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| Table S1. Demographic and clinical findings in Controls and iNO patients. | | | |
| Variable | Control-patients | iNO -patients | p-value |
| Age (years) | 71.75 (11.79) | 67.97 (10.53) | 0.15 |
| Female sex (%) | 18 (25.35) | 14 (51.85) | 0.01 |
| BSA (m2) | 1.98 [1.85 - 2.10] | 1.99 [1.83 - 2.19] | 0.70 |
| BMI (kg/m2) | 29.68 (7.23) | 30.44 (7.26) | 0.64 |
| Chronic Ischemic Disease (%) | 6 (8.45) | 2 (7.41) | 0.87 |
| Diabetes (%) | 14 (19.72) | 4 (14.81) | 0.57 |
| Hypertension (%) | 41 (57.75) | 15 (55.56) | 0.84 |
| Chronic Kidney Disease (%) | 8 (11.27) | 1 (3.70) | 0.25 |
| Neoplasm (%) | 11 (15.49) | 2 (7.41) | 0.29 |
| Obesity (%) | 25 (35.21) | 13 (48.15) | 0.24 |
| COPD (%) | 14 (19.72) | 11 (40.74) | 0.03 |
| Autoimmune Disease (%) | 8 (11.27) | 2 (7.41) | 0.57 |
| Prior Stroke (%) | 4 (5.6) | 3 (11.10) | 0.39 |
| Charlson Comorbidity Index (points) | 4 [3 - 5] | 3 [2 - 5] | 0.27 |
| SOFA Score (points) | 6 [4 -8] | 7 [4 - 8] | 0.40 |
| Persistent Hipoxiemia (%) | 64 (90.10) | 27 (100.00) | 0.18 |
|  |  |  |  |
| Noradrenaline (%) | 47 (66.20) | 16 (59.26) | 0.52 |
| Dobutamine (%) | 2 (2.82) | 0 (0.00) | 0.38 |
| Baricitimab (%) | 7 (9.86) | 4 (14.81) | 0.48 |
| Rendesemir (%) | 15 (21.13) | 3 (11.11) | 0.25 |
| Furosemide (%) | 60.00 [40.00 - 80.00] | 75.00 [55.00 - 90.00] | 0.10 |
|  |  |  |  |
| PH | 7.40 [7.30 - 7.46] | 7.40 [7.33 - 7.49] | 0.19 |
| PaO2 (mmHg) | 81.65 (30.62) | 69.04 (1.33) | 0.04 |
| PaCO2 (mmHg) | 50.73 (19.53) | 55.43 (24.33) | 0.22 |
| PaO2/FiO2 Ratio (mmHg) | 124 (51) | 95 (28) | 0.00 |
| Arterial Lactate (mMol/l) | 1.86 (1.33) | 1.73 (0.57) | 0.64 |
| SpO2 (%) | 95.00 [91.00 - 98.00] | 94 .00 [91.50 - 96.00] | 0.35 |
|  |  |  |  |
| NIMV\* (%) | 54 (76.06) | 26 (96.30) | 0.02 |
| PC ventilation (%) | 56 (78.90) | 24 (88.90) | 0.38 |
| VC ventilation (%) | 15 (21.10) | 3 (11.10) | 0.38 |
| Prone position (%) | 66 (92.96) | 27 (100.00) | 0.15 |
| Effective prone position^ (%) | 60 (84.51) | 25 (92.59) | 0.79 |
| Support Pressure (cmH2O) | 15.74 (4.32) | 19.00 (3.41) | 0.83 |
| PEEP (cmH2O) | 9.54 (2.42) | 9.04 (2.65) | 0.35 |
| Peak Pressure (cmH2O) | 26.50 [23 - 28] | 28.00 [26 – 31.50] | 0.00 |
| Pplat (cmH2O) | 20.37 (4.67) | 17.56 (8.26) | 0.07 |
| Driving Pressure (cmH2O) | 11.61 (2.98) | 14.38 (3.69) | 0.00 |
| Mechanical Power (J/min) | 19.86 (5.77) | 17.45 (9.50) | 0.19 |
| RR (b/min) | 19.51 (5.62) | 20.26 (3.94) | 0.53 |
| Tidal Volume (ml) | 513.52 (97.33) | 478.89 (88.24) | 0.12 |
| C-stat (ml cmH2O-1) | 42.69 (13.91) | 32.65 (8.41) | 0.00 |
| FiO2 | 0.70 [0.60 – 0.80] | 0.70 [0.70 – 0.80] | 0.10 |
|  |  |  |  |
| Body temperature (°C) | 36.00 [36.00 – 36.70] | 36.50 [36.00 – 37.15] | 0.17 |
| PAm (mmHg) | 86.50 (14.60) | 83.74 (0.86) | 0.37 |
| Heart Rate (bpm) | 82.00 [70.50 - 100.00] | 71.00 [66.00 – 95.50] | 0.11 |
| Prior Atrial Fibrillation (%) | 27 (38.03) | 4 (14.81) | 0.03 |
|  |  |  |  |
| LVEF% | 56.69 (10.29) | 62.96 (5.23) | 0.00 |
| VDX D-Shape (%) | 0 (0.00) | 1 (3.70) | 0.25 |
| Tapse (mm) | 20.69 (1.09) | 20.48 (1.31) | 0.48 |
| sPAP (mmHg) | 25.00 [20.00 - 30.00] | 20.00 [20.00 – 31.50] | 0.34 |
| IC diameter (cm) | 1.92 (0.29) | 1.75 (0.43) | 0.05 |
|  |  |  |  |
| Hemoglobin (g/dl) | 12.90 [11.25 – 13.95] | 12.20 [10.30 – 12.60] | 0.04 |
| IL-6 (pg/L) | 42.30 [24.45 - 135.00] | 29.80 [19.45 – 58.60] | 0.11 |
| White Cell (x10^3/uL) | 11.22 (5.32) | 13.13 (5.82) | 0.13 |
| Troponin (ng/dl) | 21.20 [13.85 – 31.80] | 15.20 [11.10 – 24.20] | 0.02 |
| Glycemia (mg%) | 176.52 (59.30) | 175.85 (47.32) | 0.96 |
