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RESEARCH PAPER

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Tracheostomy is associated with decreased in-hospital mortality during severe COVID-19 infection

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Abstract

Objective: Tracheostomy is often performed in patients with a prolonged course of endotracheal intubation. This study sought to examine the clinical utility of tracheostomy during severe Coronavirus disease 2019 (COVID-19) infection.

Study Design: A retrospective single-system, multicenter observational cohort study was performed on patients intubated for COVID-19 infection. Patients who received intubation alone were compared with patients who received intubation and subsequent tracheostomy. Patient demographics, comorbidities, and hospital courses were analyzed.

Setting: The University of Pennsylvania Health System from 2020 to 2021.

Methods: Logistic regression analysis was performed on patient demographics and comorbidities. Kaplan–Meier survival curves were generated depending on whether patients received a tracheostomy.

Results: Of 777 intubated patients, 452 were male (58.2%) and 325 were female (41.8%) with a median age of 63 (interquartile range [IQR]: 54–73) years. One-hundred and eighty-five (23.8%) patients underwent tracheostomy. The mean time from intubation to tracheostomy was (17.3 ± 9.7) days. Patients who underwent tracheostomy were less likely to expire during their hospitalization than those who did not undergo tracheostomy (odds ratio [OR] = 0.31, $P < 0.001$), and patient age was positively associated with mortality (OR = 1.04 per year, $P < 0.001$). Likelihood of receiving tracheostomy was positively associated with being on extra-corporeal membranous oxygenation (ECMO) (OR = 101.10, $P < 0.001$), immunocompromised status (OR = 3.61, $P = 0.002$), and current tobacco smoking (OR = 4.81, $P = 0.041$). Tracheostomy was also associated with a significantly longer hospital length of stay ([57.5 ± 32.2] days vs. [19.9 ± 18.1] days, $P < 0.001$).

Conclusions: Tracheostomy was associated with reduced in-hospital mortality, despite also being associated with increased comorbidities. Tracheostomy should

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not be held back from patients with comorbidities for this reason alone and may even improve survival in high-risk patients.

KEYWORDS
ARDS, COVID-19, intubation, tracheostomy

Key points

- Tracheostomy is associated with increased comorbidities and hospital length of stay in patients with severe COVID-19 (requiring intubation and mechanical ventilation).
- However, tracheostomy is also associated with reduced in-hospital mortality in these patients.
- Further research is needed to define the clinical utility of tracheostomy for high-risk patients with COVID-19.

INTRODUCTION

During the global Coronavirus disease 2019 (COVID-19) pandemic, acute respiratory distress syndrome (ARDS) was a common complication of COVID-19 infection associated with a significantly increased risk of death, ranging from 30% to 70%.[1–7] Despite the progress made by vaccines,[8] new variants have emerged that may be associated with higher levels of infectivity and transmission, even in vaccinated individuals. Anywhere from 5% to 88% of ICU patients with COVID-19 infection are intubated, with a subset of intubated patients undergoing tracheostomy.[9] Thus, the management of COVID-induced respiratory distress remains a chief concern in the COVID-19 patient population.[10]

In patients receiving intubation, tracheostomy is often performed in cases where a prolonged course of endotracheal intubation is expected to minimize sedation, facilitate ventilator weaning, or to address other clinical complexities. However, the clinical benefit of tracheostomy during COVID-19 infection is not fully understood. Some prior studies suggest that tracheostomy may be associated with decreased overall mortality.[11–13] Additionally, tracheostomy indications and timing remain controversial.[13–16] For instance, Flinspach et al. describe a two-fold increase in mortality when tracheostomy is performed within 10 days compared to after 10 days, while Ji et al. observed no difference in mortality between tracheostomy occurring before or after 14 days. Given this lack of understanding, the benefits of tracheostomy in severe COVID-19 remain ambiguous, and more information is needed to best establish clinical management guidelines.

Throughout the pandemic, several studies assessed these treatment variables in real time and reported evidence-based recommendations that tracheostomy occur no sooner than 2–3 weeks after intubation in COVID-19 patients.[17–20] However, we performed a follow-up study and determined that tracheostomy within 2 weeks of intubation can be considered.[21] As our experience with the management of this disease has grown, the aims of this study were, therefore, to reassess our previous approach and examine the clinical utility of tracheostomy during severe COVID-19 infection.

