

CRITICAL CARE

Tracheostomy outcomes in critically ill patients with COVID-19: a systematic review, meta-analysis, and meta-regression

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Abstract

Background: We performed a systematic review of mechanically ventilated patients with COVID-19, which analysed the effect of tracheostomy timing and technique (surgical vs percutaneous) on mortality. Secondary outcomes included intensive care unit (ICU) and hospital length of stay (LOS), decannulation from tracheostomy, duration of mechanical ventilation, and complications.

Methods: Four databases were screened between January 1, 2020 and January 10, 2022 (PubMed, Embase, Scopus, and Cochrane). Papers were selected according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) and the Population or Problem, Intervention or exposure, Comparison, and Outcome (PICO) guidelines. Meta-analysis and meta-regression for main outcomes were performed.

Results: The search yielded 9024 potentially relevant studies, of which 47 ($n=5268$ patients) were included. High levels of between-study heterogeneity were observed across study outcomes. The pooled mean tracheostomy timing was 16.5 days (95% confidence interval [CI]: 14.7–18.4; $I^2=99.6\%$). Pooled mortality was 22.1% (95% CI: 18.7–25.5; $I^2=89.0\%$). Meta-regression did not show significant associations between mortality and tracheostomy timing, mechanical ventilation duration, time to decannulation, and tracheostomy technique. Pooled mean estimates for ICU and hospital LOS were 29.6 (95% CI: 24.0–35.2; $I^2=98.6\%$) and 38.8 (95% CI: 32.1–45.6; $I^2=95.7\%$) days, both associated with mechanical ventilation duration (coefficient 0.8 [95% CI: 0.2–1.4], $P=0.02$ and 0.9 [95% CI: 0.4–1.4], $P=0.01$, respectively) but not tracheostomy

Received: 1 April 2022; Accepted: 12 July 2022

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timing. Data were insufficient to assess tracheostomy technique on LOS. Duration of mechanical ventilation was 23.4 days (95% CI: 19.2–27.7; $I^2=99.3\%$), not associated with tracheostomy timing. Data were insufficient to assess the effect of tracheostomy technique on mechanical ventilation duration. Time to decannulation was 23.8 days (95% CI: 19.7–27.8; $I^2=98.7\%$), not influenced by tracheostomy timing or technique. The most common complications were stoma infection, ulcers or necrosis, and bleeding.

Conclusions: In patients with COVID-19 requiring tracheostomy, the timing and technique of tracheostomy did not clearly impact on patient outcomes.

Systematic Review Protocol: PROSPERO CRD42021272220.

Keywords: ARDS; COVID-19; mortality; outcomes; SARS-CoV-2; tracheostomy

Editor's key points

- Tracheostomy practice has changed during the COVID-19 pandemic. The benefits of a tracheostomy, its optimal timing, and technique are yet to be thoroughly investigated.
- In this systematic review and meta-analysis, the authors explore important outcomes in critically ill patients with COVID-19 and a tracheostomy, examining associations with the timing of tracheostomy and the technique (percutaneous or surgical) used.
- The timing and type of tracheostomy appeared to have no impact on outcome. The authors conclude that decisions around timing and technique should include the multidisciplinary team, considering patient and their family's wishes.

During exponential increases of novel coronavirus (COVID-19) spread, extraordinary pressure on hospitals has been exerted worldwide.¹ Patients with severe disease, requiring intensive care unit (ICU) admission and mechanical ventilation (MV) presented similar mortality rates in different pandemic periods.² Prolonged MV has been frequently observed in COVID-19,^{3,4} with tracheostomy being commonly used to facilitate weaning from respiratory support and accelerate discharge from ICU. Tracheostomy practice has changed during the pandemic with a higher rate of performance compared with patients without COVID-19.^{5–9} Considering that patients with COVID-19 typically experience longer periods of MV than those with other pneumonias, it is possible that tracheostomy yields a potential survival benefit,⁷ perhaps by facilitating weaning from ventilatory support⁸ and by streamlining the critical care management of airways.¹⁰ Nevertheless, the potential benefits of a tracheostomy; its optimal timing and technique choice; and burden for patients, staff, and resources in COVID-19 have yet to be defined.¹¹

Few meta-analyses of tracheostomy practice in COVID-19 have been published at the beginning of the pandemic,^{12–14} but none of them was able to compare outcomes beyond mortality facing the issues around timing and technique of tracheostomy. We performed an updated systematic review and meta-analysis at the tail end of the COVID-19 pandemic to summarise and assess all published evidence regarding overall mortality in patients with COVID-19 and a tracheostomy, also investigating tracheostomy timing and technique (surgical [open] vs percutaneous). Secondary outcomes included ICU and hospital length of stay (LOS); timing of tracheostomy from

intubation, proportion, and timing of decannulation after tracheostomy; MV duration; and tracheostomy complications.

Methods

This systematic review was reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA)^{15,16} and the Joanna Briggs Institute (*JBI Reviewers' Manual for Systematic Reviews of Literature*¹⁷ (Supplementary material item S1). The protocol was registered in the International Prospective Register of Systematic Reviews (PROSPERO) on August 20, 2021 (Registration number: CRD42021272220).

Search strategy and study selection

Two reviewers (DB and LP) systematically searched PubMed, Embase, Scopus, and the Cochrane trial registry for all published observational studies as of January 10, 2022, aiming to investigate the timing of tracheostomy from intubation, mortality, length of hospital and ICU stay, prevalence and timing of decannulation, duration of MV, and complications in a critically ill population with COVID-19. We used a combination of headings and keywords specific for each database based on the following Medical Subject Headings (MeSH) '(tracheostomy OR tracheotomy OR trachea*) AND (COVID-19 OR ncov OR coronavirus OR COVID OR coronavirus disease OR SARS-CoV-2 OR acute severe respiratory syndrome coronavirus)'. The extended list of MeSH terms is reported in the Supplementary material item S2. Titles and abstracts of all identified studies were independently screened by two authors (DB and LP) and retrieved for duplication checking. The references of all these papers were also reviewed to identify other studies of interest potentially missed during the primary search. In addition, peer-reviewed publications, preprints, and press releases were eligible for inclusion. There were no restrictions placed on language or geographic region. After screening the titles and abstracts, the same two authors independently screened the full text of all selected articles for possible inclusion. In the case of uncertain selection, discrepancies were resolved by a consensus. If a consensus was not reached, a third reviewer was involved in the process (IDG, FB, or MS).

The selected studies included (i) observational studies and randomised trials if present; (ii) adult patients with suspected or confirmed SARS-CoV-2 infection; (iii) patients with COVID-19, who received a tracheostomy during their ICU course; and (iv) studies including 20 or more patients. Exclusion criteria were the paediatric population and non-compliance with the aforementioned inclusion criteria.

