

Brief Report

Postacute Laryngeal Injuries and Dysfunctions in COVID-19 Patients: A Scoping Review

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Abstract: Objective: To investigate postacute laryngeal injuries and dysfunctions (PLID) in coronavirus disease 2019 (COVID-19) patients. **Methods:** Three independent investigators performed a systematic review of the current literature studying PLID in patients with a history of COVID-19. The review was performed according to PRISMA Statement. Epidemiological, clinical, hospitalization features, laryngeal diseases and voice outcomes were extracted from the included papers. **Results:** Eight papers met our inclusion criteria (393 patients) corresponding to 5 uncontrolled prospective and 3 retrospective studies. The most prevalent PLID were vocal fold dysmotility (65%), vocal fold edema (35%), laryngopharyngeal reflux (21%), and muscle tension dysphonia (21%). Posterior glottic stenosis (12%), granuloma (14%), and posterior glottic diastasis (12%) were the most common injuries. Most patients with PLID were obese and had a history of intensive care unit hospitalization, and orotracheal intubation. The delay between the discharge and the laryngology office consultation ranged from 51 to 122 days. The mean duration of intubation ranged from 10 to 34 days. Seventy-eight (49%) intubated patients were in prone position. The proportion of patients requiring surgical treatment ranged from 39% to 70% (mean=48%). There was an important heterogeneity between studies about inclusion, exclusion criteria and outcomes. **Conclusion:** COVID-19 appeared to be associated with PLID, especially in patients with a history of intubation. However, future controlled studies are needed to evaluate if intubated COVID-19 patients reported more frequently PLID than patients who were intubated for other conditions.

Keywords: COVID-19; otolaryngology; Larynx; laryngeal; laryngology; intubation; voice; Head Neck; surgery

1. Introduction

Coronavirus disease 2019 (COVID-19) was associated with more than 510 billion cases and 6,200,000 deaths as of May 1, 2022 [1]. According to studies, 5 to 20% of COVID-19 patients had severe-to-critical disease and required mechanical ventilation [2,3]. The proportion of survivors after severe or critical COVID-19 ranges from 20 to 62% regarding world regions [4-6]. The survivor follow-up highlighted that they may keep neurological, psychological and systemic post-discharge sequelae [7].

Precisely, over the past few months, an increasing number of studies suggested that COVID-19 patients may report postacute laryngeal injuries and dysfunctions (PLID), especially after hospitalization in intensive care unit (ICU) [8-12].

The aim of this scoping review was to investigate post-discharge PLID in COVID-19 patients.

2. Materials and Methods

The criteria for consideration of study inclusion were based on the population, intervention, comparison, outcome, timing and setting (PICOTS) framework [13]. Data of study were independently reviewed by three investigators (JRL, SH and MC) who extracted findings according to the PRISMA checklist for systematic reviews [14].

Patient population: Prospective and retrospective, controlled, uncontrolled, or randomized studies published between December 2019 and Mai 2022 were included if authors investigated PLID in COVID-19 patients. Studies only reporting symptom outcomes without laryngeal examination were excluded. Patients should have a positive diagnostic for COVID-19 by reverse transcriptase polymerase chain reaction (RT-PCR) testing or serology. The studies were published in English, Spanish, or French peer-reviewed journals. Case reports were not considered in the analysis. The type of study was classified according to the levels of evidence for prognostic studies (I-V) [15].

Intervention, comparison and outcomes: The following outcomes were reviewed for each study: number of patients; mean age; gender; COVID-19 severity; intubation or tracheostomy history and characteristics; duration of hospitalization; post-discharge laryngeal/voice findings and methods of laryngeal outcome assessment. The Tool to Assess Risk of Bias in Cohort Studies developed by the Clarity Group and Evidence Partners was used by two authors (JRL & SH) for the bias/heterogeneity analyses of the included studies [16]. The bias analysis consisted of evaluation of cofactors that may impact the conclusion of studies.

Timing and Setting: The patients had cured COVID-19 and were discharged from the hospital.

