ 3 months after discharge and acceptance of informed consent. Patients with dysphonia prior to SARS-CoV-2 were excluded. The following clinical and epidemiological data were considered: age, sex, smoking, cardiovascular risk factors, duration of admission, orotracheal intubation (OTI) and its duration, tracheotomy and its duration, dysphonia, dysphagia and use of inhaled corticosteroids and angiotensin converting enzyme (ACE) inhibitors. Patients who reported persistent dysphonia were assessed using the Voice Handicap Index (VHI) 10, the maximum phonation time (MPT), the s/z ratio and a fibrolaryngoscope examination. The fibrolaryngoscope examination was performed by three different specialists from the Voice Unit of the Department of Otorhinolaryngology. All recordings were evaluated by the same author to confirm the diagnosis. Glottic insufficiency was assessed by stroboscopy and the s/z ratio values (s/z ratio values greater than 1.4 were considered pathological). Patients who reported persistent dysphagia were assessed with the Eating Assessment Tool (EAT) 10.

Two samples of patients were obtained, one of those hospitalised in ICU and the other of those hospitalised in ward. To select ward patients, simple random sample was carried out using Excel. Informed consent was obtained orally by a telephone call, as well as clinical and epidemiological data,

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Declaration of interest: None.

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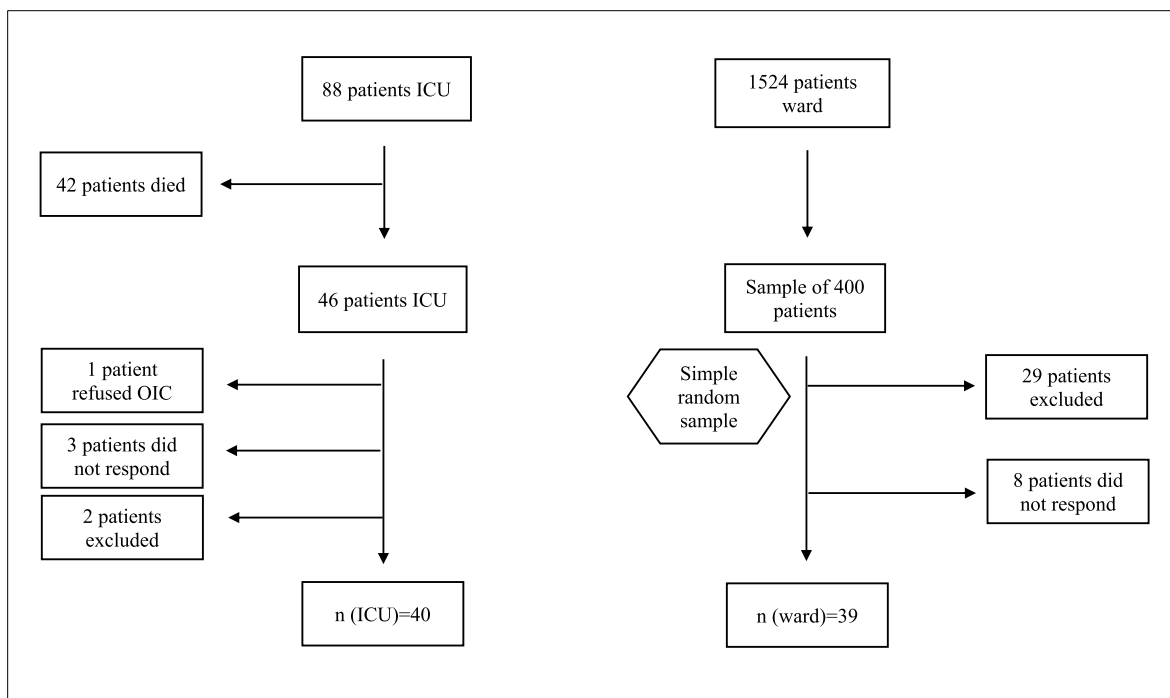
From the *Hospital Universitario de Fuenlabrada, Universidad Rey Juan Carlos, Fuenlabrada, Madrid, Spain; †Hospital Universitario de Fuenlabrada, Department of Otorhinolaryngology, Fuenlabrada, Madrid, Spain; and the ‡Hospital Universitario de Fuenlabrada, Department of Otorhinolaryngology, Universidad Rey Juan Carlos, Fuenlabrada, Madrid, Spain.