Definitions

Time to tracheostomy was defined as the mean time between initiation of MV and tracheostomy performance (days). *Time to decannulation* was defined as the mean timing between tracheostomy performance and tracheostomy removal (days). *Prevalence of decannulation* was defined as the number of alive patients who underwent decannulation from tracheostomy during their hospital stay. *MV duration* was defined as the timing between initiation of MV and its discontinuation. Primary analysis treated time to tracheostomy as a continuous variable to maximise information reported across studies. As a sensitivity analysis, we considered meta-analysis of outcomes based on published definitions of early vs late tracheostomy. *Time to tracheostomy* was defined as early when <14 or <16.5 days and late when ≥14 or ≥16.5 days. These cut-offs were based on the COVID-19 literature to date (14 days)^{9,18–20} and the mean tracheostomy time in our cohort of patients (16.5 days).

Outcomes

Primary outcome was all-cause mortality in patients with COVID-19 and tracheostomy. For this outcome, we applied meta-regression to mortality as a function of mean time to tracheostomy, study follow-up time, study start date, and study time frame to examine associations related to pandemic phase and hospital stress. Additionally, outcomes for surgical vs percutaneous tracheostomy groups were also compared. Secondary outcomes included ICU and hospital LOS in patients with COVID-19 and a tracheostomy, timing of insertion of tracheostomy, timing of decannulation of tracheostomy, duration of MV, and complications after tracheostomy.

Data extraction and risk-of-bias assessment

According to the Population or Problem, Intervention or exposure, Comparison, and Outcome (PICO) approach, two reviewers independently extracted data (DB and LP) on tracheostomy specifics and outcomes. The following data were extracted for each study: study design characteristics (case-control, cohort studies, or case series), study information (first author, date of publication, publication type, study site, and first/second wave), COVID-19 population characteristics (number of patients with or without tracheostomy, with surgical/percutaneous tracheostomy, with early/late tracheostomy, decannulated, with complications, and who died), patient characteristics (age, country, sex, total sample size, missing patients, severity of COVID-19, death, ICU LOS, and hospital LOS), and tracheostomy characteristics (type of tracheostomy, definition of timing, setting, duration of tracheostomy, duration of MV, time to decannulation, and type of tracheostomy complications [bleeding, infection of stoma, air leak, lower respiratory tract infections, hypoxia, closure, and others]). When necessary, the corresponding authors of the included studies were contacted to obtain missing data related to trial demographics, methods, and outcomes.

For each study, two reviewers (DB and LP) independently assessed the risk of bias for type and timing of tracheostomy, and outcome features, such as decannulation, ventilator weaning, complications, and mortality using the modified 8-item Newcastle–Ottawa scale (NOS) and the COVID-19 adapted NOS²¹ (see Supplementary material item S3). Disagreements amongst reviewers were discussed with a third author until a consensus was reached (IDG, FB, or MS).

Strategy for data synthesis

We provided a narrative and tabular synthesis of the findings from the included studies, structured with the aim to assess the characteristics and outcomes of critically ill patients with COVID-19 and a tracheostomy. Numerical data on the prevalence of time and type of tracheostomy and outcome features, such as mortality, LOS, decannulation, MV ventilation duration, and complications, were collected for pooled prevalence analysis.

Statistical analysis

Data were expressed as mean (standard deviation [SD]) for continuous variables and number (percentages, %) for categorical variables. Transformation from medians (inter-quartile range) to estimated means (SD) was performed using the following formula (l, lower; m, median; ss, sample size; u, upper)²²:

$$\text{Estimate mean} = (l + 2m + u) / 4 + (l - 2m + u) / 4ss$$

$$\text{Estimate SD} = 1/12 \{ [(l - 2m + u)^2 / 4] + (u - l)^2 \}$$

A meta-analysis was conducted to obtain pooled estimates for timing of tracheostomy, type of tracheostomy, mortality, ICU and hospital LOS, decannulation, MV, and complications in critically ill patients with COVID-19. Pooled estimates were obtained using a random effects model to account for expected study heterogeneity using the inverse variance method. Heterogeneity was assessed using both Cochrane Q test, τ^2 , and Higgins I^2 statistic. Confidence intervals (CIs) for binary outcomes were calculated using Wilson scores with between-study variation estimated using the DerSimonian–Laird estimator.²³

We utilised meta-regression to assess evidence of associations between outcomes and moderators as sources of between-study heterogeneity, including the possible effects of study duration and study start date. Random effects meta-regression with residual maximum likelihood (REML) model was used; residual Q statistic and Wald's χ^2 test results were also displayed. Binary outcomes were analysed on the logit scale. Ninety-five percent CIs were calculated for individual studies, and pooled estimates with 95% CI were displayed using Forest plots. Statistical significance was set at $P < 0.05$. All statistical analyses were computed with STATA® (StataCorp LLC, College Station, TX, USA) and R® software (R Foundation for Statistical Computing, Vienna, Austria).

Results

The initial search yielded 9024 potentially relevant studies, of which 3520 were excluded as duplicate studies and 3194 were excluded after revision of titles and abstracts. After full-text review, 47 studies were included in this systematic review and meta-analysis.^{6–9,18,19,24–64} The search and selection strategies are shown in Fig 1.

Characteristics of included studies and patients

All included studies were published in English between January 1, 2020 and January 10, 2022. Table 1 depicts the main characteristics of the 47 included studies, comprising 5268 patients (2252 males, 891 females, and 2125 unknowns, with a male/female ratio of 2.53). The mean age (SD) of patients was

