Pulmonology 28 (2022) 18—27

PULMONOLOGY

www.journalpulmonology.org

ORIGINAL ARTICLE

Practice of tracheostomy in patients with acute respiratory failure related to COVID—19 — Insights from the PRoVENT—COVID study

A.M. Tsonas[a,*], M. Botta[a], J. Horn[a,b], M.J. Brenner[c,d], M.S. Teng[e], B.A. McGrath[f], M.J. Schultz[a,g,h], F. Paulus[a,i], A. Serpa Neto[a,j], for the PRoVENT—COVID Collaborative Group [1,2,3]

[a] *Department of Intensive Care, Amsterdam UMC, location 'AMC', Amsterdam, the Netherlands*
[b] *Amsterdam Neuroscience, Amsterdam UMC Research Institute, Amsterdam, the Netherlands*
[c] *Department of Otolaryngology—Head & Neck Surgery, University of Michigan Medical School, Ann Arbor, Michigan, USA*
[d] *Global Tracheostomy Collaborative, Raleigh, North Carolina, USA*
[e] *Department of Otolaryngology—Head & Neck Surgery, Icahn School of Medicine at Mount Sinai, New York, New York, USA*
[f] *Anaesthesia & Intensive Care Medicine, University NHS Foundation Trust, Manchester, UK*
[g] *Mahidol—Oxford Tropical Medicine Research Unit (MORU), Mahidol University, Bangkok, Thailand*
[h] *Nuffield Department of Medicine, University of Oxford, Oxford, United Kingdom*
[i] *ACHIEVE, Centre of Applied Research, Amsterdam University of Applied Sciences, Faculty of Health, Amsterdam, the Netherlands*
[j] *Department of Critical Care Medicine, Australian and New Zealand Intensive Care Research Centre (ANZIC—RC), Monash University, Melbourne, Australia*

Received 19 April 2021; accepted 4 August 2021
Available online 20 September 2021

* Corresponding author at: Department of Intensive Care, G3—228, Amsterdam UMC, location 'AMC' Meibergdreef 9 1105 AZ Amsterdam, the Netherlands.
E-mail address: a.m.tsonas@amsterdamumc.nl (A.M. Tsonas).

[1] PRactice of VENTilation in COVID—19' study.
[2] collaborators are listed on page 3.
[3] **PRoVENT—COVID Collaborators** (in alphabetic order): S. Ahuja; J.P. van Akkeren; A.G. Algera; C.K. Algoe; R.B. van Amstel; A. Artigas; O. L. Baur; P. van de Berg; A.E. van den Berg; D.C.J.J. Bergmans; D.I. van den Bersselaar; F.A. Bertens; A.J.G.H. Bindels; M.M. de Boer; S. den Boer; L.S. Boers; M. Bogerd; L.D.J. Bos; M. Botta; J.S. Breel; H. de Bruin; S. de Bruin; C.L. Bruna; L.A. Buiteman—Kruizinga; O.L. Cremer; R. M. Determann; W. Dieperink; D.A. Dongelmans; H.S. Franke; M.S. Galek—Aldridge; M.J. de Graaff; L.A. Hagens; J.J. Haringman; S.T. van der Heide; P.L.J. van der Heiden; N.F.L. Heijnen; S.J.P. Hiel; L.L. Hoeijmakers; L. Hol; M. W. Hollmann; M.E. Hoogendoorn; J. Horn; R. van der Horst; E.L.K. Ie; D. Ivanov; N.P. Juffermans; E. Kho; E.S. de Klerk; A.W.M.M. Koopman-van Gemert; M. Koopmans; S. Kucukcelebi; M.A. Kuiper; D.W. de Lange; N. van Mourik; S.G. Nijbroek; M. Onrust; E.A.N. Oostdijk; F. Paulus; C.J. Pennartz; J. Pillay; L. Pisani; I.M. Purmer; T.C.D. Rettig; J.P. Roozeman; M.T.U. Schuijt; M.J. Schultz; A. Serpa Neto; M.E. Sleeswijk; M.R. Smit; P.E. Spronk; W. Stilma; A.C. Strang; A. M. Tsonas; P.R. Tuinman; C.M.A. Valk; F.L. Veen—Schra; L.I. Veldhuis; P. van Velzen; W.H. van der Ven; A.P.J. Vlaar; P. van Vliet; P.H.J. van der Voort; L. van Welie; H.J.F.T. Wesselink; H.H. van der Wier—Lubbers; B. van Wijk; T. Winters; W.Y. Wong; A.R.H. van Zanten.

https://doi.org/10.1016/j.pulmoe.2021.08.012

KEYWORDS
Ventilation management;
Tracheostomy;
Acute respiratory failure;
ARDS;
Covid-19;
Coronavirus 2019;
SARS-COV-2

Abstract
Objective: Invasively ventilated patients with acute respiratory failure related to coronavirus disease 2019 (COVID—19) potentially benefit from tracheostomy. The aim of this study was to determine the practice of tracheostomy during the first wave of the pandemic in 2020 in the Netherlands, to ascertain whether timing of tracheostomy had an association with outcome, and to identify factors that had an association with timing.
Methods: Secondary analysis of the 'PRactice of VENTilation in COVID—19' (PRoVENT—COVID) study, a multicenter observational study, conducted from March 1, 2020 through June 1, 2020 in 22 Dutch intensive care units (ICU) in the Netherlands. The primary endpoint was the proportion of patients receiving tracheostomy; secondary endpoints were timing of tracheostomy, duration of ventilation, length of stay in ICU and hospital, mortality, and factors associated with timing.
Results: Of 1023 patients, 189 patients (18.5%) received a tracheostomy at median 21 [17 to 28] days from start of ventilation. Timing was similar before and after online publication of an amendment to the Dutch national guidelines on tracheostomy focusing on COVID—19 patients (21 [17—28] vs. 21 [17—26] days). Tracheostomy performed $\leq$ 21 days was independently associated with shorter duration of ventilation (median 26 [21 to 32] vs. 40 [34 to 47] days) and higher mortality in ICU (22.1% vs. 10.2%), hospital (26.1% vs. 11.9%) and at day 90 (27.6% vs. 14.6%). There were no patient demographics or ventilation characteristics that had an association with timing of tracheostomy.
Conclusions: Tracheostomy was performed late in COVID—19 patients during the first wave of the pandemic in the Netherlands and timing of tracheostomy possibly had an association with outcome. However, prospective studies are needed to further explore these associations. It remains unknown which factors influenced timing of tracheostomy in COVID—19 patients.

