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ORIGINAL RESEARCH

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# Risk factors for developing subglottic and tracheal stenosis from the medical intensive care unit

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## Abstract

**Objective:** Endotracheal intubation is a common procedure in the medical intensive care unit (MICU), but it carries risk of complications including, but not limited to, subglottic stenosis (SGS) and tracheal stenosis (TS). Current literature suggests identifiable risk factors for the development of airway complications. This study is a comprehensive evaluation of potential risk factors in patients who developed SGS and TS following endotracheal intubation in our MICU.

**Methods:** Patients intubated in our MICU were identified from 2013 to 2019. Diagnoses of SGS or TS within 1 year of MICU admission were identified. Data extracted included age, sex, body measurements, comorbidities, bronchoscopies, endotracheal tube size, tracheostomy, social history, and medications. Patients with prior diagnosis of airway complication, tracheostomy, or head and neck cancer were excluded. Univariate and multivariate logistic regressions were performed.

**Results:** A total of 136 patients with TS or SGS were identified out of a sample of 6603 patients intubated in the MICU. Cases were matched to controls who did not develop airway stenosis based on identical Charlson Comorbidity Index scores. Eighty six controls were identified with a complete record of endotracheal/tracheostomy tube size, airway procedures, sociodemographic data, and medical diagnosis. Regression analysis showed that SGS or TS were associated with tracheostomy, bronchoscopy, chronic obstructive pulmonary disease, current tobacco use, gastroesophageal reflux disease, systemic lupus erythematosus, pneumonia, bronchitis, and numerous medication classes.

**Conclusion:** Various conditions, procedures, and medications are associated with an increased risk of developing SGS or TS.

**Level of evidence:** 4.

KEYWORDS
intubation, subglottic stenosis, tracheal stenosis

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## 1 | INTRODUCTION

Endotracheal intubation is an important and regularly performed procedure in the medical intensive care unit (MICU) setting. As with all medical interventions, it is not without risk. The larynx, vocal folds, and trachea are subject to injury both from initial endotracheal tube (ETT) placement and from prolonged intubation duration.[1] Long-term complications include vocal fold fixation/immobility, posterior glottic stenosis, subglottic stenosis (SGS), tracheal stenosis (TS), and posterior glottic granulomas.[2] These complications cause difficulties with phonation, deglutition, and respiration, and repeated surgical interventions with airway dilations and even tracheostomy are often required following these complications. These diagnoses follow the patient well past their initial hospitalization and result in significant morbidity, healthcare costs, and decreased quality of life.[3] Thus, identification and reduction of risk factors that contribute to these complications is an area of interest.

The current literature suggests that there are identifiable risk factors for the development of airway complications after endotracheal intubation which include diabetes, length of intubation, ETT size, patient height, and obstructive sleep apnea, among others.[1–9] Controversy exists regarding appropriate ETT size.[3] The rationale given for larger ETT size is for ease of bronchoscopy, which is thought to decrease length of time intubated and thus laryngotracheal irritation.

The purpose of this study is to create a comprehensive evaluation of the potential risk factors in patients who have developed airway stenosis and/or airway complications after endotracheal intubation in the MICU setting. This paper focuses specifically on the factors associated with the development of SGS and TS.

## 2 | MATERIALS AND METHODS

This retrospective case-control study was approved by the University of Kentucky Institutional Review Board. A retrospective chart review was conducted using CPT codes (31,500, 31,603, 31,605, 31,622, 31,600, and 43,246) for intubation, bronchoscopy, tracheostomy, percutaneous endoscopic gastrostomy, or emergency intubation between January 1, 2013 and July 31, 2019. ICD10 codes (J95.5, J38.6, J38.7, J39.8, J95) for "subglottic stenosis, postprocedural", "larynx stenosis", "other diseases of larynx", "other specified diseases of upper respiratory tract", and "intraoperative and postprocedural complications and disorders of respiratory system, not elsewhere classified" were utilized. Similarly, ICD9 codes (478.74, 478.79, 519.19) for "stenosis of larynx and glottis", "other diseases of larynx, not elsewhere classified", and "other diseases of trachea and bronchus" were utilized. All patients aged 18–100 that were intubated in the MICU setting from January 1, 2013 to July 31, 2019 at the University of Kentucky were identified. Patients with a diagnosis of TS and/or SGS within 1 year after discharge were included among the cases within each cohort.

The University of Kentucky Center for Clinical and Translational Science was used to query clinical data from the electronic medical record (grant number UL1TR001998). Data collected included age, gender, body-mass index (BMI), weight, height, emergent versus planned intubation, size of ETT, bronchoscopies, and mechanical ventilation settings. In addition, comorbidities such as cardiopulmonary disease, obstructive sleep apnea (OSA), gastroesophageal reflux disease (GERD), and smoking status were collected, along with the Charlson Comorbidity Index (CCI). Medication history was obtained including use of proton pump inhibitors (PPIs), H2 antagonists, oral/intravenous (IV) steroids, inhaled steroids, immunosuppressants, and anticoagulants. Specific diagnoses of impaired laryngeal function and airway stenosis within 1 year of hospital admission were identified using the previously mentioned codes. Additionally, otolaryngology consultation and presence/absence of laryngeal examination were noted. Patients with a prior diagnosis of airway stenosis, prior airway procedures, and head and neck cancer diagnosis were flagged on the dataset and excluded. For patients diagnosed with SGS and/or TS, controls with identical CCI scores and a complete record of endotracheal/tracheostomy tube size, airway procedures, sociodemographic data, and medical diagnosis were identified from the database. For the cases and controls, patient data sets were reviewed by the investigators, and data missing from the initial extraction were manually inputted into our database of intubated patients. This data was compiled in Microsoft Excel (Microsoft Corp., Redmond, WA).