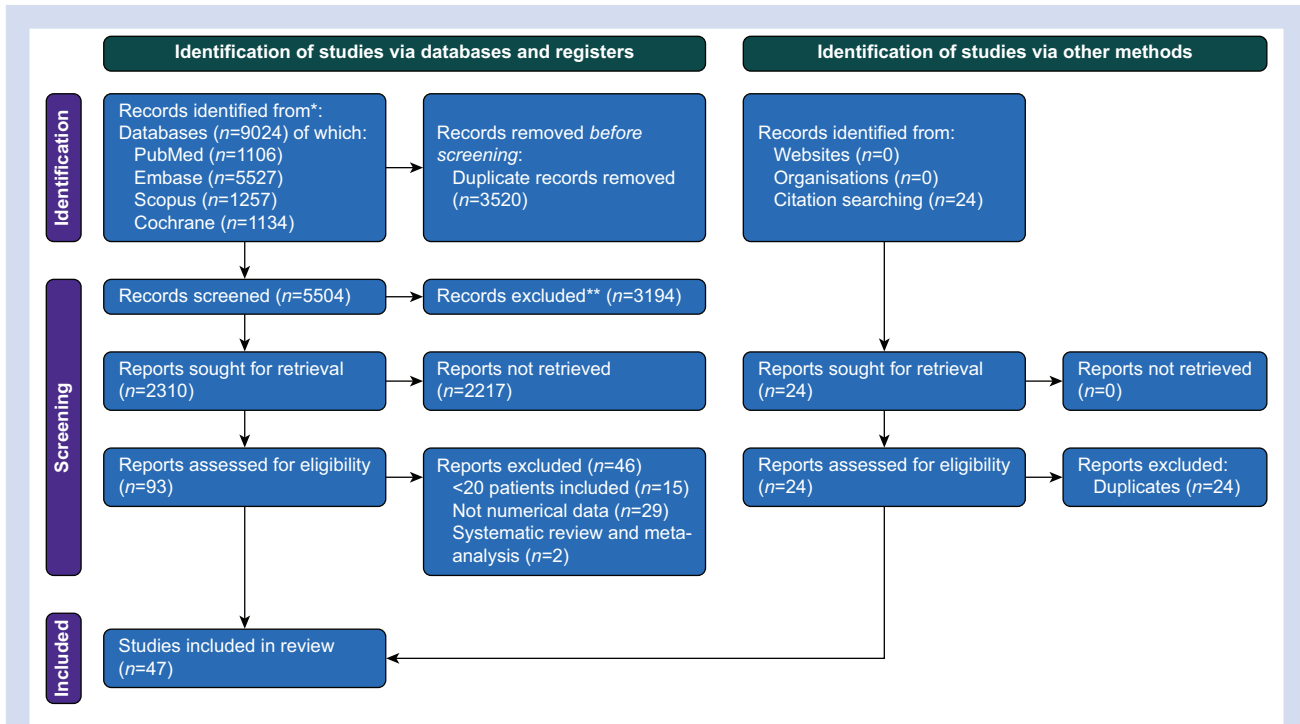


Fig 1. Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flowchart. PRISMA 2020 flow diagram for systematic reviews, which include searches of databases, registers, and other sources. This figure depicts the number of records identified from each database or register searched (rather than the total number across all databases/registers); from Page and colleagues.¹⁶

60.1 (25.3) yr. In the overall study population, the mean pooled estimate timing of tracheostomy was 16.5 (95% CI: 14.7–18.4; $I^2=99.6\%$) days. There were 2202 patients who underwent percutaneous tracheostomy and 2798 surgical tracheostomies, and for 268 patients the method of insertion was not clearly defined (surgical technique adopting percutaneous dilators or percutaneous technique completed by surgical approach). Forty-five studies reported mortality data, including 5218 patients of whom 1067 died (12 studies comprised the surgical group and 19 the percutaneous group). ICU and hospital LOS were reported in 10 and 15 studies, respectively. Thirty-three studies provided information on decannulation outcome; of 3093 patients, 1785 were decannulated (six studies in the surgical and 10 in the percutaneous groups). Duration of MV was reported in 18 studies.

Quality and bias assessment

Supplementary material item S4 presents the methods used for the assessment of methodological quality of the included studies using the NOS. Twenty-six studies were rated as high quality, 21 as moderate, and no studies were indicated as low quality. Supplementary material item S5 provides funnel plots for each outcome of interest.

Mortality

Mortality data were reported in 45 of 47 included studies. The pooled mortality in the overall population of patients who received tracheostomy was 22.1% (95% CI: 18.7–25.5; $I^2=89.0\%$; Fig 2). Where study characteristics (start date and

duration) were included as moderators, meta-regression failed to indicate any association between tracheostomy timing and mortality (coefficient -0.6 [95% CI: -1.5 to 0.2]; $P=0.13$) (Fig 3; Supplementary material item S6). Similarly, time to decannulation (coefficient 0.4 [95% CI: -0.2 to 1.0]; $P=0.15$) and MV duration (coefficient 0.6 [95% CI: -0.3 to 1.4]; $P=0.20$) were not associated with mortality (after accounting for study characteristics) (Supplementary material item S6). When applying definitions of early and late tracheostomy timing, the late group showed higher mortality than the early group (cut-off 16.5 days; $P=0.02$; Supplementary material item S7).

Grouping by follow-up time revealed a small mortality increase in studies with follow-up time >30 days compared with those with ≤ 30 days (Supplementary material items S8 and S9). In Supplementary material item S10, mortality is represented by study. Pooled mortality estimates were similar between percutaneous and surgical tracheostomy groups (22.8 [95% CI: 17.2–28.3; $I^2=80.9\%$] vs 16.5 [95% CI: 9.4–23.52; $I^2=87.7\%$]; $P=0.17$).

Hospital and ICU lengths of stay

The pooled estimated mean ICU and hospital LOS of all patients with a tracheostomy were 29.6 (95% CI: 24.0–35.2; $I^2=98.5\%$) and 38.8 (95% CI: 32.1–45.6; $I^2=95.7\%$) days, respectively (Fig 4). Neither hospital LOS nor ICU LOS was associated with mean time to tracheostomy or time to decannulation (Supplementary material item S6). Notably, ICU and hospital LOS were significantly associated with duration of MV, although the strength of correlation was weak (coefficient 0.8

Table 1 Characteristics of included studies. NC, not clear; NR, not reported; P, percutaneous; P/S, percutaneous and surgical; S, surgical. Data are expressed as mean (standard deviation [SD]).

