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Mortality in patients with severe COVID-19 who underwent tracheostomy due to prolonged mechanical ventilation

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Background: *The usefulness of tracheostomy has been questioned in patients with COVID-19 and prolonged invasive mechanical ventilation (IMV).* ***Aim:*** *To compare the 90-day mortality rate of patients who underwent a tracheostomy due prolonged IMV with those that did not receive this procedure.* ***Material and Methods:*** *We studied a historical cohort of 92 patients with COVID-19 and prolonged IMV (> 10 days). The primary outcome was the 90-day mortality rate. Secondary outcomes included days on IMV, hospital/intensive care unit (ICU) length of stay, frequency of nosocomial infections, and thrombotic complications demonstrated by images. A logistic regression was performed to adjust the effect of tracheostomy by SOFA score and days on IMV.* ***Results:*** *Forty six patients aged 54 to 66 years (72% males) underwent tracheostomy. They had a median of two comorbidities, and received the procedure after a median of 20.5 days on IMV (interquartile range: 17–26). 90-day mortality was lower in patients who were tracheostomized than in the control group (6.5% vs. 32.6%, p-value < 0.01). However, after controlling for confounding factors, no differences were found in mortality between both groups (relative risk = 0.303, p-value = 0.233). Healthcare-associated infections and hospital/ICU length of stay were higher in patients with tracheostomy than in controls. Thrombotic complications occurred in 42.4% of the patients, without differences between both groups. No cases of COVID-19 were registered in the healthcare personnel who performed tracheostomies.* ***Conclusions:*** *In patients with COVID-19 undergoing prolonged IMV, performing a tracheostomy is not associated with excess mortality, and it is a safe procedure for healthcare personnel.*

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Key words: *COVID-19; Critical Care; Pneumonia; Tracheostomy.*

Mortalidad en pacientes con COVID-19 grave sometidos a traqueostomía por ventilación mecánica prolongada

Antecedentes: *La utilidad de la traqueostomía en pacientes COVID-19 sometidos a ventilación mecánica invasiva (VMI) prolongada ha sido cuestionada.* ***Objetivo:*** *Comparar la mortalidad a 90 días en estos pacientes, con y* *sin traqueostomía.* ***Material y Métodos:*** *Estudiamos una cohorte histórica de 92 pacientes COVID-19 con VMI prolongada (>10 días). El desenlace primario fue mortalidad a 90 días. Se consideraron desenlaces secundarios los días en VMI, estadía hospitalaria/UCI, frecuencia de infecciones nosocomiales, y eventos trombóticos. Mediante regresión logística se ajustó el efecto de la traqueostomía en la mortalidad, por SOFA y días de VMI.* ***Resultados:*** *Cuarenta y seis pacientes de 54 a 66 años (72% hombres) fueron traqueostomizados. Ellos tenían una mediana de dos comorbilidades, y recibieron el procedimiento luego de una mediana de 20,5 días en VMI (rango intercuartílico: 17-26). En el análisis crudo, la mortalidad a 90 días fue menor en los pacientes con traqueostomía que en el grupo control (6,5% vs. 32,6%; p < 0,001). No obstante, luego de controlar por factores de confusión, no se encontraron diferencias en mortalidad (riesgo relativo 0,303; p = 0,233). Las infecciones asociadas a la atención de salud y la estadía en hospital/UCI fueron mayores en los pacientes traqueostomizados que en los controles. Los eventos trombóticos ocurrieron en el 42,4% de los pacientes, sin diferencias entre grupos. No hubo casos de COVID-19 en el personal de salud que realizó las traqueostomías.* ***Conclusiones:*** *En pacientes con COVID-19 sometidos a VMI prolongada, la realización de una traqueostomía no se asocia a un exceso de mortalidad, y es un procedimiento seguro para el personal sanitario.*

Palabras clave: *COVID-19; Neumonía; Cuidados Críticos; Traqueostomía.*

The month of December 2019 marked the beginning of COVID-19, a disease caused by the SARS-CoV-2 virus, which became a pandemic that has taken millions of lives globally[1]. A high proportion of patients who develop severe SARS-CoV-2 pneumonia require invasive mechanical ventilation (IMV), and it is often necessary to employ strategies of ventilatory rescue such as neuromuscular blockade, ventilation in prone position, or extracorporeal membrane oxygenation (ECMO)[2-4]. Given the severity of the respiratory compromise, it is frequent for these patients to be in IMV for prolonged periods of time[5,6].