Introduction

Tracheostomy is a frequently performed intervention in critically ill patients who require prolonged invasive ventilation, facilitating liberation from the ventilator and possibly reducing sedation needs due to increased patient comfort.[1] Patients with acute respiratory failure related to coronavirus disease 2019 (COVID—19) often need prolonged ventilation[2-4] and therefore, a substantial proportion of COVID—19 patients might benefit from tracheostomy.[5]

It is uncertain how long after start of invasive ventilation tracheostomy should be performed, in both non COVID—19 [6-8] and COVID—19 patients. Early in the pandemic, adjusted tracheostomy guidelines for COVID—19 patients were released worldwide,[9,10] with over 90% of these adjusted guidelines advising to wait at least 14 days after intubation before performing a tracheostomy.[10] Factors in favor of delaying tracheostomy included an expected decrease in risk of contamination of healthcare workers, and high risk of dangerous deteriorations in gas exchange during the procedure.[11] Timing could also have been influenced by shortages in personal protection equipment (PPE) and tracheostomy kits, and lack of experienced health care workers able to perform or guide the procedure.

The practice of tracheostomy in invasively ventilated patients with acute respiratory failure related to COVID—19 in the Netherlands is largely unknown. We explored the database of the 'PRactice of VENTilation in COVID—19' (PRoVENT—COVID) study, which contains epidemiological characteristics, granular ventilation data, and outcomes of more than 40% of all COVID—19 patients who needed invasive ventilation during the first 3 months of the outbreak in the Netherlands.[12] The aim of this study was to determine the practice of tracheostomy and to ascertain whether timing of tracheostomy had an association with duration of ventilation, length of stay and mortality. We also aimed to identify factors that had an association with timing of tracheostomy.

Methods

Study design, patients and data collection

This is a secondary analysis of the PRoVENT—COVID study (**eMethods** in **Online Supplement**). Patients were enrolled if: (1) aged $\geq$18 years; (2) admitted to one of the participating ICUs; and (3) had received invasive ventilation for respiratory failure related to COVID—19. Patients with unknown tracheostomy status due to transfer to a non—participating hospital, were excluded from this analysis.

Baseline characteristics were collected at start of invasive ventilation or ICU admission. Detailed variables and parameters of ventilation management were collected over the first 4 calendar days thereafter. ICU complications, including thromboembolic events, acute kidney injury and use of renal replacement therapy (RRT) were collected until day 28, as was reintubation status. Admission status and life status were collected until day 90.

Endpoints

The primary endpoint of this analysis was incidence of tracheostomy. Secondary endpoints were timing of

tracheostomy (counted as the number of days between start of invasive ventilation and tracheostomy procedure), outcomes including duration of ventilation, ICU− and hospital−length of stay (LOS), and ICU−, hospital−, and day 28− and day 90−mortality, and factors associated with timing.

National Dutch guidelines on tracheostomy

Before the pandemic, Dutch guidelines regarding tracheostomy practice in invasively ventilated ICU patients advised to 'consider a tracheostomy as soon as it is apparent that weaning from artificial ventilation is unlikely to happen within 2 weeks after endotracheal intubation', and also 'because this prediction is difficult, it is advised to generally delay the procedure until at least 10 days after intubation'.[13] The amendment focusing on tracheostomy in COVID−19 patients was released on April 23, 2020[14] and advised to wait at least 2 weeks before performing tracheostomy and if possible, to further delay the procedure to reduce the risk of viral transmission.

Statistical analysis

Continuous variables are presented as medians with interquartile ranges, and categorical variables as number and percentages. Timing of tracheostomy is shown in cumulative distribution plots stratified by (1) month of admission; (2) the median timing of tracheostomy of this cohort; and (3) admission before and after introduction of the amended national guideline.

Baseline characteristics and outcomes were compared between groups defined by tracheostomy status and by the median timing of this cohort. Wilcoxon rank−sum test for continuous variables and Fisher exact test for categorical variables were used accordingly. Duration of ventilation was compared through a clustered Fine−Gray competing risk model, with death before extubation treated as competing risk. Both survivors and non−survivors were included in this analysis. Binary outcomes were compared with adjusted odds ratios from a mixed−effect generalized linear model with a binomial distribution. Twenty−eight and 90−day mortality and ICU− and hospital−LOS were compared with adjusted hazard ratios from a Cox proportional hazard model. All models were adjusted for variables with a known or suspected relationship with outcome in COVID−19 patients, including age, gender, body mass index (BMI), partial arterial oxygen pressure to oxygen fraction (PaO_2/FiO_2) and plasma creatinine level at baseline, hypertension, diabetes mellitus, use of angiotensin converting enzyme inhibitors, use of angiotensin II receptor blockers, use of inotrope or vasopressor at start of ventilation, fluid balance, arterial pH, mean arterial pressure, heart rate, and respiratory system compliance at start of ventilation. The center and week of admission were considered as random effect. The group receiving tracheostomy and the group with timing greater than the median were used as references. In addition, duration of ventilation, LOS in survivors and 90−day mortality were compared using Kaplan−Meier estimators.

To ascertain which clinical factors had an independent association with timing of tracheostomy, a mixed−effect generalized linear model with Gaussian distribution and with center as random effect was used and reported as mean difference and 95% confidence interval (CI). The following variables with a known or suspected relationship with timing of tracheostomy were selected: 1) week of admission in participating hospital, the first week being determined by the date of the first COVID−19 admission in the ICU of that particular hospital; 2) demographic characteristics (age, gender, BMI, diabetes, hypertension, heart failure, asthma, and obstructive sleep apnea syndrome); 3) ventilatory and oxygenation variables in the first day after intubation or admission, aggregated as the median from a maximum of six assessments (tidal volume, positive end−expiratory pressure, respiratory system compliance, and PaO_2/FiO_2); 4) laboratory tests and vital signs in the first day after intubation or admission, aggregated as the median from a maximum of six assessments (arterial pH, lactate, creatinine, heart rate and mean arterial pressure); 5) organ support during the first day after intubation or admission (use of vasopressors, use of neuromuscular blocking agents (NMBA) and fluid balance); 6) use of prone positioning in the first 4 days of ventilation; 7) incidence of complications (thromboembolic events, acute kidney injury, use of RRT); 8) need of reintubation; and 9) being admitted after the online publication of the COVID−19 amendment to the Dutch national guidelines for tracheostomy. Missing data in predictors, when present in less than 5% of the patients, were imputed by the median.

In a post hoc analysis, we also examined whether the abovementioned variables were independently associated with performance of tracheostomy.

All analyses were conducted in R v.4.0.2 (R Foundation, Vienna, Austria) and significance level was set at 0.05.

Results

Patients

Between March 1 and June 1, 2020, 31 ICUs were invited for participation in the PRoVENT−COVID study and 22 met inclusion criteria. Of 1340 screened patients, 1023 were included in the current analysis (eFig. 1); the main reasons for exclusion were not having received invasive ventilation, unknown tracheostomy status due to transfer to a non−participating hospital, or having received ventilation for something other than COVID−19.

