**Practice of Tracheostomy in Patients with Acute Respiratory Failure related to COVID–19 – insights from the PRoVENT–COVID study**

ONLINE SUPPLEMENT

**eMethods**

The PRoVENT–COVID study is an investigator–initiated, national, multicenter, observational study conducted in the Netherlands 1. The protocol with a preliminary statistical analysis plan was prepublished 2. Study sites were approached for participation through direct contact by members of the steering committee. The study was approved by the institutional review boards of all participating hospitals, and need for informed consent was waived due to the observational nature of the study. Data was collected by trained data collectors and assisted local doctors, according to the International Conference of Harmonization’s Good Clinical Practice Guideline. All data was entered into a password-secured, internet-based electronic case report form (Castor EDC).

The statistical analysis plan for this current analysis was finalized before assessing the closed database 3.

**eFigure 1 - Consort**



| **eTable 1 - Baseline Characteristics of Patients According to Performance of Tracheostomy** |
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|  | **Performance of Tracheostomy** |  |
|  | **Tracheostomy****(*n* = 189)** | **No Tracheostomy****(*n* = 834)** | ***p* value** |
| Age, years | 65.0 (59.0 - 72.0) | 65.0 (57.0 - 72.0) | 0.562 |
| Male gender – no (%) | 152 (80.4) | 592 (71.0) | 0.009 |
| Body mass index, kg/m2 | 27.2 (25.0 - 30.5) | 27.7 (25.3 - 30.9) | 0.226 |
| Transferred under invasive ventilation | 39 (20.6) | 152 (18.2) | 0.469 |
|  Days between intubation and admission | 0.0 (0.0 - 0.0) | 0.0 (0.0 - 0.0) | 0.587 |
| Use of non-invasive ventilation – no (%) | 11 (6.7) | 63 (8.4) | 0.634 |
| Duration of non-invasive ventilation, hours | 8.0 (1.0 - 17.0) | 8.0 (2.0 - 14.0) | 0.666 |
| Timing of tracheostomy, days | 21.0 (17.0 - 28.0) | -- | -- |
| ≤ 7 days | 6 (3.2) |  |  |
| 7 - 14 days | 28 (14.8) |  |  |
| > 14 days | 155 (82.0) |  |  |
| Admitted after the publication of guidelinea | 16 (8.5) | 57 (6.8) | 0.435 |
| Week of admission within the centerb | 3.0 (2.0 - 5.0) | 3.0 (2.0 - 5.0) | 0.836 |
| Chest CT scan performed – no (%) | 58 (32.2) | 277 (34.6) | 0.602 |
|  Lung parenchyma affected – no (%) |  |  | 0.426 |
|  0% | 0 (0.0) | 11 (3.9) |  |
|  25% | 20 (34.5) | 90 (32.1) |  |