Counts and percentages were recorded for each variable. Dichotomous variables were compared using Chi-squared testing for univariate analysis and logistic regression for multivariate comparison. Continuous or categorical variables were compared between groups using the Mann–Whitney U test. A *P*-value of .05 or less was considered statistically significant. Odds ratios and confidence intervals were recorded for univariate and multivariate analysis. Both univariate logistic regression analysis and multivariate logistic regression analysis were used to predict associated risk factors. Results were considered statistically significant if the resulting *P*-value was less than .05. Statistical analysis was performed using STATA 12.1 (College Station, TX).

## 3 | RESULTS

### 3.1 | Demographics for patients developing subglottic stenosis and tracheal stenosis

A total of 6603 patients were intubated in the MICU during the study period. A total of 267 (4.04%) patients with post-intubation airway complications were identified. 136 (2.01%) patients with SGS or TS were identified. Patients excluded from this analysis were those with posterior glottic stenosis, glottic stenosis not otherwise specified, vocal cord immobility, posterior glottic granulomas, and airway stenosis not otherwise specified. Cases were matched to controls who did not develop airway stenosis based on identical Charlson Comorbidity Index (CCI) scores. Eighty six controls were identified with a complete record of endotracheal/tracheostomy tube size, airway procedures, sociodemographic data, and medical diagnosis but who did not develop SGS or TS. Table 1 details the demographic data of the controls and patients that developed SGS or TS. 52.5% of patients who developed TS were male, and the mean age was 52.9. For SGS, 56.3% were male, and the mean age was 51.8.

**TABLE 1** Demographics table for controls and patients developing subglottic and tracheal stenosis.

| Variable | Controls *n* = 86 *N* (%) | Subglottic stenosis *n* = 48 *N* (%) | Tracheal stenosis *n* = 122 *N* (%) | Subglottic stenosis and tracheal stenosis *n* = 34 *N* (%) |
|---|---|---|---|---|
| *Sex* | | | | |
| Male | 40 (46.5) | 27 (56.3) | 64 (52.5) | 19 (55.9) |
| Female | 46 (53.5) | 21 (43.8) | 58 (47.5) | 15 (44.1) |
| Total | 86 (100) | 48 (100) | 122 (100) | 34 (100) |
| *Race* | | | | |
| White | 77 (89.5) | 42 (87.5) | 112 (91.8) | 29 (85.3) |
| Black | 9 (10.5) | 6 (12.5) | 10 (8.20) | 5 (14.7) |
| American Indian/Alaskan | 0 (0) | 0 (0) | 0 (0) | 0 (0) |
| *Ethnicity* | | | | |
| Hispanic | 2 (2.33) | 1 (2.08) | 1 (0.82) | 1(2.94) |
| Non-Hispanic | 81 (94.2) | 47 (97.9) | 120 (98.4) | 33 (97.1) |
| Not reported | 3 (3.49) | 0 (0) | 1 (0.82) | 0 (0) |
| | Mean (SD) | Mean (SD) | Mean (SD) | Mean (SD) |
| *Age* (year) | 57.5 (16.3) | 51.7 (16.1) | 52.9 (14.7) | 51.4 (14.1) |
| *BMI* | 27.0 (8.8) | 31.9 (10.1) | 31.5 (10.9) | 32.3 (8.35) |
| *Height* (cm) | 171 (10.6) | 168 (12.8) | 169 (12.4) | 169 (12.5) |
| *Weight* (kg) | 78.5 (24.3) | 90.7 (32.3) | 90.2 (32.1) | 92.5 (28.1) |
| *Length of admission* (days) | 22.8 (40.9) | 23.8 (18.4) | 27.7 (24.8) | 25.1 (20.1) |

Further details regarding body habitus and length of admission are described in Table 1. For TS, the mean for BMI, height, and weight was 31.5, 169 cm, and 90.2 kg, respectively. The same for SGS was 31.9, 168 cm, and 90.7 kg, respectively. The average length of admission was 27.7 days for TS and 23.7 days for SGS. Table 2 shows the frequency and percentiles of analyzed variables, and Tables 3 and 4 detail univariate and multivariate regression outcomes, respectively.

## 3.2 | Conditions associated with subglottic stenosis and tracheal stenosis

On univariate analysis, medical conditions associated with TS were asthma (odds ratio (OR) = 3.18, 95% confidence interval (95%CI) [1.90, 5.33]; $P < .001$), chronic obstructive pulmonary disease (COPD) (OR = 3.64, 95%CI [2.36, 5.64]; $P < .001$), tobacco smoking (OR = 1.91, 95%CI [1.25, 2.91]; $P = .003$), GERD (OR = 2.99, 95%CI [1.93, 4.63]; $P < .001$), systemic lupus erythematosus (SLE) (OR = 8.41, 95%CI [1.67, 42.2]; $P = .01$), OSA (OR = 3.15, 95%CI [1.87, 5.31]; $P < .001$), coronary artery disease (OR = 1.66, 95%CI [1.09, 2.53]; $P = .02$), pneumonia (OR = 4.25, 95%CI [2.67, 6.78]; $P < .001$), and bronchitis (OR = 7.33, 95%CI [4.38, 12.3]; $P < .001$). Conditions associated with SGS on univariate analysis included asthma (OR = 2.34, 95% CI [1.19, 4.62]; $P = .01$), COPD (OR = 2.65, 95%CI [1.43, 4.91]; $P = .002$), tobacco smoking (OR = 2.18, 95%CI [1.16, 4.09]; $P = .02$), GERD (OR = 3.40, 95%CI [1.85, 6.27]; $P < .001$), pneumonia (OR = 2.07, 95%CI [1.10, 3.89]; $P = .02$), and bronchitis (OR = 3.05, 95%CI [1.60, 5.78]; $P = .001$). Conditions associated with developing either TS or SGS on univariate analysis included tobacco smoking (OR = 1.83, 95%CI [1.21, 2.75]; $P = .004$), GERD (OR = 3.21, 95%CI [2.10, 4.93]; $P < .001$), SLE (OR = 7.18, 95%CI [1.43, 36.0]; $P = .02$), OSA (OR = 3.18, 95%CI [1.90, 5.33]; $P < .001$), and pneumonia (OR = 4.17, 95%CI [2.67, 6.51]; $P < .001$).