Search strategy: The paper search was conducted with PubMed, Cochrane Library and Scopus databases by three independent laryngologists (JRL, SH and MC). Databases were screened for abstracts and titles referring to the inclusion criteria of the present study. Authors analyzed full texts of the selected publications. The following keywords were considered for the literature search: 'COVID-19'; 'SARS-CoV-2'; 'Larynx'; 'Voice'; 'Laryngeal'; 'Complications'; 'Intubation'; and 'Otolaryngology'.

3. Results

Eight papers met our inclusion criteria, accounting for 393 patients (Figure 1) [8-12,17-19]. Five studies were uncontrolled prospective [8,10,12,17,19] and three publications were retrospective case-series [9,11,18]. Two studies were initially excluded because lack of laryngeal examination. The characteristics of studies are described in Table 1. The mean age of patients ranged from 42 to 63 yo. Patients consisted of individuals with a history of intensive care unit (ICU) hospitalization and orotracheal intubation [9,10,12,19]; non-intubated individuals [17]; or mixed populations [8,11,18]. Inclusion, exclusion criteria and comorbidities of patients are reported in Table 2. Comorbidity data were not reported in one study [17]. Studies included patients with the following

comorbidities: hypertension (N=124/237; 52%); tobacco consumption (N=44/89; 49%); diabetes (N=100/237; 42%); laryngopharyngeal or gastroesophageal reflux disease (N=11/34; 33%); obesity (N=55/207; 27%); asthma (N=15/71; 21%); coronary disease (N=15/88; 17%); COPD (N=13/104; 13%); obstructive sleep apnea syndrome (N=13/122; 11%) and stroke (N=2/25; 8%) (Table 2). Exclusion criteria were specified in four papers, and included patients with laryngeal disorders or dysphonia prior COVID-19 episode and those without confirmation of the COVID-19 diagnosis (RT-PCR, serology) [11,12,17,18]. Azzam *et al.* also excluded patients with voice disorders occurred >1-month post-infection, or with a history of head and neck cancer or trauma [17].

