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New perspectives on tracheal resection for COVID-19–related stenosis: A propensity score matching analysis

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ABSTRACT

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Objective: The large number of patients with COVID-19 subjected to prolonged invasive mechanical ventilation has been expected to result in a significant increase in tracheal stenosis in the next years. The aim of this study was to evaluate and compare postoperative outcomes of patients who survived COVID-19 critical illness and underwent tracheal resection for postintubation/posttracheostomy tracheal stenosis with those of non–COVID-19 patients.

Methods: It was single-center, retrospective study. All consecutive patients with postintubation/posttracheostomy tracheal stenosis who underwent tracheal resection from February 2020 to March 2022 were enrolled. A total of 147 tracheal resections were performed: 24 were in post–COVID-19 patients and 123 were in non–COVID-19 patients. A 1:1 propensity score matching analysis was performed, considering age, gender, body mass index, and length of stenosis. After matching, 2 groups of 24 patients each were identified: a post–COVID-19 group and a non–COVID group. **Results:** No mortality after surgery was registered. Posttracheostomy etiology of stenosis resulted more frequently in post–COVID-19 patients ($n = 20$ in the post– COVID-19 group vs $n = 11$ in the non–COVID-19 group; $P = .03$), as well as intensive care unit admissions during the postoperative period (16 vs 9 patients; $P = .04$). Need for postoperative reintubation for glottic edema and respiratory failure was higher in the post–COVID-19 group (7 vs 2 postoperative reintubation procedures; $P = .04$). Postoperative dysphonia was observed in 11 (46%) patients in the post-COVID-19

Tracheal surgery after COVID-19.

CENTRAL MESSAGE

Post–COVID-19 patients affected by tracheal stenosis who underwent tracheal resection showed higher postoperative complications rate and increased ICU admission stay compared with non–COVID-19 patients.

PERSPECTIVE

COVID-19 and mechanical ventilation significantly influence the etiology of tracheal stenosis. The aim of the present study is to investigate how COVID-19 could influence tracheal surgery in terms of postoperative outcomes.

See Commentary on page XXX. See Discussion on page XXX.

The COVID-19 pandemic during early 2020 presented a challenge for surgery worldwide.^{[1](#page-7-0)} Although the clinical presentation of COVID-19 could be extremely heterogeneous, varying from asymptomatic to severe respiratory failure,

group versus 4 (16%) patients in the non–COVID-19 group ($P = .03$).

Conclusions: Tracheal resection continues to be safe and effective in COVID-19– related tracheal stenosis scenarios. Intensive care unit admission rates and postoperative complications seem to be higher in post–COVID-19 patients who underwent tracheal resection compared with non–COVID-19 patients. (J Thorac Cardiovasc

invasive mechanical ventilation (IMV) has been necessary in 9.8% to 15.2% 15.2% 15.2% of patients.^{2[,3](#page-7-2)} The mechanical and

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Abbreviations and Acronyms

- $ETT = endotracheal tube$
- $ICU =$ intensive care unit
- $IMV =$ invasive mechanical ventilation
- $LMA =$ laryngeal mask airway
- $PSM =$ propensity score matching

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ischemic damage caused by prolonged intubation and tracheostomy on the tracheal wall is a well-known risk factor for the production of fibrotic tracheal scarring.^{[4](#page-7-3)[,5](#page-7-4)} Moreover, the SARS-CoV-2 virus worsens this ischemic tracheal mucosa damage by causing a prothrombotic and antifibrinolytic state, producing microvascular injury and necrosis and requiring chronic high-dose systemic steroids use.^{[6](#page-7-5)[,7](#page-7-6)} As already published, the supine-to-prone position change, frequently used in intensive care settings to improve the prognosis in intubated COVID-19 patients with respiratory distress, induces modification of endotracheal tube cuff pressure associated with tube displacement.⁸ In addition, tracheal epithelial changes caused by the SARS-CoV-2 virus itself should be considered as a predisposing factor for tracheal stenosis in a patient with COVID-19. $\frac{9,10}{9}$ $\frac{9,10}{9}$ $\frac{9,10}{9}$ Prolonged need for IMV in COVID-19 patients, along with the intrinsic capacity of the virus itself to damage the tracheal mucosa, have led to an increased incidence in postintubation/tracheostomy airway complications, including tracheal stenosis, tracheomalacia, and tracheoesophageal fistulas.¹¹

