Timing of Tracheostomy for Prolonged Respiratory Wean in Critically Ill Coronavirus Disease 2019 Patients: A Machine Learning Approach

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Objectives: To propose the optimal timing to consider tracheostomy insertion for weaning of mechanically ventilated patients recovering from coronavirus disease 2019 pneumonia. We investigated the relationship between duration of mechanical ventilation prior to tracheostomy insertion and in-hospital mortality. In addition, we present a machine learning approach to facilitate decision-making.

Design: Prospective cohort study.

Setting: Guy's & St Thomas' Hospital, London, United Kingdom.

Patients: Consecutive patients admitted with acute respiratory failure secondary to coronavirus disease 2019 requiring mechanical ventilation between March 3, 2020, and May 5, 2020.

Interventions: Baseline characteristics and temporal trends in markers of disease severity were prospectively recorded. Tracheostomy was performed for anticipated prolonged ventilatory wean when levels of respiratory support were favorable. Decision tree was constructed using C4.5 algorithm, and its classification performance has been evaluated by a leave-one-out cross-validation technique.

Measurements and Main Results: One-hundred seventy-six patients required mechanical ventilation for acute respiratory failure, of which 87 patients (49.4%) underwent tracheostomy. We identified that optimal timing for tracheostomy insertion is between day 13 and day 17. Presence of fibrosis on CT scan (odds ratio, 13.26; 95% CI [3.61–48.91]; $p \leq 0.0001$) and Pao_2:Fio_2 ratio (odds ratio, 0.98; 95% CI [0.95–0.99]; $p = 0.008$) were independently associated with tracheostomy insertion. Cox multiple regression analysis showed that chronic obstructive pulmonary disease (hazard ratio, 6.56; 95% CI [1.04–41.59]; $p = 0.046$), ischemic heart disease (hazard ratio, 4.62; 95% CI [1.19–17.87]; $p = 0.027$), positive end-expiratory pressure (hazard ratio, 1.26; 95% CI [1.02–1.57]; $p = 0.034$), Pao_2:Fio_2 ratio (hazard ratio, 0.98; 95% CI [0.97–0.99]; $p = 0.003$), and C-reactive protein (hazard ratio, 1.01; 95% CI [1–1.01]; $p = 0.005$) were independent late predictors of in-hospital mortality.

Conclusions: We propose that the optimal window for consideration of tracheostomy for ventilatory weaning is between day 13 and 17. Late predictors of mortality may serve as adverse factors when

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considering tracheostomy, and our decision tree provides a degree of decision support for clinicians.

Key Words: coronavirus disease 2019; mechanically ventilated patients; severe acute respiratory syndrome coronavirus-2; tracheostomy

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To date, there have been 12,539 admissions to critical care in United Kingdom, Wales, and Northern Ireland with coronavirus disease 2019 (COVID-19) pneumonia (1). Of those requiring mechanical ventilation (MV), the time to death of nonsurvivors has been reported as 10 days (5–17 d) (1), whereas the duration of ventilation in survivors is between 20 and 27 days (1, 2). Tracheostomy insertion to facilitate ventilatory weaning has an established role in the ICU, reducing the frequency of ventilator-associated pneumonia, duration of sedation, duration of MV, and length of stay in critical care (3,4). Although the timing of tracheostomy insertion is controversial, with no survival benefit demonstrated with earlier tracheostomy insertion (5), the general clinical consensus is tracheostomy insertion for weaning should be considered between 5 and 10 days of MV (4–6).

There are currently limited data regarding tracheostomy in critically ill coronavirus disease 2019 (COVID-19) patients. Some early case series have reported mortality rates of 7–12% when performing tracheostomy between 10 and 20 days of MV (7–9); however, these reports have limited follow-up periods and lack meaningful outcomes analysis. In our institution, tracheostomy has been performed in patients with COVID-19 for weaning of ventilation according to a standardized published protocol since the start of the pandemic (10).

A number of guidelines have been published with recommendations for the timing of tracheostomy in COVID-19 patients. In the United Kingdom, 14 days has been proposed (11, 12), whereas North American guidelines have recommended 21 days (13, 14). Most recently, an international consensus statement suggested that tracheostomy be delayed until at least day 10 of MV and considered only when patients are showing signs of clinical improvement (15, 16). These approaches seek to balance the potential maximizing of clinical benefit to the patient while minimizing the risk of healthcare worker transmission and futility of intervention (15).

The aim of this study was to propose the optimal timing of tracheostomy insertion to facilitate ventilatory weaning by investigating the relationship between duration of MV prior to tracheostomy insertion and in-hospital mortality. Collected data were used to produce a decision tree using a machine-learning algorithm.