Authors	Year	Country	Age, mean (SD) (yr)	Overall population, n patients	Tracheostomy timing, mean, (SD) (days)	S, P, or p/s	Mortality, n patients
Ahmed and colleagues ⁵³	2021	USA	63.00 (11.85)	64.00	20.00 (7.04)	P/S	21.00
Ahn and colleagues ⁶⁴	2021	Korea	68.80 (41.72)	27.00	15.80 (9.00)	P/S	11.00
Angel and colleagues ¹⁸	2021	USA	NR	178.00	NR	P	44.00
Arnold and colleagues ²⁴	2022	USA	66.00 (7.41)	59.00	19.00 (5.19)	P	23.00
Avilés-Jurado and colleagues ⁶⁰	2020	Spain	63.80 (9.70)	50.00	9.00 (16.30)	P	8.00
Bartier and colleagues ⁶¹	2021	France	56.00 (12.00)	59.00	NR	P/S	6.00
Battaglini and colleagues ⁹	2021	Italy	63.40 (9.34)	153.00	15.00 (15.75)	P/S	65.00
Botti and colleagues ²⁵	2021	Italy	64.00 (11.25)	47.00	NR	P/S	14.00
Boujaoude and colleagues ²⁶	2021	USA	54.00 (12.00)	32.00	22.00 (8.00)	P	9.00
Breik and colleagues ⁷	2020	UK	55.00 (12.00)	100.00	13.90 (4.50)	P/S	15.00
Cagino and colleagues ²⁷	2021	USA	56.00 (15.75)	25.00	22.00 (17.03)	P/S	NR
Cardasis and colleagues ²⁸	2022	USA	61.10 (10.00)	24.00	18.60 (10.37)	S	3.00
Chao and colleagues ²⁹	2020	USA	62.00 (14.30)	53.00	19.70 (6.90)	P/S	6.00
Cohen and colleagues ³⁰	2022	USA	59.90 (15.10)	24.00	31.90 (12.30)	P	9.00
Courtney and colleagues ³²	2021	UK	54.00 (8.60)	20.00	16.50 (3.70)	S	0.00
COVIDTrach Collaborative ³³	2020	UK	NR	563.00	16.75 (6.94)	P/S	62.00
Floyd and colleagues ³⁴	2020	USA	NR	38.00	24.00 (5.33)	P/S	2.00
Forni and colleagues ⁶²	2020	Switzerland	NR	53.00	NR	P	8.00
Glibbery and colleagues ¹⁹	2020	UK	60.50 (12.40)	28.00	17.00 (4.40)	P/S	2.00
Illuzzi and colleagues ³⁵	2020	Not clear	NR	111.00	NR	P	33.00
Krishnamoorthy and colleagues ³⁶	2020	USA	62.54 (13.55)	143.00	25.00 (6.60)	P/S	13.00
Kumar and colleagues ³⁷	2021	India	45.50 (9.59)	38.00	11.60 (4.63)	P	6.00
Kwak and colleagues ³⁸	2021	USA	58.10 (15.80)	148.00	12.23 (6.82)	P/S	30.00
Livneh and colleagues ³⁹	2021	USA	64.00 (21.33)	38.00	7.50 (4.08)	NC	22.00
Long and colleagues ⁵⁹	2021	USA	62.00 (0.00)	67.00	20.00 (22.96)	P/S	5.00
Mahmood and colleagues ⁴⁰	2021	USA	53.87 (42.19)	118.00	21.75 (4.10)	P/S	18
Martin-Villares and colleagues ⁸	2021	Spain	NR	1890.00	17.50 (130.42)	P/S	383.00
Mata-Castro and colleagues ⁴¹	2021	Spain	66.40 (6.20)	29.00	15.20 (9.50)	P/S	5.00
Picetti and colleagues ⁴²	2020	Italy	58.70 (8.70)	66.00	6.10 (2.10)	S	9.00
Riestra-Ayora and colleagues ⁴³	2020	Spain	67.55 (10.60)	27.00	NR	P/S	11.00
Rosano and colleagues ⁴⁴	2022	Italy	64.00 (9.00)	121.00	6.00 (1.48)	P	54.00
Rouhani and colleagues ⁴⁵	2021	UK	57.00 (11.25)	41.00	24.00 (29.63)	P/S	4.00
Rovira and colleagues ⁴⁶	2021	UK	55.60 (11.20)	201.00	17.00 (5.93)	P/S	29.00
Sifrer and colleagues ⁴⁷	2022	Slovenia	65.50 (26.67)	25.00	NR	S	NR
Singh and colleagues ³¹	2020	UK	55.70 (9.50)	47.00	18.60 (6.70)	S	1.00
Taboada and colleagues ⁴⁸	2021	Spain	69.59 (8.16)	29.00	15.00 (4.07)	NC	12.00
Takhar and colleagues ⁴⁹	2020	UK	52.94 (172.10)	87.00	16.00 (5.19)	NC	7.00
Tang and colleagues ⁵⁰	2020	China	63.90 (14.00)	80.00	17.50 (11.63)	P/S	43.00
Tornari and colleagues ⁶⁰	2021	UK	57.28 (45.77)	78.00	16.25 (4.10)	P/S	0.00
Turri-Zanoni and colleagues ⁵¹	2020	Italy	62.00 (53.00)	32.00	15.00 (15.00)	P/S	5.00
Valchanov and colleagues ⁵²	2021	India	45.50 (9.59)	38.00	11.66 (4.63)	P	9.00
Volo and colleagues ⁵³	2021	Italy	69.00 (31.11)	23.00	13.00 (0.00)	P/S	9.00
Weiss and colleagues ⁵⁴	2021	USA	55.19 (253.10)	28.00	26.00 (9.00)	P/S	3.00
Williamson and colleagues ⁵⁵	2021	UK	66.00 (8.15)	29.00	4.00 (8.88)	P	7.00
Yeung and colleagues ⁵⁶	2020	UK	57.70 (10.48)	72.00	17.00 (5.19)	P/S	7.00
Yokokawa and colleagues ⁵⁷	2021	Japan	NR	35.00	NR	S	17.00
Zuazua-Gonzalez and colleagues ⁵⁸	2020	Spain	60.80 (8.43)	30.00	NR	S	17.00

[95% CI: 0.2–1.4], $P=0.02$ and 0.9 [95% CI: 0.4–1.4], $P=0.01$, respectively). Applying definitions of early and late tracheostomy timing indicated differences in hospital LOS favouring the early tracheostomy group. Between-group comparisons for ICU LOS indicate similar outcomes between the early and late groups (Supplementary material item S7). Hospital and ICU LOS were not computable between surgical and percutaneous groups because of insufficient data.

Decannulation

The pooled prevalence of decannulation in the overall population was 47.5% (95% CI: 35.4–59.6; $I^2=98.6%$). Average

times to tracheostomy did not appear to impact the prevalence of decannulation (Supplementary material item S6), with no differences between early and late tracheostomy (Supplementary material item S7). Prevalence of decannulation did not significantly differ between percutaneous and surgical groups (47.5 [95% CI: 26.6–68.4; $I^2=98.0%$] vs 46.6 [95% CI: 20.2–72.9; $I^2=96.2%$]; $P=0.96$). In the overall study population, the time to decannulation was 23.8 (95% CI: 19.7–27.8; $I^2=98.7%$) days (Fig 4). Time to decannulation was not associated with timing of tracheostomy (Supplementary material item S6). No differences in decannulation time were observed based on definitions of early and late