On multivariate analysis, a history of COPD was associated with the development of TS (OR = 2.08, 95%CI [1.02, 4.22]; $P = .04$) and either SGS or TS (OR = 2.28, 95%CI [1.13, 4.59]; $P = .02$). Tobacco smoking was associated with TS (OR = 2.01, 95%CI [1.02, 3.98]; $P = .04$) and either SGS or TS (OR = 1.95, 95%CI [1.00, 3.78]; $P = .05$) but not SGS alone ($P = .21$). GERD was associated with TS (OR = 2.19, 95%CI [1.11, 4.34]; $P = .02$), SGS (OR = 2.79, 95%CI [1.15, 6.81]; $P = .02$) and either SGS or TS (OR = 2.48, 95%CI [1.26, 4.88]; $P = .01$). SLE was associated with TS (OR = 14.3, 95%CI [1.13, 181]; $P = .04$) or either SGS or TS (OR = 16.22, 95%CI [1.22, 216.12]; $P = .04$) but not SGS alone ($P = .06$). Bronchitis was similarly associated with TS (OR = 3.80, 95%CI [1.78, 8.10]; $P < .001$) and either SGS or TS (OR = 3.71, 95%CI [1.75, 7.87]; $P < .001$) but not SGS alone ($P = .18$).

## 3.3 | Procedures associated with subglottic stenosis and tracheal stenosis

On univariate analysis, procedures associated with TS included intubation (OR = 0.17, 95%CI [0.09, 0.31]; $P < .001$), therapeutic bronchoscopy (OR = 3.44, 95%CI [2.21, 5.35]; $P = .001$), tracheostomy

**TABLE 2** Incidences (*N*) and percentages (%) of comorbid diagnosis, procedures, and medications for patients that developed SGS and TS.

| Variable | Tracheal stenosis *N* (%) | Subglottic stenosis *N* (%) |
|---|---|---|
| Asthma | 36 (29.5) | 14 (29.2) |
| COPD | 78 (63.9) | 30 (62.5) |
| Emphysema | 14 (11.5) | 6 (12.5) |
| Rheumatoid arthritis | 6 (4.92) | 3 (6.25) |
| Sjogren's syndrome | 0 (0) | 0 (0) |
| GPA | 1 (0.82) | 0 (0) |
| Relapsing polychondritis | 4 (3.28) | 1 (2.08) |
| Sarcoidosis | 1 (0.82) | 0 (0) |
| Current smoker | 75 (61.5) | 32 (66.7) |
| GERD | 59 (48.4) | 27 (56.3) |
| SLE | 6 (4.92) | 2 (4.17) |
| Alcohol use | 14 (11.5) | 7 (14.6) |
| Obstructive sleep apnea | 35 (28.7) | 12 (25.0) |
| Hemorrhagic shock | 13 (10.7) | 2 (4.17) |
| Anaphylactic shock | 2 (1.64) | 2 (4.17) |
| PVD | 10 (8.20) | 6 (12.5) |
| Carotid stenosis | 3 (2.46) | 1 (2.08) |
| Coronary artery disease | 59 (48.4) | 22 (45.8) |
| Stroke | 12 (9.84) | 5 (10.4) |
| Pneumonia | 92 (75.4) | 32 (66.7) |
| Bronchitis | 53 (43.4) | 18 (37.5) |
| Sepsis | 64 (52.5) | 24 (50.0) |
| SIRS | 2 (1.64) | 1 (2.08) |
| Intubation | 89 (73.0) | 39 (81.3) |
| Therapeutic bronchoscopy | 59 (48.4) | 20 (41.7) |
| EGD | 2 (1.64) | 2 (4.17) |
| Tracheostomy | 23 (18.9) | 8 (16.7) |
| Diagnostic bronchoscopy | 32 (26.2) | 10 (20.8) |
| Bronchoscopy count | 91 (74.6) | 30 (62.5) |
| Tube size | — | — |
| CCI | — | — |
| ENT note | 2 (1.64) | 1 (2.08) |
| Extubation count | 30 (24.6) | 16 (33.3) |
| PPIs | 43 (35.2) | 25 (52.1) |
| H2 antagonists | 20 (16.4) | 15 (31.3) |
| Vasopressors | 0 (0) | 0 (0) |
| Oral and IV steroids | 59 (48.4) | 26 (54.2) |
| Inhaled steroids | 12 (9.84) | 5 (10.4) |
| Immunosuppressants | 21 (17.2) | 4 (8.33) |
| Anticoagulants | 59 (48.4) | 30 (62.5) |

Abbreviations: CCI, Charlson Comorbidity Index; COPD, chronic obstructive pulmonary disease; EGD, esophagogastroduodenoscopy; GERD, gastroesophageal reflux disease; GPA, granulomatosis with polyangiitis; PPIs, proton pump inhibitors; PVD, peripheral vascular disease; SIRS, systemic inflammatory response syndrome; SLE, systemic lupus erythematosus.