|  50% | 21 (36.2) | 79 (28.2) |  |
|  75% | 14 (24.1) | 86 (30.7) |  |
|  100% | 3 (5.2) | 14 (5.0) |  |
| Chest X-ray performed – no (%) | 103 (87.3) | 438 (85.4) | 0.663 |
|  Quadrants affected – no (%) |  |  | 0.426 |
|  1 | 13 (12.5) | 27 (6.2) |  |
|  2 | 29 (27.9) | 92 (21.1) |  |
|  3 | 27 (26.0) | 126 (29.0) |  |
|  4 | 35 (33.7) | 190 (43.7) |  |
| Severity of ARDS – no (%) |  |  | 0.091 |
|  Mild | 39 (21.0) | 166 (20.2) |  |
|  Moderate | 134 (72.0) | 551 (67.2) |  |
|  Severe | 13 (7.0) | 103 (12.6) |  |
| Co-existing disorders – no (%) |  |  |  |
|  Hypertension | 62 (32.8) | 284 (34.1) | 0.799 |
|  Heart failure | 10 (5.3) | 38 (4.6) | 0.703 |
|  Diabetes | 43 (22.8) | 181 (21.7) | 0.770 |
|  Chronic kidney disease | 11 (5.8) | 34 (4.1) | 0.324 |
|  Baseline creatinine, µmol/Lc | 77.0 (65.0 - 95.2) | 78.0 (62.0 - 98.0) | 0.781 |
|  Liver cirrhosis | 1 (0.5) | 2 (0.2) | 0.459 |
|  Chronic obstructive pulmonary disease | 14 (7.4) | 67 (8.0) | 0.882 |
|  Active hematological neoplasia | 4 (2.1) | 11 (1.3) | 0.498 |
|  Active solid neoplasia | 5 (2.6) | 23 (2.8) | 0.999 |
|  Neuromuscular disease | 1 (0.5) | 6 (0.7) | 0.999 |
|  Immunosuppression | 5 (2.6) | 19 (2.3) | 0.790 |
|  Asthma | 19 (10.1) | 39 (4.7) | 0.008 |
|  Obstructive sleep apnea syndrome | 10 (5.3) | 48 (5.8) | 0.999 |
| Previous medication – no (%) |  |  |  |
|  Systemic steroids | 7 (3.7) | 29 (3.5) | 0.828 |
|  Inhalation steroids | 20 (10.6) | 98 (11.8) | 0.707 |
|  Angiotensin converting enzyme inhibitor | 33 (17.5) | 145 (17.4) | 0.999 |
|  Angiotensin II receptor blocker | 23 (12.2) | 89 (10.7) | 0.522 |
|  Beta-blockers | 41 (21.7) | 157 (18.8) | 0.361 |
|  Insulin | 14 (7.4) | 58 (7.0) | 0.875 |
|  Metformin | 27 (14.3) | 130 (15.6) | 0.738 |
|  Statins | 60 (31.7) | 244 (29.3) | 0.537 |
|  Calcium channel blockers | 28 (14.8) | 154 (18.5) | 0.249 |
| Organ support at start of ventilation – no (%) |  |  |  |
|  Continuous sedation | 179 (94.7) | 801 (96.3) | 0.309 |
|  Inotropic or vasopressor | 143 (75.7) | 646 (77.6) | 0.565 |
|  Vasopressor | 143 (75.7) | 645 (77.5) | 0.566 |
|  Inotropic | 5 (2.6) | 35 (4.2) | 0.408 |
|  Fluid balance, mL | 456.8 (-38.8 - 1354.1) | 555.5 (12.2 - 1318.5) | 0.434 |
|  Urine output, mL | 720.0 (403.8 - 1173.8) | 667.5 (350.0 - 1130.0) | 0.120 |
| Ventilation support at start of ventilation |  |  |  |
|  Assisted ventilation – no (%) | 52 (27.7) | 248 (29.9) | 0.595 |