MATERIAL AND METHODS

Institutional Review Board exemption was obtained from the University of Pennsylvania. A single-system multicenter retrospective observational cohort study was conducted including five hospitals within the University of Pennsylvania Health System (Hospital of the University of Pennsylvania, Penn Presbyterian Medical Center, Pennsylvania Hospital, Chester County Hospital, Medical College of Pennsylvania). Inclusion criteria were all patients admitted with COVID-19 between 2020 and 2021 who underwent intubation with or without subsequent tracheostomy during their hospital stay. Exclusion criteria were intubation for non-COVID-related reasons and prior history of tracheostomy.

For regression and survival analyses, patients who (1) died within 5 days, (2) received a tracheostomy within 5 days, or (3) did not receive a tracheostomy but were extubated within 5 days, were excluded. This cutoff of 5 days was chosen based on standard practices at our institution to consider elective tracheostomy beginning 5 days after intubation or later. A 5-day cutoff also eliminates the potential confounding variable of patients who were not eligible for tracheostomy due to death or extubation within 5 days.

Data including demographic information, past medical history, admission information, presence of ARDS, duration of ventilator requirement, tracheostomy procedure details, complications, length of stay, and disposition information was collected from the electronic health record and stored in REDCap. Patients were identified by ICD-10 and CPT codes.

Comorbidities were defined as conditions identified by the Centers for Disease Control and Prevention as high-risk factors for severe illness from COVID.[22] Ventilator liberation was defined as the first full 24-h period without ventilator assistance. Descriptive variables were summarized by mean (SD) for continuous variables and *n* (%) for categorical variables.

The primary analysis was a multivariate logistic regression performed wherein the dependent variable was whether a patient passed away in the hospital and the predictors being a list of patient demographics, comorbidities, and tracheostomy status (Table 1). Assumption testing and model validation are as follows: multicollinearity was assessed via variance inflation factor (VIF). All terms were found to have a VIF < 3, and all continuous predictors exhibited a linear relationship with the logit of the outcome. To test for influential events, Cook's distance was used to identify outliers (Cook's distance > 4/*n*). Removal of these outliers was not seen to substantively change the model, and therefore all events were included in the model. The secondary analysis was a multivariate logistic regression, conducted with the same methodology as above, wherein the dependent variable is whether the patient received a tracheostomy.

Survival curves based on tracheostomy status were generated by the Kaplan–Meier method, with time from hospital admission to death in days as the dependent variable. As described above, only patients who were intubated for at least 5 days were included in this comparison. As patients were only followed up until death or recovery and discharge, the following assumption was made regarding right-censored data (patients who had recovered and been discharged): recovered patients were assumed to still be alive at the final timepoint. The final timepoint was the length from admission to discharge/death for the longest hospital stay. Cox regression was not used, as multiple variables of interest were seen to violate the proportional hazards assumption, as determined via Schoenfeld test. Instead, nonparametric log-rank tests were employed for a further secondary analysis investigating the relationship between timing of tracheostomy and survival. All patients who underwent tracheostomy were considered for this analysis.

Statistical significance was set at $P < 0.05$ for all analyses. All statistical analysis was performed in RStudio.

TABLE 1 Patient study group.

Term	Total cohort (*n* = 777)	Regression and survival analyses (*n* = 478)
Tracheostomy, *n* (%)	185 (24%)	167 (35%)
Age [years, median (Q_1, Q_3)]	63 (54, 73)	64 (54, 72)
Gender, *n* (%)		
Male	452 (58%)	291 (61%)
Female	325 (42%)	187 (39%)
Race, *n* (%)		
Caucasian	239 (31%)	37 (8%)
Hispanic	88 (11%)	204 (43%)
Black	334 (43%)	142 (30%)
Asian	57 (7%)	62 (13%)
Other	29 (4%)	15 (3%)
Unknown	30 (4%)	18 (4%)
Patient on extra-corporeal membranous oxygenation, *n* (%)	49 (6%)	42 (9%)
Diabetes, *n* (%)	241 (31%)	152 (32%)
Cardiovascular disease, *n* (%)	397 (51%)	255 (53%)
Non-COVID pulmonary disease	139 (18%)	93 (19%)
Chronic kidney disease, *n* (%)	152 (20%)	94 (20%)
Chronic liver disease, *n* (%)	56 (7%)	32 (7%)
Immunocompromised, *n* (%)	55 (7%)	39 (8%)
Smoking, *n* (%)	22 (3%)	15 (3%)
Any comorbidities, *n* (%)	535 (69%)	344 (72%)