| Creatinine (mg/dl) | 0.96 [0.75 – 1.23] | 0.87 [0.57 – 1.11] | 0.10 |
| D-Dimer (mg/L) | 1.45 [0.91 – 4.54] | 2.00 [1.09 – 3.50] | 0.58 |
| CRP (mg/dl) | 8.59 [4.50 – 15.61] | 13.21 [5.32 – 16.44)] | 0.30 |
|  |  |  |  |
| The onset of symptoms to ICU admission (days) | 11.99 (9.39) | 10.17 (5.42) | 0.32 |
| Ward to ICU admission (days) | 4.65 (70.73) | 5.22 (4.66) | 0.69 |
|  |  |  |  |
| Categorical variables: number (percentage); continuous variables: median [25–75 percentile] or mean (SD).; **Control,** not iNO administration. Abbreviation: **iNO**, inhaled nitric oxide; **BSA,** body surface area; **BMI,** body mass index; **COPD,** chronic obstructive pulmonary disease; **CT,** computed tomography; **PaO2**, partial pressure of oxygen; **PaCO2,** partial pressure of carbon dioxide; **NIMV,** non-invasive mechanical ventilation; **PEEP,** positive End-Expiratory Pressure; **FiO2,** inspired fraction of oxygen; **C-stat,** static pulmonary compliance; **PAm,** mean arterial pressure; **LVEF%,** left ventricular ejection fraction; **IC,** inferior cava; **IL-6,** interleukin 6; **sPAP**, systolic pulmonary arterial pressure; **CRP,** C-reactive protein; **ICU,** intensive care unit; **RR,** respiratory rate; **Pplat,** pressure plateau; **SpO2**, pulse oximetry saturation.  *\*: non-invasively ventilated patients for contraindications.*  *^: the prone position was not performed on patients due to contraindications.* | | | |

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| Table S2. Changes in respiratory and inflammatory variables during the treatment: the difference between Non-responders and Responders. | | | | |  |
|  |
| Variable |  | Non-responders | Responders | p-value |  |
| PaO2/FiO2 ratio (mmHg) | T0 | 97 (31) | 93 (27) | 0.19 |  |
|  | T1 | 97.14 (35.5) | 128.9 (42.9) |  |  |
|  | T2 | 119 (58) | 144 (51) |  |  |
|  |  |  |  |  |  |
| PaCO2 (mmHg) | T0 | 58.6 (29.58) | 49.24 (8.74) | 0.04 |  |
|  | T1 | 58.01 (19.36) | 48.44 (8.67) |  |  |
|  | T2 | 66.37 (28.75) | 46.41 (5.91) |  |  |
|  |  |  |  |  |  |
| Arterial Lactate (mMol/l) | T0 | 1.76 (0.53) | 1.56 (0.65) | 0.46 |  |
|  | T1 | 1.78 (0.48) | 1.68 (0.59) |  |  |
|  | T2 | 1.95 (0.75) | 1.72 (0.66) |  |  |
|  |  |  |  |  |  |
| Support Pressure (cmH2O) | T0 | 18.8 (4.03) | 19.17 (2.59) | 0.18 |  |
|  | T2 | 15.53 (2.87) | 13.00 (2.66) |  |  |
|  |  |  |  |  |  |
| PEEP (cmH2O) | T0 | 8.53 (2.9) | 10.00 (2.05) | 0.56 |  |
|  | T2 | 8.2 (2.65) | 9.18 (1.60) |  |  |
|  |  |  |  |  |  |
| C-stat (ml cmH2O-1) | T0 | 31.13 (10.40) | 34.7 (4.37) | 0.28 |  |
|  | T2 | 39.73 (22.73) | 47.3 (16.52) |  |  |
|  |  |  |  |  |  |
| CRP (mg/dl) | T0 | 11.00 [4.53 – 13.31] | 16.07 [11.38 – 21.46] | 0.92 |  |
|  | T2 | 11.69 [5.16 – 14.71] | 7.29 [3.26 – 9.57] |  |  |
|  |  |  |  |  |  |
| D-Dimer (mg/L) | T0 | 2.21 [0.17 – 12.54] | 1.53 [0.80 – 2.18] | 0.12 |  |
|  | T2 | 2.66 [1.23 – 4.96] | 2.61 [1.31 – 3.38] |  |  |
|  |  |  |  |  |  |
| IL-6 (pg/L) | T0 | 27.90 [16.32 – 42.65] | 23.40 [11.99 – 69.03] | 0.74 |  |
|  | T2 | 43.85 [16.35 – 51.77] | 30.90 [24.85 – 45.40] |  |  |

Categorical variables: number (percentage); continuous variables: median [25–75 percentile] or mean (SD). Abbreviation: **T0**, the time before iNO administration; **T1**, time at 1 hour of iNO administration; **T2**, time after the end of iNO administration; **PaO2**, partial pressure of oxygen; **PaCO2**, partial pressure of carbon dioxide; **FiO2**, inspired fraction of oxygen; **PEEP**, Positive End-Expiratory Pressure; **C-stat**, static pulmonary compliance; **IL-6**, interleukin 6; **CRP**, C-reactive protein.