BRIEF REPORT

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Risk of Post-Intubation Laryngotracheal Stenosis With Respect to COVID-19 Status in a Large Multicenter Cohort Cross-Sectional Study

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OBJECTIVES: Occurrence of post-intubation laryngotracheal stenosis (LTS) with respect to COVID-19 status.

DESIGN: Retrospective cross-sectional inpatient database.

SETTING: Eleven Midwest academic and community hospitals, United States.

PATIENTS: Adults, mechanically ventilated, from January 2020 to August 2022, who were subsequently readmitted within 6 months with a new diagnosis of LTS.

INTERVENTIONS: None.

MEASUREMENTS AND MAIN RESULTS: Six thousand eight hundred fifty-one COVID-19 negative and 1316 COVID-19 positive patients were intubated and had similar distribution by age (median 63.77 vs. 63.16 yr old), sex (male, 60.8%; $n = 4173$ vs. 60%; $n = 789$), endotracheal tube size (≥ 7.5, 75.8%; $n = 5192$ vs. 75.5%; $n = 994$), and comorbidities. The ICU length of stay (median [interquartile range (IQR)], 7.23 d [2.13–16.67 d] vs. 3.95 d [1.91–8.88 d]) and mechanical ventilation days (median [IQR], 5.57 d [1.01–14.18 d] vs. 1.37 d [0.35–4.72 d]) were longer in the COVID-19 positive group. The occurrence of LTS was double in the COVID-19 positive group (12.7%, $n = 168$ vs. 6.4%, $n = 440$; $p < 0.001$) and was most commonly diagnosed within 60 days of intubation. In multivariate analysis, the risk of LTS increased by 2% with each additional ICU day (hazard ratio [HR], 1.02; 95% CI, 1.02–1.03; $p < 0.001$), by 3% with each additional day of ventilation (HR, 1.03; 95% CI, 1.02–1.04; $p < 0.001$), and by 52% for each additional reintubation (HR, 1.52; 95% CI, 1.36–1.71; $p < 0.001$). We observed no significant association COVID-19 status and risk of LTS.

CONCLUSIONS: The occurrence of post-intubation LTS was double in a COVID-19 positive cohort, with higher risk with increasing number of days intubated, days in the ICU and especially with the number of reintubations. COVID-19 status was not an independent risk factor for LTS.

KEYWORDS: airway stenosis; laryngotracheal stenosis; stridor

During the COVID-19 pandemic, 15–30% of hospitalized patients had severe disease (1) requiring prolonged endotracheal intubation, which is the main risk factor for iatrogenic laryngotracheal stenosis (LTS) (2). Risk factors for LTS overlap with risk factors for severe COVID-19 disease, including older age, diabetes mellitus (DM), and obesity (1, 2). Additionally, pandemic practice patterns included the use of large endotracheal tubes (ETTs) for pulmonary toilet and delayed tracheotomy placement, which are also known risk factors for LTS (3). At the same time, it has been proposed that COVID-19 itself could increase the risk of LTS via high viral replication within the tracheal

DOI: 10.1097/CCE.0000000000001081

KEY POINTS

Question: Is positive COVID-19 status associated with increased occurrence of post-intubation laryngotracheal stenosis (LTS)?

Findings: LTS occurrence was double in the COVID-19 positive cohort (12.7%, *n* = 168/1316) compared with the COVID-19 negative cohort (6.4%, *n* = 440/6851). COVID-19 positive status was not independently associated with LTS risk.

Meaning: COVID-19 positive status itself was not associated with increased LTS risk, pointing to increased risk of LTS in the COVID positive cohort less likely due to the presence of severe acute respiratory syndrome coronavirus 2 in the airway, but rather due to selection and predisposition for risk factors known to increase risk of LTS.

epithelium and the associated prothrombotic state resulting in microvascular injury and necrosis of the central airway mucosa (4).