Incidence of tracheostomy

Of 1023 patients, 189 patients (18.5%) underwent tracheostomy. Tracheostomized patients were more often males and more likely to have asthma. On the first day of ventilation, tracheostomized patients had a higher respiratory compliance and $etCO_2$, and underwent longer duration of prone positioning (eTable 1). Performance of tracheostomy was independently associated with reintubation, pulmonary embolism, AKI and use of RRT. Additionally, tracheostomy was independently associated with longer duration of ventilation and lower ICU−, hospital−, and 28− and 90−day mortality (eTable 2).

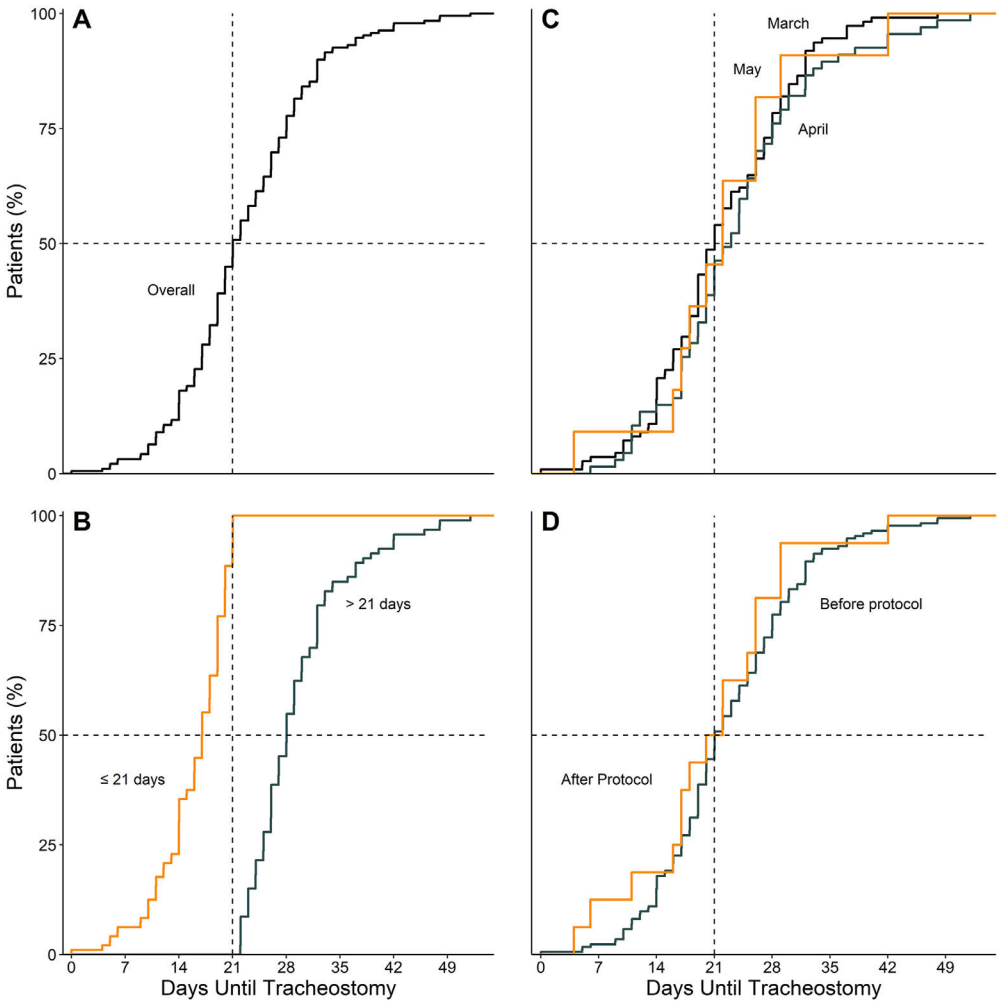

Figure 1 Cumulative Distribution Curves of Timing of Tracheostomy (A): All tracheostomized patients; (B): Stratified by month of admission; (C): Stratified by timing of tracheostomy before or on the median, or after; (D): Stratified by admission before and after the protocol.

Timing of tracheostomy

Time between start of invasive ventilation and tracheostomy was median 21 [17–28] days. Time until tracheostomy in March (21 [16–28] days), April (23 [17–28] days) and May (22 [17–26] days) was similar and seemed unaffected by the online publication of the amendment (21 [17–28] vs. 21 [17–26] days) (Fig. 1).

Compared to patients who were tracheostomized > 21 days, patients who were tracheostomized ≤ 21 days had a lower plasma creatinine and higher respiratory compliance and were ventilated with a higher tidal volume at baseline (Table 1). Tracheostomy ≤ 21 days was independently associated with shorter duration of ventilation, but higher ICU–, hospital– and 90–day mortality (Table 2 and Fig. 2).

Factors associated with timing and performance of tracheostomy

None of the clinical factors were associated with timing of tracheostomy (eTable 3). In the post hoc analysis, independent predictors of performance of tracheostomy were asthma, respiratory system compliance, occurrence of thromboembolic complications, need for RRT and reintubation (eTable 4).

Discussion

The findings of this secondary analysis of the PRoVENT–COVID study can be summarized as follows: (1) roughly 1 in every 5 patients were tracheostomized, (2) median timing of tracheostomy was 21 days, and this remained after online publication of the amendment of the national guideline, (3) tracheostomy ≤ 21 days had an independent association with shorter duration of ventilation and higher mortality rates, and (4) timing was not influenced by clinical factors. In a post hoc analysis, asthma, respiratory system compliance, occurrence of thromboembolic complications, need for RRT and reintubation were associated with performance of tracheostomy.

This analysis has several strengths. First, it is one of the largest cohorts of COVID–19 patients in which tracheostomy practice was analyzed. Second, we used data captured over the entire first wave of the pandemic in the Netherlands, encompassing about 40% of all ICU patients admitted during

Table 1 Baseline characteristics of patients receiving tracheostomy according to timing.