Address correspondence and reprint requests to Carlos Leis-Cofiño, Hospital Universitario de Fuenlabrada, Universidad Rey Juan Carlos, Camino del Molino, 2, Fuenlabrada, Madrid 28942, Spain. E-mail: carlosleis2402@gmail.com

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Abbreviation: OIC (oral informed consent)

FIGURE 1. Sample selection process. OIC, oral informed consent.

which were checked using the medical record. ICU and ward samples were paired by age and previous diseases. The sample selection process is depicted in Figure 1. Once anonymised, the data collected were included in a database.

The statistical analysis was performed using SPSS v27 programme. A descriptive analysis of all variables was carried out using the appropriate statistical tools in each case. Qualitative variables were given as numbers and percentages and quantitative variables as mean and standard deviation or median plus interquartile range. Chi-square test was used for comparing qualitative variables and the Mann-Whitney U-test for comparing qualitative and quantitative variables. In cases where the sample size was not large enough to perform Chi-square, Fisher's exact test or calculation of exact bilateral significance (instead of asymptotic significance) was used. A P value <0.05 was considered statistically significant.

RESULTS

A total of 79 patients were included in the study (48 men and 31 women). Male patients were younger than female patients, although no significant differences were found ($P = 0.623$). No significant differences in age were found between patients admitted to the ICU and those admitted to the ward ($P = 0.064$).

The clinical and epidemiological characteristics of patients admitted to the ICU are shown in Table 2. In the group of patients with persistent dysphonia admitted to the ICU ($n = 10$) the median age was 64.5 years (interquartile range, 58.5-69.25), a higher percentage of women (60%)

than men (40%) was observed, the mean duration of admission was 41.30 ± 14.97 days, of which 18.5 days (interquartile range, 13-23.5) were in the ICU; 100% of patients required OTI with a mean duration of 15.70 ± 6.27 days, no patient underwent tracheotomy and the most frequent cardiovascular risk factor was obesity (80%). Persistent dysphonia in patients admitted to the ICU is associated with persistent dysphagia ($P = 0.002$), also the age of patients with persistent dysphonia is significantly higher than the age of non-dysphonic patients ($P = 0.046$). There is a higher frequency of persistent dysphonia in patients admitted to the ICU (71.4%) compared to ward patients (28.6%), but no statistically significant association was found between admission to the ICU and persistent dysphonia ($P = 0.139$) (Table 1).

The clinical and epidemiological characteristics of patients admitted to the ward are shown in Table 3. In the group of patients with persistent dysphonia admitted to the ward ($n = 4$) the mean age was 56.75 ± 18.14 years, a higher percentage of women (75%) than men (25%) was observed, the median duration of admission was 7 days (interquartile range, 3-16.25) and the most frequent cardiovascular risk factor were obesity, arterial hypertension and dyslipidaemia (50%).

The clinical and epidemiological data and exploratory findings of patients with persistent dysphonia are listed in Tables 1 and 4. The most frequent exploratory finding was vocal cord paresis/paralysis (64.3%), followed by atrophy (28.6%) and granuloma (7.1%), one patient (7.1%) had no lesions on fibrolaryngoscopy; distinguishing between ICU and ward, the most frequent finding in those admitted to

TABLE 1.
Characteristics and Frequency of Acute Dysphonia and Persistent Dysphonia in Hospitalised COVID-19 Patients