MATERIALS AND METHODS

Study Design and Subjects

This is a prospective, observational cohort study. We included consecutive patients (age ≥ 18 yr old) admitted to the ICU at Guy's and St Thomas' National Health Service (NHS) Foundation Trust between March 3, 2020, and May 5, 2020. As a regional referral center for extracorporeal membrane oxygenation (ECMO), and due to the creation of additional surge capacity for the South London operational delivery network, patients included both those admitted directly from within our institution and those transferred to us for clinical or capacity reasons. All patients included were diagnosed with laboratory-confirmed COVID-19 and were critically ill with acute hypoxemic respiratory failure receiving MV, of whom some underwent tracheostomy. Exclusion criteria were as follows: 1) patients who underwent tracheostomy for indications other than prolonged respiratory wean and 2) patients in whom baseline data were unavailable.

Laboratory confirmation of severe acute respiratory syndrome coronavirus-2 infection was confirmed with reverse transcriptase polymerase chain reaction of nasopharyngeal, oropharyngeal, or tracheal samples. Patients were followed up until discharge from hospital or death. For patients still receiving inpatient care at the time of reporting, only those who had at least a 28-day follow-up period were included in the study. A sample size calculation was not performed, but a convenience sample of the defined time window of the study was selected. Using the NHS Health Research Authority decision tool, this project was determined to be a service evaluation, thereby not requiring ethical approval, and was registered with the institutional review board (Audit No: 10811) on March 23, 2020.

Data Collection

All data were collected from electronic medical records and collected in line with the severe acute respiratory infection data tool (17). Baseline characteristics collected included age, gender, ethnicity, body mass index (BMI), comorbidities, and the Acute Physiology and Chronic Health Evaluation II (APACHE) II score. We screened past medical history for diabetes mellitus, hypertension, ischemic heart disease, chronic obstructive pulmonary disease, asthma, chronic kidney disease, and smoking status. We assessed whether the patients were diagnosed with (1) thromboembolism (pulmonary, venous, or multiple) confirmed with imaging or (2) the presence of lung fibrosis was confirmed on reports of computerized tomography (recorded as a binary measure), as these have been recognized as disease-specific sequelae that adversely affect outcomes (18,19).

We collected vital signs, markers of acute respiratory failure, and serum-based biomarkers of disease severity that were recorded at different time points during ICU admission. These variables were recorded at baseline (within first 24 hr of critical care admission) and at days 7, 10, and 14. If the patient was successfully weaned from MV or died prior to day 14, we used the last recorded measurements prior to that event. Variables included levels of respiratory support required the following: positive end-expiratory pressure (PEEP), F_{IO_2}, Pa_{O_2}, $Pa_{O_2}{:}F_{IO_2}$ (PF) ratio, and requirement for ECMO. Serum biomarkers and vital signs included temperature, high-sensitivity C-reactive protein (CRP), D-dimers, and ferritin. We also collected data on other organ support requirements delivered including vasopressor agents and renal replacement therapy. These variables are herein collectively referred to as "clinical course".

Primary and Secondary Outcome Measures

The primary outcome measure was in-hospital mortality. Secondary outcome measures were total duration of MV, requirement for tracheostomy, and time to hospital discharge.

For the purposes of analysis, we categorized the cohort into four groups:

- tracheostomy/alive (TT/A),
- tracheostomy/died (TT/D),
- no tracheostomy/alive (nTT/A), and
- no tracheostomy/dead (nTT/D).

Study Objectives

The aim of the current study was to investigate the relationship between duration of MV prior to tracheostomy insertion and in-hospital mortality and to propose the optimal time window for consideration of tracheostomy. We also sought to define the optimal timing based on clinical course of the disease, identify factors associated with tracheostomy insertion, and identify late predictors of in-hospital mortality.

Timing of Tracheostomy Insertion

Performing the tracheostomy was deemed unsafe in patients requiring very high levels of ventilatory support as a period of apnea, or derecruitment was likely to lead to clinical deterioration. Requirement for prone positioning was also a contraindication to tracheostomy insertion in our institution due to potential risk of tube dislodgement or blockage. Thus, patients only received a tracheostomy if: 1) they were showing signs of clinical improvement (15), 2) there was no active or anticipated requirement for proning, and 3) they were on lower levels of ventilatory support. This was defined as a PEEP of less than or equal to 10 cm H_2O and F_{IO_2} of less than or equal to 0.5.

Statistical Analysis

Data were summarized using frequency tables and summary statistics. The preferred method of analysis for continuous variables was parametric. Nonparametric analysis methods were used only if parametric assumptions could not be satisfied, even after data transformation attempts. Parametric model assumptions were assessed using Kolmogorov test and Levene's test for verification of homogeneity of variances. Missing data were not imputed.

Kaplan-Meier estimates were used to identify the optimal window for timing of tracheostomy. Limits were defined as days (since start of MV) when survival (nTT/D) and probability of not being extubated (nTT/A) reached 10%. In addition, variables associated with tracheostomy insertion were obtained at day 14. Starting with the most significant variable in univariate analysis, we used a multiple binary logistic regression model to estimate odds ratios (ORs) for associated factors.