	Timing of tracheostomy[a]		p value
	≤ 21 days (*n* = 96)	> 21 days (*n* = 93)	
Age, years	65.0 (59.0 - 72.0)	65.0 (60.0 - 71.0)	0.947
Male gender — no (%)	75 (78.1)	77 (82.8)	0.466
Body mass index, kg/m^2	26.5 (24.7 - 31.0)	28.0 (26.1 - 29.9)	0.265
Transferred under invasive ventilation	21 (21.9)	17 (18.3)	0.589
Days between intubation and admission	0.0 (0.0 - 0.0)	0.0 (0.0 - 0.0)	0.922
Use of non-invasive ventilation — no (%)	4 / 79 (5.1)	7 / 86 (8.1)	0.539
Duration of non-invasive ventilation, hours	8.0 (5.0 - 36.0)	4.5 (1.0 - 14.8)	0.356
Timing of tracheostomy, days	17.0 (14.0 - 19.0)	28.0 (25.0 - 32.0)	< 0.001
Admitted after the publication of guideline[b]	8 (8.3)	8 (8.6)	0.999
Week of admission within the center[c]	2.5 (1.0 - 4.0)	3.0 (2.0 - 4.0)	0.269
Chest CT scan performed — no (%)	26 / 91 (28.6)	32 / 89 (36.0)	0.339
Lung parenchyma affected — no (%)			0.681
25%	11 / 26 (42.3)	9 / 32 (28.1)	
50%	9 / 26 (34.6)	12 / 32 (37.5)	
75%	5 / 26 (19.2)	9 / 32 (28.1)	
100%	1 / 26 (3.8)	2 / 32 (6.2)	
Chest X-ray performed — no (%)	55 / 63 (87.3)	49 / 55 (89.1)	0.999
Quadrants affected — no (%)			0.583
1	5 / 55 (9.1)	8 / 50 (16.0)	
2	14 / 55 (25.5)	15 / 50 (30.0)	
3	17 / 55 (30.9)	11 / 50 (22.0)	
4	19 / 55 (34.5)	16 / 50 (32.0)	
Severity of ARDS — no (%)			0.198
Mild	18 (18.8)	21 / 90 (23.3)	
Moderate	74 (77.1)	60 / 90 (66.7)	
Severe	4 (4.2)	9 / 90 (10.0)	
Co-existing disorders — no (%)			
Hypertension	29 (30.2)	33 (35.5)	0.536
Heart failure	4 (4.2)	6 (6.5)	0.532
Diabetes	22 (22.9)	21 (22.6)	0.999
Chronic kidney disease	6 (6.2)	5 (5.4)	0.999
Baseline creatinine, μmol/L[d]	74.0 (65.0 - 85.5)	81.0 (65.0 - 105.0)	0.032
Liver cirrhosis	1 (1.0)	0 (0.0)	0.999
Chronic obstructive pulmonary disease	6 (6.2)	8 (8.6)	0.588
Active hematological neoplasia	1 (1.0)	3 (3.2)	0.363
Active solid neoplasia	3 (3.1)	2 (2.2)	0.999
Neuromuscular disease	0 (0.0)	1 (1.1)	0.492
Immunosuppression	4 (4.2)	1 (1.1)	0.369
Asthma	10 (10.4)	9 (9.7)	0.999
Obstructive sleep apnea syndrome	5 (5.2)	5 (5.4)	0.999
Previous medication — no (%)			
Systemic steroids	5 (5.2)	2 (2.2)	0.445
Inhalation steroids	11 (11.5)	9 (9.7)	0.814
Angiotensin converting enzyme inhibitor	17 (17.7)	16 (17.2)	0.999
Angiotensin II receptor blocker	9 (9.4)	14 (15.1)	0.270
Beta-blockers	22 (22.9)	18 (19.4)	0.596
Insulin	9 (9.4)	5 (5.4)	0.407
Metformin	13 (13.5)	14 (15.1)	0.837
Statins	32 (33.3)	28 (30.1)	0.643
Calcium channel blockers	13 (13.5)	15 (16.1)	0.685
Organ support at start of ventilation — no (%)			
Continuous sedation	92 (95.8)	87 (93.5)	0.532
Inotropic or vasopressor	77 (80.2)	66 (71.0)	0.175
Vasopressor	77 (80.2)	66 (71.0)	0.175
Inotropic	1 (1.0)	5 (5.4)	0.114
Fluid balance, mL	585.5 (43.5 - 1438.6)	357.9 (-61.5 - 965.5)	0.138
Urine output, mL	682.5 (347.5 - 1172.5)	762.5 (411.2 - 1171.2)	0.579

Table 1 (*Continued*)

	Timing of tracheostomy[a]		p value
	≤ 21 days (*n* = 96)	> 21 days (*n* = 93)	
Ventilation support at start of ventilation			
Assisted ventilation — no (%)	29 (30.2)	23 / 92 (25.0)	0.514
Tidal volume, mL/kg PBW	6.7 (6.1 - 7.6)	6.4 (5.8 - 6.9)	0.019
PEEP, cmH_2O	13.0 (11.2 - 14.6)	12.5 (10.7 - 14.3)	0.478
Peak pressure, cmH_2O	26.0 (23.4 - 29.1)	25.7 (23.9 - 29.0)	0.734
Driving pressure, cmH_2O	13.0 (11.0 - 15.1)	14.0 (12.0 - 15.9)	0.090
Mechanical power, J/min	18.9 (15.5 - 22.7)	19.1 (15.7 - 23.2)	0.882
Compliance, mL/cmH_2O	37.7 (30.9 - 45.3)	33.5 (26.4 - 40.1)	0.037
Total respiratory rate, mpm	21.2 (19.0 - 24.0)	22.3 (19.4 - 24.5)	0.352
FiO_2	0.60 (0.49 - 0.69)	0.56 (0.47 - 0.66)	0.344
$etCO_2$, mmHg	36.9 (33.3 - 41.6)	38.4 (34.2 - 44.8)	0.290
Vital signs at start of ventilation			
Heart rate, bpm	88.5 (76.4 - 101.1)	84.0 (77.0 - 100.2)	0.429
Mean arterial pressure, mmHg	80.3 (73.5 - 87.5)	79.9 (75.3 - 91.3)	0.484
Laboratory tests at start of ventilation			
pH	7.36 (7.30 - 7.40)	7.36 (7.31 - 7.41)	0.473
PaO_2, mmHg	81.4 (74.1 - 94.3)	81.8 (73.1 - 98.0)	0.896
PaO_2 / FiO_2, mmHg	123.9 (93.4 - 160.8)	140.6 (109.0 - 200.7)	0.074
$PaCO_2$, mmHg	45.5 (40.3 - 51.9)	45.0 (39.8 - 50.5)	0.553
Lactate, mmol/L	1.1 (0.9 - 1.5)	1.1 (1.0 - 1.4)	0.555
Adjunctive therapies at start of ventilation			
Prone positioning - no. (%)	30 / 93 (32.3)	303 / 92 (32.6)	0.999
Duration of prone positioning, hours	9.5 (6.0 - 14.4)	10.0 (7.0 - 13.5)	0.897
Recruitment maneuvers - no. (%)	1 / 84 (1.2)	33 / 80 (3.8)	0.358
ECMO - no. (%)	0 / 95 (0.0)	0 (0.0)	—
Use of NMBA - no. (%)	29 (30.2)	20 (21.5)	0.188
Duration of neuromuscular blocking agents, hours	0.0 (0.0 - 8.0)	0.0 (0.0 - 0.0)	0.200

Data are median (quartile 25% - quartile 75%) or No (%). Percentages may not total 100 because of rounding
CT: computed tomography; ARDS: Acute Respiratory Distress Syndrome; PBW: predicted body weight; PEEP: positive end expiratory pressure; ECMO: extracorporeal membrane oxygenation; NMBA: neuromuscular blocking agent
[a] Groups defined by the median timing of this cohort.
[b] National guideline on practice of tracheostomy on COVID-19 patients published on April 23, 2020.
[c] First week determined as the week when the first patient was admitted in the center.
[d] Most recent measurement in 24 hours before intubation, or at ICU admission under invasive ventilation.

that time. Third, university, non—university, teaching and non—teaching centers were involved, increasing the generalizability of this study. Fourth, hospitals that were invited but did not participate were unable to do so only because of administrative and regulatory barriers, unrelated to the workload and possible lack of time on the ICU. This makes selection bias unlikely. Fifth, the exact date of publication of the tracheostomy guideline amendment was known, giving accurate insight into its influence on practice of tracheostomy. Sixth, our statistical analysis plan was published before analysis of the data, preventing reporting bias.