	Patients (N = 79)	Persistent Dysphonia(n = 14)	P value	No Persistent Dysphonia(n = 65)
Age	64 [54-71]	64.5 [58.5-69.25]	-	63 [53.5-72]
Gender			-	
Female	31 (39.2%)	9 (64.3%)		22 (33.8%)
Male	48 (60.8%)	5 (35.7%)		43 (66.2%)
BMI (kg/m ²)			-	
18.5-24.9	11 (13.9%)	0 (0.0%)		11 (16.9%)
25.0-29.9	22 (27.8%)	2 (14.3%)		20 (30.8%)
≥30	37 (46.8%)	10 (71.4%)		27 (41.5%)
Unknown	9 (11.4%)	2 (14.3%)		7 (10.8%)
Diabetes Mellitus	20 (25.3%)	3 (21.4%)	-	17 (26.2%)
Arterial hypertension	43 (54.4%)	8 (57.1%)	-	35 (53.8%)
Dyslipidaemia	41 (51.9%)	4 (28.6%)	-	37 (56.9%)
Smoking			-	
Non-smoker	39 (49.4%)	9 (64.3%)		30 (46.2%)
(Ex-)Smoker	40 (50.6%)	5 (35.7%)		35 (53.8%)
Pack-year	38 [15.25-51.75]	34.5 [20.63-81.38]		38 [12.75-51.75]
Duration of admission (days)	18 [10-36]	32.00 ± 20.01	-	16 [9.5-35.5]
ICU	40 (50.6%)	10 (71.4%)	0.139*	30 (46.2%)
Days of ICU	14.5 [10-23.75]	18.5 [13-23.5]		14 [9.5-24.5]
Acute dysphonia	24 (30.3%)	14 (100%)		10 (15.4%)
Acute dysphagia	8 (10.1%)	6 (42.9%)		2 (3.1%)
Persistent	7 (8.9%)	6 (42.9%)	-	1 (1.5%)
Usual treatment				
Inhaled corticosteroids	10 (12.7%)	2 (14.3%)	-	8 (12.3%)
ACE inhibitors	21 (26.6%)	4 (28.6%)	-	17 (26.2%)

Notes: N (percentage). Mean ± Standard deviation. Median [interquartile range].

* Fisher's exact test. Abbreviation: BMI, Body Mass Index.

ICU was paresis, while in those admitted to ward it was atrophy. The vocal cords were most frequently affected unilaterally (50%). No patient with persistent dysphonia was smoker, but 5 (35.7%) of them were former smokers with a median pack-year of 34.5 (interquartile range, 21-81.38). The MPT values and the s/z ratio show that 28.57% of the patients had glottic insufficiency. The median VHI 10 was 13 (interquartile range, 7.5-26.75). 6 patients (42.9%) had persistent dysphagia with a median EAT-10 of 15.5 (interquartile range, 10-24.5). Male patients were younger than female patients, although no statistically significant differences were found ($P = 1.000$). No significant differences were found between the age of patients admitted to the ICU and those admitted to the ward ($P = 0.733$).

DISCUSSION

This study shows a prevalence of persistent dysphonia of 25% in hospitalised COVID-19 patients admitted to the ICU and 10.3% in patients admitted to the ward. Reviewing the available literature, there are no studies that assess the persistence of this symptom at least 3 months after hospital discharge. In a previous study by Cantarella et al⁶ in a sample of non-hospitalised patients,

it was observed that in 15% of patients dysphonia lasted more than 1 month.

The aetiology of dysphonia and its permanence in these patients is unknown, but it may be due to multiple causes. On the one hand, 100% of patients with persistent dysphonia admitted to the ICU underwent OTI, which is a potential cause of airway injury, dysphonia and dysphagia.^{9,10} Laryngeal injury is a frequent consequence of OTI and is exacerbated with its duration; one of the most common injuries is vocal cord paralysis,^{7,8} which is usually unilateral and of the left vocal cord due to fixation of the endotracheal tube in the right corner of the mouth.⁹ The risk of vocal cord paralysis after OTI increases with age over 50 years, diabetes mellitus and arterial hypertension.^{8,9} The most widely accepted mechanism of paralysis is compression of the recurrent laryngeal nerve.¹¹

On the other hand, in our study no patient with persistent dysphonia underwent tracheotomy. Although there is wide disparity between studies on the benefits of early tracheotomy and the definition of prolonged mechanical ventilation,¹² Bishop et al¹³ observed in an animal model that laryngeal injury due to OTI reached its maximum severity between days 1 and 7, thereafter there was no relationship with duration. Despite the results of this study, during the COVID-19