We performed a logistic regression analysis to identify early (baseline) and late factors (day 14) associated with in-hospital mortality. Starting with the most significant variable in the univariate analysis, log-likelihood ratio was used to determine whether inclusion of a new variable improved the fit of the Cox regression multiple model. We then estimated hazard ratios (HRs) for

death using the Cox proportional hazards model. We confirmed the proportional hazards assumption of the Cox models using the Schoenfeld residuals test.

Continuous variables representing markers of acute hypoxemic respiratory failure and disease severity were analyzed using a repeated-measures analysis of variance to test for within-subject differences for individual parameters. For variables that violated Mauchly's test for sphericity, the Greenhouse-Geisser and Huynh-Feldt adjustments corrections were applied. Where significant differences were displayed, the Scheffe multiple range test was used post hoc to identify which time points were significantly different from the others included in this comparison. In case of dichotomous variables, the Cochran Q statistic was calculated. p value of less than 0.05 was considered statistically significant. Statistical analysis was performed with SPSS v. 20.0 (IBM Corp., Armonk, NY).

A machine learning analytic process was used to produce a decision tree (21) of risk factors associated with in-hospital mortality as outcome based on day 14 variables and baseline characteristics. The goal of machine learning analysis is to create a model that predicts the value of a target variable (class) by learning simple decision rules inferred from the data features. Algorithms break down a dataset into smaller and smaller subsets, whereas at the same time an associated decision tree is incrementally developed. The final result is a tree with decision nodes and leaf nodes. We applied the C4.5 algorithm, and its classification performance has been evaluated by a leave-one-out cross-validation technique (22, 23). This dataset was split into three subsets: training subset, test subset, and validation subset. The training subset was used to build the decision trees, and the test one was used to evaluate the generated classifiers, whereas the validation subset was used to clinically validate the developed prediction system. Separately, we calculated HRs for each final outcome using Cox regression analysis for enhanced clinical relevance.

RESULTS

A total of 263 patients with laboratory-confirmed COVID-19 patients were admitted to ICU for MV between March 3, 2020, and May 5, 2020. Eighty-seven patients were excluded from analysis; 85 due to inadequate baseline data, and two due to alternative indication for tracheostomy (neurologic wean).

One-hundred seventy-six patients were subsequently included for analysis with an overall mortality rate of 25% (44 nonsurvivors). Eighty-seven (49.4%) underwent tracheostomy at a median of 16 days (13–21 d) post intubation, and there were seven deaths (8.0%). For patients undergoing tracheostomy, the total duration of MV was 30 days (25–36 d). Of the 89 patients (50.6%) who did not receive a tracheostomy, 52 (58.4%) were successfully liberated from MV by day 7 (3–10.5), and 37 (41.6%) died at day 10 (6–13). Baseline characteristics, disease-specific sequelae, and outcomes are summarized in the **Table 1**.

Clinical Course

Markers of acute respiratory failure, serum biomarkers, vital signs, and requirements for organ support were collected at different time

TABLE 1. Baseline Characteristics, Disease-Specific Sequelae, and Outcomes

Variables	Overall (*n* = 176)	TT/A (*n* = 80)	TT/D (*n* = 7)	No TT/A (*n* = 52)	No TT/D (*n* = 37)	Univariate Analysis, % *p*	Multiple Regression Hazard Ratio (95% CI); *p*
Female gender, *n* (%)		24 (30.0)	2 (28.6)	14 (26.9)	10 (27)	NS	
Age (yr), median (range)	55.5 (22–82)	54 (26–77)a	54 (33–72)	53.5 (25–46)a	62 (37–82)	< 0.0001	1.84 (1.81–2.08), 0.014
Body mass index, median (range)	28.9 (21–61.7)	29.7 (22.3–61.7)	29.3 (22.5–46.0)	27.7 (21–39.1)	28.1 (22.9–48.4)	NS	
Ethnicity, *n* (%)							
White	78 (44.3)	30 (37.5)	5 (71.4)	25 (48.1)	18 (48.6)	NS	
Black	57 (32.4)	25 (30.5)	1 (14.3)	17 (32.7)	14 (37.8)	NS	
Asian	26 (14.8)	19 (23.2)	1 (14.3)	4 (7.7)	2 (5.4)	NS	
Mixed	5 (2.8)	4 (4.9)	0 (0)	0 (0)	1 (2.7)	NS	
Other	10 (5.7)	2 (2.4)	0 (0)	6 (11.5)	2 (5.4)	NS	
Diabetes, *n* (%)	60 (34.1)	27 (32.9)	1 (14.3)	13 (25)	19 (51.4)	NS	
Hypertension, *n* (%)	67 (38.1)	27 (33.8)a	1 (14.3)	17 (32.7)a	22 (59.5)	0.01	
Ischemic heart disease, *n* (%)	10 (5.7)	4 (4.9) a	0 (0)	0 (0)a	6 (16.2)	0.011	
Chronic obstructive pulmonary disease, *n* (%)	11 (6.3)	2 (2.4) a	0 (0)	1 (1.9)a	8 (21.6)	< 0.0001	3.25 (1.36–7.79), 0.008
Asthma, *n* (%)	25 (14.2)	11 (13.8)	2 (28.6)	5 (9.6)	7 (18.9)	NS	
Chronic kidney disease, *n* (%)	12 (6.8)	9 (11)	0 (0)	2 (3.8)	1 (2.7)	NS	
Smokingb, *n* (%)	2 (1.3)	1 (1.6)	0 (0)	0 (0)	1 (2.8)	NS	
Acute Physiology and Chronic Health Evaluation II score, median (range)	14 (2–34)	14 (8–22)c	13 (10–17)	11 (3–21) a	16 (8–25)	0.001	1.49 (1.39–1.68), 0.044
Thromboembolism, *n* (%)	53 (15.1)	34 (42)ac	3 (42.6)	8 (15.7)	8 (25)	< 0.0001	
Fibrosis on CT scan, *n* (%)	50 (14.2)	38 (47.5)a,c	5 (71.4)	4 (12.9)	3 (15)	< 0.0001	
Mortality, *n* (%)	44 (25.0)	7 (8.0)		37 (41.6)		< 0.0001	
Days to death from start of MVd, median (range)	11 (6.25–15.75)	NA	29 (28–34)	NA	10 (6–14)	NA	
Duration of MVd	NA	30 (25–36)	NA	7 (3–10.5)	N/A	NA	
Day of tracheostomyd	NA	16 (13–20)	19 (10–34)	NA	N/A	NA	