The incidence of tracheostomy in the current cohort of COVID—19 patients is slightly higher than in LUNG SAFE,[15] a large service review in which 13% of ARDS patients received a tracheostomy.[16] LUNG SAFE patients were ventilated for a shorter duration and represent a more heterogeneous population of ARDS patients, possibly explaining this difference. Also, thromboembolic complications and AKI are prevalent among COVID—19 ARDS patients,[17,18] factors which were shown to be predictors of performing a tracheostomy in this study.

The timing of tracheostomy was substantially later in this study than in LUNG SAFE, which showed a median timing of 14 days.[16] This may be due to the larger proportion of patients with moderate—severe ARDS seen in this study, as well as lower PaO_2/FiO_2 and use of higher PEEP at baseline. Placement of a tracheostomy canula can be unsafe in patients with severely compromised gas—exchange because of the unavoidable loss in positive airway pressure, delaying the procedure until improvement of oxygenation is seen. In addition, tracheostomy could have been postponed by health care providers out of fear of viral transmission, preferably waiting for a decrease in viral load.

Practice of tracheostomy is difficult to compare to other cohorts of invasively ventilated COVID—19 patients because of the large variability seen in both incidence and timing in a number of identified studies. Incidence of tracheostomy in

Table 2 Clinical outcomes of patients receiving tracheostomy according to timing.

	Timing of tracheostomy[a]		Adjusted effect estimate* (95% Confidence Interval)	*p* value
	≤ 21 days (*n* = 96)	> 21 days (*n* = 93)		
Duration of ventilation, days	26.0 (21.0 - 32.0)	40.0 (33.5 - 46.5)	SHR, 13.74 (5.48 to 34.47)[c]	< 0.001
In survivors at day 28, days	26.5 (21.8 - 33.3)	40.0 (33.5 - 46.5)		
Reintubation – no (%)	24 / 95 (25.3)	24 (25.8)	OR, 0.96 (0.46 to 1.99)[d]	0.902
Thromboembolic complications – no (%)	38 (39.6)	45 (48.4)	OR, 0.65 (0.35 to 1.22)[d]	0.181
Pulmonary embolism	32 (33.3)	38 (40.9)	OR, 0.70 (0.37 to 1.33)[d]	0.279
Deep vein thrombosis	3 (3.1)	9 (9.7)	OR, 0.26 (0.01 to 4.95)[d]	0.369
Ischemic stroke	3 (3.1)	5 (5.4)	OR, 0.13 (0.01 to 2.07)[d]	0.150
Myocardial infarction	2 (2.1)	1 (1.1)	–	–
Systemic arterial embolism	0 (0.0)	0 (0.0)	–	–
Acute kidney injury – no (%)	53 / 94 (56.4)	53 (57.0)	OR, 1.24 (0.58 to 2.62)[d]	0.578
Need for RRT – no (%)	26 (27.1)	35 (37.6)	OR, 0.59 (0.27 to 1.30)[d]	0.192
Need of rescue therapy – no (%)[b]	71 / 95 (74.7)	72 (77.4)	OR, 0.65 (0.29 to 1.49)[d]	0.312
Prone positioning	51 / 95 (53.7)	61 / 92 (66.3)	OR, 0.43 (0.18 to 1.04)[d]	0.060
Recruitment maneuver	5 / 85 (5.9)	6 / 82 (7.3)	OR, 0.73 (0.14 to 3.91)[d]	0.715
Use of NMBA	53 (55.2)	46 (49.5)	OR, 1.05 (0.50 to 2.19)[d]	0.894
ECMO	1 / 95 (1.1)	0 (0.0)	–	–
Use of continuous sedation – no (%)[b]	95 (99.0)	90 (96.8)	OR, ∞ (0.00 to ∞)[d]	0.999
Use of inotropic or vasopressor – no (%)[b]	90 (93.8)	85 (91.4)	OR, 0.00 (0.00 to ∞)[d]	0.407
Use of vasopressor	90 (93.8)	85 (91.4)	OR, 0.00 (0.00 to ∞)[d]	0.407
Use of inotropic	5 (5.2)	8 (8.6)	OR, 0.09 (0.00 to 2.67)[d]	0.166
ICU length of stay, days	29.0 (24.3 - 36.8)	44.0 (37.5 - 51.0)	HR, 1.18 (0.82 to 1.69)[e]	0.370
In survivors, days	29.0 (25.0 - 38.0)	43.5 (37.0 - 50.0)		
Hospital length of stay, days	39.0 (30.0 - 50.0)	58.0 (50.0 - 66.0)	HR, 1.05 (0.72 to 1.52)[e]	0.810
In survivors, days	43.0 (33.5 - 53.5)	58.0 (52.0 - 65.8)		
ICU mortality – no (%)	21 / 95 (22.1)	9 / 88 (10.2)	OR, 3.24 (1.24 to 8.46)[d]	0.016
Hospital mortality – no (%)	24 / 92 (26.1)	10 / 84 (11.9)	OR, 3.76 (1.44 to 9.85)[d]	0.007
28-day mortality – no (%)	11 (11.5)	0 (0.0)	–	–
90-day mortality – no (%)	24 / 87 (27.6)	12 / 82 (14.6)	HR, 3.24 (1.45 to 7.25)[e]	0.004

Data are median (quartile 25% - quartile 75%) or No (%). Percentages may not total 100 because of rounding
RRT: renal replacement therapy; NMBA: neuromuscular blocking agent; ECMO: extracorporeal membrane oxygenation; ICU: intensive care unit

* All models adjusted for age, gender, body mass index, PaO_2 / FiO_2, creatinine, hypertension, diabetes mellitus, use of angiotensin converting enzyme inhibitors, use of angiotensin II receptor blockers, use of inotrope or vasopressor at start of ventilation, fluid balance, pH, mean arterial pressure, heart rate, and respiratory system compliance at start of ventilation.