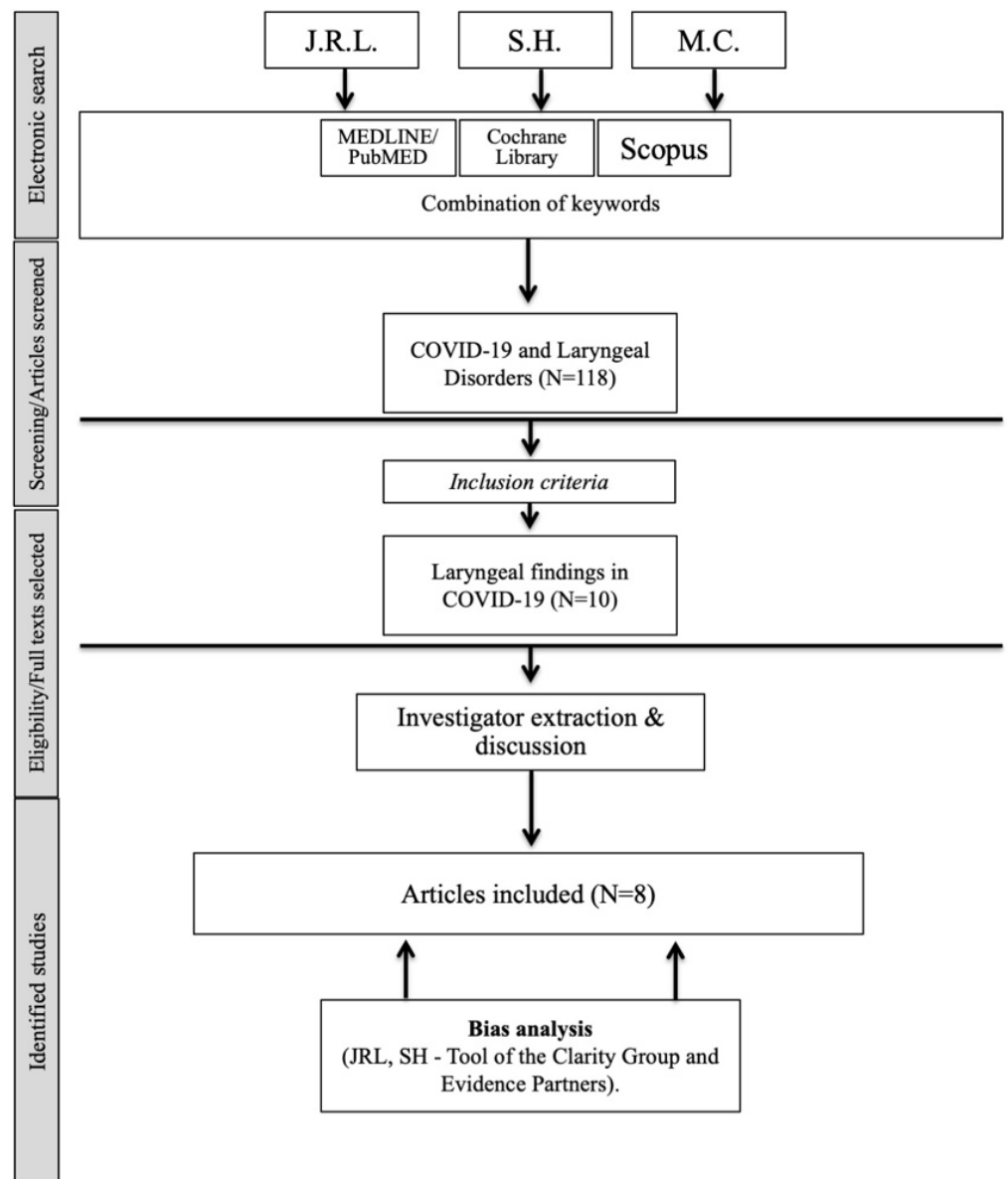


Figure 1. flow chart.

Among patients presenting with voice disorders post-discharge, there were 184 females and 209 males. The mean body mass index was provided in two studies and was elevated (>25) [10,11]. The mean delay

between the discharge and the laryngology office consultation ranged from 51 to 122 days [11,12,17,18,19].

The features of patients who were hospitalized in ICU are presented in Table 1. The mean duration of intubation ranged from 10 to 34 days, while the size of the tube ranged from 7 to 8. Seventy-eight (49%) intubated patients were in prone position during the ICU stay. There were 88/237 patients (37%) with a tracheostomy, which was removed after a mean duration ranging from 16 to 70 days.

Table 1. Studies investigating laryngeal disorders and injuries in COVID-19 patients.

Authors	Study	EL	Population	ICU outcomes	Voice/laryngeal outcomes	Results	Conclusion
Naunheim (8) USA	Prospective Uncontrolled	III	N=13 dysphonic ICU N=7 non-ICU patients Age= 59 yo F/M=5/15 BMI= NP Delay= NP	Intubation (13): 22d Tube size: 7.5 Prone: 9 Tracheostomy: 9 Duration: 16d Proning: NP	Prevalence of disorders Voice-breath Stroboscopy abnormalities Vocal fold immobility Posterior glottic stenosis Subglottis stenosis Posterior glottic diastasis Laryngopharyngeal reflux MTD Intervention need	12 (60)-7 (35) 17 (85) 8 (40) 3 (15) 2 (10) 2 (10) 2 (10) 1 (5) 9 (45)	1. Most patients with dysphonia and history of COVID-19 had history of intubation. The occurrence of laryngeal lesions was found in post-intubated patients. 2. Nine patients required procedural interventions; 4 in operating room.
Scholfield (9) UK	Retrospective Case-series	IV	N=3 post-intubated ICU Age= 49 yo F/M=1/2 BMI=NP Delay= NP	Intubation (3): 34d Tube size: 8 Tracheostomy: 3 Duration: 30d Tube: 7-9 Proning: N.P.	Prevalence of Subglottis stenosis	N=3	1. Subglottis stenosis may occur early in COVID-19 patients who were long-time intubated or tracheotomized.
Sandblom (10) Germany	Prospective Uncontrolled	III	N=25 post-intubated ICU Age= 63 yo F/M= 2/23 BMI= 28 Delay= NP	Intubation (25): 10d Tube size: NP Tracheostomy: 20 Duration: 30d Tube: NP Proning: 12	FEES penetration Vocal fold dysmotility Vocal fold immobility Granuloma Vocal fold hematoma Vocal fold ulceration	23 (96) 19 (76) 2 (8) 2 (8) 1 (4) 1 (4)	1. Vocal fold movement disorders are prevalent in post-intubated patients. 2. There was positive correlation between ICU hospitalization duration and dysphagia severity.
Neevel (11) USA	Retrospective Case-series	IV	N=18 dysphonic ICU N=2 non-ICU patients Age= 50 yo F/M= 12/12 BMI= 29 Delay= 107d	Intubation (18): 14d Tube size: 8 Tracheostomy: 10 Duration: 18d Tube: NP Proning: 10	V-RQOL score (N=14) Intubated patients (N=18): VF motion impairments VF edema/erosion Subglottis stenosis Posterior glottic diastasis Posterior glottic stenosis Unilateral VF immobility	73 9 (50) 7 (39) 4 (22) 4 (22) 3 (17) 4 (22)	1. Most patients had multiple chief voice complaints. 2. Intubated patients reported high prevalence of laryngeal injuries. 3. Non-intubated patients reported tension muscle dysphonia (4), glottic edema (1), laryngitis (1), and unilateral VF paresis (1)