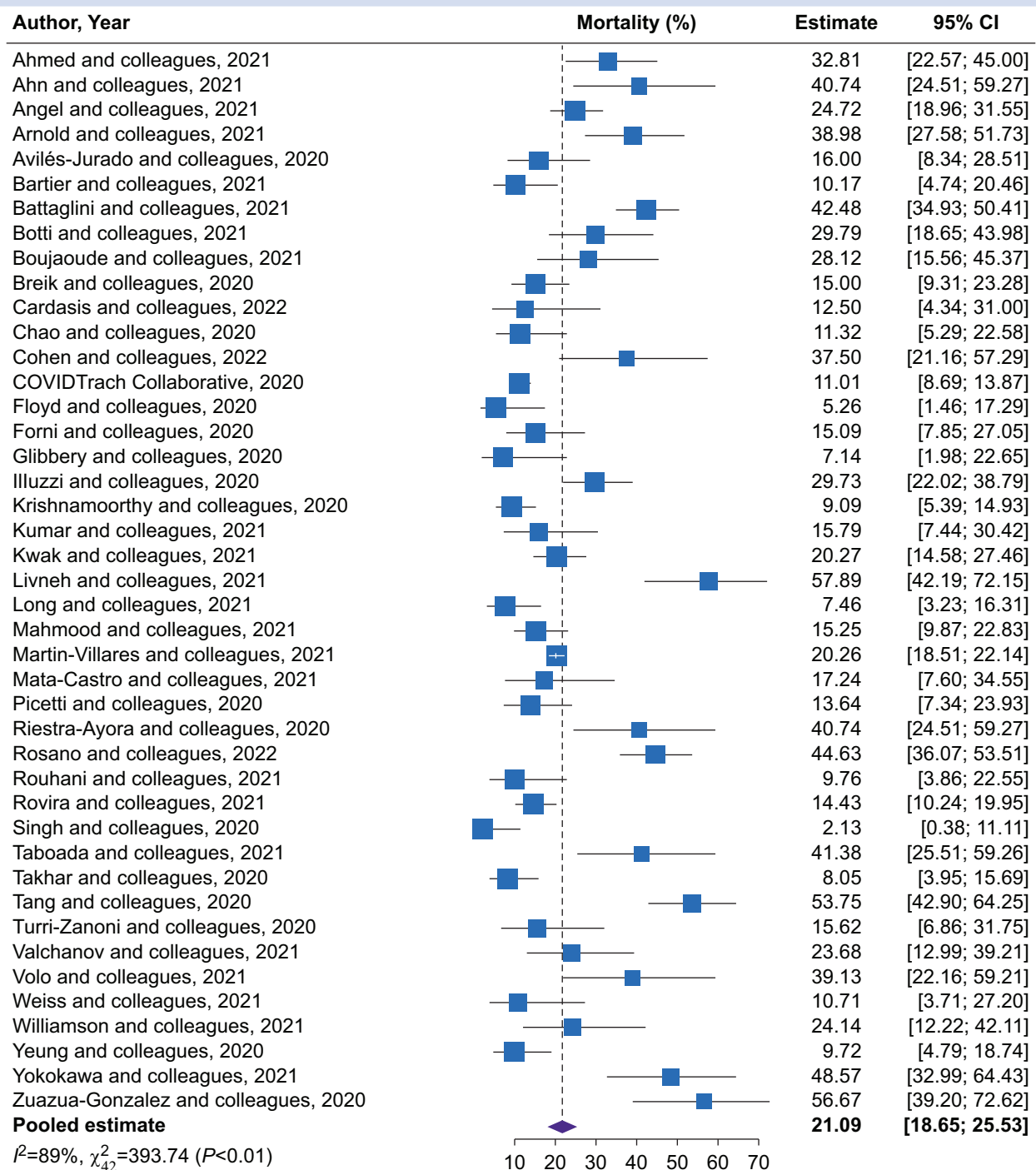


Fig 2. Forest plot of mortality in the overall population. This figure depicts the forest plots of prevalence of mortality in the overall population of patients with COVID-19 and a tracheostomy. CI, confidence interval.

tracheostomy timing (Supplementary material item S7). Time to decannulation was similar for percutaneous and surgical groups (21.0 [95% CI: 15.7–26.3] vs 18.4 [95% CI: 12.4–24.3] days; difference: 2.6 [95% CI: –5.4 to 10.6]; $P=0.52$).

Duration of mechanical ventilation

In the overall population of patients with COVID-19 and a tracheostomy, the mean MV duration was 23.4 days (95% CI:

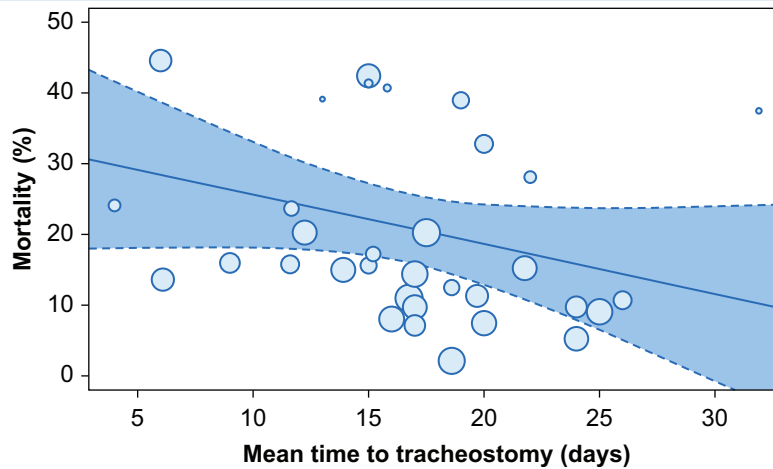


Fig 3. Meta-regression of mortality with mean time to tracheostomy as moderator. Red line represents proposed linear trend, where coefficient 0.70 (−1.55 to 0.15); $P=0.10$; and constant 32.64 (17.67–47.60); $P=0.00$ (meta-regression outputs with moderators are reported in Supplementary material item S3).

19.2–27.7; $I^2=99.3\%$; Fig 4). MV duration was not associated with tracheostomy timing (Supplementary material item S6), and no differences in MV duration were found between early and late tracheostomy timing (Supplementary material item S7). MV duration was not computable between surgical and percutaneous groups because of insufficient data. MV duration did not correlate with decannulation timing, ICU LOS, or hospital LOS (Supplementary material item S11).

Tracheostomy complications

Data regarding complications were not always available for comparison between the groups. Table 2 presents pooled prevalence of tracheostomy complications. Where available for comparison, tracheostomy complications for timing and surgical vs percutaneous tracheostomy groups are reported in the table legend.

Discussion

The main findings of our study were (i) the pooled prevalence of mortality in patients with COVID-19 and a tracheostomy was 22.1% without influence of timing to tracheostomy, tracheostomy technique, time to decannulation, and duration of MV. When applying definitions for early and late tracheostomy timing, the late tracheostomy group showed greater mortality than the early group (cut-off 16.5 days). (ii) The pooled estimated mean ICU and hospital LOS of all patients with a tracheostomy were 29.6 and 38.8 days, respectively, being both influenced by MV duration but not tracheostomy timing. No data for surgical vs percutaneous comparison were available. (iii) The mean time to decannulation was 23.8 days, and the pooled prevalence of decannulation was 47.5% of patients, both without influence by tracheostomy timing and technique. (iv) The mean duration of MV was 23.4 days, and it was not influenced by tracheostomy time. No data for surgical vs percutaneous comparison were available. (v) The most prevalent complications of tracheostomy were stoma infection/breakdown/ulcers or necrosis, followed by bleeding.

To the best of our knowledge, this is the first systematic review, meta-analysis, and meta-regression in critically ill patients with COVID-19 and a tracheostomy, which reports the associations between outcomes and moderators as sources of between-study heterogeneity accounting for the effects of study duration (partial accounting for time-varying associations) and study start date (hospital strain), and the comparison between early vs late at different cut-offs and technique (surgical vs percutaneous tracheostomy) for several outcomes, including mortality, hospital and ICU LOS, decannulation, duration of MV, and complications. Previous meta-analyses reported the comparison between such subgroups of patients only for a few outcomes.^{12–14,65}

Mortality

Considering 45 studies for the outcome mortality, our results showed a pooled tracheostomy mortality in COVID-19 of 22.1% (95% CI: 18.7–25.5; $I^2=89.0\%$), similarly to that previously reported by Ferro and colleagues¹³ of 19.2% (95% CI: 15.2–23.6), including 37 studies, and Ji and colleagues,¹⁴ including 14 studies but higher than that reported by Benito and colleagues¹² of 13.1% (95% CI: 8.5–18.4), including 14 studies. Ferro and colleagues¹³ reported no differences in cumulative mortality between early and late tracheostomy (relative risk [RR] 1.6; 95% CI: 0.2–11.8) and surgical vs percutaneous tracheostomy (RR 2.0; 95% CI: 0.2–20.4). Other meta-analyses by Benito and colleagues¹² and Chong and Tan⁶⁶ used a cut-off at 7 and 14 and 10 and 14 days, finding no differences in mortality between the early and late groups. In our study, the mean timing of tracheostomy in patients with COVID-19 was 16.5 days. To reduce heterogeneity and the bias related to pandemic phase and hospital stress, and to face the unclear benefit of using the tracheostomy timing as dichotomic variable, we performed a meta-regression for mortality using the mean time to tracheostomy as continuous variable, and accounting for the effects of study duration (partial accounting for time-varying associations) and study start date (hospital strain). We found that neither time to tracheostomy nor