TABLE 2.
Characteristics of Patients Admitted to the ICU

	ICU Patients (N = 40)	Persistent Dysphonia (n = 10)	P value	No Persistent Dysphonia (n = 30)
Age	62.5 [52.5-66.75]	64.5 [58.5-69.25]	0.046[†]	60 [51.75-66]
Gender			0.159*	
Female	16 (40.0%)	6 (60.0%)		10 (33.3%)
Male	24 (60.0%)	4 (40.0%)		20 (66.7%)
BMI (kg/m ²)			0.618 ^{‡,§}	
18.5-24.9	5 (12.5%)	0 (0.0%)		5 (16.7%)
25-29.9	4 (10.0%)	1 (10.0%)		3 (10.0%)
≥30	26 (65.0%)	8 (80.0%)		18 (60.0%)
Unknown	5 (12.5%)	1 (10.0%)		4 (13.3%)
Diabetes mellitus	11 (27.5%)	3 (30.0%)	1.000*	8 (26.7%)
Arterial hypertension	20 (50.0%)	6 (60.0%)	0.716*	14 (46.7%)
Dyslipidaemia	18 (45.0%)	2 (20.0%)	0.082*	16 (53.3%)
Smoking			0.471*	
Non-smoker	23 (57.5%)	7 (70.0%)		16 (53.3%)
(Ex-)Smoker	17 (42.5%)	3 (30.0%)		14 (46.7%)
Pack-year	40.5 [20-56.88]	56.50 ± 50.91	0.549 [†]	39.63 ± 23.57
Duration of admission (days)	37.85 ± 18.22	41.30 ± 14.97	0.414 [†]	36.70 ± 19.27
OTI	38 (95.0%)	10 (100%)	0.077*	28 (93.3%)
Days of OTI	12.73 ± 5.85	15.70 ± 6.27	0.084 [†]	11.63 ± 5.39
Tracheotomy	8 (10.1%)	0 (0.0%)	0.338*	8 (12.3%)
Days of tracheotomy	12.25 ± 3.20	-	-	12.25 ± 3.20
Acute dysphonia	15 (37.5%)	10 (100%)		5 (16.7%)
Acute dysphagia	7 (17.5%)	5 (50.0%)		2 (6.7%)
Persistent	6 (15.0%)	5 (50.0%)	0.002^{‡,§}	1 (3.3%)
Usual treatment				
Inhaled corticosteroids	4 (10.0%)	0 (0.0%)	0.556*	4 (13.3%)
ACE inhibitors	14 (35.0%)	4 (40.0%)	0.718*	10 (33.3%)

Notes: N (percentage). Mean ± Standard deviation. Median [interquartile range].

* Fisher's exact test.

† Mann Whitney U test.

‡ Chi square test.

§ Calculation of exact bilateral significance instead of asymptotic significance.

pandemic many authors have concurred in the recommendation to delay tracheostomy until at least day 14¹⁴ to reduce the risk of infection of healthcare workers. In our hospital, a late tracheotomy protocol was followed, taking into consideration the recommendations of the majority of guidelines.¹⁵ The decision to perform a tracheotomy was made by consensus between intensive care professionals, anaesthesiologists and otorhinolaryngologists. This decision was individualised for each patient, taking into consideration whether the weaning objectives were met.¹⁵ Tracheotomies were performed 17 days on average from the start of OTI and mortality in these patients was lower compared to those not tracheostomised.¹⁵ These data could explain the high prevalence of persistent dysphonia in ICU patients found in our study, despite we did not find a significant association between dysphonia, OTI and its duration, which could be due to the small sample.

Another possible aetiology is corditis caused by the presence of SARS-CoV-2 in the larynx. Studies have shown the presence of the ACE-2 receptor in the larynx, including the vocal cords,^{16,17} which is the SARS-CoV-2 receptor.¹⁸ Acute dysphonia as a symptom of COVID-19 may be due to direct entry of SARS-CoV-2 into laryngeal cells, leading to laryngeal and vocal cord inflammation.⁵ However, we have not found signs indicative of corditis in patients with persistent dysphonia. According to Lechien et al,⁵ infection-related dysfunction of the lung and thoracoabdominal musculature could also lead to dysphonia, as the ACE-2 receptor is also expressed in these regions.