[a] Groups defined by the median timing of this cohort; group tracheostomized after 21 days is the reference.

[b] Assessed in the first four days of ventilation.

[c] Subdistribution hazard ratio from a Fine-Gray competing risk model with death before extubation in 28 days treated as a competing risk and with center as clustering effect.

[d] Odds ratio from a mixed-effect generalized linear model with a binomial distribution and with center as random effect.

[e] Hazard ratio from a (shared-frailty) Cox proportional hazard model (for the ICU and hospital length of stay analyses, all patients who died prior to discharge were assigned the maximum length of stay to account for death as a competing risk in this model) with center as frailty. P value for the Schoenfeld residuals; < 0.001 (ICU length of stay); < 0.001 (hospital length of stay); < 0.001 (90-day mortality)

invasively ventilated COVID−19 patients has been shown to range from 8 to 77%,[3,19-35] and mean or median timing from 4 to 23 days.[5,19,22,24,27-42] As many of these identified studies are single center, this may reflect differences in local practices irrespective of national guidelines. This idea is supported by the fact that most of the identified studies showed a timing of ≤ 14 days,[19,22,24,27,28,32,33,35,39,42] despite 90% of international guidelines recommending waiting at least 14 days before performing a tracheostomy in COVID−19 patients.[10] The timing in our cohort, however, is in line with the majority of international guidelines, as well as the amendment of national Dutch tracheostomy guidelines. Therefore, it is possible that international advice regarding tracheostomy practice, released early on in the pandemic of 2020, was followed even before publication of the amendment of national guidelines. As it was already national practice to delay tracheostomy until at least 10 days after intubation, it would not have been a significant change in mindset.

Earlier timing of tracheostomy had an association with shorter duration of ventilation in this cohort. Freeing patients from the ventilator as soon as possible is particularly valuable when there is a surge of patients needing to be treated in a pandemic. However, earlier tracheostomy was also associated with a higher mortality. This association was found after correcting for factors possibly having an

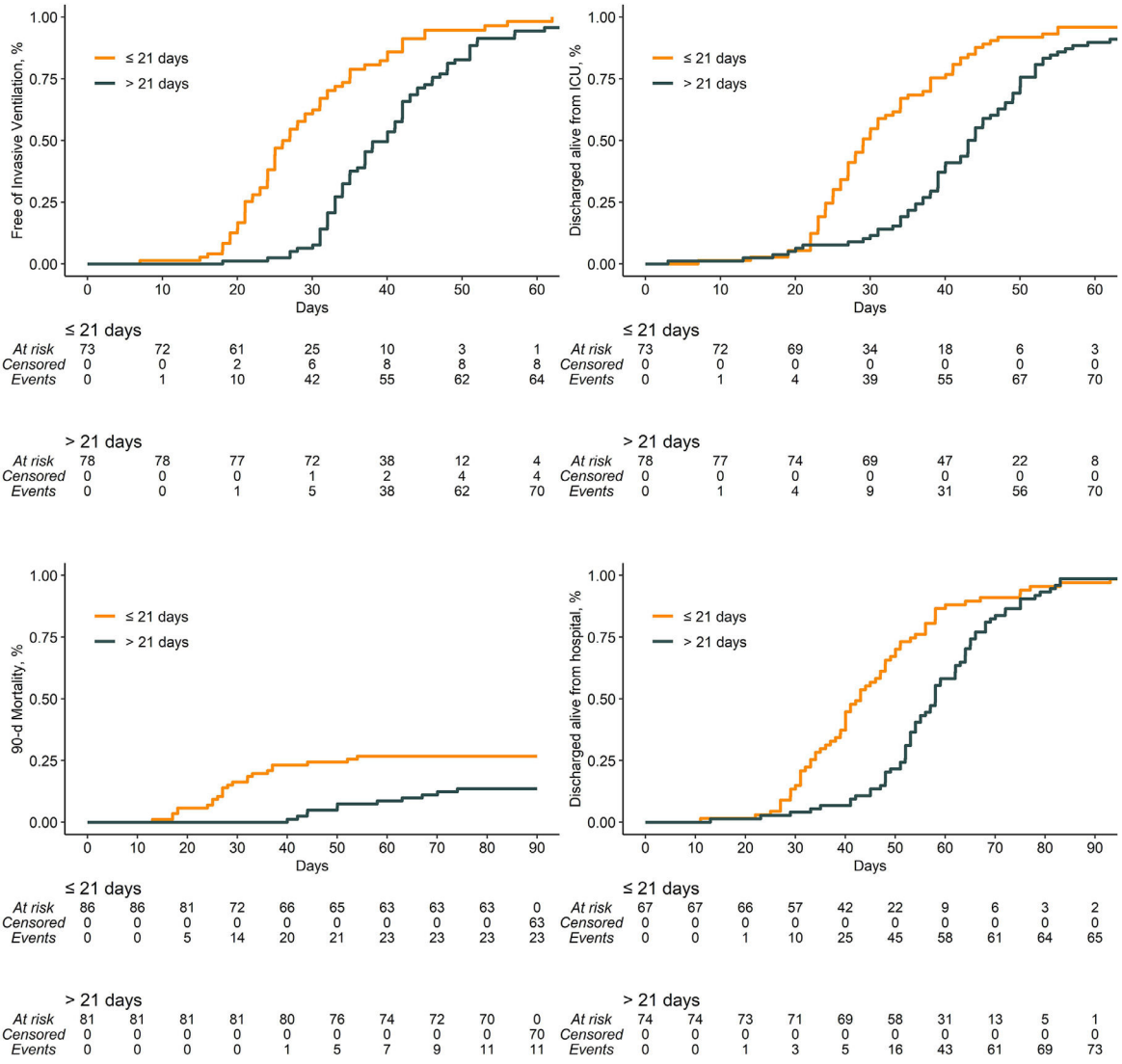

Figure 2 Kaplan–Meier Curves stratified by Timing of Tracheostomy (A): Duration of Ventilation in Survivors; (B): 90–day survival; (C): Duration of ICU stay in survivors; (D): Duration of hospital stay in survivors

independent association with outcome, such as hemodynamic and respiratory problems. It is likely that this association is the result of immortal time bias and not an actual cause and effect. This phenomenon is introduced when patients cannot experience a certain outcome during a period of follow–up. In this analysis, patients in the later tracheostomy group already had survived 21 days before being categorized. This period is quite long, which may have increased the magnitude of bias.[43]

This study has limitations. We had 99 patients with an unknown tracheostomy status due to transfer to a non–participating hospital. In addition, we did not collect local guidelines on tracheostomy practice, making it unclear what decisions were precisely based on. Different approaches to clinical decisions from each center may have influenced outcomes. We didn't collect data on PPE and tracheostomy kit shortages and cannot determine the effect this had on timing. Whether a surgical or percutaneous technique was used for placement of tracheostomy was not recorded, which could have given additional insight into tracheostomy practice in the Netherlands. Ventilation data was restricted to the first four days of admission and therefore are unknown directly before placement of tracheostomy. Furthermore, data regarding incidence of ventilator associated pneumonia (VAP), other infections and sepsis were not collected; as these factors could influence both timing of tracheostomy and outcome, this is a limitation. Finally, use of additional therapies such as antibiotics, steroids and anticoagulants is unknown in our cohort, which could also have influenced outcome.