A = alive, D = dead, MV = invasive mechanical ventilation, NA = not applicable, NS = not significant, TT = tracheostomy.

aSignificant compared with no TT/D (nTT/D) (Mann-Whitney/χ^2 of independence where applicable).

b21 missing cases (overall), 19 (TT/A), 1 (no TT/A [nTT/A]), 1 (nTT/D).

cSignificant compared with nTT/A (Mann-Whitney *U* test).

dDescribed as median and interquartile range/quartile I–quartile III.

Univariate analysis: Differences between groups TT/A, TT/D, nTT/A, nTT/D were compared using the Kruskal-Wallis test. Multiple analysis: Cox regression survival analysis (hazard ratio) was used. Characteristics are displayed separately for overall cohort, and patients who received tracheostomy and survived (TT/A) received tracheostomy and died (TT/D), received MV, were extubated and alive (nTT/A), received MV and died (nTT/D).

points during the first 14 days of MV (**Online Supplementary Table 1**, Supplemental Digital Content 1, http://links.lww.com/CCX/A421). In the nTT/A group, median (range) baseline PEEP score, PF ratio, and CRP were 10 cm H_2O (8–12 cm H_2O), 178.9 mm Hg (101.1–318.3 mm Hg), and 124 mg/L (45–245 mg/L), respectively. The last measurement before stopping MV was median (range) 7 cm H_2O (5–10 cm H_2O) (PEEP), 247.5 mm Hg (72.3–309.7 mm Hg) (PF ratio), and 78 mg/L (29–296 mg/L) (CRP).

Baseline PEEP score, PF ratio, and CRP in nTT/D group were similar: 10 cm H_2O (10–14 cm H_2O), 157.5 mm Hg (86.3–204.5 mm Hg), and 192 mg/L (40–229 mg/L), respectively. However, last measurements before death significantly differed: 12 cm H_2O (10–12 cm H_2O) (PEEP), 95.3 mm Hg (70.5–166.9 mm Hg) (PF ratio), and 292 mg/L (256–348 mg/L) (CRP) (all $p < 0.05$). Changes of selected markers over time are displayed in **Figure 1**.

Optimal Timing for Consideration of Tracheostomy Insertion

The time to successful liberation from MV in nTT/A group was 7 days (3–10.5 d), and the day of death in nTT/D group was 10 (6–14). In relation to the clinical course of disease, we observed that severely unwell patients (nTT/D) deteriorate rapidly despite maximal therapy. On the contrary, patients in the nTT/A group showed rapid signs of clinical improvement, and ventilation was ceased early. Finding the time points where the majority of patients in groups nTT/A and nTT/D are off MV or did not survive, would leave a group of patients that plateaued and would be suitable for consideration of tracheostomy to facilitate ventilatory weaning.

Using Kaplan-Meier estimates, we identified days (since start of MV) when survival in nTT/D group and probability of not being extubated in nTT/A group dropped to 10%. These served as lower and upper bound of optimal timing window. By these criteria, the optimal time window for consideration of tracheostomy is day 13–17 post intubation (**Fig. 2**).

Factors Associated With Tracheostomy Insertion

Univariate analysis showed that PEEP, Pao_2, PF ratio, radiological lung fibrosis, and thromboembolism were factors significantly associated with tracheostomy insertion. Multiple binary regression analysis displayed PF ratio (OR, 0.98; 95% CI [0.95–0.99]; $p = 0.008$) and presence of fibrosis on CT scan (OR, 13.26; 95% CI [3.61–48.91]; $p \leq 0.0001$) as independently associated factors (**Table 2**).