(OR = 2.69, 95%CI [1.47, 4.93]; $P = .001$), diagnostic bronchoscopy (OR = 3.39, 95%CI [1.96, 5.87]; $P < .001$), and increased bronchoscopy count (OR = 3.13, 95%CI [2.21, 4.44]; $P < .001$). Similarly, procedures associated with SGS on univariate analysis included therapeutic bronchoscopy (OR = 1.91, 95%CI [1.03, 3.54]; $P = .04$), and an increased bronchoscopy count (OR = 1.71, 95%CI [1.10, 2.68]; $P = .02$). On univariate analysis, procedures associated with the development of either SGS or TS include intubation (OR = 0.17, 95%CI [0.09, 0.31]; $P < .001$), therapeutic bronchoscopy (OR = 3.39, 95%CI [2.20, 5.23]; $P < .001$), tracheostomy (OR = 2.98, 95%CI [1.63, 5.44]; $P < .001$), diagnostic bronchoscopy (OR = 3.81, 95%CI [2.20, 6.60]; $P < .001$), and increased bronchoscopy count (OR = 3.27, 95%CI [2.31, 4.62]; $P < .001$).

When analyzed continuously, SGS was associated with decreased ETT size on univariate analysis (OR = 0.41, 95%CI [0.22, 0.78]; $P = .01$) and multivariate analysis (OR = 0.37, 95%CI [0.15, 0.93]; $P = .03$). On univariate analysis, the ratio of ETT size to height in mm/m (ETT/ht) was not associated with the development of TS or SGS. However, when analyzed ordinally, patients with an ETT/ht ratio greater than 4.5 were associated with an increased risk of TS alone (OR = 1.68, 95%CI [1.10, 2.57]; $P = .02$) and either SGS or TS (OR = 1.62, 95%CI [1.08, 2.44]; $P = .02$) but not SGS alone.

On multivariate analysis, procedures associated with TS included therapeutic bronchoscopy (OR = 2.68, 95%CI [1.35, 5.34]; $P = .01$), tracheostomy (OR = 4.64, 95%CI [1.86, 11.60]; $P = .001$), and diagnostic bronchoscopy (OR = 2.39, 95%CI [1.07, 5.34]; $P = .03$). On multivariate analysis, procedures associated with the development of both SGS or TS included therapeutic bronchoscopy (OR = 2.80, 95% CI [1.41, 5.58]; $P = .003$), tracheostomy (OR = 5.03, 95%CI [2.02, 12.6]; $P = .001$), and diagnostic bronchoscopy (OR = 2.83, 95%CI [1.27, 6.30]; $P = .01$).

### 3.4 | Medications associated with subglottic stenosis or tracheal stenosis

Of the medications analyzed, those associated with TS alone on univariate analysis included PPIs (OR = 1.77, 95%CI [1.13, 2.77]; $P = .01$), oral/IV steroids (OR = 3.92, 95%CI [2.50, 6.15]; $P < .001$), inhaled steroids (OR = 3.85, 95%CI [1.58, 9.40]; $P = .003$), immunosuppressants (OR = 4.65, 95%CI [2.28, 9.48]; $P < .001$), and anticoagulants (OR = 2.16, 95%CI [1.41, 3.30]; $P < .001$). On univariate analysis, medications associated with SGS included PPIs (OR = 3.50, 95%CI [1.90, 6.45]; $P < .001$), H2 antagonists (OR = 4.34, 95%CI [2.17, 8.71]; $P < .001$), oral/IV steroids (OR = 3.75, 95%CI [2.04, 6.93]; $P < .001$), and anticoagulants (OR = 3.55, 95%CI [1.91, 6.61]; $P < .001$). All medication categories were associated with the development of either SGS or TS on univariate analysis.

On multivariate analysis, oral/IV steroids (OR = 2.87, 95%CI [1.20, 6.88]; $P = .02$) and immunosuppressants (OR = 0.17, 95%CI [0.03, 0.87]; $P < .03$) were associated with the development of SGS. No medications were associated with the development of TS on multivariate analysis. Only oral/IV steroid use was statistically associated

**TABLE 3** Univariate analysis odds ratios (OR) and 95% confidence intervals (95%CI) for the development of tracheal and subglottic stenosis.