Although elective surgery was postponed during pandemic, 12 some diseases could potentially become life-threatening and surgery could not be delayed.^{[13](#page-8-5)} Among these conditions, tracheal stenosis, which usually becomes symptomatic when 50% obstruction is reached, emerged as an unavoidable surgical entity culminating in the increased incidence of trachea resection during the past 2 years.

Considering a dual etiology of postintubation tracheal stenosis, COVID-19 survivors could have a different postoperative course after tracheal surgery. The aim of this study was to report our experience with post–COVID-19 patients who underwent tracheal resection and reconstruction, comparing the postoperative outcomes with those of non–COVID-19 patients ([Figure 1\)](#page-2-0).

METHODS

Patients

This single-center retrospective study was performed following the Strengthening the Reporting of Observational Studies in Epidemiology

guidelines. Institutional approval was granted for this study (RIF. CE 6451_2021; September 15, 2021). Individual written informed consent was obtained from each patient or legally authorized representative or parent(s) for this study.

From February 2020 to March 2022, 147 consecutive patients with postintubation/posttracheostomy tracheal stenosis underwent tracheal or laryngotracheal resection and reconstruction with an end-to-end anastomosis via cervicotomy at the Thoracic Surgery Unit of Sant'Andrea Hospital of Sapienza University of Rome, the referral center for tracheal surgery in Italy. Generally, cases arrive from the north to the south of Italy. A significant part of the study population has transferred from intensive care units (ICUs) or rehabilitation institutions in the central regions of Italy after brain injury, coma, or heart/respiratory failure. Ear, nose, and throat specialists do not address tracheal surgery in Italy. Patients with idiopathic tracheal stenosis or neoplastic tracheal stenosis, patients who underwent an extended tracheal resection for long-segment tracheal stenosis (>5 cm), as well as patients who underwent a tracheal replacement by a cryopreserved aortic graft were not considered in this series. Of the 147 patients we considered, 24 were post–COVID-19 patients who survived a critical illness that required IMV through intubation or tracheostomy during the pandemic, whereas 123 were patients with tracheal stenosis who received an endotracheal tube (ETT) or a tracheostomy for other causes and not for COVID-19 respiratory failure. Preoperative assessment included fiberoptic bronchoscopy and neck-thorax computed tomography scan, which were used to verify the vocal cords' motility and to evaluate the tracheal stenosis; that is, its length from vocal cords, the extent, the site, and the severity grade according to Cotton-Meyer classification ([Figure 2\)](#page-3-0). Tracheal resection-anastomosis was performed in accordance with Pearson's technique. Intraoperative ventilation was achieved by endotracheal intubation with a wire-reinforced small caliber tube (4-4.5 mm) passed through the stenosis or by the insertion of a laryngeal mask airway (LMA) device. The choice to use an ETT or LMA was done according to patients' physical characteristics and clinic history, features of the stenosis (distance from vocal cords and grade of stenosis). During surgery, all patients underwent traditional cross-field ventilation after tracheal resection by an armored 5 mm ETT. When possible, immediate extubation or removal of the LMAwould be attempted for every patient in the operating room. However, at the end of the cross-field ventilation, when the end-to-end anastomosis is performed, the anesthesiologist could decide to place a nasotracheal tube, with a 7- to 7.5-mm caliber, as described in our previous series^{[14](#page-8-6)} and defined as a traditional early reintubation also when an LMA was used during the first phases of the surgical procedure (ie, induction, resection, and anastomosis). The anesthesiologist's choice is based on evaluation of the patient, on the anatomical glottis status, on the patient's stability, and his or her preoperative cooperation. Thus, a patient can be moved to an ICU or to the thoracic surgery unit with a 7- or 7.5-mm nasotracheal tube in place and a deflated cuff, awake, spontaneously breathing. The tube is removed after 24 hours under broncoscopic vision. The unexpected reintubation was defined as a new EET positioning (2 times), occurring because of a respiratory failure, after the removal of the LMA or the EET at the end of surgery in the operating room or within the first 24 to 48 hours from surgery (delayed reintubation).