Predictors of In-Hospital Mortality as Adverse Factors for Tracheostomy

We analyzed early (baseline) and late (day 14) predictors of in-hospital mortality that may serve as adverse factors when considering tracheostomy.

Multiple Cox regression analysis of early predictors showed that age (HR, 1.84; 95% CI [1.81–2.08]; $p = 0.014$), hypertension (HR, 1.92; 95% CI [1.01–3.65]; $p = 0.047$), ischemic heart disease (HR, 1.92; 95% CI [1.01–3.65]; $p = 0.047$), chronic obstructive pulmonary disease (COPD) (HR, 3.25; 95% CI [1.36–7.79]; $p = 0.008$), and APACHE II score (HR, 1.49; 95% CI [1.39–1.68]; $p = 0.044$) were significantly associated with in-hospital mortality (Table 1).

Cox multiple regression analysis showed that COPD (HR, 6.56; 95% CI [1.04–41.59]; $p = 0.046$), ischemic heart disease (HR, 4.62; 95% CI [1.19–17.87]; $p = 0.027$), PEEP (HR, 1.26; 95% CI [1.02–1.57]; $p = 0.034$), PF ratio (HR, 0.98; 95% CI [0.97–0.99]; $p = 0.003$), and CRP (HR, 1.01; 95% CI [1–1.01]; $p = 0.005$) were independent late predictors associated with in-hospital mortality (Table 2).

Decision Tree of Risk Factors for Late In-Hospital Mortality

A decision tree based on gain ratio variable selection is presented in **Figure 3**. The dataset used for tree induction consisted of 170 samples described by 20 variables. The target of classification was survival. The analysis of classification performance of the tree was focused on precision, recall, and classification accuracy. The classification evaluation shows that the accuracy is 74.9%, precision is 85.4%, and recall is 81.0%. We decided to reduce the decision tree to its clinically relevant section that does not visualize the branching of a small subset of patients.

DISCUSSION

In this study, we analyzed the characteristics and clinical course of critically ill patients receiving MV and propose that optimal timing for consideration of tracheostomy to facilitate ventilatory weaning is between day 13 and 17. Since the tracheostomy group is arbitrary, and some factors such as age or PEEP may have a bimodal effect on risk ratio, we sought to identify a predictor that would reflect the natural disease course when considering tracheostomy. As a result, we chose in-hospital mortality to serve as the primary adverse factor. At the time-point identified, clinical variables and outcomes become sufficiently divergent to enable the clinician to
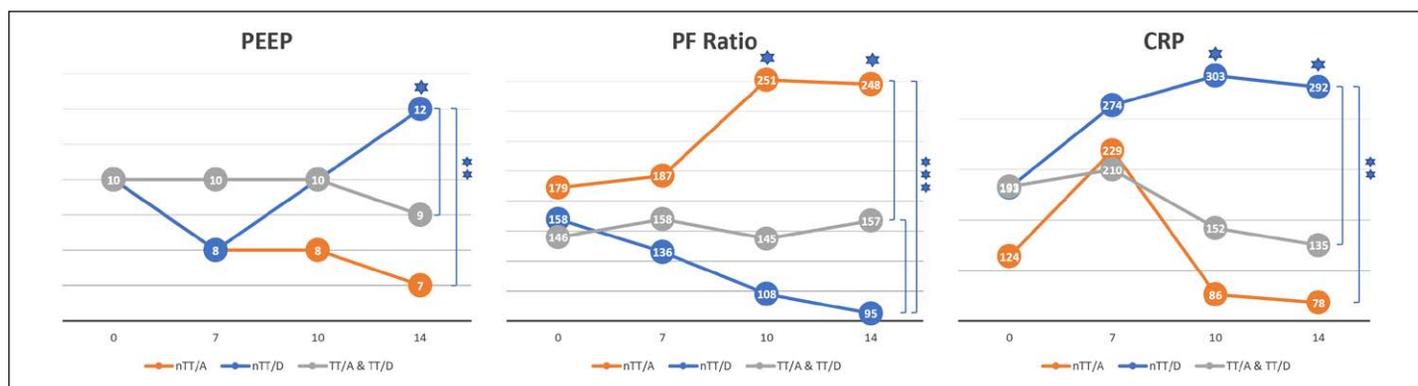
Figure 1. Temporal trends in positive end-expiratory pressure (PEEP), Pao_2:Fio_2 (PF) ratio, and C-reactive protein (CRP). *Significant ($p < 0.05$) difference between measurement at one time point within group, overall significance marker with * above variable tested with Kruskal-Wallis, intergroup significances tested with Mann-Whitney *U* test and marked with * displayed on the right side of each figure. nTT/A = no tracheostomy/extubated/alive, nTT/D = no tracheostomy/dead, TT/A = tracheostomy/alive, TT/D = tracheostomy/dead.

identify patients that are likely to benefit from tracheostomy and minimize the risk of performing futile procedures.