| Univariate Variable | Tracheal stenosis | | Subglottic stenosis | | Tracheal or subglottic stenosis | |
|---|---|---|---|---|---|---|
| | OR (95%CI) | *p* | OR (95%CI) | *p* | OR (95%CI) | *p* |
| Age | 1.00 (0.98–1.01) | .518 | 0.99 (0.98–1.01) | .403 | 1.00 (0.98–1.01) | .481 |
| BMI | 1.02 (1.00–1.03) | .116 | 1.02 (0.99–1.04) | .244 | 1.02 (1.00–1.03) | .103 |
| Height (cm) | 0.99 (0.97–1.01) | .247 | 0.98 (0.96–1.01) | .179 | 0.99 (0.97–1.00) | .121 |
| Weight (kg) | 1.00 (1.00–1.01) | .227 | 1.00 (0.99–1.01) | .421 | **1.00 (1.00–1.01)** | .259 |
| Death | **0.27 (0.14–0.52)** | ***.0001*** | **0.06 (0.01–0.45)** | ***.006*** | **0.23 (0.12–0.43)** | ***.0001*** |
| Race | 1.07 (0.50–2.29) | .866 | 1.82 (0.71–4.63) | .21 | 1.05 (0.50–2.21) | .9 |
| Male | 1.40 (0.92–2.13) | .112 | 1.56 (0.85–2.86) | .147 | 1.46 (0.98–2.19) | .064 |
| Ethnicity | 0.50 (0.06–4.31) | .527 | 1.58 (0.18–13.8) | .678 | 0.43 (0.05–3.68) | .437 |
| Rurality | 0.95 (0.88–1.04) | .26 | 0.93 (0.82–1.05) | .223 | 0.96 (0.89–1.04) | .287 |
| Appalachian | **0.55 (0.36–0.84)** | ***.005*** | 0.65 (0.35–1.18) | .156 | **0.56 (0.37–0.84)** | ***.005*** |
| Distance to hospital (miles) | 1.00 (0.99–1.00) | .06 | 0.99 (0.99–1.00) | .095 | 1.00 (0.99–1.00) | .057 |
| Median household income ($) | 1.00 (1.00–1.00) | .708 | 1.00 (1.00–1.00) | .35 | 1.00 (1.00–1.00) | .508 |
| Asthma | **3.18 (1.90–5.33)** | ***.0001*** | **2.34 (1.19–4.62)** | ***.014*** | 3.19 (1.91–5.33) | *.0001* |
| COPD | **3.64 (2.36–5.64)** | ***.0001*** | **2.65 (1.43–4.91)** | ***.002*** | 3.72 (2.44–5.67) | *.0001* |
| Emphysema | 1.80 (0.89–3.64) | .103 | 1.77 (0.70–4.49) | .232 | 1.72 (0.86–3.46) | .125 |
| Rheumatoid arthritis | 1.83 (0.64–5.25) | .262 | 2.16 (0.59–7.95) | .246 | 1.56 (0.54–4.47) | .409 |
| GPA | 1.34 (0.12–14.9) | .81 | – | – | 1.15 (0.10–12.8) | .908 |
| Relapsing polychondritis | 5.51 (1.00–30.5) | .051 | 1.69 (0.19–14.7) | .637 | 4.71 (0.85–26.0) | .076 |
| Current smoker | **1.91 (1.25–2.91)** | ***.003*** | **2.18 (1.16–4.09)** | ***.016*** | **1.83 (1.21–2.75)** | ***.004*** |
| GERD | **2.99 (1.93–4.63)** | ***.0001*** | **3.40 (1.85–6.27)** | ***.0001*** | **3.21 (2.10–4.93)** | ***.0001*** |
| SLE | **8.41 (1.67–42.2)** | ***.01*** | 2.86 (0.56–14.6) | .206 | **7.18 (1.43–36.0)** | ***.017*** |
| Alcohol use | 0.75 (0.40–1.42) | .383 | 1.07 (0.46–2.51) | .869 | 0.85 (0.47–1.55) | .597 |
| Obstructive sleep apnea | **3.15 (1.87–5.31)** | ***.0001*** | 1.89 (0.93–3.85) | .077 | **3.18 (1.90–5.33)** | ***.0001*** |
| Hemorrhagic shock | 1.27 (0.64–2.55) | .494 | 0.40 (0.09–1.73) | .221 | 1.08 (0.54–2.15) | .836 |
| Anaphylactic shock | 5.43 (0.49–60.5) | .169 | **17.4 (1.55–196)** | ***.021*** | 4.66 (0.42–51.8) | .211 |
| PVD | 1.08 (0.50–2.32) | .846 | 1.83 (0.72–4.67) | .204 | 1.22 (0.59–2.53) | .593 |
| Carotid stenosis | 1.15 (0.29–4.53) | .839 | 0.93 (0.11–7.48) | .943 | 0.99 (0.25–3.87) | .984 |
| Coronary artery disease | **1.66 (1.09–2.53)** | ***.018*** | 1.34 (0.74–2.45) | .337 | 1.51 (1.00–2.27) | .049 |
| Stroke | 1.16 (0.57–2.37) | .674 | 1.22 (0.45–3.27) | .698 | 1.12 (0.56–2.24) | .75 |
| Pneumonia | **4.25 (2.67–6.78)** | ***.0001*** | **2.07 (1.10–3.89)** | ***.024*** | **4.17 (2.67–6.51)** | ***.0001*** |
| Bronchitis | **7.33 (4.38–12.3)** | ***.0001*** | **3.05 (1.60–5.78)** | ***.001*** | **7.13 (4.25–11.9)** | ***.0001*** |
| Sepsis | 1.72 (1.13–2.61) | .012 | 1.39 (0.76–2.53) | .285 | 1.73 (1.15–2.60) | .008 |
| SIRS | 0.44 (0.10–1.98) | .284 | 0.64 (0.08–4.96) | .665 | 0.37 (0.08–1.70) | .202 |
| Intubation | **0.17 (0.09–0.31)** | ***.0001*** | 0.52 (0.24–1.15) | .106 | **0.17 (0.09–0.31)** | ***.0001*** |
| Therapeutic bronchoscopy | **3.44 (2.21–5.35)** | ***.0001*** | **1.91 (1.03–3.54)** | ***.038*** | **3.39 (2.20–5.23)** | ***.0001*** |
| EGD | 1.35 (0.24–7.44) | .734 | 4.32 (0.77–24.2) | .097 | 2.33 (0.46–11.7) | .304 |
| Tracheostomy | **2.69 (1.47–4.93)** | ***.001*** | 1.76 (0.77–4.01) | .181 | **2.98 (1.63–5.44)** | ***.0001*** |
| Diagnostic bronchoscopy | **3.39 (1.96–5.87)** | ***.0001*** | 1.73 (0.81–3.67) | .155 | **3.81 (2.20–6.60)** | ***.0001*** |
| Bronchoscopy count | **3.13 (2.21–4.44)** | ***.0001*** | **1.71 (1.10–2.68)** | ***.018*** | **3.27 (2.31–4.62)** | ***.0001*** |
| Tube size | 1.40 (0.84–2.33) | .200 | **0.41 (0.22–0.78)** | ***.006*** | 0.94 (0.59–1.52) | .81 |
| ETT/height | 1.78 (1.02–3.26) | .052 | 0.88 (0.46–1.85) | .709 | 0.38 (0.87–2.58) | .168 |
| ETT/height >=4.5 (mm/m) | **1.68 (1.10–2.57)** | ***.017*** | 1.18 (0.65–2.16) | .597 | **1.62 (1.08–2.44)** | ***.021*** |
| CCI | 1.06 (1.00–1.12) | .052 | 0.97 (0.89–1.06) | .478 | 1.04 (0.99–1.10) | .123 |
| ENT note | 5.43 (0.49–60.5) | .169 | 4.24 (0.38–47.7) | .242 | – | – |
| Extubation count | 0.69 (0.44–1.10) | .121 | 1.16 (0.63–2.14) | .638 | 0.78 (0.50–1.21) | .261 |