Conclusion

This study gives insight into the practice of tracheostomy in invasively ventilated COVID–19 patients in the Netherlands. The results suggest that earlier timing of tracheostomy is associated with a shorter duration of ventilation, which would be of crucial benefit in overloaded ICUs. However, because this study also suggested a higher mortality in patients who received earlier tracheostomy, future studies are needed to determine whether earlier tracheostomy has a positive influence on outcome in COVID–19 patients. It

remains unclear which factors influenced timing of tracheostomy during the first wave of the pandemic.

Conflicts of interest

The authors have no conflicts of interest to declare.

Supplementary materials

Supplementary material associated with this article can be found in the online version at doi:10.1016/j.pulmoe.2021.08.012.

References

1. Mahmood K, Wahidi MM. The changing role for tracheostomy in patients requiring mechanical ventilation. Clin Chest Med. 2016;37(4):741—51. https://doi.org/10.1016/j.ccm.2016.07.013.
2. Ferrando C, Suarez-Sipmann F, Mellado-Artigas R, et al. Clinical features, ventilatory management, and outcome of ARDS caused by COVID-19 are similar to other causes of ARDS. Intensive Care Med. 2020;46(12):2200—11. https://doi.org/10.1007/s00134-020-06192-2.
3. Cummings MJ, Baldwin MR, Abrams D, et al. Epidemiology, clinical course, and outcomes of critically ill adults with COVID-19 in New York City: a prospective cohort study. Lancet. 2020;395 (10239):1763—70. https://doi.org/10.1016/S0140-6736(20)31189-2.
4. Grasselli G, Zangrillo A, Zanella A, et al. Baseline characteristics and outcomes of 1591 patients infected with SARS-CoV-2 admitted to ICUs of the Lombardy Region, Italy. JAMA. 2020;323 (16):1574—81. https://doi.org/10.1001/jama.2020.5394.
5. Saad M, Laghi FA, Brofman J, Undevia NS, Shaikh H. Long-term acute care hospital outcomes of mechanically ventilated patients with coronavirus disease 2019. Crit Care Med. 2021.
6. Young D, Harrison DA, Cuthbertson BH, Rowan K, TracMan C. Effect of early vs late tracheostomy placement on survival in patients receiving mechanical ventilation: the TracMan randomized trial. JAMA. 2013;309(20):2121—9. https://doi.org/10.1001/jama.2013.5154.
7. Huang H, Li Y, Ariani F, Chen X, Lin J. Timing of tracheostomy in critically ill patients: a meta-analysis. PLoS One. 2014;9(3): e92981. https://doi.org/10.1371/journal.pone.0092981.
8. Siempos II, Ntaidou TK, Filippidis FT, Choi AMK. Effect of early versus late or no tracheostomy on mortality and pneumonia of critically ill patients receiving mechanical ventilation: a systematic review and meta-analysis. Lancet Respir Med. 2015;3 (2):150—8. https://doi.org/10.1016/s2213-2600(15)00007-7.
9. Chiesa-Estomba CM, Lechien JR, Calvo-Henriquez C, et al. Systematic review of international guidelines for tracheostomy in COVID-19 patients. Oral Oncol. 2020;108:104844. https://doi.org/10.1016/j.oraloncology.2020.104844.
10. Bier-Laning C, Cramer JD, Roy S, et al. Tracheostomy during the COVID-19 pandemic: comparison of international perioperative care protocols and practices in 26 countries. Otolaryngol Head Neck Surg. 2020;164(6):1136—47. https://doi.org/10.1177/0194599820961985.
11. McGrath BA, Ashby N, Birchall M, et al. Multidisciplinary guidance for safe tracheostomy care during the COVID-19 pandemic: the NHS National Patient Safety Improvement Programme (NatPatSIP). Anaesthesia. 2020. https://doi.org/10.1111/anae.15120.
12. NICE. COVID-19 op de Nederlandse Intensive Cares; Patiëntkarakteristieken en uitkomsten vergeleken met pneumonie patiënten op de IC in 2017-2019, https://www.stichting-nice.nl/COVID_rapport.p df [accessed 17 March 2021].
13. Fikkers BG, Breedveld P, Delwig H, et al. Tracheostomy on the Intensive Care Unit for Adult Patients. 2013. https://nvic.nl/sites/nvic.nl/files/Richtlijnen%20aanmaken/NVIC%20guideline%20tracheostomy%202013.pdf [accessed 17 March 2021].
14. Fikkers BG, Dieperink P, Frenzel T, et al. NVIC Tracheotomieprotocol COVID-19 (definitief, 23 april 2020) https://nvic.nl/sites/nvic.nl/files/Richtlijnen%20aanmaken/NVIC%20tracheotomieprotocol2020%20definitief%20april2020%20versie2_0.pdf. 2020 [accessed 17 March 2021].
15. Bellani G, Laffey JG, Pham T, et al. Epidemiology, patterns of care, and mortality for patients with acute respiratory distress syndrome in intensive care units in 50 countries. JAMA. 2016;315 (8):788—800. https://doi.org/10.1001/jama.2016.0291.
16. Abe T, Madotto F, Pham T, et al. Epidemiology and patterns of tracheostomy practice in patients with acute respiratory distress syndrome in ICUs across 50 countries. Crit Care. 2018;22 (1):195. https://doi.org/10.1186/s13054-018-2126-6.
17. Gabarre P, Dumas G, Dupont T, Darmon M, Azoulay E, Zafrani L. Acute kidney injury in critically ill patients with COVID-19. Intensive Care Med. 2020;46(7):1339—48. https://doi.org/10.1007/s00134-020-06153-9.
18. Jenner WJ, Kanji R, Mirsadraee S, et al. Thrombotic complications in 2928 patients with COVID-19 treated in intensive care: a systematic review. J Thromb Thrombol. 2021;51(3):595—607. https://doi.org/10.1007/s11239-021-02394-7.
19. Angel L, Kon ZN, Chang SH, et al. Novel percutaneous tracheostomy for critically ill patients with COVID-19. Ann Thorac Surg. 2020;110(3):1006—11. https://doi.org/10.1016/j.athoracsur.2020.04.010.
20. Hur K, Price CPE, Gray EL, et al. Factors associated with intubation and prolonged intubation in hospitalized patients with COVID-19. Otolaryngol Head Neck Surg. 2020;163(1):170—8. https://doi.org/10.1177/0194599820929640.
21. Karagiannidis C, Mostert C, Hentschker C, et al. Case characteristics, resource use, and outcomes of 10 021 patients with COVID-19 admitted to 920 German hospitals: an observational study. Lancet Respir Med. 2020;8(9):853—62. https://doi.org/10.1016/S2213-2600(20)30316-7.
22. Martin-Villares C, Perez Molina-Ramirez C, Bartolome-Benito M, Bernal-Sprekelsen M. Group COEC. Outcome of 1890 tracheostomies for critical COVID-19 patients: a national cohort study in Spain. Eur Arch Otorhinolaryngol. 2020;278(5):1605—12. https://doi.org/10.1007/s00405-020-06220-3.
23. McWilliams D, Weblin J, Hodson J, et al. Rehabilitation levels in COVID-19 patients admitted to intensive care requiring invasive ventilation: an observational study. Ann Am Thorac Soc. 2020;18(1):122—9. https://doi.org/10.1513/AnnalsATS.202005-560OC.
24. Morvan JB, Riviere D, Danguy des Deserts M, Bonfort G, Mathais Q, Pasquier P. Percutaneous dilatational tracheostomy for saturating influx of COVID-19 patients: experience of military ENT physicians deployed in Mulhouse, France. Eur Ann Otorhinolaryngol Head Neck Dis. 2020;137(4):263—8. https://doi.org/10.1016/j.anorl.2020.06.016.
25. Mukherjee V, Toth AT, Fenianos M, et al. Clinical outcomes in critically ill coronavirus disease 2019 patients: a unique New York city public hospital experience. Crit Care Explor. 2020;2 (8):e0188. https://doi.org/10.1097/CCE.0000000000000188.
26. Primmaz S, Le Terrier C, Suh N, et al. Preparedness and reorganization of care for coronavirus disease 2019 patients in a Swiss ICU: characteristics and outcomes of 129 patients. Crit Care Explor. 2020;2(8):e0173. https://doi.org/10.1097/CCE.0000000000000173.