Although independent variables associated with in-hospital mortality identified in this study were consistent with existing large studies and national reports on critically ill COVID-19 patients (1, 2, 24, 25), analysis of temporal changes in clinical course facilitated the additional identification of PEEP, PF ratio, and CRP as late factors that are independently associated with in hospital mortality. Despite the statistical significance of PF ratio, the association is marginal; therefore, its clinical significance is low.

Our analysis of the clinical course identified that those who died underwent a rapid deterioration despite maximal management. The time to death for nonsurvivors in our study was 10 days (6–14 d) which is consistent with other studies of this population (1, 25, 28). Waiting until after day 13, when probability of being extubated reached 90% appears a pragmatic recommendation that will both minimize futility and reduce the potential of performing unnecessary procedures on patients likely to recover irrespective of intervention.

Particularly interesting findings were the increased prevalence of thromboembolism in the group of patients that had a tracheostomy. Additionally, a novel factor—presence of lung fibrosis—was an independent predictor of tracheostomy insertion. CRP also emerged as an independent predictor of both early and late mortality, with late pyrexia also associated. It is recognized that some patients with COVID-19 develop a severe hyperinflammatory state that is associated with cytokine storm syndrome (29). CRP, ferritin, and persistent pyrexia are some of the factors that can help identify patients with hyperinflammation (30). This process may account for our findings and supports the existing evidence (18, 19, 28, 29). These findings suggest that patients with the sequelae of hyperinflammation who survive early critical care are more likely to require tracheostomy. Treatments that improve survival, such as dexamethasone (31), are rapidly emerging, and this may have further implications upon these findings.

Decision tree algorithms are considered as one of the most methodologically accepted classification techniques (21). In our study, we applied the C4.5 algorithm which has been used in various medical disciplines, including intensive care (22, 23, 32). The accuracy achieved in other studies was higher compared with our decision tree, and the limiting factors specific to this analysis were a relatively small sample size and increased disease complexity. For future work, applying the model on larger database would improve the accuracy of its prediction value. Despite these limitations, the accuracy was adequate to provide decision support for clinicians or at least provide them a second opinion.

The main strengths of this study were to identify and provide an evidence-base to support an optimal timeframe for consideration of tracheostomy insertion for anticipated prolonged ventilatory weaning; this was further augmented by identifying late predictors of in-hospital mortality. The analysis, therefore, can aid clinicians in predicting which patients are likely to survive but may require tracheostomy. It can in turn be hypothesized that these are likely factors associated with prolonged ventilation, given the duration of ventilation in this group was 29 days, compared with 7 days in those who did not require a tracheostomy.

The general limitations of this study include the population demographics, which were younger compared with the national cohort of patients receiving critical care (1). Furthermore, it represents a single-institution experience with a high volume of tertiary and regional referrals, with access to advanced therapies such as ECMO. We are aware that there are numerous factors, both clinical and nonclinical, that may influence decision-making and timing of tracheostomy in different institutions, which may
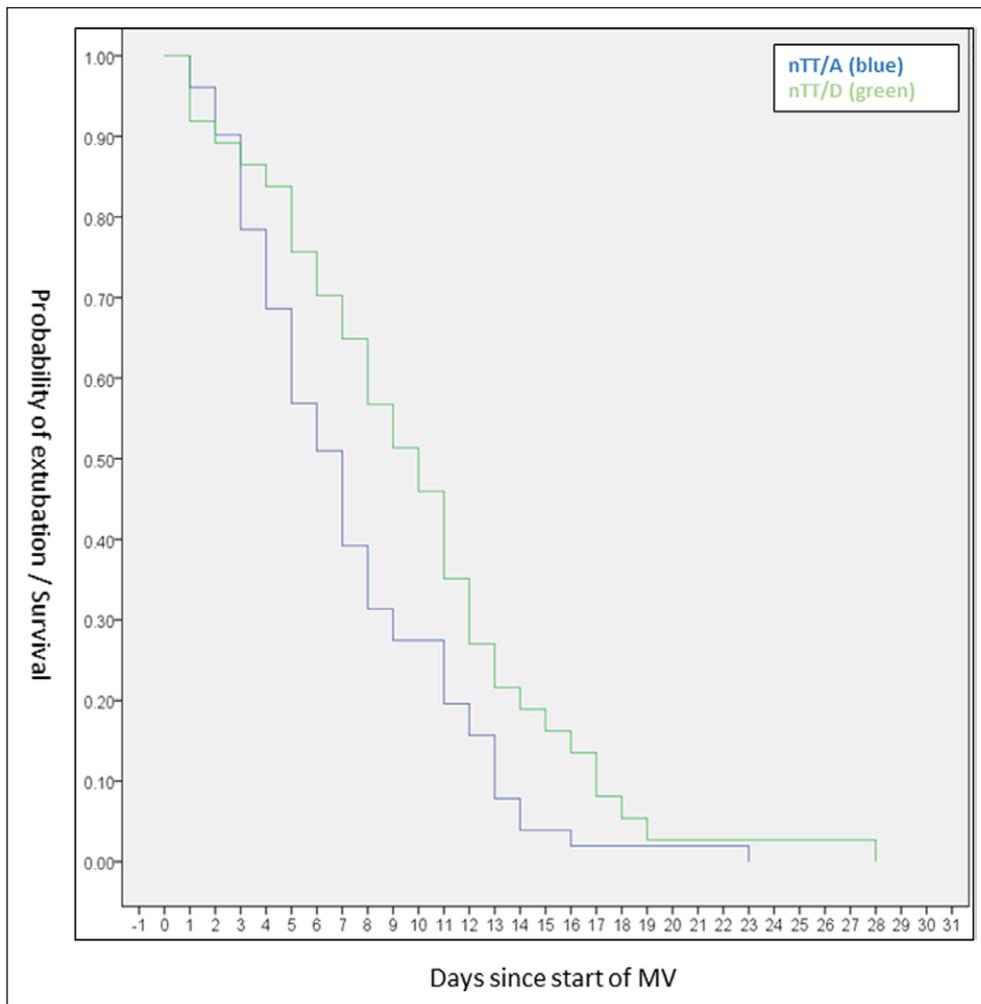
Figure 2. Kaplan-Meier estimates to determine optimal window for consideration of tracheostomy. MV = mechanical ventilation, nTT/A = no tracheostomy/extubated/alive, nTT/D = no tracheostomy/dead.