The performance of a tracheostomy is one of the interventions that facilitate ventilatory support in these patients[7]. Among the advantages of tracheostomy in patients with prolonged IMV are providing a secure airway, avoiding injuries in the oral mucosa, larynx, and vocal cords, facilitating airway aspiration and mouth care, reducing the need for analgesia and sedation, lowering IMV days and intensive care unit (ICU) stay, enabling communication and oral feeding, and improving patient comfort[8-10]. Both open and percutaneous tracheostomy have been found to be equivalent in their outcomes[11-13]. Recently, Long et al.[14] reported the security of both tracheostomy techniques in patients with COVID-19. While it has been documented that between 10 and 15% of critical patients require a tracheostomy[7], these numbers may be higher in COVID-19 (36–53%)[13,15,16].

Some series have reported a high mortality in COVID-19 patients who had undergone prolonged IMV[3,17,18]. Also, due to the inherent risk of transmission to health workers, being a procedure that generates aerosol sprays, the utility of doing a tracheostomy in this group of patients has been questioned[19,20]. On the contrary, some more recent observational studies have reported a mortality of between 18 and 25% in this population of critical patients[15,21]. Thus, there still lack information about tracheostomy in COVID-19.

This study aims to establish the 90-day mortality rate of patients who have undergone tracheostomy because of prolonged IMV (> 10 days) and compare it with patients of similar severity but who did not undergo this procedure, adjusting by potential confusion factors.

Methods

A historical cohort of patients with severe COVID-19 pneumonia and respiratory failure that required prolonged IMV. We screened all confirmed cases of COVID-19 admitted to any ICU at Hospital Clínico Universidad de Chile (Santiago, Chile) since March 3, 2020 up to July 31, 2020 (the first wave of the COVID-19 in Chile). Adult patients with a positive PCR test for SARS-CoV-2 and ventilator support for 10 days or more were included. COVID-19 cases occurred in pregnant women, patients younger than 18 years, and those without available data because their transfer were excluded (Figure 1). This clinical trial was approved by the institutional bioethics board (Scientific and Research Ethics Committee, Hospital Clínico Universidad de Chile) and registered in ClinicalTrials.gov (NCT04642703). Patients were treated following local, national, and international protocols[22,23]. Medical care was delivered by trained staff and supervised by certified physicians in critical care medicine.

Clinical data

Clinical records were reviewed by trained personnel to obtain pre-specified information based on a standardized form. We registered the following information: a) Along hospital admission: admission/discharge dates, sociodemographic characteristics, comorbidities, thromboembolic events, survival status, and transfer to other hospitals; b) Along ICU stay: admission/transfer dates, laboratory data, disease severity, ventilatory support, rescue therapies, infections (ventilator-associated pneumonia [VAP], urinary tract and blood-stream infections), and tracheostomy performance.

Tracheostomy intervention

The indication of tracheostomy, as part of our standard of care, was determined by a team of certified critical care physicians, following national guidelines[24] and consented by the patient's family. The following were the indications of tracheostomy registered: prolonged IMV (more than 10 days), weaning failure, lower level of consciousness without the ability to protect the airway during IMV weaning, and ICU-acquired weakness with expected prolonged IMV.

All the percutaneous tracheostomies were elective and performed by one intensivist (CMR) using a modified standard technique of single-step dilation previously described[9,25]; bedside ultrasound guidance was used to prevent viral dissemination[24,26]. Open tracheotomies were performed by two specialized surgeons (RZ, DR), according to our institutional protocol. COVID-19 symptoms were followed-up in all the team that performed tracheostomies.

Tracheostomy date and laboratory data were obtained from clinical records. If the patient did not receive a tracheostomy, data at day 10 of IMV were obtained.

Outcomes

The 90-day mortality rate was the primary outcome. Vital status was checked by hospital records and national death certificates 90 days after IMV onset. Secondary outcomes included days on IMV, hospital/ICU length of stay, and the frequency of VAP, urinary and blood-stream infections along ICU stay, all of three with positive cultures and clinical manifestations of infection. Thrombotic complications demonstrated by images (limbs Doppler ultrasound or chest computed tomography angiography) was also a secondary outcome. The primary outcome was right censored 90 days after IMV onset, and secondary outcomes follow-up to hospital discharge or 90 days after IMV onset (whatever occurred first).