Investigations into the anticipated deluge of LTS (5) after the COVID-19 pandemic have been limited to series with small sample sizes relative to the extent of COVID-19 cases, with variable findings (4, 6, 7). For example, Félix et al (6) reported a 17% occurrence (*n* = 16/95) and Ayten et al (7) reported a 3.3% occurrence (*n* = 7/208) of post-intubation LTS in COVID-19 patients. Two studies compared the occurrence of post-intubation LTS in COVID-19 positive and negative cohorts, with group sizes ranging from 16 to 45 patients (4, 8). Fiacchini et al (8) reported a 5% occurrence (*n* = 8/16) of LTS in the COVID-19 positive cohort vs. 0% occurrence (*n* = 0/16) of LTS in a case-controlled COVID-19 negative cohort. In another study by the Fiacchini et al (4) group, they observed a 47% occurrence of full-thickness tracheal lesions and tracheoesophageal fistulas in the COVID-19 positive (*n* = 14/30) vs. 2.2% in the COVID-19 negative (1/45) cohorts. The small sample sizes in the existing literature make it difficult to determine the extent to which COVID-19 itself vs. other potential risk factors of COVID-19 infection or severity may contribute to LTS occurrence.

The aim of this study was to evaluate the occurrence of post-intubation LTS in a large cohort with both COVID-19 negative and positive disease, using data from 11 Midwest U.S. hospitals representing greater than 8000 patients. We hypothesized that COVID-19 positive patients requiring intubation would have a higher occurrence of LTS than COVID-19 negative patients. Secondarily, we aimed to identify risk factors for development of LTS, including COVID-19 status itself.

METHODS

We conducted a retrospective cohort analysis of inpatient acute care data from 11 U.S. Midwest hospitals from January 1, 2020, to August 31, 2022. Adult patients requiring invasive mechanical ventilation who were subsequently readmitted within 6 months with a new diagnosis of airway stenosis were included. Airway stenosis was identified by *International Classification of Diseases*, 10th Edition diagnosis code (J38.6, J39.8, J95.03, J95.5, and Z87.09) or by Current Procedural Terminology (CPT) code (dilation, repair, resection surgery, 31528, 31529, 31592, 31630, 31641, 31780, and 31781). Patients with a diagnosis of airway stenosis at initial admission were excluded. The University of Minnesota Institutional Review Board approved this study (STUDY00015824, airway stenosis post-endotracheal intubation, approved July 11, 2022). The study followed all procedures in accordance with the ethical standards of the responsible committee on human experimentation and with the Helsinki Declaration of 1975.

COVID-19 status, determined by polymerase chain reaction, was the independent variable. Key covariates included as follows:

1) Demographics: age, sex, and race.
2) Patient comorbidities: tobacco smoking status, body mass index (BMI), and Elixhauser comorbidities (9).
3) Endotracheal intubation variables: number of intubation instances during index admission, number of intubation attempts, and ETT size.
4) Hospital stay variables: admission diagnoses, medications administered during admission, inpatient length of stay (LOS), ICU LOS, total invasive mechanical ventilation days, and death during index admission.

The primary outcome was the occurrence of LTS. Continuous variables with less than 40% missingness were imputed using predictive mean matching. Categorical variables with less than 40% missingness

TABLE 1.
Univariate Analysis of COVID-19 Positive and Negative Cohort Characteristics

Variable	COVID Status		p
	Negative, *n* (%), 6851	Positive, *n* (%), 1316	
Demographics			
Age, median (IQR)	63.77 (52.30–72.90)	63.16 (51.79–72.31)	0.518
Sex			
Female	2686 (39.2)	527 (40.0)	0.589
Male	4165 (60.8)	789 (60.0)	
Race			
Asian	377 (5.5)	172 (13.1)	**< 0.001**
Black	470 (6.9)	144 (10.9)	
Latinx	62 (0.9)	35 (2.7)	
Native American/Alaskan	107 (1.6)	29 (2.2)	
Other	32 (0.5)	11 (0.8)	
Patient declined	215 (3.1)	54 (4.1)	
White	5588 (81.6)	871 (66.2)	
Medical comorbidities			
Tobacco smoking history			
Never smoker	2672 (39.0)	586 (44.5)	**< 0.001**
Current smoker	1222 (17.8)	112 (8.5)	
Former smoker	2471 (36.1)	495 (37.6)	
Unknown	486 (7.1)	123 (9.3)	
Body mass index			
< 30	4006 (58.5)	673 (51.1)	**< 0.001**
30–35 (class I)	1419 (20.7)	304 (23.1)	
35–40 (class II)	759 (11.1)	174 (13.2)	
> 40 (class III)	667 (9.7)	165 (12.5)	
Elixhauser comorbidities at the time of admission			
Iron deficiency anemia	1627 (23.7)	413 (31.4)	**< 0.001**
Diabetes, uncomplicated	345 (5.0)	113 (8.6)	**< 0.001**
Diabetes, complicated	727 (10.6)	216 (16.4)	**< 0.001**
Obesity	772 (11.3)	224 (17.0)	**< 0.001**
Weight loss	1878 (27.4)	512 (38.9)	**< 0.001**
Endotracheal intubation			
Number of intubations, mean (SD)	1.11 (0.42)	1.14 (0.47)	0.023
Number of total intubation attempts, median (IQR)	1.00 (0.00–1.00)	0.00 (0.00–1.00)	**< 0.001**
Endotracheal tube size			
7.5 and above	5192 (75.8)	994 (75.5)	0.872
7 and under	1659 (24.2)	322 (24.5)	