|  Tidal volume, mL/kg PBW | 6.6 (5.9 - 7.2) | 6.4 (5.9 - 7.0) | 0.102 |
|  PEEP, cmH2O | 12.7 (11.0 - 14.5) | 12.7 (11.0 - 14.7) | 0.863 |
|  Peak pressure, cmH2O | 26.0 (23.5 - 29.0) | 26.8 (23.7 - 30.0) | 0.083 |
|  Driving pressure, cmH2O | 13.0 (11.5 - 15.7) | 14.0 (11.8 - 16.2) | 0.158 |
|  Mechanical power, J/min | 19.0 (15.5 - 23.0) | 18.3 (15.2 - 22.4) | 0.405 |
|  Compliance, mL/cmH2O | 35.4 (28.8 - 43.1) | 33.0 (26.6 - 40.2) | 0.021 |
|  Total respiratory rate, mpm | 21.7 (19.0 - 24.3) | 21.8 (19.5 - 24.0) | 0.788 |
|  FiO2 | 0.6 (0.5 - 0.7) | 0.6 (0.5 - 0.7) | 0.932 |
|  etCO2, mmHg | 38.2 (33.6 - 43.9) | 36.7 (32.5 - 42.0) | 0.050 |
| Vital signs at start of ventilation |  |  |  |
|  Heart rate, bpm | 86.0 (76.8 - 100.7) | 84.0 (73.5 - 97.0) | 0.075 |
|  Mean arterial pressure, mmHg | 80.0 (74.3 - 88.7) | 81.0 (73.8 - 88.0) | 0.495 |
|  Laboratory tests at start of ventilation |  |  |  |
|  pH | 7.4 (7.3 - 7.4) | 7.4 (7.3 - 7.4) | 0.485 |
|  PaO2, mmHg | 81.8 (73.5 - 95.0) | 81.5 (72.0 - 95.4) | 0.417 |
|  PaO2 / FiO2, mmHg | 133.9 (99.8 - 178.1) | 131.8 (100.4 - 174.4) | 0.734 |
|  PaCO2, mmHg | 45.0 (40.1 - 51.0) | 44.5 (39.3 - 49.9) | 0.294 |
|  Lactate, mmol/L | 1.1 (0.9 - 1.4) | 1.2 (1.0 - 1.5) | 0.581 |
| Adjunctive therapies at start of ventilation |  |  |  |
|  Prone positioning – no. (%) | 60 (32.4) | 254 (31.1) | 0.726 |
|  Duration of prone positioning - hours | 10.0 (6.5 - 13.8) | 8.0 (4.0 - 13.0) | 0.046 |
|  Recruitment maneuvers – no. (%) | 4 (2.5) | 17 (2.5) | 0.999 |
|  Extracorporeal membrane oxygenation – no. (%) | 0 (0.0) | 4 (0.5) | 0.999 |
|  Neuromuscular blocking agents – no. (%) | 50 (26.5) | 234 (28.2) | 0.719 |
|  Duration of neuromuscular blocking agents, hours | 0.0 (0.0 - 8.0) | 0.0 (0.0 - 8.0) | 0.653 |
| Data are median (quartile 25% - quartile 75%) or No (%). Percentages may not total 100 because of rounding*CT: computed tomography; ECMO: extracorporeal membrane oxygenation; ICU: intensive care unit; NMBA: neuromuscular blocking agent; PEEP positive end expiratory pressure; RRT: renal replacement therapy*at start of ventilation.a National guideline on practice of tracheostomy on COVID-19 patients published on April 23, 2020.b First week determined as the week when the first patient was admitted in the center.c Most recent measurement in 24 hours before intubation - or at ICU admission under invasive ventilation. |