RESULTS

The study population details are shown in Table 1. Of 777 patients, 452 were male (58%) and 325 were female (42%) with a median age of 63 (interquartile range [IQR]: 54–73) years. Comorbidities analyzed included being on extra-corporeal membranous oxygenation (ECMO, *n* = 49, 6.3%), diabetes (*n* = 241, 31%), cardiovascular disease (*n* = 397, 51%), non-COVID pulmonary disease (*n* = 139, 18%), chronic kidney disease (*n* = 152, 20%), chronic liver disease (*n* = 56, 7.2%), immunocompromise (*n* = 55, 7.1%), current smoker (*n* = 22, 2.8%). Five hundred and thirty-five patients (69%) had one or more of these comorbidities. One-hundred and eighty-five (24%) patients underwent tracheostomy and the mean time from endotracheal intubation to tracheostomy was (17.3 ± 9.7) days (Figure 1A). Of the original 777 patient cohort, 478 patients were intubated for at least 5 days. Two hundred and ninety-one were male (61%) and 187 were female (39%) with a median age of 64 (IQR: 54–72) years. Comorbidities analyzed included being on ECMO (*n* = 42, 8.8%), diabetes (*n* = 152, 32%), cardiovascular disease (*n* = 255, 53%), non-COVID pulmonary disease (*n* = 93, 19%), chronic kidney disease (*n* = 94, 20%), chronic liver disease (*n* = 32, 6.7%), immunocompromise (*n* = 39, 8.2%), current smoker (*n* = 15, 3.1%). Three hundred and forty-four patients (72%) had one or more of these comorbidities. An overall Kaplan–Meier survival curve is shown in Figure 1B.

To determine what effect tracheostomy had on patient mortality, a logistic regression was performed, with whether the patient passed away in the hospital as the dependent variable and demographic and comorbidity information as predictors (Table 2). Among patients who remained intubated at 5 days, tracheostomy was associated with a significant decrease in mortality ($P < 0.001$, odds ratio [OR] = 0.31). We also observed a significant association between patient age and