(*Continued*)

TABLE 1. (*Continued*)
Univariate Analysis of COVID-19 Positive and Negative Cohort Characteristics

Variable	COVID Status		p
	Negative, *n* (%), 6851	Positive, *n* (%), 1316	
Hospital stay			
Inpatient length of stay, d, median (IQR)	10.74 (5.57–20.25)	18 (9.02–30.0)	**< 0.001**
ICU length of stay, d, median (IQR)	3.95 (1.91–8.88)	7.23 (2.13–16.67)	**< 0.001**
Total invasive ventilation days, d, median (IQR)	1.37 (0.35–4.72)	5.57 (1.01–14.18)	**< 0.001**
Death during index admission	1681 (24.5)	435 (33.1)	**< 0.001**
Admission diagnosis			
Cardiac and circulatory conditions	2320 (33.9)	224 (17.0)	**< 0.001**
Gastrointestinal	217 (3.2)	42 (3.2)	
Mental health	102 (1.5)	10 (0.8)	
Neurologic disorders	573 (8.4)	65 (4.9)	
Respiratory	967 (14.1)	536 (40.7)	
Other	2580 (37.7)	431 (32.8)	
Other cancer	92 (1.3)	8 (0.6)	
Medications during admission			
Steroids	1778 (26.0)	513 (39.0)	**< 0.001**
Blood thinners	739 (10.8)	276 (21.0)	**< 0.001**
Respiratory	233 (3.4)	106 (8.1)	**< 0.001**
Vasopressors	2558 (37.3)	373 (28.3)	**< 0.001**
Primary outcome			
Laryngotracheal stenosis post-intubation	438 (6.4)	168 (12.8)	**< 0.001**

IQR = interquartile range.

were imputed using multinomial regression. Variables with greater than or equal to 40% missingness were excluded. Student *t* test, chi-square test, or Fisher exact test were used for univariate analyses. All univariate analyses were performed using the "tableone" package (https://cran.r-project.org/web/packages/tableone/). Kaplan-Meier curves assessed the risk of LTS and were compared using log-rank and Wilcoxon tests. Cox proportional hazard regression—adjusted for demographics and clinical characteristics—was used to estimate the hazard ratio (HR) and related statistical significance, including CIs. The proportional hazards assumption of the model was checked using Schoenfeld residuals. All analyses were performed using R V4.1.2, running in RStudio V 2022.07.2 (R Core Team [2023]: R: A Language and Environment for Statistical Computing. Vienna, Austria, R Foundation for Statistical Computing. Available at: https://www.R-project.org/).

RESULTS

Eight thousand one hundred sixty-seven patients were intubated during the study period, including 83.9% (n = 6851) COVID-19 negative and 16.1% (n = 1316) COVID-19 positive. Overall occurrence of LTS within 6 months of discharge was 7.42% (n = 606), with a higher occurrence in the COVID-19 positive patients (12.8%, n = 168) compared with the COVID-19 negative cohort (6.4%, n = 438) (**Table 1**). Most post-intubation LTS was diagnosed within 60 days (**Fig. 1*A***).