TABLE 2. Factors Associated With Tracheostomy Insertion and Late Predictors of In-Hospital Mortality.

Variables	Univariate Analysis		Multiple Analysis	
	OR (95% CI)	*p*	OR (95% CI)	*p*
Factors associated with tracheostomy insertion				
Age	0.98 (0.96–1.00)	0.062	0.95 (0.91–1.00)	0.086
APACHE II	1.02 (0.95–1.01)	0.59		
PEEP	1.24 (1.08–1.43)	0.003	1.16 (0.93–1.46)	0.18
PF ratio	0.99 (0.99–1.00)	< 0.0001	0.98 (0.95–0.99)	0.008
CRP	0.99 (0.99–1.00)	0.136		
D-dimer	1.00 (0.99–1.02)	0.62		
Temperature	1.18 (0.92–1.51)	0.2		
Vasopressors	0.93 (0.77–1.13)	0.48		
CT fibrosis	8.45 (3.37–21.18)	< 0.0001	13.26 (3.61–48.91)	< 0.0001
Thromboembolism	3.16 (1.58–6.32)	0.001	2.71 (1.91–4.41)	0.17
	Hazard Ratio (95% CI)	*p*	Hazard Ratio (95% CI)	*p*
Late predictors of in-hospital mortality				
Age	1.08 (1.04–1.11)	< 0.0001		
APACHE II	1.13 (1.03–1.24)	0.01		
Chronic obstructive pulmonary disease	10.28 (2.59–40.82)	0.001	6.56 (1.04–41.59)	0.046
Hypertension	2.18 (1.08–4.4)	0.03		
Ischemic heart disease	5.42 (1.45–20.23)	0.012	4.62 (1.19–17.87)	0.027
PEEP	1.37 (1.14–1.65)	0.001	1.26 (1.02–1.57)	0.034
PF ratio	0.98 (0.97–0.99)	< 0.0001	0.98 (0.97–0.99)	0.003
CRP	1.01 (1.01–1.02)	< 0.0001	1.01 (1–1.01)	0.005
Ferritin	1 (1)	0.111		
D-dimer	1.01 (0.99–1.03)	0.216		
Temperature	1.8 (1.23–2.62)	0.002		
Vasopressors	4.48 (2.1–9.55)	< 0.0001		
Renal replacement therapy	1.77 (0.8–3.87)	0.157		
Extracorporeal membrane oxygenation	0.45 (0.15–1.38)	0.162		

APACHE II = Acute Physiology and Chronic Health Evaluation II, CRP = C-reactive protein, OR = odds ratio, PEEP = positive end-expiratory pressure, PF = Pao_2:Fio_2.
Univariate analysis: logistic regression model was used. Multiple analysis: Multiple binary regression analysis (likelihood ratio) was used for factors associated with tracheostomy insertion and Cox-regression survival analysis (likelihood ratio) was used for late predictors of in-hospital mortality. PEEP, PF ratio, CRP, ferritin, D-dimer, temperature: we analyzed variables obtained on day 14. If patient had tracheostomy prior to day 14, we included latest measurement prior to procedure.

subsequently limit the application of the decision tree. These complex interactions include variation in local protocols, as well as broader disease-specific treatment approaches, and resource implications such as bed numbers and clinical skill levels. However, the largest multicenter study to date of COVID tracheostomy in the United Kingdom has highlighted that timing of tracheostomy and respiratory variables were similar to those found in this study cohort (9). Although this limits the generalizability of our findings, it conversely improves the homogeneity of intervention and reliability of data. These data can only be interpreted as hypothesis-generating,

and prospective randomized trials would be required to definitively determine the optimal time frame for tracheostomy insertion in patients with COVID-19.