There are reported cases of vagus and glossopharyngeal nerve neuropathy in patients with COVID-19,¹⁹ and post-viral vagal neuropathy is postulated as a possible aetiology of dysphonia in these patients,²⁰ which could explain

TABLE 3.
Characteristics of Patients Admitted to the Ward

	Ward Patients (N = 39)	Persistent Dysphonia (n = 4)	P value	No Persistent Dysphonia (n = 35)
Age	69 [57-76]	56.75 ± 18.14	0.249 [†]	69 [57-76]
Gender			0.279*	
Women	15 (38.5%)	3 (75.0%)		12 (34.3%)
Male	24 (61.5%)	1 (25.0%)		23 (65.7%)
BMI (kg/m ²)			0.350 ^{†,§}	
18.5-24.9	6 (15.4%)	0 (0.0%)		6 (17.1%)
25-29.9	18 (46.1%)	1 (25.0%)		17 (48.6%)
≥30	11 (28.2%)	2 (50.0%)		9 (25.7%)
Unknown	4 (10.3%)	1 (25.0%)		3 (8.6%)
Diabetes Mellitus	9 (23.1%)	0 (0.0%)	0.556*	9 (25.7%)
Arterial hypertension	24 (61.5%)	2 (50.0%)	1.000*	21 (60.0%)
Dyslipidaemia	23 (59.0%)	2 (50.0%)	1.000*	21 (60.0%)
Smoking			1.000*	
Non-smoker	16 (41.0%)	2 (50.0%)		14 (40.0%)
(Ex-)Smoker	23 (59.0%)	2 (50.0%)		21 (60.0%)
Pack-year	31 [10.5-51]	34.50 ± 19.09	0.791 [†]	31 [10.25-55.5]
Duration of admission (days)	10 [7-15]	7 [3-16.25]	0.212 [†]	10 [8-15]
Acute dysphonia	9 (23.1%)	4 (100%)	-	5 (14.3%)
Acute dysphagia	1 (2.6%)	1 (25.0%)	-	0 (0.0%)
Persistent	1 (2.6%)	1 (25.0%)	0.103*	0 (0.0%)
Usual treatment				
Inhaled corticosteroids	6 (15.4%)	2 (50.0%)	0.104*	4 (11.4%)
ACE inhibitors	7 (17.9%)	0 (0.0%)	1.000*	7 (20.0%)

Notes: N (percentage). Mean ± Standard deviation. Median [interquartile range].

* Fisher's exact test.

† Chi square test.

‡ Mann Whitney U test.

§ Calculation of exact bilateral significance instead of asymptotic significance.

persistent dysphonia and its association with the permanence of dysphagia in ICU patients, as well as the fibrolaryngoscopic findings. Coronaviruses are neurotropic and can induce neuronal injury mainly in the most severe patients.^{11,21} Three main mechanisms have been proposed to explain the neurological disease in these patients: cardio-respiratory failure and metabolic abnormalities triggered by the infection, direct invasion of the nervous system and an autoimmune response to the virus.²² It appears that the

autoimmune response may be due to shared amino acid sequences between SARS-CoV-2 and human antigens, such as heat shock proteins.²³ In addition, the ACE-2 receptor is also present in both central and peripheral nervous system,²¹ which allows the virus to invade it, mainly via two pathways: retrograde axonal transport and the haematogenous pathway.²⁴

The most frequent finding on fibrolaryngoscopic examination in patients with persistent dysphonia was paresis and