| **eTable 2 - Clinical Outcomes of Patients According to Performance of Tracheostomy** |
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|  | **Performance of Tracheostomya** |  |  |
|  | **Tracheostomy****(*n* = 189)** | **No Tracheostomy****(*n* = 834)** | **Adjusted Effect Estimate\*****(95% Confidence Interval)** | ***p* value** |
|  |  |  |  |  |
|  Duration of ventilation, days | 33.0 (25.0 - 42.0) | 12.0 (7.0 - 18.0) | SHR, 0.32 (0.23 to 0.44)c | <0.001 |
|  In survivors at day 28, days | 34.0 (26.3 - 42.0) | 12.0 (8.0 - 19.0) |
|  Reintubation– no (%) | 48 (25.5) | 87 (10.5) |  OR, 3.15 (2.07 to 4.8)d | <0.001 |
|  Thromboembolic complications – no (%) | 82 (43.4) | 228 (27.3) | OR, 2.13 (1.51 to 3.02)d | <0.001 |
|  Pulmonary embolism | 70 (37.0) | 172 (20.6) | OR, 2.36 (1.65 to 3.37)d | <0.001 |
|  Deep vein thrombosis | 12 (6.3) | 44 (5.3) | OR, 1.71 (0.79 to 3.69)d | 0.172 |
|  Ischemic stroke | 8 (4.2) | 22 (2.6) | OR, 1.49 (0.62 to 3.56)d | 0.374 |
|  Myocardial infarction | 2 (1.1) | 13 (1.6) | OR, 0.52 (0.11 to 2.6)d | 0.428 |
|  Acute kidney injury – no (%) | 105 (56.1) | 366 (44.0) | OR, 1.63 (1.14 to 2.32)d | 0.007 |
|  Need for RRT – no (%) | 60 (31.7) | 140 (16.8) | OR, 2.42 (1.63 to 3.6)d | <0.001 |
|  Need of rescue therapy – no (%)b | 143 (76.1) | 629 (76.2) | OR, 1.09 (0.72 to 1.66)d | 0.679 |
|  Prone positioning | 112 (59.9) | 482 (58.2) | OR, 1.22 (0.82 to 1.8)d | 0.321 |
|  Recruitment maneuver | 11 (6.6) | 49 (7.1) | OR, 1.14 (0.54 to 2.4)d | 0.738 |
|  Use of NMBA | 99 (52.4) | 404 (48.4) | OR, 1.02 (0.71 to 1.46)d | 0.915 |
|  ECMO | 1 (0.5) | 11 (1.3) | OR, 0.32 (0.03 to 3.82)d | 0.397 |
|  Use of continuous sedation – no (%)b | 185 (97.9) | 829 (99.4) | OR, 0.24 (0.03 to 1.79)d | 0.165 |
|  Use of inotropic or vasopressor – no (%)b | 175 (92.6) | 779 (93.4) | OR, 0.92 (0.41 to 2.09)d | 0.846 |
|  Use of vasopressor | 175 (92.6) | 778 (93.3) | OR, 0.96 (0.43 to 2.15)d | 0.917 |
|  Use of inotropic | 12 (6.3) | 84 (10.1) | OR, 0.52 (0.23 to 1.18)d | 0.120 |
|  ICU length of stay, days | 37.0 (27.0 - 45.0) | 13.0 (8.0 - 20.0) | HR, 0.92 (0.76 to 1.11)e | 0.400 |
|  In survivors, days | 38.0 (28.0 - 46.5) | 14.0 (9.0 - 22.0) |
|  Hospital length of stay, days | 49.5 (36.0 - 60.5) | 20.0 (12.0 - 30.0) | HR, 0.96 (0.79 to 1.17)e | 0.710 |
|  In survivors, days | 52.0 (41.0 - 62.0) | 26.0 (18.0 - 36.0) |
|  ICU mortality – no (%) | 30 (16.4) | 308 (37.1) | OR, 0.25 (0.16 to 0.4)d | <0.001 |
|  Hospital mortality – no (%) | 34 (19.3) | 315 (38.9) | OR, 0.28 (0.18 to 0.44)d | <0.001 |
|  28-day mortality – no (%) | 11 (5.8) | 293 (35.3) | HR, 0.10 (0.05 to 0.18)e | <0.001 |
|  90-day mortality – no (%) | 36 (21.4) | 326 (42.2) | HR, 0.28 (0.19 to 0.40)e | <0.001 |
| 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; PEEP positive end expiratory pressure*\* All models adjusted for age, gender, body mass index, PaO2 / FiO2, 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 Group receiving tracheostomy is reference group.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) |