During the postoperative period, according to noninvasive protocols, patients received steroids, air humidification, diuretics therapy, nebulized epinephrine, and high-flow oxygen therapy (AIRVO2; Fisher & Paykel Healthcare) to prevent and to treat laryngeal edema. Fiberoptic bronchoscopy was performed when necessary and at discharge, and then at 1, 3, 6, and 12 months after surgery for every patient.

Specimens of the trachea resected from the patients who underwent tracheal surgery were sent for pathologic examination. Squamous metaplasia, ulceration, dense fibrosis, acute flogosis, gigantocellular flogosis, necrosis, gland atrophy, and neoangiogenesis were evaluated on surgical specimens.

FIGURE 1. Graphical abstract of the study.

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Propensity Score Matching and Statistical Analysis

To identify 2 balanced groups according to potential confounding baseline variables, a 1:1 propensity score matching (PSM) analysis was performed using a logistic regression model and considering age, gender, body mass index, and length of stenosis (1-4 cm). A greedy algorithm with calipers of 0.2 of the SD of the logit of the propensity score was used. The distributions of the PSM results between groups were evaluated using standardized mean difference. Groups were defined as comparable for all confounders if standardized mean difference is ≤ 0.10 . After matching, 2 groups of 24 patients each were identified: a post–COVID-19 group and a non–COVID-19 group ([Figure 3\)](#page-3-1). Characteristics of patients and postoperative results were analyzed before and after matching. For the estimation of the treatment effect, matched data were analyzed using procedures for matched analyses, such as paired t tests for continuous variables, whereas McNemar's test, conditional logit, doubly robust, and mixed effect (matched pairs as random effect) logistic regression were used for binary outcomes. Tracheal specimens resected from patients of both groups were evaluated to assess possible similarities or differences. Data were collected and stored in an Excel database (Microsoft Corp) and were analyzed using SPSS version 25.0 (IBM-SPSS Software Inc). Quantitative variables were expressed as mean \pm SD, whereas nominal variables were expressed binarily as presence (1) or absence (0) of the event. Comparison of categorical variables was performed by χ^2 test using the Fisher exact test. Comparison of continuous variables was performed by Student t test. No missing data are present in the dataset.

RESULTS

Pre- and postmatching characteristics of patients and intraoperative variables are shown in [Table 1](#page-4-0). Postmatching results are shown in [Table 2.](#page-5-0) Male patients were $n = 14$ (58%) in the post–COVID-19 group and n = 14 (58%) in the non–COVID-19 group ($P = 1.00$). The mean age was 59.29 ± 9.84 in the post–COVID-19 group and

 52.33 ± 18.28 in the non–COVID-19 group ($P = .10$). None of the other preoperative characteristics, including American Society of Anesthesiologists score, body mass index, distance from vocal cords, and preoperative dilation procedures (rigid bronchoscopy or laser vaporization) presented statistically significant differences between the 2 groups ($P = .69, P = .18, P = .23,$ and $P = .41$, respectively), except for the etiology of the stenosis: 4 (17%) patients in the post–COVID-19 group versus 13 (54%) patients in the non–COVID-19 group experienced postintubation stenosis, whereas 20 (83%) patients in the post–COVID-19 group versus 11 (46%) patients in the non–COVID-19 group had a posttracheostomy stenosis ($P = .03$). In the post– COVID-19 group, 14 (58%) patients required laryngotracheal intervention versus 12 (50%) in the non–COVID-19 group ($P = .76$). In the post–COVID-19 group, 22 (92%) patients were operated with LMA intraoperative assistance, whereas 2 (8%) patients were operated with traditional ETT. In the post–COVID-19 group, 19 (79%) patients were operated with LMA intraoperative assistance, whereas 5 (21%) patients were operated with traditional ETT $(P = .20)$. Early reintubation was reported in 9 (37%) patients in the post–COVID-19 group and in 8 (32%) patients in the non–COVID-19 group ($P = .12$). Preoperative comorbidities such as chronic obstructive pulmonary disease, diabetes, and Charlson Comorbidity Index were analyzed before and after matching, not showing statistically significant differences ($P = .72, P = .11,$ and $P = .21$, respectively, before matching, and P .89, $P = 1.00$, and $P = .34$ after