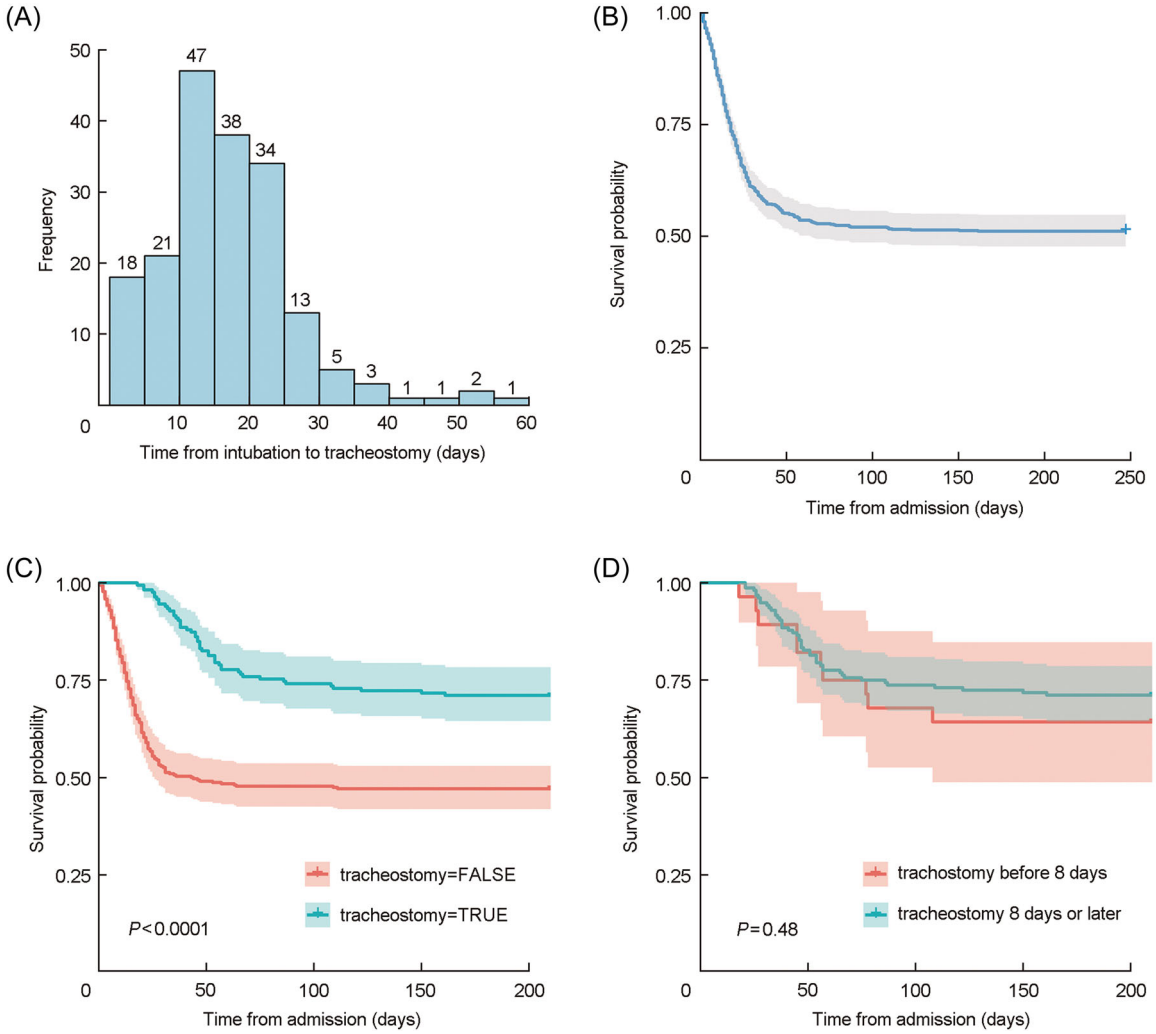

FIGURE 1 Timing and survival characteristics of patients intubated for severe COVID-19 receiving or not receiving tracheostomy. (A) Histogram showing time in days from intubation to tracheostomy; (B) Kaplan–Meier survival curve showing time from hospital admission to death in days, Gray area denotes 95% confidence interval; (C) Kaplan–Meier survival curve comparing patients who underwent tracheostomy ($n = 167$, blue) versus those who did not ($n = 311$, red), with corresponding 95% confidence interval, P-value reflects results of log-rank test; (D) Kaplan–Meier survival curve comparing patients who underwent tracheostomy at least 8 days following intubation (blue) versus those who received an intubation before 8 days of intubation (red), with corresponding 95% confidence interval, P-value reflects results of log-rank test.

mortality ($P < 0.001$, OR = 1.04 per year). No significant association was observed between race, gender, or comorbidities with mortality. Consistent with these results, tracheostomy was associated with increased survival on a Kaplan–Meier survival curve with associated log-rank test ($P < 0.001$, Figure 1C).

To determine which predictors are associated with receiving a tracheostomy while intubated for COVID-19 infection, logistic regression was performed, with whether the patient underwent a tracheostomy as the dependent variable and demographic and comorbidity information as predictors (Table 3). Neither age, gender, nor race were associated with a significant change in odds of receiving a tracheostomy. Having any comorbidities was associated with receiving a tracheostomy ($P < 0.001$, OR = 5.47), as were the specific comorbidities of being on ECMO ($P < 0.001$, OR = 101.10), being immunocompromised ($P = 0.003$, OR = 3.61), and smoking ($P < 0.040$, OR = 4.81).

To investigate whether the timing of tracheostomy influenced patient survival, a Kaplan–Meier survival curve was generated comparing patients who received a tracheostomy before 8 days of intubation with those who received a tracheostomy at least 8 days following intubation (Figure 1D). No significant difference was observed by log-rank test ($P = 0.480$). Tracheostomy was furthermore associated with an increased hospital length of stay, as assessed by two-sided Wilcoxon–Mann–Whitney U test ([57.5 ± 32.2] days vs. [19.9 ± 18.1] days; $P < 0.001$).