In multivariate analysis, the risk of LTS increased by 2% for each additional day in the ICU (HR, 1.02; 95% CI: 1.02–1.03; $p < 0.001$), by 3% for each additional day intubated (HR, 1.03; 95% CI, 1.02–1.04; $p < 0.001$), and by 52% for each additional intubation during admission (HR, 1.52; 95% CI, 1.36–1.71; $p < 0.001$) (**Fig. 1*B***). We observed no significant

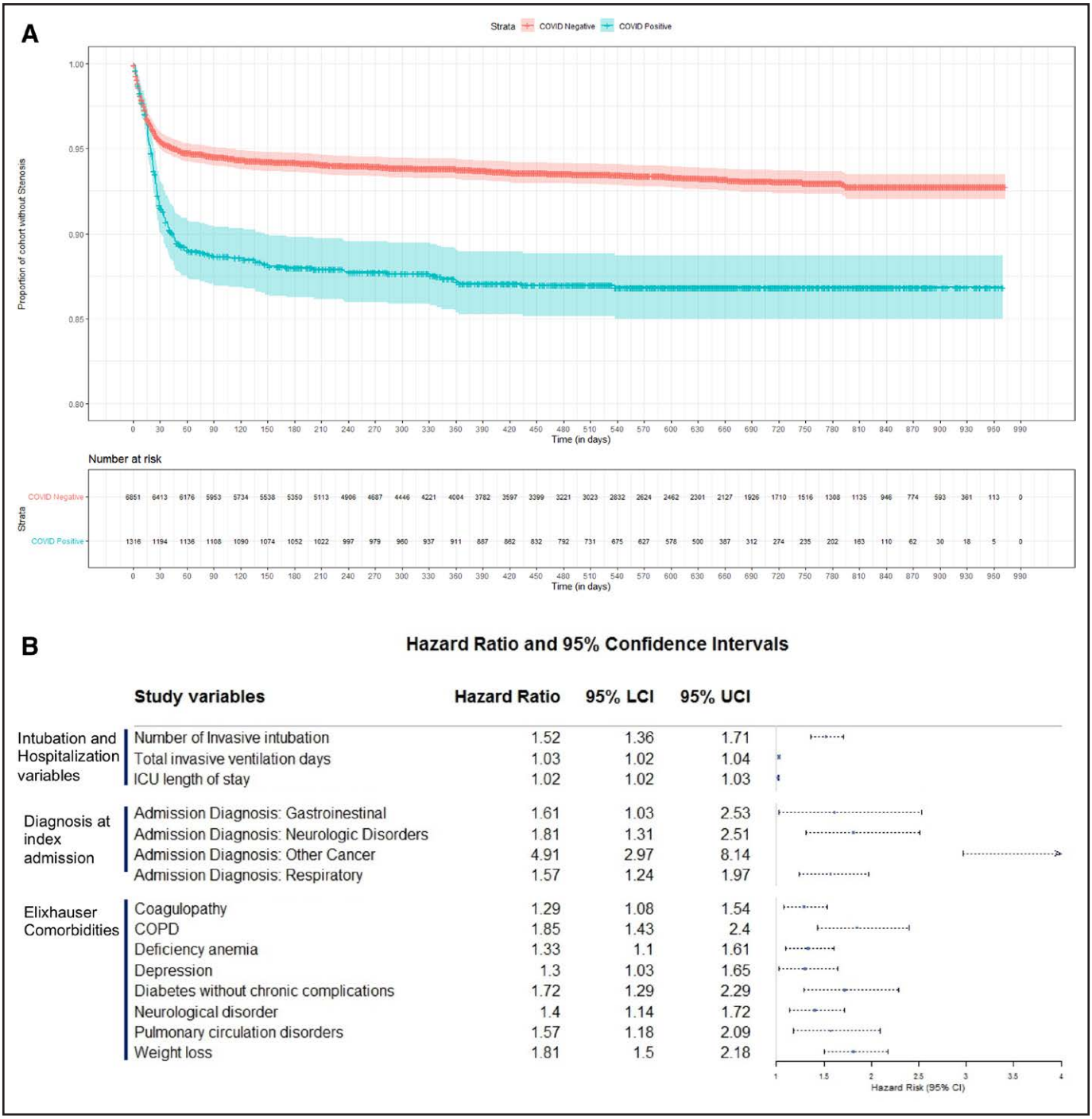

Figure 1. Kaplan-Meier analysis of laryngotracheal stenosis (LTS)-free survival. **A**, Kaplan-Meier analysis for LTS-free survival in COVID-19 positive and negative cohorts along with the CIs. It includes the number of patients at risk for both cohorts across time (d). One-mo (30 d) LTS-free survival for COVID-19 negative was 95.5% (95% CI, 95–96%) compared with 91.5% (95% CI, 90–93.1%) for COVID-19 positive cohorts. The nonoverlapping CIs for the two groups suggest that the difference is significant. The significant *p* value for log-rank test ($p < 0.001$) and Wilcoxon test ($p < 0.001$) suggests that the COVID-19 positive cohort were more vulnerable to developing LTS. **B**, Hazard ratios based on Cox regression modeling for factors associated with increased risk of LTS. COPD = chronic obstructive pulmonary disease, LCI = lower CI, UCI = upper CI.

association with demographic factors, smoking status, BMI, COVID-19 status, length of hospital stay, ETT size, and medications administered during admission.