| **eTable 3 - Univariable Assessment of Factors Associated with Tracheostomy Timing** |
| --- |
|  | **Mean Difference****(95% CI)** | ***p* value** |
| **General characteristics** |  |  |
|  Week of admission | 0.24 (-0.34 to 0.81) | 0.418 |
|  Admission after the national guideline | -1.74 (-6.16 to 2.65) | 0.439 |
| **Baseline characteristics** |  |  |
|  Age | 0.35 (-0.90 to 1.61) | 0.586 |
|  Male gender | 1.45 (-1.61 to 4.50) | 0.352 |
|  Body mass index | 0.51 (-0.75 to 1.74) | 0.421 |
| **Co-existing disorders** |  |  |
|  Diabetes | 1.57 (-1.39 to 4.49) | 0.294 |
|  Hypertension | 1.89 (-0.71 to 4.47) | 0.153 |
|  Heart failure | 3.60 (-1.86 to 9.14) | 0.199 |
|  Asthma | 2.56 (-1.50 to 6.65) | 0.219 |
|  Obstructive sleep apnea syndrome | 2.12 (-3.33 to 7.60) | 0.447 |
| **Ventilatory variables in the first day** |  |  |
|  PEEP | -0.02 (-1.32 to 1.24) | 0.978 |
|  Tidal volume per predicted body weight | -0.96 (-2.27 to 0.38) | 0.157 |
|  Respiratory system compliance | -0.43 (-1.80 to 0.93) | 0.536 |
| **Laboratory tests in the first day** |  |  |
|  PaO2 / FiO2 | -0.13 (-1.37 to 1.11) | 0.841 |
|  pH | 0.89 (-0.36 to 2.14) | 0.164 |
|  Lactate | -0.16 (-1.46 to 1.13) | 0.805 |
|  Creatinine | 0.64 (-0.57 to 1.85) | 0.299 |
| **Vital signs in the first day** |  |  |
|  Heart rate | -0.19 (-1.42 to 1.03) | 0.758 |
|  Mean arterial pressure | 0.48 (-0.75 to 1.70) | 0.443 |
| **Organ support in the first day** |  |  |
|  Use of vasopressor or inotropic | 0.19 (-4.62 to 4.89) | 0.937 |
|  Fluid balance | -0.63 (-1.89 to 0.62) | 0.329 |
| **Rescue therapy in the first 4 days** |  |  |
|  Use of neuromuscular blocking agents | -0.72 (-3.30 to 1.81) | 0.577 |
|  Prone positioning | 2.59 (-0.01 to 5.22) | 0.054 |
| **Complication** |  |  |
|  Thromboembolic complications | 1.27 (-1.18 to 3.75) | 0.313 |
|  Acute kidney injury | 0.33 (-2.19 to 2.85) | 0.797 |
|  Renal replacement therapy | 1.72 (-0.89 to 4.36) | 0.199 |
|  Reintubation | 1.86 (-0.97 to 4.73) | 0.201 |
| Mixed-effect generalized linear model with Gaussian distribution and center as random effect.Continuous variables were included after standardization and mean difference represents the increase in one standard deviation of the variable. |