Statistical analysis

Normal data distribution was assessed by a Shapiro-Wilk test. Baseline characteristics and outcomes were reported as mean ± standard deviation or median (interquartile range [IQR]: p25–p75) for continuous variables and as an absolute count (%) for categorical variables. Patients who were tracheostomized were compared with patients without tracheostomy (controls) through a t-Student's test or Mann-Whitney's U for continuous variables, whereas Fisher's exact test was used for categorical variables. Available-cases analysis was performed when missing data were found (Table 1). Because the presence of confounding by indication was anticipated, we proposed that physicians were likely to perform a tracheostomy in patients with longer days in IMV and based on Sequential Organ Failure Assessment (SOFA), which was tested by a logistic regression. Only three independent variables were included considering the number of events[28]. Finally, to exploratorily graph the time from IMV onset to death in both groups, crude and adjusted survival curves were obtained based on predictions from a Cox regression model with the same independent variables. All statistical analyses were performed in Stata v12.0 (StataCorp, TX, USA) and plots in Prism v8.0 (GraphPad Software, California, USA). A p-value < 0.05 was interpreted as strong evidence against the statistical null hypothesis.

Results

During the study period, 169 patients with COVID-19 pneumonia were admitted to the ICU for IMV. We included 92 ventilated patients in the final analysis, 46 of whom underwent tracheostomy and 46 controls with IMV by 10 days or more (Figure 1).

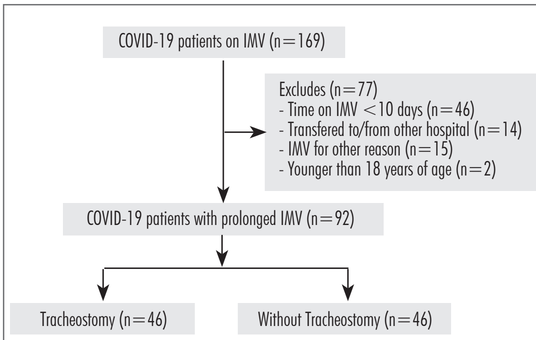

Figure 1. Flowchart of COVID-19 patients included in the study.

Table 1. Characteristics of COVID-19 patients with prolonged mechanical ventilation

Characteristics	Control patients (n = 46)	Tracheostomy (n = 46)	p-value
Age, years	61.5 (54.0–66.0)	63.5 (54.0–70.0)	0.251
Male sex	33 (71.7%)	29 (63.0%)	0.505
BMI, kg/m^2	30.0 (26.3–33.5)	29.0 (25.2–34.0)	0.845
Comorbidity number	2.0 (1.0–3.0)	2.0 (1.0–3.0)	0.387
Hypertension	24 (52.2%)	28 (60.9%)	0.528
Type 2 Diabetes mellitus	18 (39.1%)	24 (52.2%)	0.295
Obesity	18 (39.1%)	21 (45.7%)	0.673
Chronic airway obstruction	4 (8.7%)	4 (8.7%)	1.000
Cardiovascular disease	1 (2.2%)	4 (8.7%)	0.361
Tobacco smoking	34 (73.9%)	36 (78.3%)	0.936
Cancer	3 (6.5%)	0 (0.0%)	0.242
Other comorbidity	7 (15.2%)	7 (15.2%)	1.000
At ICU admission			
SOFA score	7.0 (6.0–8.0)	6.0 (6.0–8.0)	0.204
Use of vasopressors	41 (89.1%)	34 (73.9%)	0.105
Hemoglobin, g/dL	12.3 ± 1.8	12.8 ± 1.6	0.178
Leucocytes, 103/mL	11.8 (8.3–14.4)	10.6 (7.5–14.9)	0.525
Platelets, 103/mL	292 (215–365)	258 (191–368)	0.363
C Reactive Protein (mg/L)	333.6 (218.8– 508.2)	260.6 (180.0–387.9)	0.060
LDH, U/L	464.5 (412.0–591.0)	574.0 (420.0–771.0)	0.120
Troponin, (ng/mL)	0.01 (0.01–0.01)	0.01 (0.01– 0.04)	0.038
D-Dimer, (ng/mL)	2646 (1330–6619)	1756 (1100–3771)	0.060
Creatinine, mg/dL	0.8 (0.6–1.3)	0.6 (0.5–1.0)	0.150
pCO_2, mmHg	47.1 (43.0–53.2)	44.5 (41.6–53.2)	0.248
HCO_3, mmol/L	22.4 ± 3.1	22.6 (3.2)	0.848
pO_2, mmHg	82.6 ± 15.6	69.2 ± 12.8	<0.001
FiO_2, %	69.8 ± 18.2	69.5 ± 23.5	0.941
PaO_2/FiO_2 ratio	119.9 (96.75–151.3)	103.3 (77.8–143.6)	0.092
PaO_2/FiO_2 pre IMV onset	75.0 (66.0–98.0)	84.0 (64.0–128.0)	0.281