(Continues)

**TABLE 3** (Continued)

| Univariate Variable | Tracheal stenosis | | Subglottic stenosis | | Tracheal or subglottic stenosis | |
|---|---|---|---|---|---|---|
| | OR (95%CI) | *p* | OR (95%CI) | *p* | OR (95%CI) | *p* |
| PPIs | **1.77 (1.13–2.77)** | ***.013*** | **3.50 (1.90–6.45)** | ***.0001*** | **1.92 (1.24–2.98)** | ***.004*** |
| H2 antagonists | 1.75 (0.96–3.18) | .068 | **4.34 (2.17–8.71)** | ***.0001*** | **2.10 (1.17–3.76)** | ***.013*** |
| Oral and IV steroids | **3.92 (2.50–6.15)** | ***.0001*** | **3.75 (2.04–6.93)** | ***.0001*** | **4.33 (2.78–6.74)** | ***.0001*** |
| Inhaled steroids | **3.85 (1.58–9.40)** | ***.003*** | 2.80 (0.98–8.02) | .055 | **3.27 (1.34–7.95)** | ***.009*** |
| Immunosuppressants | **4.65 (2.28–9.48)** | ***.0001*** | 1.09 (0.37–3.22) | .883 | **3.90 (1.92–7.93)** | ***.0001*** |
| Anticoagulants | **2.16 (1.41–3.30)** | ***.0001*** | **3.55 (1.91–6.61)** | ***.0001*** | **2.48 (1.63–3.76)** | ***.0001*** |

*Note*: Statistically significant results have been bolded with the *P*-values italicized.
Abbreviations: BMI, body mass index; CCI, Charlson Comorbidity Index; COPD, chronic obstructive pulmonary disease; EGD, esophagogastroduodenoscopy; ETT, endotracheal tube; GERD, gastroesophageal reflux disease; GPA, granulomatosis with polyangiitis; PPIs, proton pump inhibitors; PVD, peripheral vascular disease; SIRS, systemic inflammatory response syndrome; SLE, systemic lupus erythematosus.

**TABLE 4** Multivariate analysis odds ratios (OR) and 95% confidence intervals (95%CI) for the development of tracheal and subglottic stenosis.

| Multivariate Variable | Tracheal stenosis | | Subglottic stenosis | | Tracheal or subglottic stenosis | |
|---|---|---|---|---|---|---|
| | OR (95%CI) | *p* | OR (95%CI) | *p* | OR (95%CI) | *p* |
| Age | 0.98 (0.96–1.01) | .162 | 1.01 (0.98–1.05) | .532 | 0.99 (0.96–1.01) | .344 |
| BMI | 0.95 (0.79–1.16) | .630 | 0.82 (0.63–1.08) | .158 | 0.98 (0.81–1.18) | .799 |
| Height (cm) | 0.98 (0.90–1.06) | .604 | 0.94 (0.84–1.06) | .301 | 0.98 (0.91–1.06) | .659 |
| Weight (kg) | 1.02 (0.95–1.09) | .568 | 1.07 (0.97–1.17) | .165 | 1.01 (0.95–1.08) | .732 |
| Length of stay (days) | 0.99 (0.98–1.00) | .175 | 0.98 (0.96–1.01) | .129 | 0.99 (0.98–1.00) | .099 |
| Race | 0.86 (0.28–2.71) | .803 | 2.37 (0.59–9.46) | .223 | 1.12 (0.38–3.30) | .834 |
| Male | 1.88 (0.78–4.50) | .157 | 1.48 (0.42–5.29) | .543 | 1.79 (0.77–4.14) | .176 |
| Ethnicity | 0.49 (0.01–19.8) | .704 | 2.50 (0.03–210) | .686 | 0.25 (0.00–13.4) | .494 |
| Rurality | 1.13 (0.95–1.36) | .168 | 0.88 (0.68–1.15) | .356 | 1.12 (0.94–1.33) | .213 |
| Appalachian | **0.30 (0.12–0.71)** | ***.007*** | 1.38 (0.39–4.84) | .613 | **0.34 (0.15–0.80)** | ***.013*** |
| Distance to hospital (miles) | 1.00 (0.99–1.00) | .231 | 1.00 (0.98–1.01) | .503 | 1.00 (0.99–1.00) | .380 |
| Median household income ($) | 1.00 (1.00–1.00) | .892 | 1.00 (1.00–1.00) | .899 | 1.00 (1.00–1.00) | .577 |
| Asthma | 0.99 (0.44–2.25) | .988 | 0.88 (0.30–2.54) | .812 | 0.90 (0.40–2.03) | .794 |
| COPD | **2.08 (1.02–4.22)** | ***.044*** | 1.85 (0.70–4.94) | .216 | **2.28 (1.13–4.59)** | ***.021*** |
| Emphysema | 0.88 (0.29–2.63) | .815 | 2.16 (0.60–7.76) | .238 | 0.91 (0.31–2.66) | .858 |
| Rheumatoid arthritis | 1.27 (0.25–6.41) | .772 | 1.00 (0.16–6.41) | .996 | 0.83 (0.17–4.11) | .823 |
| GPA | 1.14 (0.03–47.3) | .944 | – | – | 1.26 (0.03–52.7) | .902 |
| Relapsing polychondritis | 2.50 (0.18–34.1) | .492 | 3.58 (0.28–46.4) | .329 | 2.14 (0.16–28.8) | .568 |
| Current smoker | **2.01 (1.02–3.98)** | ***.044*** | 1.81 (0.71–4.64) | .213 | **1.95 (1.00–3.78)** | ***.049*** |
| GERD | **2.19 (1.11–4.34)** | ***.024*** | **2.79 (1.15–6.81)** | ***.024*** | **2.48 (1.26–4.88)** | ***.008*** |
| SLE | **14.31 (1.13–181)** | ***.04*** | 11.31 (0.92–139) | .058 | **16.22 (1.22–216)** | ***.035*** |
| Alcohol use | 0.62 (0.24–1.56) | .309 | 1.25 (0.38–4.15) | .712 | 0.70 (0.29–1.70) | .436 |
| Obstructive sleep apnea | 1.30 (0.56–3.01) | .541 | 0.92 (0.28–3.02) | .894 | 1.38 (0.59–3.21) | .455 |
| Hemorrhagic shock | 0.85 (0.29–2.44) | .759 | 0.26 (0.04–1.71) | .162 | 0.72 (0.25–2.10) | .552 |
| Anaphylactic shock | 1.08 (0.07–16.6) | .954 | **28.8 (1.23–676)** | ***.037*** | 0.96 (0.06–16.1) | .980 |
| PVD | 0.43 (0.13–1.46) | .176 | 1.64 (0.40–6.66) | .491 | 0.59 (0.19–1.86) | .367 |
| Carotid stenosis | 1.75 (0.21–14.9) | .608 | 2.70 (0.16–45.0) | .489 | 1.64 (0.19–14.0) | .653 |
| Coronary artery disease | 1.36 (0.66–2.83) | .406 | 0.81 (0.29–2.23) | .685 | 1.12 (0.54–2.30) | .768 |
| Stroke | 1.02 (0.36–2.89) | .966 | 1.59 (0.41–6.23) | .506 | 0.96 (0.35–2.62) | .941 |
| Pneumonia | 1.41 (0.72–2.78) | .317 | 1.35 (0.51–3.56) | .539 | 1.57 (0.81–3.04) | .181 |