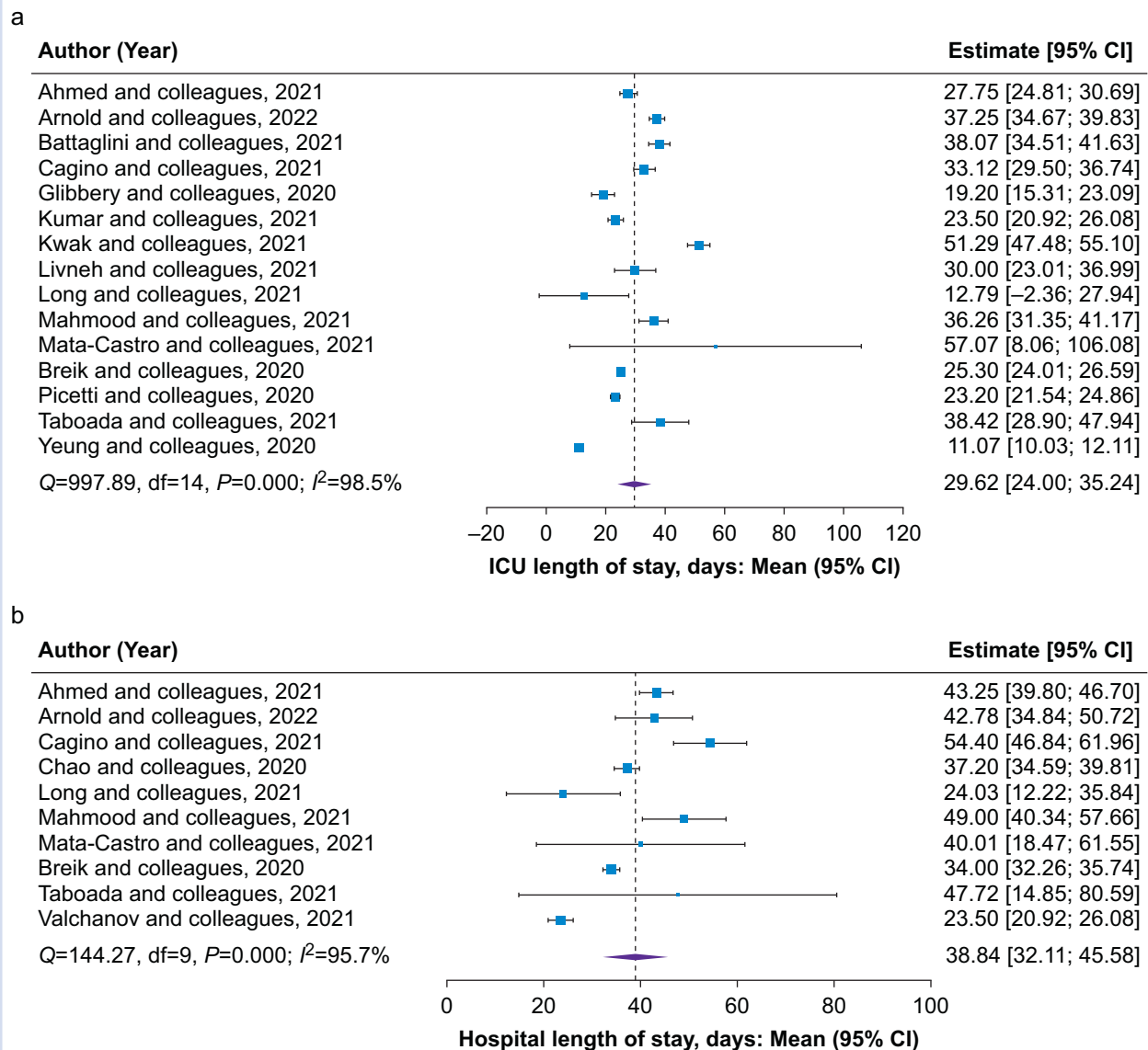
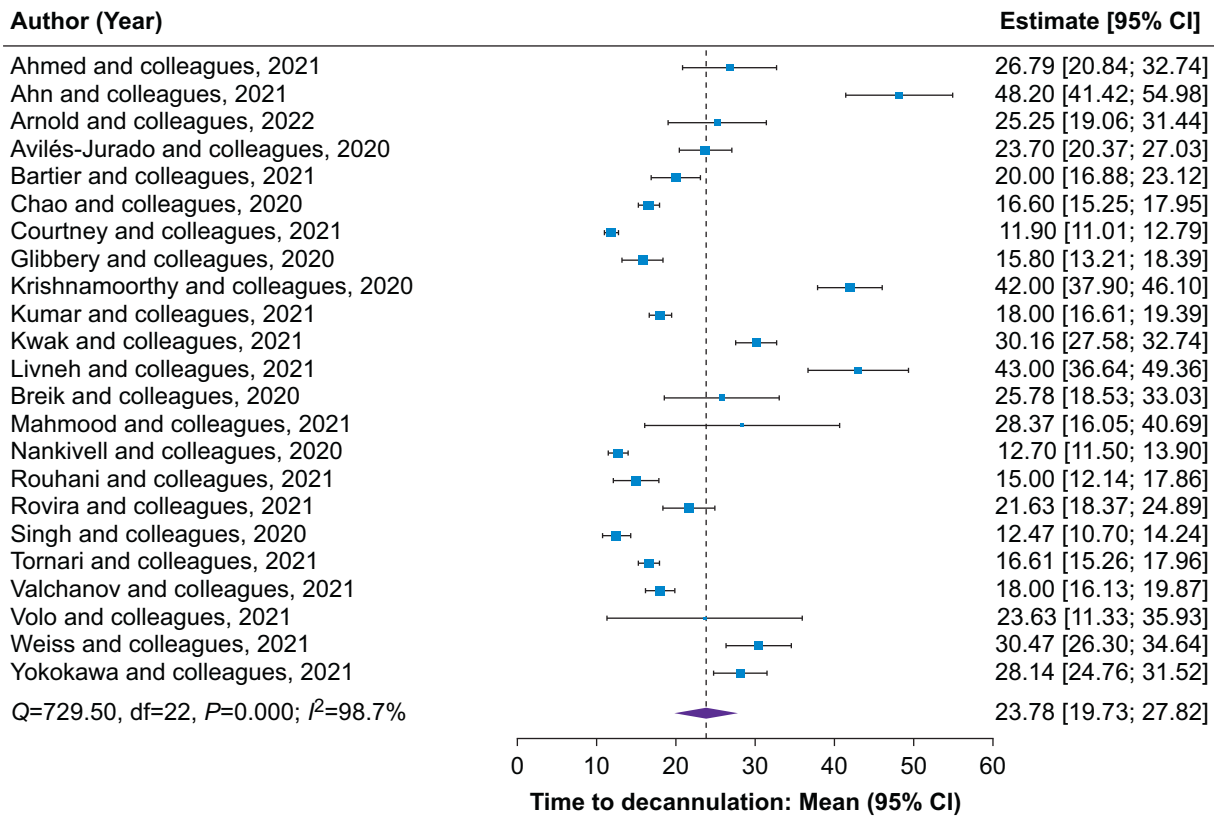