BMI: Body mass index; SOFA: Sequential organ failure assessment; IMV: Invasive mechanical ventilation.

Basal characteristics of patients are shown in Table 1. Most tracheostomized patients were males aged over 50 years, with a median of 2 comorbidities (78.3% tobacco smoking, 60.9% hypertension, 52.2% diabetes) and overweight (median body mass index [BMI][29] [IQR 25.2–34.0]). At ICU admission, COVID-19 patients in IMV showed organ dysfunction (SOFA score ≥ 6 in 75% of them) and elevated C reactive protein, LDH, and D-Dimer levels. Whereas most baseline characteristics were similar between both groups, we found higher troponin levels in patients who had undergone tracheostomy than in controls (0.01 [IQR 0.01–0.04] vs. 0.01 [IQR 0.01–0.01], p-value = 0.038) and lower PaO_2 at ICU admission (69.2 ± 12.8 vs. 82.6 ± 15.0, p-value < 0.001), with no statistical differences in PaO_2/FiO_2 ratio at admission or at orotracheal intubation.

Patients were tracheostomized after a median of 20.5 days (IQR 17–26) on IMV. Indications for tracheostomy were prolonged IMV in all patients, but 2 of them also had a lower level of consciousness. Elective percutaneous tracheostomy was performed in 35 patients, 20 at the ICU and 15 in the operating room because individual boxes were not available; open tracheostomy was done in 11 patients when percutaneous tracheostomy was not feasible, only one of them at the ICU and the others in the operating room. On the day of tracheostomy, patients showed lower severity (median SOFA score 4 [IQR 3–5]) and better lung function (mean PaO_2/FiO_2 ratio 206.9 ± 58.9). No important abnormalities in platelet count and coagulation were present at that moment. When comparing tracheostomized patients' characteristics at the day of tracheostomy with those that were not subjected to the procedure (at day 10), all of these were clinically similar (Table 2).

The clinical decision for tracheostomy was highly associated with the total days on IMV (odds ratio 1.21, p–value < 0.001). The propensity of being tracheostomized increased in patients with longer days on IMV (Figure 1). On the other hand, the odds of mortality decreased when more days on IMV were observed (Figure 2).

Table 2 shows secondary outcomes. COVID-19 patients who received a tracheostomy had longer days on IMV, and longer ICU and

Table 2. Primary and secondary outcomes (unadjusted)

Outcome	Control patients (n = 46)	Tracheostomy (n = 46)	p-value
90-day mortality	15 (32.6%)	3 (6.5%)	0.003
Hospital length of stay, days	29.5 (22–42)	73 (61–100.5)	<0.001
ICU length of stay, days	18 (15–26)	58 (43–73)	<0.001
Days on IMV time, days	16 (13–21)	46 (35–59)	<0.001
Days under NMB	9.5 (6–13)	10.5 (5- 15)	0.434
Days with prone-positioning	6.5 (4–10)	7.5 (3–12)	0.538
Renal replacement therapy	4 (8.7%)	8 (17.4%)	0.354
ECMO	0 (0.0%)	4 (8.7%)	0.117
$ECCO_2R$	1 (2.2%)	1 (2.2%)	1.000
Healthcare-associated infections[a]	9 (19.6%)	24 (52.2%)	0.002
VAP	0 (0.0%)	5 (10.9%)	0.056
Blood-stream infections	5 (10.9%)	12 (26.1%)	0.105
Urinary infections	4 (8.7%)	15 (32.6%)	0.009
Thrombotic complications[b]	16 (34.8%)	23 (50%)	0.205
Pulmonary embolism	14 (30.4%)	16 (34.8%)	0.824
Lower-extremity DVT	1 (2.2%)	5 (10.9%)	0.203
Thrombosis in other sites	1 (2.2%)	4 (8.7%)	0.361