TABLE 4.
Exploratory Findings in Patients With Persistent Dysphonia

	Age	Gender	Smoking (p-y)	ICU (days)	OTI (days)	Tracheotomy (days)	Fibrolaryngoscopy Findings	Vocal Cord	MPT (sec)	S/Z	VHI 10	Dysphagia	EAT 10	Inhaled Corticosteroids	ACE Inhibitors
Patient 1	48	M	No	Yes (25)	Yes (21)	No	Paresis	Left	4	1.25	13	Yes	14	No	Yes
Patient 2	67	M	Ex (92.5)	Yes (35)	Yes (26)	No	Paralysis	Right	4	4.25	12	Yes	10	No	Yes
Patient 3	64	F	No	Yes (21)	Yes (19)	No	Paresis	Right	6	1.7	6	No	-	No	Yes
Patient 4	65	F	Ex (21)	Yes (23)	Yes (18)	No	Paresis	Bilateral	3	2	36	Yes	17	No	No
Patient 5	74	M	No	Yes (21)	Yes (21)	No	Paralysis	Bilateral	*	*	14	No	-	No	No
Patient 6	62	F	Ex (?)	Yes (14)	Yes (9)	No	Paresis	Right	6	1	8	No	-	No	No
Patient 7	64	F	No	Yes (14)	Yes (13)	No	Paresis	Right	10	0.9	25	Yes	23	No	No
Patient 8	63	F	No	Yes (8)	Yes (7)	No	Paresis + Atrophy	Right	7	1.14	32	Yes	29	No	No
Patient 9	70	M	No	Yes (10)	Yes (9)	No	Granuloma	Left	*	*	6	No	-	No	No
Patient 10	69	F	No	Yes (16)	Yes (14)	No	No injuries	-	7	1	13	No	-	No	Yes
Patient 11	68	F	No	No	No	No	Atrophy	Left	17	1.06	4	No	-	Yes	No
Patient 12	45	F	Ex (21)	No	No	No	Atrophy	Bilateral	11	5.5	32	No	-	Yes	No
Patient 13	38	M	No	No	No	No	Atrophy	Bilateral	†	†	14	No	-	No	No
Patient 14	76	F	Ex (48)	No	No	No	Atrophy	Left	9	0.44	13	Yes	10	No	No

* Treated before the start of this study, so these data are not assessable.

† Did not attend the consultation. Abbreviations: M, male; F, female; Ex, Ex-smoker; ?, unknown; p-y, pack-year.

paralysis (60.4%), which could be explained by both mechanical ventilation techniques and the infection itself. In addition to the tests performed in this study, some patients with persistent dysphonia and vocal cord paralysis or paresis underwent laryngeal electromyography where reinnervation potentials were observed, an evidence of possible reversibility of the paresis and paralysis found. In one patient a vocal granuloma was found, a lesion associated with intubation.⁸ Two patients presented bilateral vocal cord atrophy, this lesion may be related to both the infection and the intake of inhaled corticosteroids, due to the local deposition of this drug, which can lead to mucosal atrophy and myopathy of the intrinsic laryngeal muscles.^{25,26} A single patient had no lesions on examination, probably due to functional dysphonia (dysregulation of laryngeal muscle activity in the absence of neurological or structural lesions), which is the most common laryngeal pathology that causes dysphonia.²⁷ There are also described cases of psychogenic dysphonia due to COVID-19 that could justify it, as it has been shown that viral infection can trigger psychiatric symptoms due to the inflammatory response.²⁸

Although there are numerous confounding factors such as OTI or inhaled glucocorticoids which are recognised as possible causes of dysphonia, it is possible that the virus is involved in the pathogenesis of dysphonia in some patients, as the fact that there are two dysphonic patients who have not received any treatment that causes this symptom supports the hypothesis that the virus is capable of producing it by various mechanisms that are not yet well established. Despite few patients present with persistent dysphonia without having received any of these treatments, this may be due to the small sample size. However, the aetiology of dysphonia in these patients is likely to be multifactorial and not due to a single cause.

There are several limitations present in this study. Firstly, there may be a recall bias, which we tried to correct by completing and cross-checking the data with the medical records. Secondly, some medical records are missing data such as BMI, so these data are considered as missing values. Thirdly, some patients had already been treated and the MPT and s/z ratio were not present in the medical records and could not be performed currently, as they would not be assessable due to the treatment. Fourthly, there may be a survival bias, due to the high lethality of the disease in ICU patients, which may lead to an underestimation of the frequency of dysphonia. Finally, the study design does not allow to distinguish whether the cause of dysphonia is the virus itself or the different treatments such as OTI, inhaled glucocorticoids or tracheostomy, which act as confounding factors.

CONCLUSION

Dysphonia at least 3 months after hospital discharge is found in 25% of patients admitted to the ICU and 10.3% of patients admitted to the ward, and correlates with persistence of dysphagia in those admitted to the ICU. The most

frequent findings in fibrolaryngoscopy are vocal cord paresis in those admitted to the ICU and vocal cord atrophy in those admitted to the ward, these observations justify the persistence of the symptom. This is one of the first studies to show that persistence of dysphonia may be a consequence of COVID-19, so further studies are needed to assess the evolution and prognosis of these patients and the possible association of dysphonia with the severity of the disease. Studies will also be needed to clarify the aetiology of dysphonia in COVID-19 patients.

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