					Unilateral VF hypomobility	2 (11)	4.Surgical/medical treatments were
					Bilateral VF hypomobility	3 (17)	made in 10 and 4 patients.
Felix (12)	Prospective Uncontrolled	III	N=95 post-intubated ICU Age= 59 yo F/M= 44/51 BMI= NP Delay= 100d	Intubation (95): 12d Tube size: 7-8 Tracheostomy: 20 Duration: NP Tube: NP Proning: 47	Laryngeal injuries Hyperemia Granuloma Posterior glottic stenosis Unilateral VF immobility	38 (40) 6 (6) 15 (16) 16 (17) 1 (1)	1.Laryngeal injuries were found in 40% of intubated patients. 2.Tube size and prone position were contributing factors of laryngeal injuries.
Azzam (17) Egypt	Prospective Uncontrolled	III	N=106 non-intubated Age= 42 yo F/M= 78/28 BMI= NP Delay= <30d	-	Dysphonia VF edema VF swelling Unilateral VF immobility Ventricular band edema	84 (79) 42 (40) 18 (17) 14 (13) 20 (19)	1. Dysphonia occurred in 79% of mild-to-moderate COVID-19 patients. 2. Various laryngeal findings were found in videostroboscopy.
Allisan (18) USA	Retropective Case-series	IV	Gr1=31 intubated Gr2=50 not intubated Age= 54 yo F/M= 32/49 BMI= NP Delay= 122d	Intubation (31): 17d Tube size: 8 Tracheostomy: 18 Duration: 70d Tube: 7-9 Proning: NP	Disorders Dysphonia MTD LPR VF paresis VF paralysis VF atrophy VF polyp Granuloma Glottis insufficiency Arytenoid ankylosis Posterior/subglottis stenosis Tracheal stenosis	Gr1-2, p-value 20, 38; NS 1-19; S 1-18; S 3-3, NS 5-3, NS 3-6, NS 0-8, NS 8-0, S 4-3, NS 1-5, NS 5-0, NS 5-0, NS	1.COVID-19 may be associated with laryngeal injuries and disorders in intubated and not intubated patients. 2.Granuloma, posterior glottis stenosis, VF paresis and tracheal stenosis were the most prevalent diseases.
Hans (19) France	Prospective Uncontrolled	III	N=43 intubated Age= 52 yo F/M= 10/33 BMI= NP Delay= 51d	Intubation (43): 10d Tube size: NP Tracheostomy: 8 Duration: NP Tube: 7-9 Proning: NP	Posterior glottic stenosis Laryngeal edema Granuloma Laryngeal necrosis Posterior glottic diastasis VF atrophy Subglottis stenosis	14 (33) 10 (23) 8 (19) 2 (5) 2 (5) 2 (5) 1 (2)	1. Posterior glottis stenosis, laryngeal edema and granuloma were the most prevalent laryngeal findings. 2.Prolonged intubation was associated with an increase of laryngeal injuries (posterior stenosis).