FIGURE 2. Endoscopic view (A) and computed tomography (CT) findings (C) of a postintubation non–COVID-19 tracheal stenosis. Endoscopic view (B) and CT findings (D) of a post–COVID-19 tracheal stenosis.

matching). Variables such as preoperative smoking history and diabetes mellitus were analyzed before and after matching and no statistically significant differences were found ([Table 1\)](#page-4-0). The mean time from intubation or tracheostomy and surgery was 7.67 ± 4.71 months in the post–COVID-19 group and 5.69 ± 4.29 months in the non–COVID-19 group ($P = .31$). Intraoperative and postoperative results

are shown in [Tables 1](#page-4-0) and [2](#page-5-0). The mean operative time was not different between groups: 93.70 ± 24.45 minutes in the post–COVID-19 group versus 100.83 ± 32.12 in the non–COVID-19 group ($P = .48$). Mortality was 0% in both groups and minor complications (vocal roughness, mild early temporary swallowing difficulty, and surgical incision dehiscence) were 8% in both groups. Postoperative

FIGURE 3. Patients' inclusion/exclusion flow diagram.

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TABLE 1. Patients' characteristics and intraoperative variables before and after matching

Values are presented as mean \pm SD or n (%). SMD, Standardized mean difference; ASA, American Society of Anesthesiologists; COPD, chronic obstructive pulmonary disease; DM, diabetes mellitus; CCI, Charlson Comorbidity Index; BMI, body mass index; ETT, endotracheal tube. *ETT or tracheostomy.

dysphonia was reported in 11 (46%) patients in the post– COVID-19 group and 4 (16%) patients in non–COVID-19 group ($P = .03$). Delayed reintubation rate for laryngeal edema and respiratory failure was higher in the post– COVID-19 group $(n = 7 [29\%])$ versus the non–COVID-19 group ($n = 2 [8\%]$), with a statistically significant difference ($P = .04$). ICU admission rate was higher in the post– COVID-19 group (16 [67%] vs 9 [37%]; $P = .04$). At the end, mean hospital stay was not different between groups (7.42 ± 4.21) days in the post–COVID-19 group vs 6.67 ± 3.11 days in the non–COVID-19 group; $P = .39$), with a median of 7 versus 6 days. Re-stenosis occurrence rate was 8% in both groups. One patient in the post– COVID-19 group received a permanent tracheostomy (4%). One patient in the post–COVID-19 group and 2 patients in the non–COVID-19 group are still managing the

re-stenosis with airways stenting. Mean follow-up was 12.23 ± 4.12 months.

Histologic macroscopic findings using hematoxylineosin staining showed an intense hyaline fibrosis extended to the peritracheal soft tissue, with acute inflammation demonstrated by the presence of lymphocytes and plasma cells infiltrate in specimens from both groups ([Figures 2](#page-3-0) and [4\)](#page-5-1). Occasional giant cell granulomas were present. However, no statistically significant differences were reported between groups ($P > .05$ for each histologic variable analyzed).