Fig 4. Forest plots of secondary outcomes in the overall population. Forest plots of mean estimate of (a) ICU and (b) hospital length of stay; (c) decannulation after tracheostomy and (d) mean duration of mechanical ventilation in overall patients with COVID-19 and a tracheostomy. CI, confidence interval.

tracheostomy technique (percutaneous vs surgical) explained the heterogeneity in mortality results. Adopting the statistical inverse variance REML method and the generalised linear mixed model method, a small difference in mortality was observed between groups followed-up for >30 and ≤30 days, whereas an overlap in CIs suggests no notable effect. Further significant heterogeneity was observed in both groups. The existing literature in COVID-19 reported a mean tracheostomy timing to be closer to 14 rather than 10 or 7 days described in the non-COVID-19 literature.^{67–69} When applying definitions for early and late tracheostomy timing (14 or 16.5 days as cut-offs), only 16.5 days cut-off reported differences in mortality being higher in the late group than in the early tracheostomy group, not confirming the results of other meta-analyses.^{12–14,66} An early tracheostomy performance demonstrated

possible beneficial effects on outcome in patients without COVID-19.^{70,71} However, this does not really account for the real impact in terms of benefits or harm on patients' outcomes, because critically ill patients present a high likelihood of evolving to multiple organ dysfunction that cannot be optimally predicted during the first days of ICU admission.¹¹ Early tracheostomy is often thought to be accompanied by reduced laryngeal injury and laryngeal dysfunction associated with prolonged tracheal intubation; reduced cumulative burden of sedative agents; better pulmonary hygiene through secretion clearance; earlier return to eating, drinking, and talking; and earlier rehabilitation.⁷² However, a late tracheostomy could be considered in some patients who are clinically unstable and may require prone positioning that might be at risk of tracheostomy dislodgement or who present with multi-

c



d

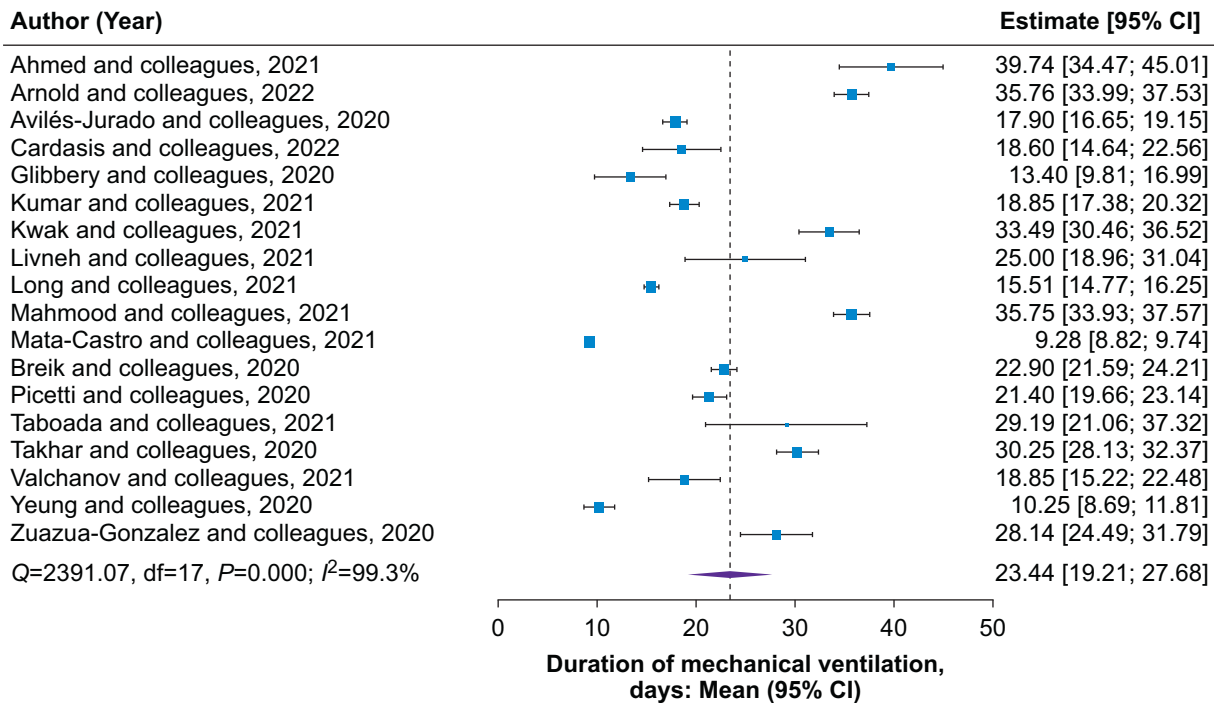


Fig 4. (continued).

Table 2 Tracheostomy complications. *False passage includes cases of dislodgement and replacement. No differences in bleeding were found between the early and late groups (6.4 [95% CI: 3.8–8.9; $I^2=11.0\%$] vs 5.0 [95% CI: 2.8–7.3; $I^2=100.0\%$]; $P=0.44$), but early tracheostomy (14 days cut-off) was more likely associated with bleeding (OR 1.6 [95% CI: 1.0–2.4]) than late. No differences in bleeding were found between percutaneous vs surgical groups (5.6 [95% CI: 2.0–9.1; $I^2=0.0\%$] vs 6.9 [95% CI: –1.6 to 15.4; $I^2=100.0\%$]; $P=0.83$; OR 0.9 [95% CI: 0.6–1.4]). Early tracheostomy (14 days cut-off) was less likely associated with false passage/dislodgement (OR 0.5 [95% CI: 0.2–1.5]) than late. CI, confidence interval; OR, odds ratio.

Complication	Overall prevalence (95% CI) (%)	Heterogeneity I^2 (%)
Bleeding	7.0 (7.4–8.7)	52.6
Cuff or air leak	2.4 (1.1–3.7)	31.7
False passage or dislodgement*	2.3 (1.0–3.6)	100.0
Peri-procedural hypoxaemia or desaturation	3.1 (0.8–5.4)	74.0
Pneumothorax or pneumomediastinum	0.0 (0.0–0.0)	0.03
Stenosis or obstruction	2.0 (0.5–3.6)	14.7
Stoma infection, breakdown/ulcers, or necrosis	7.6 (3.5–11.8)	90.0

organ failure.^{73,74} During the pandemic, some factors that may have influenced the choice of performing a tracheostomy have changed. Hence, a tracheostomy procedure in patients with COVID-19 could have been associated with staff procedural risks as a result of aerosol generation, thus delaying the procedure earlier in the pandemic.^{75,76} Therefore, we can assume that a late tracheostomy timing could have been selected in some patients with COVID-19 who were believed to be survivors or to facilitate a difficult weaning from MV, whilst early on in the COVID-19 pandemic many authorities were not recommending early tracheostomy because of infection control issues.⁷³ The selection of patients and their severity of illness may have contributed to a possible selection bias when analysing mortality in the early vs late groups and the surgical vs percutaneous, thus explaining these contrasting results on outcomes. Therefore, the optimal timing for tracheostomy insertion remains controversial.