Table 1 footnotes: Abbreviations: BMI=body mass index; FEES=fiberoptic endoscopic evaluation of swallowing; EL=evidence level; ICU=intensive care unit; LPR=laryngopharyngeal reflux; M/F=male/female; MTD=Muscle tension dysphonia; NP=not provided; VF=vocal fold; V-RQOL=voice related quality of life; yo=years old

Table 2. Inclusion, exclusion criteria and comorbidities of patients.

Authors	Inclusion	Exclusion	Comorbidities
Naunheim (8)	Voice-related disorder patients	NP	Hypertension (11), Tobacco (9), Diabetes (8), Asthma (4), Obesity (3), OSAS (2), COPD (1)
Scholfield (9)	-	-	Diabetes (2), Obesity (2), Hypertension (2), OSAS (1), LPR (1)
Sandblom (10)	Post-intubated patients with dysphonia	NP	Hypertension (16), Diabetes (11), Obesity (8), OSAS (4), Stroke (2), Coronary disease (6)
Neevel (11)	Dysphonic patients	Dysphonia before COVID-19 No confirmation of COVID-19	Diabetes (9), Hypertension (9), Tobacco history (8), Asthma/COPB (5), Coronary disease (2)
Felix (12)	Post-intubated patients with dysphonia	Dysphonia before COVID-19 No confirmation of COVID-19	Hypertension (52) Diabetes (41) Obesity (28)
Azzam (17)	Mild-to-moderate COVID-19 cases	Dysphonia before COVID-19 No confirmation of COVID-19 >1 month delay post-COVID-19 Severe COVID-19 Laryngeal lesion before COVID-19 Chemo/radiotherapy, Head Neck Trauma or cancer histories	NP
Allisan (18)	Dysphonic patients	Laryngeal disorders before COVID-19	Reflux (10), tobacco (9), Diabetes (9), Asthma (6), Anxiety (6), Obesity (4), Hypertension (4), OSAS (2), COPD (3), Depression (2) Depression (2), Panic disorder (2)
Hans (19)	Post-intubated patients with dysphonia	NP	Hypertension (30), Diabetes (20), Tobacco (18), Dyslipidemia (12), Obesity (10), Coronary disease (7), COPD (4), OSAS (4)

Table 2 footnotes: Abbreviations: COVID-19=coronavirus disease 2019; COPD=chronic obstructive pulmonary disease; LPR=laryngopharyngeal reflux; NP=not provided; OSAS=obstructive sleep apnea syndrome.

Laryngeal abnormalities

Irrespective to the definition and voice quality tools used, dysphonia was found in 70% of patients. Most patients had multiple chiefs of complaints (Table 1). PLID reported in studies are summarized in Table 3. Among COVID-19 patients with dysphonia in the post-discharge follow-up, the most prevalent PLID were vocal fold dysmotility, edema, laryngopharyngeal reflux, and muscle tension dysphonia (Table 3). The most prevalent laryngeal injuries included posterior glottic stenosis, granuloma, posterior glottic diastasis and VF immobility. Sandblom *et al.* reported a positive association between the duration of ICU stay and the severity of swallowing disorders [10]. Among contributing factors, Hans *et al.* reported that prolonged intubation was associated with an increase of laryngeal injuries, e.g. posterior glottic stenosis [19], while Felix *et al.*

observed that intubation tube size and prone position were both factors associated with laryngeal injuries [12].

Some authors reported the need of medical (botox or corticosteroid injections) or surgical (balloon dilatation or laser microsurgery procedures) treatments for the management of laryngeal injuries [8,11,19]. Overall, the proportion of patients requiring surgical approach ranged from 39% to 70% (mean=48%) [8,11,19].

Table 3. Prevalence of laryngeal disorders and injuries.