[a]Presence of one or more healthcare-associated infection; [b]Presence of one or more thrombotic complications; ICU: Intensive Care Unit; IMV: Invasive mechanical ventilation; NMB: Neuro-muscular blockade; ECMO: Extracorporeal membrane oxygenation; $ECCO_2R$: Extracorporeal carbon dioxide removal; VAP: Ventilator-associated pneumonia; DVT: Deep vein thrombosis.

hospital length of stay than patients who were not tracheostomized. In fact, 75% of tracheostomized patients were on IMV by 35 days or more and hospital length of stay was higher than 100 days in 28.26% of patients. Consequently, healthcare-associated infections were significantly higher in tracheostomized patients. Thrombotic events were confirmed in 42.4% of patients, without significant differences between patients with and without tracheostomy.

In the crude analysis, 90-day mortality was lower in patients who were tracheostomized than in the control group (6.5% vs. 32.6%, p-value < 0.001), and no deaths occurred out of the hospital. At the end of the study, 2 tracheostomized patients remained on IMV, and all patients without tracheostomy have been discharged; thus, in the worst scenario, crude 90-day mortality would be 10.9% vs. 32.6%, in tracheostomized and controls, respectively (p-value = 0.021). However, after controlling for total days on IMV and SOFA score, logistic regression models showed weak evidence against similar 90-day mortality between both groups (relative risk = 0.303, p-value = 0.233). Likewise, adjusted survival curves were similar between patients with and without tracheostomy (Figure 2).

At the end of the study, none of the five physicians than participated in the tracheostomies nor any staff from the team developed COVID-19 symptoms. Furthermore, four physicians voluntarily reported their serological assessment (IgM and IgG) and PCR test for SARS-CoV-2; all of them had negative results.

Discussion

In the present study, patients with severe SARS-CoV-2 pneumonia who underwent prolonged IMV and received tracheostomy showed a low 90-day mortality (10.9% in worst-case scenario). Additionally, by controlling for potential confounding factors, it was demonstrated that the procedure is not associated with an excess of mortality in comparison to patients who did not undergo tracheostomy.

As opposed to the reports for classic acute respiratory distress syndrome, patients who develop severe SARS-CoV-2 pneumonia require prolonged IMV with more frequency (10–21 days) and show a higher mortality[5,6,17]. In fact, SARS-CoV-2 pneumonia is the most visible expression of a much more complex pathology, with multisystemic compromise and a higher risk of bad outcome[29]. To our knowledge, this is the first study to evaluate 90-day mortality of COVID-19 patients who had undergone tracheostomy because of prolonged IMV, incorporating a control group that allowed us to adjust for confounding factors. Our results do not show a high global mortality (19.5%) despite the severity of their clinical presentation and the associated organic dysfunctions (Table 1). Additionally, we documented a strikingly low mortality in the group of

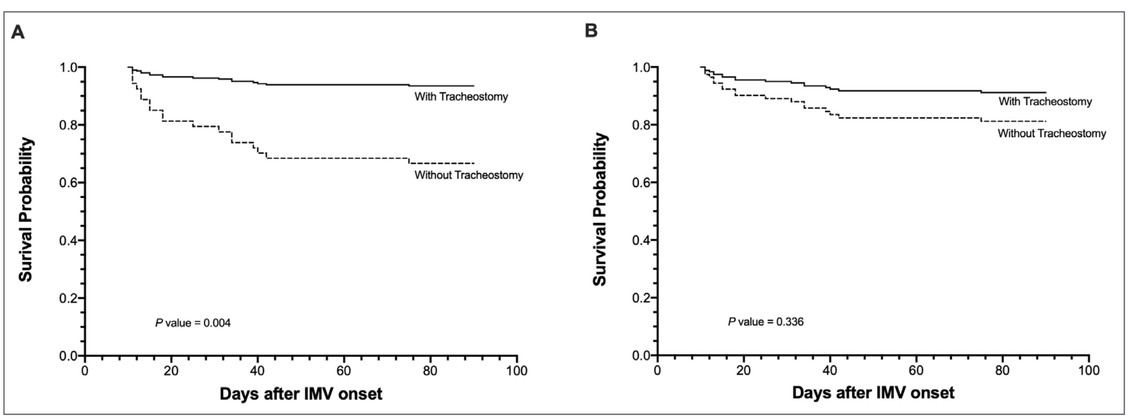

Figure 2. Crude and adjusted survival curves in COVID-19 patients with prolonged invasive mechanical ventilation by tracheostomy status. Survival plots of patients with and without tracheostomy. A, crude analysis and B, adjusted at means of covariates in Cox regression. The apparent worse survival after invasive mechanical ventilation (IMV) onset in patients without tracheostomy seems to be because of the confounding effect of SOFA score and days on IMV.

