**eTable 2:** The estimated effects, standard errors, p-values and corresponding 95% confidence intervals obtained from the fitted linear mixed models of different variables. The baseline value is included as a deviation from the overall population mean. The ‘intercept’ refers to the reference levels of other categorical variables (GroupD14 and TimePost) at the mean of the baseline value of the corresponding variables. PVRI, IL-6, IL-8 and Lung injury score were log transformed before analysis.

|  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Variable** | **Study** | **Time** | **Mean** | **SD** | **Effect** | **Estimate** | **Std.Error** | **p-value** | **95% lower CI** | **95% Upper CI** |
| Haemoglobin | Sham | Pre | 9.2 | 0.3 | (Intercept) | 12.4 | 0.3 | <0.01 | 11.8 | 12.9 |
| Sham | Post | 8.5 | 0.4 | Baseline | 0.7 | 0.2 | <0.01 | 0.4 | 1.1 |
| Sham | Day1 | 8.8 | 0.9 | GroupD14R | -1.6 | 0.3 | <0.01 | -2.3 | -0.9 |
| D14 | Pre | 8.9 | 1.6 | GroupD14W | -0.9 | 0.3 | 0.01 | -1.6 | -0.2 |
| D14 | Post | 12.5 | 1.1 | GroupSham | -3.8 | 0.4 | <0.01 | -4.6 | -2.9 |
| D14 | Day1 | 11.3 | 0.4 | TimeDay1 | -1.0 | 0.4 | 0.01 | -1.8 | -0.3 |
| D14W | Pre | 9.2 | 0.8 |  |  |  |  |  |  |
| D14W | Post | 11.4 | 1.0 |  |  |  |  |  |  |
| D14W | Day1 | 11.3 | 0.6 |  |  |  |  |  |  |
| D14R | Pre | 9.6 | 0.5 |  |  |  |  |  |  |
| D14R | Post | 11.1 | 0.6 |  |  |  |  |  |  |
| D14R | Day1 | 11.3 | 0.7 |  |  |  |  |  |  |
| Haematocrit | Sham | Pre | 0.3 | 0.0 | (Intercept) | 0.4 | 0.0 | <0.01 | 0.4 | 0.4 |
| Sham | Post | 0.3 | 0.0 | Baseline | 0.6 | 0.2 | <0.01 | 0.3 | 1.0 |
| Sham | Day1 | 0.3 | 0.0 | GroupD14R | -0.1 | 0.0 | <0.01 | -0.1 | 0.0 |
| D14 | Pre | 0.3 | 0.0 | GroupD14W | 0.0 | 0.0 | 0.05 | -0.1 | 0.0 |
| D14 | Post | 0.4 | 0.0 | GroupSham | -0.1 | 0.0 | <0.01 | -0.2 | -0.1 |
| D14 | Day1 | 0.4 | 0.0 | TimeDay1 | 0.0 | 0.0 | 0.01 | -0.1 | 0.0 |
| D14W | Pre | 0.3 | 0.0 |  |  |  |  |  |  |
| D14W | Post | 0.4 | 0.0 |  |  |  |  |  |  |
| D14W | Day1 | 0.4 | 0.0 |  |  |  |  |  |  |
| D14R | Pre | 0.3 | 0.0 |  |  |  |  |  |  |
| D14R | Post | 0.4 | 0.0 |  |  |  |  |  |  |
| D14R | Day1 | 0.4 | 0.0 |  |  |  |  |  |  |
| Central venous pressure | Sham | Pre | 8.1 | 3.7 | (Intercept) | 10.5 | 1.4 | <0.01 | 7.7 | 13.3 |
| Sham | Post | 10.0 | 1.2 | Baseline | 0.4 | 0.1 | <0.01 | 0.2 | 0.6 |
| Sham | Day1 | 5.3 | 3.0 | GroupD14R | -4.3 | 1.5 | 0.01 | -7.4 | -1.2 |
| D14 | Pre | 6.8 | 3.5 | GroupD14W | 1.9 | 1.5 | 0.21 | -1.2 | 5.0 |