Laryngeal disorders	Number/total	Prevalence	References
VF dysmotility	28/43	65.1	10,11
VF edema	59/167	35.3	11,17,19
Laryngopharyngeal reflux	21/101	20.8	8,18
MTD	21/101	20.8	8,18
Ventricular band edema	20/106	18.9	17
Bilateral VF hypo/immobility	3/18	16.7	11
Posterior glottic stenosis	42/257	16.3	8,11,12,18,19
Granuloma	33/244	13.5	10,12,18,19
Posterior glottic diastasis or atrophy	19/162	11.7	8,11,18,19
VF immobility	37/345	10.7	8,10,11,12,17,18
VF polyp	8/81	9.9	18
Subglottis stenosis	15/165	9.1	8,9,11,18,19
Glottis insufficiency	7/81	8.6	18
VF hypomobility	8/99	8.1	11,18
VF ulceration or necrosis	3/68	4.4	8,19
VF hematoma	1/25	4.0	8

Table 3 footnotes: Abbreviations: MTD=muscle tension dysphonia; VF=vocal fold.

Bias analysis

Bias analysis is reported in Appendix 1. There was no study that compared prevalence of PLID between COVID-19 discharged patients and those discharged from the hospital for another reason. Three studies were retrospective case-series (EL: IV) and 5 were prospective uncontrolled studies (EL: III). The patient populations substantially varied from one study to another according to the proportion of intubated *versus* not intubated patients, and therefore, the severity of the disease. Moreover, the delay between the discharge and the time of examination was not provided in 3 studies [8-10] and may vary from one study to another, which may lead to a comparison bias. Other factors may limit the comparison between studies, e.g. the variability in comorbidity prevalence, the proportion of tracheostomy, the duration of intubation or tracheostomy, and the methods used to evaluate laryngeal function and PLID (Appendix 1). Moreover, many important outcomes that may influence the development of PLID were not investigated in patients, including tobacco consumption, laryngopharyngeal reflux, or history of previous cancer or radiation. No author reported medical postdischarge care (drugs), which may impact the development of some laryngeal injuries.

4. Discussion

Coronavirus disease 2019 was found to be associated with many otolaryngological disorders, including smell and taste dysfunctions [20], vestibular neuritis [21], parotitis [22], facial paralysis [23] or paradoxical vocal fold movement [24]. The association between COVID-19 and laryngeal disorders was initially observed in a first-wave epidemiological study in which 26% of patients with mild-to-moderate COVID-19 reported dysphonia throughout the clinical course of the disease [25]. Since then, the follow-up of patients who were intubated or tracheotomized in ICU suggested the occurrence of mid-term PLID [8-12]. The present review summarized the PLID found in COVID-19 patients. Many factors may limit the draw of reliable conclusion.

First, most authors suggested that the prevalence of post-intubation or post-tracheostomy PLID was substantially high in COVID-19 patients who were discharged from the ICU. Our data suggested that the prevalence of bilateral or unilateral vocal fold motion disorders, vocal fold edema or posterior glottic stenosis may reach 16% to 65% of cases. A recent systematic review reported that 13% to 31% of non-COVID-19 patients who were endotracheally intubated in ICU had moderate-to-severe laryngotracheal injuries [26]. Precisely, grade 3 injuries, including stenosis, hypo/immobility of vocal folds and/or arytenoid complex, were found in 13% of cases, whereas grade 2 injuries (e.g. hematoma, ulceration, edema or granulation) concerned 31% of cases [26]. Authors reported that the prevalence of grade 3 and 2 injuries increased to 33% and 18% in patients with an average intubation duration >5 days, respectively [26]. Comparing these data with the findings of the present review, it could appear that COVID-19 patients may present higher rates of PLID but, according to the lack of controlled study, the draw of reliable conclusion remains difficult.

Second, many other biases may limit the interpretation of the study results. The primary bias is an inclusion bias because patients included in the studies were all recruited from otolaryngology or laryngology office and, therefore, consisted of a dysphonic population. There was no epidemiological study that systematically evaluated the occurrence of voice disorders and PLID in all patients who were discharged from the hospital/ICU.