CONCLUSIONS

Historical reviews can show us how similar situations that happened in the past can recur in the future. Lessons learned from what happened during the pandemic should

Values are presented as mean \pm SD, n (%), or odds ratio (95% CI) unless otherwise noted. SMD, Standardized mean difference; NA, not available; ICU, intensive care unit.

remain clear to deal with the consequences and to manage any future outbreaks. Cooper^{[15](#page-8-7)} highlighted how the worldwide epidemic of poliomyelitis in the early 1950s initiated the era of positive pressure ventilation through cuffed endotracheal or tracheostomy tubes, developing the application of ventilator assistance in specialized medical and surgical ICUs. Amongst the survivors, more than 20% developed airway complications, primarily tracheal stenosis ([Figure 5](#page-6-0)).

More recently, Fiacchini and colleagues 10 showed that the 48% of ventilated patients during the severe phase of the COVID-19 illness reported a tracheal stenosis. Accordingly, the clinical numbers are often confirmed by histologic findings: very hard and peculiar inflammatory tissues persisted in the peritracheal area during the dissection, with an infiltration of multinuclear giant cell granulomas and intravascular fibrin thrombi with perivascular mononuclear infiltrate of CD3 T lymphocytes.¹⁶ Fiacchini and colleagues^{[17](#page-8-9)} showed

FIGURE 4. Hematoxylin-eosin staining $(1 \times$ original magnification). A, In the specimen of a patient from the post-COVID-19 group, severe hyaline fibrosis restricting the tracheal lumen can be seen. Hyaline fibrosis extends to the peritracheal soft tissues and disrupts the cartilaginous arch. B, A milder fibrosis with a lower lumen restriction can be appreciated in the specimen of a patient from the non–COVID-19 group. The fibrosis mostly involves the pars membranacea and rear portion of the trachea.

FIGURE 5. Surgical specimen of a tracheal resection in a post–COVID-19 patient.

in 8 patients that a subepithelial inflammatory lymphomonocyte infiltrate was observed in tracheal biopsies of both COVID-19 and non–COVID-19 patients that was associated with vasculitis of small subepithelial vessels associated with foci of coagulative necrosis. Two gene sets (HALLMAR-K_INFLAMMATORY_RESPONSE and HALLMAR-K_ESTROGEN_RESPONSE_LATE) were significantly deregulated in COVID-19 patients compared with the control group. The authors conclude that the altered inflammatory response of the COVID-19 patients could be another possible explanation of the increasing number of laryngotracheal complications. On the contrary, Ward and colleagues¹⁸ examined the histologic findings of tracheal tissue samples obtained from COVID-19–positive mechanically ventilated patients ($n = 33$), to assess the degree of tracheal inflammation/ulceration present, comparing samples obtained from COVID-19–negative patients ($n = 5$). Histologic findings were similar between mechanically ventilated COVID-19– positive and -negative patients.

It is clear that deeper histologic and mechanistic studies, evaluating the interleukins, immunoglobulin G4 secreting plasma cells, and T-helper type 2 response, are needed to highlight the potential implication of the virus itself on the tracheal mucosa in the pathogenesis of the stenosis.

Although clinical reviews and case reports have been published in the past [2](#page-7-1) years^{2[,19,](#page-8-11)[20](#page-8-12)} showing the state of the art of COVID-19–related tracheal stenosis, including the incidence and management, the results are often circumstantial and poor for comparison. The exact number of intubated COVID-19 patients developing tracheal stenosis is unknown, ranging from 3% to 40% .^{[20](#page-8-12)} However, the worldwide incidence of tracheal stenosis is reported to be higher in COVID-19 patients than during the pre–COVID-19 era, as our group experienced, and the medical community has been alerted.