tracheostomized patients. Other series that did not include a control group nor remote tracking, have reported similar death rates[14,19,21].

Today, there is still controversy about the impact of the tracheostomy's timing in critical patients' mortality. The largest study that compared early (< 4 days) versus late (> 10 days) tracheostomy did not show differences in terms of mortality between both strategies[30]. A meta-analysis found that the performance of tracheostomy within the first 10 days of translaryngeal intubation was associated with a higher number of days free from the ventilator, lower ICU stay, reduction in the use of sedatives, and lower long-term mortality (> 2 months)[31]. In patients with COVID-19, present recommendations regarding the time of performance of the procedure are quite variable[20,27,32-34]. The lower mortality observed in the present study cannot be explained by an early tracheostomy strategy because due to the patients' clinical severity (severe hypoxemia, hemodynamic instability, prone position ventilation, ECMO), the procedure took place around 20 days after the translaryngeal ventilation, similar than other studies[14,19].

An important aspect to highlight is that the performance of a tracheostomy improves the patients' comfort[35,36], allowing the reduction of sedatives and with it a more active participation in the rehabilitation process inside the ICU, which may positively impact the final evolution of the disease. However, in COVID-19 a higher 30-day survival was found in patients who had undergone tracheostomy; but this study did not adjust the survival probability by other risk factors[37].

Until the report of the present series, there had not been a comparative evaluation between COVID-19 patients that underwent tracheostomy and patients who did not undergo this procedure, controlled by confounding factors. Our crude analyses show a lower 90-day mortality in patients that underwent tracheostomy; however, this difference disappeared after controlling for confounding factors (p-value = 0.233). It is highly likely that the lower mortality observed in patients who underwent tracheostomy can be explained by the existence of "confounding by indication"[38]. Specialists decided to tracheostomize these patients because they were convinced that their survival was highly possible.

In relation to secondary outcomes (Table 2), infections associated with healthcare and thrombotic events were frequent in our study's patients. The higher frequency of nosocomial infections in patients who had undergone tracheostomy can be explained by the longer ICU stay. On the other hand, although more thrombotic events were observed in patients with tracheostomy (50% vs. 35%), this difference did not reach statistical difference, and as with the infections' case, it may be due to a higher exposure to the outcome because of lower absolute mortality. However, thrombosis was presented with a global frequency similar to other studies[39].

In our study, there were no registered cases of COVID-19 among personnel who participated in the performance of tracheostomies. Thus, we confirmed that tracheostomy can be carried out in a safe manner as demonstrated in diverse clinical series[13,15,40].

Limitations

Our study has several limitations that must be considered. It is a series from a single center that includes a small number of tracheostomized patients. However, the fact that it was monocentric may have reduced variability in the selection criteria. Moreover, the findings are concordant with those observed by other investigators[14,19,21]. Because our patients underwent tracheostomy around the third week of translaryngeal intubation, our data did not allow us to evaluate the impact that early tracheostomy may have had in this population of patients, and even though 76% of the patients underwent percutaneous tracheostomy, we could not establish differences between open and percutaneous tracheostomy. Nonetheless, other authors have previously reported the equivalence of both techniques[14]. On the other hand, even though we attempted to control confounding by indication, a larger sample size would have allowed other complementary techniques to be performed. Finally, we could not perform serology or a PCR test to all members of the team that did the tracheostomies. However, none developed clinical manifestations or had to stay in preventive isolation.

Conclusion

Our study's data show that in COVID-19 patients undergoing prolonged IMV, the performance of a tracheostomy is not associated with excess mortality, is a safe procedure for sanitary personnel, and could improve comfort and favor ICU rehabilitation.

Execution

Competing interests

The authors declare that they have no competing interests.

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