Third, authors investigated some laryngeal disorders without consideration of other contributing factors that may be associated with the development of PLID. This is particularly the case for muscle tension dysphonia, which was reported as prevalent condition in COVID-19 patients in two studies [8,18]. Muscle tension dysphonia may develop from gastric or environmental irritants, laryngitis, or even stress, among other conditions [27], which were not investigated in both studies [8,18]. Similar observation may be made for granuloma. Although the intubation is an important cause of granuloma, other prevalent etiologies may play a key role in the development of granuloma such as reflux [28]. The patient comorbidities are important issue for the interpretation of the findings of studies. According to studies, the populations of studies considered in the present review reported high but different rates of comorbidities, which may be an additional limiting factor to precisely studied the prevalence of PLID and association with COVID-19. Indeed, some comorbidities may be associated more frequently with some PLID, such as reflux and posterior laryngeal edema; or diabetes and laryngotracheal stenosis [28,29]. Another factor that may impact the results of studies is the definition of PLID. We observed that the definition of some PLID may vary from one study to another. Precisely, authors did not define similarly vocal fold hypomobility, which was the most prevalent PLID. The observation of hypomobility of vocal folds is still subjective and many authors did not provide information about the etiology (laryngeal nerve impairment *versus* arytenoid join ankylosis) [10,11,18]. These biases have to be considered in future studies that aim to investigate PLID in COVID-19.

The present scoping review included 8 studies (393 patients), which considerably limits the draw of reliable conclusion. The low number and the low evidence level of studies are, therefore, the primary limitation of this review. The lack of controlled study comparing both prevalence and features of post-intubation/post-tracheostomy PLID between

discharged COVID-19 and individuals with a history of intubation or tracheostomy for another condition is another important limitation.

5. Conclusion:

COVID-19 appeared to be associated with PLID in patients with a history of intubation or tracheostomy. However, it remains difficult to determine if the development of post-intubation or post-tracheostomy PLID is more frequent in COVID-19 patients compared with those with a history of intubation or tracheostomy for another condition. Future controlled studies are needed to compare the prevalence of post-intubation or post-tracheostomy PLID in both populations.

6. Patents

This section is not mandatory but may be added if there are patents resulting from the work reported in this manuscript.

Author Contributions: Conceptualization, SH and JRL.; methodology, SH, JRL formal analysis, SH, JRL; writing—original draft preparation, JRL, SH.. Authorship must be limited to those who have contributed substantially to the work reported.

Data Availability Statement: Data are available on request.

Conflicts of Interest: The authors declare no conflict of interest.

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Appendix 1: Bias analysis.

Authors	Confounding factors	Population analysis	Delay	Int./trach. details	Postdischarge care
Naunheim (8)	Probably no	Probably yes	Probably yes	Yes	No
Scholfield (9)	No	Yes	Yes	Probably yes	No
Sandblom (10)	Probably no	Probably yes	Probably yes	Probably yes	No
Neevel (11)	Probably yes	Yes	Yes	Probably yes	No
Felix (12)	Probably yes	Probably yes	Probably yes	Probably yes	No
Azzam (17)	Probably yes	Yes	Probably yes	Yes	No
Allisan (18)	Probably yes	Probably yes	Probably yes	Probably yes	No
Hans (19)	Probably no	Probably yes	Probably yes	Probably yes	No

Appendix 1 footnotes: Confounding factors: Yes=authors excluded patients with laryngeal disorders prior the COVID-19 and carefully assessed the other conditions associated with PLID (i.e. reflux, tobacco exposition, trauma or radiation histories); probably yes=authors excluded patients with laryngeal disorders prior the COVID-19 or carefully assessed the other conditions associated with PLID (i.e. reflux, tobacco exposition, trauma or radiation histories); Probably no=authors excluded some confounding factors; No=no information was provided about exclusion criteria. Population analysis: Yes=authors performed different analyses or provided data to perform such analyses regarding the following types of patients: intubated vs non-intubated & tracheotomized vs non-tracheotomized patients. No=they did not provide information. Delay: Yes=authors provided information about the delay between the discharge of hospital and the occurrence of PLID in the different populations of patients (if applicable; intubated vs non-intubated; tracheotomized vs non-tracheotomized). Probably Yes= authors provided details for the entire cohort; Probably no= Only delay between COVID-19 diagnosis and PLID occurrence were available; No=authors did not provide such information. Intubation/tracheostomy details: Yes=authors provided full information for concerned patients (duration, tube size, proning); probably yes= >50% of information were provided; probably no= <50% of information were provided; No=no information were provided. Postdischarge care: Yes=authors provided information about postdischarge medication/care (e.g. speech therapy) that may influence the development of PLID. No=authors did not provide such information.