ICU and hospital lengths of stay

In the present study, the mean ICU and hospital LOS for patients with a tracheostomy were significantly influenced by the duration of MV. A recent meta-analysis by Deng and colleagues⁷⁷ in patients without COVID-19 in the ICU revealed that early tracheostomy was associated with MV duration and a shorter ICU stay.⁷⁷ Other studies in patients without COVID-19 reported that early tracheostomy was associated with shorter overall ICU stay when compared with late tracheostomy,^{78,79} confirming an association between tracheostomy timing and hospital and ICU LOS,⁸⁰ but this was not clearly confirmed in our study. A late group might be expected to survive and be less sick at the time of tracheostomy, whereas an early group of patients might be expected to be sicker, being less clear whether they will survive, thus with possible longer hospital LOS.¹¹ However, our results did not confirm the influence of tracheostomy

timing on ICU and hospital LOS. In COVID-19, two previous meta-analyses reported reduced ICU stay with early tracheostomy (less than 14 days)^{14,65}; this contrasting result can be explained by the limited number of studies included and the different definition of early and late tracheostomy timing. However, despite its other potential advantages, early tracheostomy in patients in general ICU and in COVID-19 to shorten the LOS is not clearly supported by the literature.^{77,79,81–83} However, based on our new findings, we can suppose that the duration of MV and its consequences might play a pivotal role on the outcomes of patients with COVID-19.

Tracheostomy decannulation

This study found that time to decannulation was 23.8 days with a prevalence of 47.5%, with no significant impact of timing and technique of tracheostomy, not different from Ferro and colleagues.¹³ Benito and colleagues¹² reported an incidence of decannulation of 34.9 (25.4–44.9) by including 15 studies with a mean duration of 18.6 days (SD 5.7). Staibano and colleagues⁶⁵ reported no association between early tracheostomy (<14 days) and decannulation. A pre-pandemic survey revealed that patient level of consciousness, cough effectiveness, secretions, and oxygenation are important determinants of clinicians' decision to decannulate⁸⁴; however, the association between tracheostomy timing, decannulation, and outcome remains unclear.

Tracheostomy and duration of mechanical ventilation

In the current study, the mean duration of MV was 23.4 days, and the duration of MV significantly influenced the ICU and hospital LOS. Additionally, the duration of MV was not influenced by the tracheostomy timing. Previous study in patients without COVID-19 found a correlation between tracheostomy timing and duration of MV,⁸⁰ a result not duplicated in this study. A systematic review in non-COVID-19 concluded a shorter duration of MV for early tracheostomy,⁸⁵ again not confirmed by other studies.⁸² In COVID-19, Staibano and colleagues⁶⁶ found no association between early tracheostomy (<14 days) and duration of MV, whereas in our study we found an interesting effect of duration of MV on LOS. The supposed benefit of earlier tracheostomy is that it allows for decreased sedation and earlier mobilisation. However, this analysis suggests that even with early tracheostomy, patients are subjected to prolonged periods of ventilatory support, likely because of protracted severe respiratory failure that might affect the patients' outcomes.

Tracheostomy complications

The most prevalent complication of tracheostomy was stoma infection/breakdown/ulcers or necrosis, followed by bleeding. These findings are not clearly supported by the non-COVID-19 and previous COVID-19 literature.^{13,86} Our results showed that early tracheostomy was more likely associated with bleeding and less likely associated with stoma infection/breakdown or ulcers than late. The reason for such results could be explained by the increased risk of bleeding, anticoagulant therapies, or anti-platelet medications that often characterise the initial phase of disease treatment.^{87–89} No clear advantages for percutaneous or surgical technique were found with regard to bleeding. A percutaneous approach involves less

dissection and a smaller stoma but with limited direct visualisation that may have an impact on peri-procedural complications.⁷³

Limitations

This study has several limitations to address. First, possibly related to the nature of the COVID-19 pandemic, the qualities of some included studies were low with absence of long-term follow-up, short periods of available research, and incomplete data. Second, the weighted means are estimated with assumption of normal distribution, probably causing a selection bias. Moreover, it was not possible to report the values as medians because of insufficient data from the selected studies. The selection of patients (not evaluated for severity of illness) included in the mortality analysis may lead to a significant bias, impossible to control for by meta-regression analysis. We were not able to look at trends in tracheostomy performance, but it may change with time. Important, we found a huge heterogeneity across studies, which was impossible to explain even accounting immortality time bias in meta-regression. Inferring causal relationships from observational studies is difficult to ascertain, particularly in the context of meta-analyses, which are constrained by the availability of published data on both potential moderators and outcomes. In our analysis, we have examined evidence of potential associations between the mean time to tracheostomy (as a continuous variable) and expected outcomes, without implying causality attributable to limited data. Finally, by pooling studies from across the world across the period examined, it was impossible to control for the effect of the evolving treatment strategies and infection control measures (impacting tracheostomy practice) used by the various studies (i.e. the introduction of steroids, etc.), even when assessing a meta-regression analysis. An analysis able to adjust for such secular trends would be of interest.

Conclusions

Our findings suggest that in mechanically ventilated patients with COVID-19, the timing (early vs late) and type (surgical vs percutaneous) of tracheostomy have no clear impact on outcome. Decisions surrounding optimal timing and technique should include a multidisciplinary team, and patients' and families' wishes, and be informed by further evidence generation.

Authors' contributions

Study conception: DB

Study design: DB, PP

Database screening: DB, LP, AS, CR, S-MC, IDG, FB, BHC, MS

Literature search: DB, LP

Statistical analysis: DB, LP, NW

Writing of article: DB

Editing of article: DB, AS, CR, S-MC, IDG, FB, BHC, MS, GLB, JS, JFF, PP

Approval of article: AS, CR, S-MC, IDG, FB, BHC, MS, NW, GLB, JS, JFF, PP

Acknowledgements

GLB acknowledges receipt of a Biomedicine International Training Research programme for Excellent Clinician-

Scientists (BITRECS) fellowship. The BITRECS project has received funding from the European Union's Horizon 2020 research and innovation program under the Marie Skłodowska-Curie grant agreement no. 754550 and from the "La Caixa" Foundation (ID 100010434) under the agreement LCF/PR/GN18/50310006.

Declarations of interest

MS received consultancy fees from Teleflex Medical (Athlone, Ireland) and from Verathon Medical (USA), Boston Scientific (France), and MSD (Italy). The other authors declare that they have no conflicts of interest.

Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.bja.2022.07.032>.

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Handling editor: Jonathan Hardman