**TABLE 4** (Continued)

| Multivariate Variable | Tracheal stenosis | | Subglottic stenosis | | Tracheal or subglottic stenosis | |
|---|---|---|---|---|---|---|
| | OR (95%CI) | *p* | OR (95%CI) | *p* | OR (95%CI) | *p* |
| Bronchitis | **3.80 (1.78–8.10)** | ***.001*** | 1.93 (0.73–5.11) | .183 | **3.71 (1.75–7.87)** | ***.001*** |
| Sepsis | 0.84 (0.43–1.61) | .591 | 0.50 (0.21–1.21) | .126 | 0.87 (0.46–1.66) | .681 |
| SIRS | 0.43 (0.08–2.33) | .330 | 0.98 (0.10–9.47) | .986 | 0.34 (0.06–1.98) | .232 |
| Therapeutic bronchoscopy | **2.68 (1.35–5.34)** | ***.005*** | 2.29 (0.82–6.41) | .115 | **2.80 (1.41–5.58)** | ***.003*** |
| EGD with PEG placement | 0.71 (0.07–7.03) | .769 | 11.50 (0.75–176) | .079 | 1.70 (0.17–17.2) | .652 |
| Tracheostomy | **4.64 (1.86–11.6)** | ***.001*** | 1.72 (0.53–5.59) | .369 | **5.03 (2.02–12.6)** | ***.001*** |
| Diagnostic bronchoscopy | **2.39 (1.07–5.34)** | ***.033*** | 2.28 (0.73–7.10) | .155 | **2.83 (1.27–6.30)** | ***.011*** |
| Tube size | 1.51 (0.75–3.03) | .249 | **0.37 (0.15–0.93)** | ***.034*** | 0.82 (0.40–1.66) | .573 |
| CCI | 1.06 (0.95–1.17) | .301 | 0.87 (0.74–1.03) | .104 | 1.03 (0.93–1.14) | .594 |
| ENT note | 5.19 (0.35–77.6) | .233 | 1.61 (0.06–45.0) | .780 | — | — |
| Extubation count | 1.03 (0.51–2.05) | .943 | 1.44 (0.59–3.56) | .426 | 1.31 (0.68–2.52) | .425 |
| PPIs | 0.75 (0.37–1.52) | .418 | 1.64 (0.71–3.78) | .243 | 0.70 (0.35–1.43) | .333 |
| H2 antagonists | 0.75 (0.32–1.77) | .510 | 2.47 (0.94–6.48) | .065 | 0.83 (0.36–1.90) | .652 |
| Oral and IV steroids | 1.96 (0.94–4.06) | .071 | **2.87 (1.20–6.88)** | ***.018*** | **2.48 (1.21–5.08)** | ***.013*** |
| Inhaled steroids | 2.30 (0.68–7.85) | .182 | 1.93 (0.46–8.05) | .369 | 1.50 (0.44–5.12) | .520 |
| Immunosuppressants | 1.59 (0.46–5.55) | .465 | **0.17 (0.03–0.87)** | ***.033*** | 0.96 (0.28–3.30) | .946 |
| Anticoagulants | 0.88 (0.45–1.72) | .714 | 1.88 (0.80–4.41) | .147 | 1.18 (0.60–2.30) | .633 |

*Note*: Statistically significant results have been bolded with the *P*-values italicized.
Abbreviations: BMI, body mass index; CCI, Charlson Comorbidity Index; COPD, chronic obstructive pulmonary disease; EGD, esophagogastroduodenoscopy; GERD, gastroesophageal reflux disease; GPA, granulomatosis with polyangiitis; PPIs, proton pump inhibitors; PVD, peripheral vascular disease; SIRS, systemic inflammatory response syndrome; SLE, systemic lupus erythematosus.

with the development of either SGS or TS (OR = 2.48, 95%CI [1.21, 5.08]; $P = .01$) on multivariate analysis.