CONCLUSIONS

There is increasing evidence that tracheostomy is indicated to aid the rehabilitation of ventilated COVID-19 patients. We propose that the optimal timing for tracheostomy insertion in terms of clinical outcome is between day 13 and day 17. This hypothesis will need
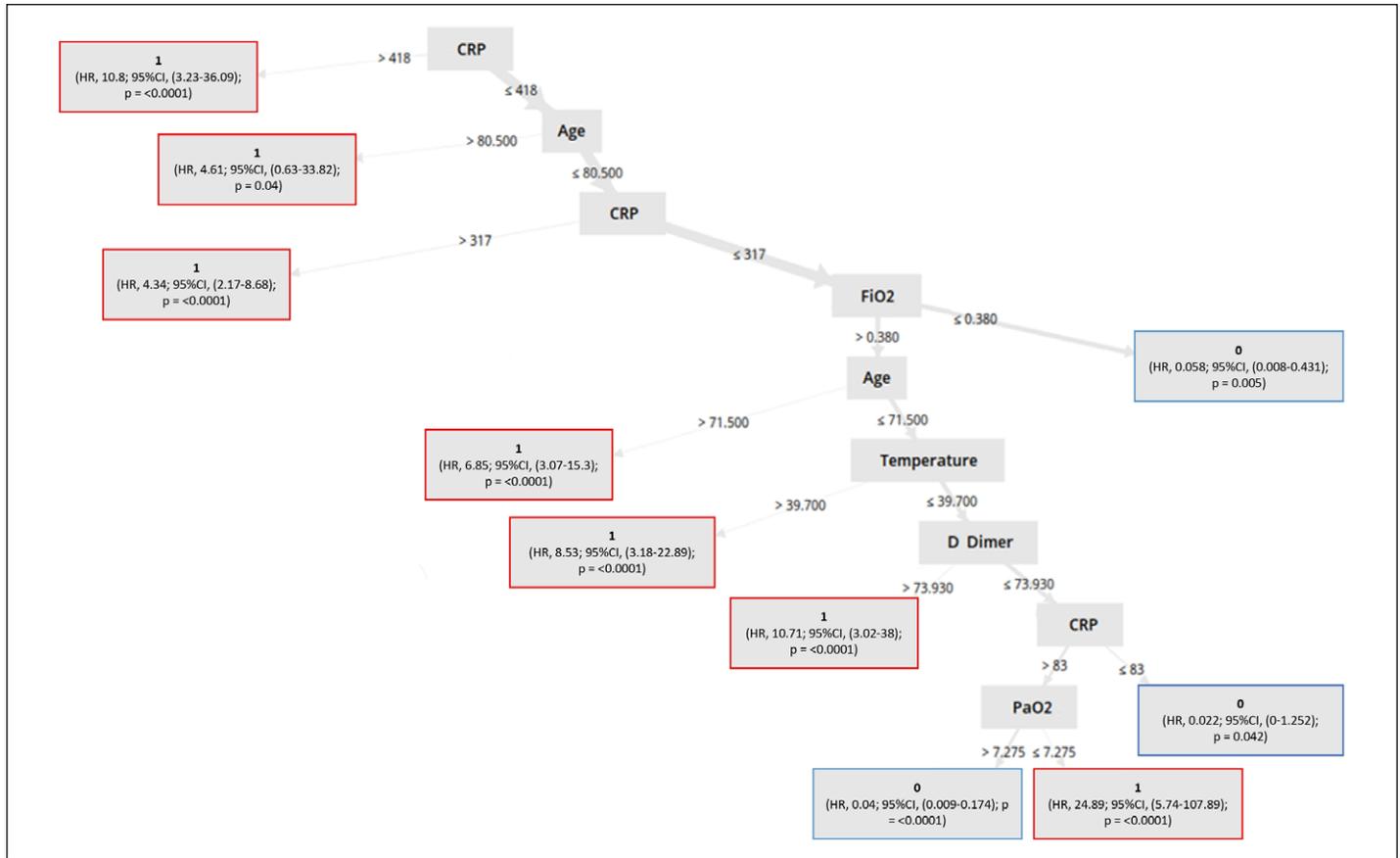
Figure 3. Decision tree of late risk factors associated with in-hospital mortality. The outcome was survival where 1 = death and 0 = alive. Hazard ratios (HRs) were separately calculated using Cox regression analysis and are displayed for each outcome. CRP = C-reactive protein.

to be tested in prospective, randomized clinical trials should further waves of the COVID-19 pandemic ensue. Last, our decision tree analysis may provide a degree of decision support for clinicians.

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