The present study tries to evaluate a pure surgical aspect, considering a unique high-volume center for tracheal surgery in the country: The postoperative complications in patients experiencing COVID-19–related tracheal stenosis who underwent tracheal resection [\(Figure 6](#page-7-7)). Following laryngotracheal and tracheal resection-anastomosis, laryngeal edema is among the most challenging intra- and postoperative nonanastomotic complications, eventually requiring reintubation of the patient. Postoperative care for patients after tracheal surgery include judicious use of steroids, ambient humidification, and diuretics to prevent the risk of edema of the glottis. All the published series demonstrated that tracheal resection is a safe and effective proced-ure.^{[14](#page-8-6)[,21](#page-8-13)} Laryngeal edema can be the main cause for the unexpected reintubation after extubation or laryngeal mask removal (ie, delayed reintubation). The present study suggests that, compared with the control group, the COVID-19 etiology could increase the delayed reintubation occurrence, ICU admission rate, and postoperative dysphonia. These data could be a consequence of the increased delayed reintubation in this set of patients. The laryngotracheal resection, required for very high and subglottic stenosis, can be a direct risk factor for intra- and postoperative laryngeal edema, the closeness to vocal cords, the involvement of lymphatic vessels, and the need for extending resection to the cricoid are the major difficulties, especially in idiopathic or acquired subglottic stenosis. In fact, the closer to the vocal cords is the stenosis, the greater is the risk for inflammation involving vocal cords, and so a consequent edema and a consequent respiratory failure. However, the matching analysis of the present study and the exclusion of the patients with idiopathic stenosis from the study should overcome this bias. Moreover, the use of LMA seems not to be a variable with a clinical influence or a potential risk factor, as demonstrated in a previous study.^{[22](#page-8-14)} Preoperative comorbidities were accurately analyzed before and after matching. However, no statistically significant differences were found. Comorbidities seem not to influence postoperative outcomes in this cohort of patients.

To the best of our knowledge, this is the first study exploring the potential influence of COVID-19 etiology on postoperative complications in patients who underwent tracheal surgery compared with a control group (non– COVID-19 patients). However, several limitations are present. It is a single-center retrospective study, and it deals with a small group of patients, although it is the largest in the literature. Postintubation tracheal stenosis is a rare condition with an estimated incidence of 4.9 cases per million per year in the general population.^{[23](#page-8-15)} There are still no reliable data about the occurrence of postintubation tracheal stenosis in recovered COVID-19 patients. Actually, this is the largest report of post–COVID-19–related tracheal stenosis. In the literature, no more than case series are present,

FIGURE 6. Postoperative findings of the study. ICU, Intensive care unit.

not exceeding a dozen patients. Nevertheless, limitations are present: PSM was chosen to allow regression on multiple variables in a small sample size, which is an imperfect method of controlling confounders, but at least a way to attempt to increase comparability between groups; PSM cannot account for unmeasured variables (eg, maybe those who survived COVID-19 are more robust than average and this is why outcomes were similarly good); however, no statistical methods analyzing retrospective data could be representative of the population as a whole; Acknowledging that tracheal stenosis is a rare disease, there is an increased likelihood of a Type II error occurring when the cohort of the study is small.

The tracheostomy etiology seems to have an implication because it is a more frequent preoperative variable in COVID-19 patients, due to both cuff damage and cartilage injury caused during the stoma procedure with no differences. However, this is a fact that should be taken into account by surgeons at the preoperative evaluation, explaining to the patient the potential risks. Further prospective multicentric studies would be useful to confirm the results and to identify a real preventive strategy.

Finally, severe SARS-CoV-2 disease is becoming more infrequent at the moment. However, the disease and its consequences are still present. Moreover, the current experience may represent know-how useful in future, unpredictable situations involving intracellular respiratory infection with intense local inflammation and requiring prolonged intubation, and determining tracheal stenosis.

In conclusion, Tracheal resection continues to be effective in COVID-19–related tracheal stenosis scenarios, with no differences in long-term postoperative outcomes. ICU admission rate and postoperative complications seem to be higher in post–COVID-19 patients who underwent tracheal resection compared with non–COVID-19 patients.

Webcast (\triangle)

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Conflict of Interest Statement

The authors reported no conflicts of interest.

The Journal policy requires editors and reviewers to disclose conflicts of interest and to decline handling manuscripts for which they may have a conflict of interest. The editors and reviewers of this article have no conflicts of interest.

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