## 4 | DISCUSSION

Endotracheal intubation in the MICU is not without risk. Understanding the factors associated with the development of SGS and TS following intubation in the MICU may decrease the frequency of these complications. This study noted several variables associated with SGS and TS.

In contrast to prior literature, our study did not show a significant association between ETT size and the development of airway stenosis.[10] However, an ETT/ht ratio greater than our population mean of 4.5 was associated with the development of TS and either SGS or TS on univariate analysis. Therefore, there is likely a threshold ETT size for a given height that predisposes patients to airway stenosis. Appropriate ETT size based on patient height should be utilized when performing endotracheal intubation to reduce the risk of airway stenosis.

Bronchoscopy was associated with stenosis on multivariate analysis. Part of the rationale for larger ETT size in the MICU is the need for bronchoscopy and possible earlier extubation because of bronchoscopy. Seeing as increases in ETT size were not associated with stenosis, these results are likely due to confounding variables given that patients with more difficult airway diseases such as pneumonia or prolonged intubation may have an increased need for bronchoscopies. In that way, stenosis may be more related to airway inflammation due to acute or chronic conditions and less associated with procedural damage due to bronchoscopy. Nevertheless, larger tube sizes are generally required for bronchoscopy, and though our results were unable to demonstrate a discrete association between ETT size and stenosis, it could be that our sample size was too small to show significance. There is a relatively small range of discrete ETT sizes used for intubation, and thus it can be challenging to detect significant differences.

Additionally, we noted an association between autoimmune disorders such as SLE with the development of SGS and TS. It has been established that autoimmune disorders can cause SGS and TS without the presence of mechanical injury such as intubation.[4] It could be that the added insult of trauma during intubation may precipitate the onset of autoimmune-related SGS or TS. It could also be that autoimmune disorders cause susceptibility of inflamed tracheal and glottic tissues to be more severely affected by intubation. Patients with autoimmune conditions comprised a small portion of our patient population (see Table 2), and further analysis on these associations is required in the future.

Steroid use was also associated with SGS and TS. This contrasts with the thought that steroids decrease inflammation and thus decrease the risks of scarring that may lead to stenosis.[11] This protective function may exist for local steroids, but it may be that oral/IV steroids decrease the immune response to pathogens, which may make the tracheal and subglottic mucosa more susceptible to permanent

injury. Additionally, it is unclear how steroids affect the microbiome of the trachea and how this affects healing and scarring.[12] More investigation into this hypothesis is warranted, perhaps looking at specific pathogens. It is also likely that patients might have been given steroids after a diagnosis of stenosis was established, as a form of treatment. We are unable to delineate which factor preceded the other from our data.

Multivariate analysis and univariate analysis both demonstrated an association between GERD and the development of SGS and TS. Digestive acids and enzymes that reflux up the esophagus may enter the airway, again leading to injury that allows for scarring of the tracheal and subglottic tissues.[12] Tracheal fibroblasts transition to myofibroblasts on exposure to gastric juices, which thus can lead to scarring and airway stenosis. Just like steroids, GERD may influence the microbiome of the trachea and affect wound healing.

Unsurprisingly, respiratory problems such as COPD and pneumonia were associated with SGS and TS. Patients with impaired respiratory function are more likely to require longer periods of intubations.[7] They also may require procedures such as bronchoscopies, which require a larger tube size. The same processes that injure the lungs may injure the trachea, again leading to scarring. Smoking tobacco was also associated with stenosis development. This, again, may be secondary to associated respiratory compromise. It may also be due to the established detrimental effects of tobacco on wound healing, including decreased vascularization.

There are limitations to this study that may impede the generalizability of the results. Primarily, the small sample size increases the possibility of error and decreases the overall power of the study. The nature of a retrospective case-control study also introduces inherent limitations that may limit this study's ability to highlight any causal relationship with associated diagnosis, therapies, or medication administration. However, this information may be used to inform clinical decision making and guide more rigorous studies in the future. Additionally, given the single-institution nature of this study, patients may have presented to outside facilities for follow-up or they may have been lost to follow-up due to barriers to care such as distance to hospital.[13] Therefore, the reported incidence of SGS and TS may be an underestimate. For the univariate and multivariate analysis regarding medications, it was not possible to discern whether these medications were pre-intubation medications or whether they were transiently prescribed during the intubation period. Finally, although our multivariate regression evaluated the effect of numerous comorbidities on the development of TS and SGS, we did not analyze the effect of diabetes mellitus. In our MICU population, many patients experience large shifts in glucose levels due to their acute illness and treatments. Therapy for these patients in the MICU is, therefore, almost identical to patients with chronic diabetes. Diabetes was excluded from the analysis to prevent confounding results.

## 5 | CONCLUSION

Multiple variables in a MICU setting may result in damage to a patient's airway and increase a patient's susceptibility to develop airway stenosis. This study demonstrates various clinical factors including patient demographics, comorbid conditions, airway procedures, and medications associated with the development of both TS and SGS. Further research is warranted to investigate how these factors can be recognized in a clinical setting and subsequently altered in a way that decreases the incidence of both SGS and TS.

## CONFLICT OF INTEREST STATEMENT

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