| **eTable 4 - Univariable and Multivariable Assessment of Factors Associated with Performance of Tracheostomy** |
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|  | **Univariable Model** | **Multivariable Model** |
|  | **Odds Ratio****(95% CI)** | ***p* value** | **Odds Ratio****(95% CI)** | ***p* value** |
| **General characteristics** |  |  |  |  |
|  Week of admission | 1.04 (0.96 to 1.14) | 0.359 | --- | --- |
|  Admission after the national guideline | 1.17 (0.64 to 2.14) | 0.601 | --- | --- |
| **Baseline characteristics** |  |  |  |  |
|  Age | 1.14 (0.96 to 1.35) | 0.143 | --- | --- |
|  Male gender | 1.71 (1.15 to 2.54) | 0.008 | 1.53 (0.96 to 2.45) | 0.075 |
|  Body mass index | 0.87 (0.71 to 1.06) | 0.160 | --- | --- |
| **Co-existing disorders** |  |  |  |  |
|  Diabetes | 1.08 (0.73 to 1.59) | 0.715 | --- | --- |
|  Hypertension | 0.95 (0.67 to 1.34) | 0.763 | --- | --- |
|  Heart failure | 1.04 (0.50 to 2.18) | 0.915 | --- | --- |
|  Chronic obstructive pulmonary disease | 1.03 (0.56 to 1.90) | 0.932 | --- | --- |
|  Asthma | 2.34 (1.29 to 4.24) | 0.005 | 3.24 (1.67 to 6.27) | 0.001 |
|  Obstructive sleep apnea syndrome | 0.99 (0.49 to 2.03) | 0.986 | --- | --- |
| **Ventilatory variables in the first day** |  |  |  |  |
|  PEEP | 0.91 (0.77 to 1.08) | 0.289 | --- | --- |
|  Tidal volume per predicted body weight | 1.07 (0.91 to 1.25) | 0.429 | --- | --- |
|  Respiratory system compliance | 1.21 (1.02 to 1.43) | 0.028 | 1.20 (1.00 to 1.45) | 0.049 |
| **Laboratory tests in the first day** |  |  |  |  |
|  PaO2 / FiO2 | 1.01 (0.85 to 1.19) | 0.929 | --- | --- |
|  pH | 0.97 (0.82 to 1.15) | 0.744 | --- | --- |
|  Lactate | 0.75 (0.52 to 1.09) | 0.132 | --- | --- |
|  Creatinine | 0.94 (0.75 to 1.18) | 0.603 | --- | --- |
| **Vital signs in the first day** |  |  |  |  |
|  Heart rate | 1.15 (0.98 to 1.35) | 0.086 | --- | --- |
|  Mean arterial pressure | 1.09 (0.93 to 1.28) | 0.270 | --- | --- |
| **Organ support in the first day** |  |  |  |  |
|  Use of vasopressor or inotropic | 0.75 (0.40 to 1.41) | 0.372 | --- | --- |
|  Fluid balance | 0.93 (0.78 to 1.11) | 0.416 | --- | --- |
| **Rescue therapy in the first 4 days** |  |  |  |  |
|  Use of neuromuscular blocking agents | 1.06 (0.76 to 1.49) | 0.727 | --- | --- |
|  Prone positioning | 1.14 (0.80 to 1.63) | 0.463 | --- | --- |
| **Complication** |  |  |  |  |
|  Thromboembolic complications | 2.10 (1.50 to 2.95) | < 0.001 | 1.87 (1.25 to 2.80) | 0.002 |
|  Acute kidney injury | 1.53 (1.10 to 2.13) | 0.012 | 1.15 (0.73 to 1.80) | 0.552 |
|  Renal replacement therapy | 2.17 (1.49 to 3.15) | < 0.001 | 1.73 (1.02 to 2.92) | 0.042 |
|  Reintubation | 3.20 (2.11 to 4.86) | < 0.001 | 3.40 (2.12 to 5.46) | < 0.001 |
| Mixed-effect generalized linear model with Gaussian distribution and center as random effect.Continuous variables were included after standardization and mean difference represents the increase in one standard deviation of the variable. |

REFERENCES

1. Botta M, Tsonas AM, Pillay J, Boers LS, Algera AG, Bos LDJ, et al. Ventilation Management and Clinical Outcome in Invasively Ventilated COVID–19 Patients (PRoVENT–COVID) – a national, multicentre, observational cohort study. The Lancet Respiratory Medicine 2020; 9(2):139-148. https://doi.org/10.1016/S2213-2600(20)30459-8

2. Boers NS, Botta M, Tsonas AM, Algera AG, Pillay J, Dongelmans DA, et al. PRactice of VENTilation in Patients with Novel Coronavirus Disease (PRoVENT-COVID): rationale and protocol for a national multicenter observational study in The Netherlands. Ann Transl Med 2020; 8(19): 1251. https://doi.org/10.21037/atm-20-5107.

3. PRoVENT-COVID collaborators. Tracheostomy practice in COVID–19; preliminary statistical analysis plan. 23 November, 2020. <https://sites.google.com/view/provent-covid/tracheostomy-practice-preliminary-sap> [assessed 17 March 2021].