DISCUSSION

This is the largest retrospective cross-sectional cohort study evaluating post-intubation LTS occurrence with attention to COVID-19 status. Post-intubation LTS occurrence was twice as high in COVID-19 positive patients, 12.8% vs. 6.4%, with the highest risk within 60 days of intubation. In multivariate analysis, COVID-19 status itself was not associated with increased LTS occurrence.

With respect to post-intubation LTS occurrence in COVID-19 positive cohorts, our findings were similar to prior reports. Félix et al (6) has the prior largest cohort in the literature and found a 17% rate of LTS. The authors compared this to a historical cohort with similar methodology, which showed a rate of stenosis of 8.2% (10), concluding that the rate of stenosis in COVID-19 positive patients was twice that in non-COVID-19 patients.

With respect to overall risk factors associated with LTS occurrence, multivariate analysis in our study identified similar factors as previously reported (2, 3) to include number of days intubated, number of reintubations, ICU LOS, respiratory-related admission diagnosis, and comorbidities of DM and COPD.

With respect to COVID-19-specific risk factors for LTS occurrence, the need for airway clearance with large caliber ETT tubes and long durations of intubation with delay in tracheotomy placement have been proposed as risks. Regarding ETT size, Félix et al (6) reported five times higher risk of LTS in patients intubated with a size greater than or equal to eight ETT compared with less than or equal to 7.5 ETT. In contrast, in our cohort, over 75% of all patients were intubated with greater than or equal to 7.5 ETT, and no effect of ETT size was identified. Interestingly, the observed LTS rate was lower in our study as well. The contrasting findings may be related to differences in dichotomization of ETT size and/or other practice differences that were not readily apparent. Regarding intubation length, Ayten et al (7) observed longer intubation duration in COVID-19 positive patients who developed LTS (28 ± 13 d) vs. those who did not (11 ± 9 d). In our cohort, the COVID-19 positive group had a longer duration of intubation, and in multivariate analysis, each additional intubation day increased the risk of LTS by 3%, pointing to the significance of prolonged intubation as a risk factor regardless of COVID-19 status and highlighting the need for appropriately timed conversion to tracheotomy.

Regarding COVID-19 status itself and the risk of LTS, in this study, COVID-19 status itself was not an independent risk factor for LTS once other relevant clinical factors were taken into account, but LTS was more common among the COVID positive patients. This suggests that the presence of severe acute respiratory syndrome coronavirus 2 in the central airway may not necessarily change the pathophysiology of LTS development itself. Instead, it likely selects for patients already at risk for LTS. Fiacchini et al (4) have identified potential management differences that may contribute to LTS in COVID positive patients: pronation maneuvers, the use of higher steroid doses, and lower Pao_2/Fio_2 ratios during intubation.

Strengths of this study include cohort size, inclusion of both COVID-19 positive and negative patients, study span of 3 years to include both early and later pandemic phases, and inclusion of patients from both academic and community centers accounting for different practice patterns and disease severity levels. The study also identified symptomatic LTS rather than acute phase laryngotracheal lesions. Last, the study looked at COVID-19 status itself as a risk factor for LTS.

Limitations include the retrospective and aggregated nature of the data source. Data on ETT cuff pressures and pronation were not available. LTS was defined by proxy of CPT and diagnosis codes without an independent assessment of airway endoscopic findings. Last, the occurrence of LTS is limited to patients who had subsequent hospitalizations, thus excluding those who did not survive (a differential effect given lower survival among those COVID-19 positive) or who left the health system for subsequent care.

This large study underscores the need for vigilance for post-intubation LTS in COVID-19 survivors, particularly those who required multiple and/or prolonged intubations, with special attention to diagnosis in the first few months after hospitalization.

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Preliminary data was presented as a poster at the 4th Vienna European Society of Thoracic Surgeons Laryngotracheal Course, Vienna, Austria, March 2–24, 2023.

The authors have disclosed that they do not have any potential conflicts of interest.

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