DISCUSSION

In this study, we found that, of patients who remained intubated at 5 days, subsequent tracheostomy was associated with reduced in-hospital mortality compared to those who did not receive

TABLE 2 Primary endpoint: logistic regression with in-hospital mortality as a dependent variable.

Term	Odds ratio (OR)	Standard error (SE)	Statistic	*P* value	Confidence interval low (CI_{low})	Confidence interval high (CI_{high})
(Intercept)	0.09	0.539	−4.460	8.26×10^{-6}	0.031	0.254
Age	1.04	0.008	5.430	5.75×10^{-8}	1.030	1.060
Gender						
Male	–	–	–	–	–	–
Female	0.66	0.216	−1.930	0.054	0.431	1.000
Race						
Caucasian	–	–	–	–	–	–
Hispanic	1.42	0.341	1.040	0.300	0.729	2.780
Black	1.09	0.248	0.357	0.721	0.672	1.780
Asian	1.34	0.422	0.694	0.488	0.588	3.100
Other	0.99	0.567	−0.012	0.991	0.315	2.990
Unknown	1.22	0.494	0.411	0.681	0.462	3.260
Patient on extra-corporeal membranous oxygenation (ECMO)						
No	–	–	–	–	–	–
Yes	1.81	0.426	1.390	0.163	0.773	4.150
Diabetes						
No	–	–	–	–	–	–
Yes	0.64	0.245	−1.820	0.068	0.394	1.030
Cardiovascular disease						
No	–	–	–	–	–	–
Yes	0.81	0.284	−0.730	0.466	0.465	1.42
Non-COVID pulmonary disease						
No	–	–	–	–	–	–
Yes	0.99	0.278	−0.026	0.980	0.574	1.710
Chronic kidney disease						
No	–	–	–	–	–	–
Yes	1.14	0.267	0.484	0.628	0.673	1.920
Chronic liver disease						
No	–	–	–	–	–	–
Yes	0.96	0.442	−0.088	0.930	0.396	2.270
Immunocompromised						
No	–	–	–	–	–	–
Yes	1.29	0.396	0.642	0.521	0.589	2.810
Smoking						
No	–	–	–	–	–	–
Yes	0.85	0.665	−0.252	0.801	0.206	2.960
Any comorbidities						
No	–	–	–	–	–	–
Yes	1.27	0.349	0.676	0.499	0.639	2.517
Tracheostomy						
No	–	–	–	–	–	–
Yes	0.31	0.257	−4.590	4.44×10^{-6}	0.183	0.504

TABLE 3 Secondary endpoint: logistic regression with tracheostomy status as a dependent variable.

Term	Odds ratio (OR)	Standard error (SE)	Statistic	*P* value	Confidence interval low (CI_{low})	Confidence interval high (CI_{high})
(Intercept)	0.093	0.642	−3.690	<0.001	0.025	0.316
Age	1.000	0.008	0.480	0.631	0.988	1.020
Gender						
Male	–	–	–	–	–	–
Female	0.658	0.247	−1.690	0.090	0.402	1.060
Race						
Caucasian	–	–	–	–	–	–
Hispanic	1.040	0.414	0.089	0.929	0.453	2.310
Black	0.741	0.280	−1.070	0.284	0.428	1.280
Asian	0.658	0.545	−0.769	0.442	0.209	1.820
Other	0.969	0.691	−0.045	0.964	0.230	3.610
Unknown	0.880	0.635	−0.201	0.841	0.228	2.880
Patient on extra-corporeal membranous oxygenation (ECMO)						
No	–	–	–	–	–	–
Yes	101.100	1.05	4.410	<0.001	19.850	1, 858.140
Diabetes						
No	–	–	–	–	–	–
Yes	0.950	0.255	−0.203	0.839	0.576	1.570
Cardiovascular disease						
No	–	–	–	–	–	–
Yes	1.140	0.308	0.433	0.665	0.629	2.120
Non-COVID pulmonary disease						
No	–	–	–	–	–	–
Yes	1.590	0.295	1.560	0.118	0.888	2.830
Chronic kidney disease						
No	–	–	–	–	–	–
Yes	0.759	0.283	−0.970	0.330	0.432	1.310
Chronic liver disease						
No	–	–	–	–	–	–
Yes	0.413	0.533	−1.660	0.097	0.134	1.110
Immunocompromised						
No	–	–	–	–	–	–
Yes	3.610	0.424	3.030	0.003	1.600	8.540
Smoking						
No	–	–	–	–	–	–
Yes	4.810	0.767	2.050	0.041	1.150	25.400
Any comorbidities						
No	–	–	–	–	–	–
Yes	5.470	0.437	3.890	<0.001	2.360	13.200