27. Queen Elizabeth Hospital Birmingham COVID-19 airway team. Safety and 30-day outcomes of tracheostomy for COVID-19: a prospective observational cohort study. Br J Anaesth. 2020;125 (6):872—9. https://doi.org/10.1016/j.bja.2020.08.023.
28. Rosano A, Martinelli E, Fusina F, et al. Early percutaneous tracheostomy in coronavirus disease 2019: association with hospital mortality and factors associated with removal of tracheostomy tube at ICU discharge. A cohort study on 121 patients. Crit Care Med. 2021;49(2):261—70. https://doi.org/10.1097/CCM.0000000000004752.
29. Taboada M, Rama P, Pita-Romero R, et al. Critically ill COVID-19 patients attended by anesthesiologists in northwestern Spain: a multicenter prospective observational study. Rev Esp Anestesiol Reanim. 2021;68(1):10—20. https://doi.org/10.1016/j.redar.2020.08.004.
30. Thomson RJ, Hunter J, Dutton J, et al. Clinical characteristics and outcomes of critically ill patients with COVID-19 admitted to an intensive care unit in London: a prospective observational cohort study. PLoS One. 2020;15(12):e0243710. https://doi.org/10.1371/journal.pone.0243710.
31. Tornari C, Surda P, Takhar A, et al. Tracheostomy, ventilatory wean, and decannulation in COVID-19 patients. Eur Arch Otorhinolaryngol. 2020;1:1—10. https://doi.org/10.1007/s00405-020-06187-1.
32. Volo T, Stritoni P, Battel I, et al. Elective tracheostomy during COVID-19 outbreak: to whom, when, how? Early experience from Venice, Italy. Eur Arch Otorhinolaryngol. 2020;12:1—9. https://doi.org/10.1007/s00405-020-06190-6.
33. Yeung E, Hopkins P, Auzinger G, Fan K. Challenges of tracheostomy in COVID-19 patients in a tertiary centre in inner city London. Int J Oral Maxillofac Surg. 2020;49(11):1385—91. https://doi.org/10.1016/j.ijom.2020.08.007.
34. Ziehr DR, Alladina J, Petri CR, et al. Respiratory pathophysiology of mechanically ventilated patients with COVID-19: a cohort study. Am J Respir Crit Care Med. 2020;201(12):1560—4. https://doi.org/10.1164/rccm.202004-1163LE.
35. Zuazua-Gonzalez A, Collazo-Lorduy T, Coello-Casariego G, et al. Surgical tracheostomies in COVID-19 patients: indications, technique, and results in a second-level Spanish hospital. OTO Open. 2020;4(3). 2473974X20957636https://doi.org/10.1177/2473974X20957636.
36. Chao TN, Harbison SP, Braslow BM, et al. Outcomes after tracheostomy in COVID-19 patients. Ann Surg. 2020;272(3):e181—6. https://doi.org/10.1097/SLA.0000000000004166.
37. COVIDTrach collaborative. the outcomes of mechanically ventilated COVID-19 patients undergoing tracheostomy in the UK: Interim Report. Br J Surg. 2020;107(12):e583—e4. https://doi.org/10.1002/bjs.12020.
38. D'Ascanio L, Pandolfini M, Cingolani C, Latini G, Giardini D. Letter to the editor regarding "How to avoid nosocomial spread during tracheostomy for Covid-19 patients". Head Neck. 2020;42(9):2768—9. https://doi.org/10.1002/hed.26333.
39. Piccin O, Albertini R, Caliceti U, et al. Early experience in tracheostomy and tracheostomy tube management in Covid-19 patients. Am J Otolaryngol. 2020;41(4):102535. https://doi.org/10.1016/j.amjoto.2020.102535.
40. Riestra-Ayora J, Yanes-Diaz J, Penuelas O, Molina-Quiros C, Sanz-Fernandez R, Martin-Sanz E. Safety and prognosis in percutaneous vs surgical tracheostomy in 27 patients with COVID-19. Otolaryngol Head Neck Surg. 2020;163(3):462—4. https://doi.org/10.1177/0194599820931801.
41. Takhar A, Tornari C, Amin N, et al. Safety and outcomes of percutaneous tracheostomy in coronavirus disease 2019 pneumonitis patients requiring prolonged mechanical ventilation. J Laryngol Otol. 2020: 1—10. https://doi.org/10.1017/S0022215120002303.
42. Williamson A, Roberts MT, Phillips J, Saha R. Early percutaneous tracheostomy for patients with COVID-19. Anaesthesia. 2020;76 (1):138—9. https://doi.org/10.1111/anae.15197.
43. Levesque LE, Hanley JA, Kezouh A, Suissa S. Problem of immortal time bias in cohort studies: example using statins for preventing progression of diabetes. BMJ. 2010;340:b5087. https://doi.org/10.1136/bmj.b5087.