tracheostomy. A 5-day cutoff was chosen according to standard practice in the University of Pennsylvania Health System and to eliminate the potential confounding variable of patients who were not eligible for tracheostomy due to death or extubation within 5 days.

This is the largest study to date to demonstrate a difference in in-hospital mortality between patients who received intubation and those who received both intubation and tracheostomy. Our results suggest an association between tracheostomy and improved outcomes in the setting of severe COVID-19 infection, in agreement with other studies examining similar questions.[13,23] For example, Rozenblat et al. showed a 29.8% reduction in mortality in patients undergoing tracheostomy. However, Rozenblat et al. also reported lower observed mortality in "late" (≥8 days) tracheostomy patients, in contrast to this study, wherein no such effect was observed. Recently, a meta-analysis examining 47 studies on the effect of tracheostomy timing and technique on COVID-19 mortality found that while mortality was significantly reduced in patients who received tracheostomy, the timing of tracheostomy did not affect mortality, the duration of mechanical ventilation, or the time to decannulation.[24] These data support the results of our study, in which we found an inverse relationship between tracheostomy and in-hospital mortality but no relationship between timing of tracheostomy and days to ventilator or sedation weaning. This finding is also in agreement with other studies, such as Kwak et al., who reported noninferiority of early (≤10 days) tracheostomy during New York City outbreak in 2020 and Polok et al. who observed no significant difference between early (≤10 days) and late tracheostomy in an older age group with critical COVID-19 illness.[25,26]

In this study, logistic regression analysis determined that multiple comorbidities were associated with an increased likelihood of undergoing tracheostomy, which is contrary to other studies which report no association between any particular comorbidity and likelihood of receiving tracheostomy.[13] Even though patients with comorbidities have a higher risk of severe infection and death compared to healthy individuals,[27] we observed no significant association of any comorbidities (other than advanced age) with patient mortality, as assessed with multivariate logistic regression. This suggests that tracheostomy should not be withheld from patients with comorbidities for this reason alone. On the other hand, these data may also suggest that more aggressive management of higher-risk patients may be reasonable. Regardless, the present study supports treating intubated COVID-19 patients similarly to other patients receiving prolonged mechanical ventilation.

Limitations of this study include its inherent bias as a retrospective, nonrandomized cohort study, as well as its lack of long-term follow-up of the study population. In addition, the study is limited by its inability to evaluate for possible additional factors that may have helped determine tracheostomy candidacy, such as specific markers of clinical stability. In addition, receiving a tracheostomy may itself be a confounder as there may be unidentifiable factors at play during the surgical decision-making process that portend a positive prognosis. Further research is needed to explain these observations and better predict outcomes in patients with severe COVID-19 infection.

CONCLUSIONS

The likelihood of receiving tracheostomy during severe COVID-19 infection was associated with characteristics including ECMO, immunocompromised states, and smoking. Of patients who remained intubated after 5 days, subsequent tracheostomy was associated with reduced in-hospital mortality compared to those who did not receive tracheostomy after 5 days of intubation. Further research is needed to assess this observed association between tracheostomy and in-hospital survival as new variants of COVID-19 arise and demand optimal management for at-risk patients.

AUTHOR CONTRIBUTIONS

Ahab Alnemri: Collection and analysis of data; presentation of research; writing of the manuscript. **Kaley Ricciardelli**: Collection of data. **Stephanie Wang**: Analysis of data; writing of methods section; editing of the manuscript. **Michael Baumgartner**: Analysis of data; editing of the manuscript. **Tiffany N. Chao**: Design and oversight of study; editing of the manuscript.

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CONFLICT OF INTEREST STATEMENT

The authors declare no conflict of interest.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

ETHICS STATEMENT

Given the deidentified study group and privately stored retrospective data, this study was exempted from Institutional Review Board approval.

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