| D14 | Post | 10.4 | 4.5 | GroupSham | -0.8 | 1.5 | 0.60 | -4.0 | 2.4 |
| D14 | Day1 | 8.3 | 4.3 | TimeDay1 | -2.7 | 2.0 | 0.19 | -6.9 | 1.5 |
| D14W | Pre | 9.9 | 2.0 | GroupD14R:TimeDay1 | 1.8 | 2.2 | 0.43 | -2.7 | 6.3 |
| D14W | Post | 13.5 | 1.5 | GroupD14W:TimeDay1 | -3.6 | 2.1 | 0.10 | -8.0 | 0.8 |
| D14W | Day1 | 7.1 | 1.5 | GroupSham:TimeDay1 | -1.9 | 2.2 | 0.39 | -6.5 | 2.7 |
| D14R | Pre | 5.1 | 2.0 |  |  |  |  |  |  |
| D14R | Post | 5.1 | 1.6 |  |  |  |  |  |  |
| D14R | Day1 | 4.1 | 1.9 |  |  |  |  |  |  |
| Pulmonary capilary artery wedge pressure | Sham | Pre | 15.0 | 3.9 | (Intercept) | 15.0 | 1.9 | <0.01 | 11.0 | 18.9 |
| Sham | Post | 14.6 | 3.8 | Baseline | 0.4 | 0.2 | 0.04 | 0.0 | 0.7 |
| Sham | Day1 | 8.6 | 2.5 | GroupD14R | -4.8 | 2.2 | 0.04 | -9.2 | -0.3 |
| D14 | Pre | 12.6 | 4.3 | GroupD14W | 1.7 | 2.1 | 0.43 | -2.7 | 6.1 |
| D14 | Post | 15.0 | 6.2 | GroupSham | -1.4 | 2.3 | 0.57 | -6.2 | 3.5 |
| D14 | Day1 | 10.8 | 4.0 | TimeDay1 | -4.8 | 2.9 | 0.11 | -10.8 | 1.2 |
| D14W | Pre | 13.7 | 1.7 | GroupD14R:TimeDay1 | 3.7 | 3.1 | 0.25 | -2.7 | 10.0 |
| D14W | Post | 17.1 | 2.8 | GroupD14W:TimeDay1 | -1.5 | 3.2 | 0.63 | -8.2 | 5.1 |
| D14W | Day1 | 10.6 | 2.5 | GroupSham:TimeDay1 | -1.2 | 3.4 | 0.73 | -8.2 | 5.8 |
| D14R | Pre | 9.1 | 1.5 |  |  |  |  |  |  |
| D14R | Post | 8.9 | 1.4 |  |  |  |  |  |  |
| D14R | Day1 | 7.8 | 2.3 |  |  |  |  |  |  |
| Cardiac index | Sham | Pre | 3.9 | 1.0 | (Intercept) | 4.6 | 0.3 | <0.01 | 4.0 | 5.2 |
| Sham | Post | 4.9 | 1.0 | Baseline | 0.4 | 0.1 | 0.01 | 0.1 | 0.7 |
| Sham | Day1 | 4.1 | 0.7 | GroupD14R | -0.4 | 0.3 | 0.19 | -1.1 | 0.2 |
| D14 | Pre | 4.3 | 1.2 | GroupD14W | -0.2 | 0.4 | 0.62 | -1.0 | 0.6 |
| D14 | Post | 4.6 | 0.7 | GroupSham | 0.5 | 0.4 | 0.18 | -0.3 | 1.3 |
| D14 | Day1 | 3.5 | 0.5 | TimeDay1 | -1.1 | 0.2 | <0.01 | -1.5 | -0.6 |
| D14W | Pre | 3.9 | 0.7 |  |  |  |  |  |  |
| D14W | Post | 3.9 | 0.7 |  |  |  |  |  |  |
| D14W | Day1 | 3.8 | 0.8 |  |  |  |  |  |  |
| D14R | Pre | 4.5 | 0.6 |  |  |  |  |  |  |
| D14R | Post | 4.5 | 0.8 |  |  |  |  |  |  |
| D14R | Day1 | 3.0 | 0.5 |  |  |  |  |  |  |
| Lung injury score | Sham | Pre | 1.1 | 0.7 | (Intercept) | 0.5 | 0.1 | <0.01 | 0.3 | 0.7 |
| Sham | Post | 1.3 | 0.7 | Baseline | 0.7 | 0.1 | <0.01 | 0.6 | 0.9 |
| Sham | Day1 | 1.1 | 0.7 | GroupD14R | -0.4 | 0.1 | 0.01 | -0.6 | -0.1 |
| D14 | Pre | 0.9 | 0.3 | GroupD14W | -0.2 | 0.1 | 0.19 | -0.5 | 0.1 |
| D14 | Post | 1.8 | 0.4 | GroupSham | -0.3 | 0.1 | 0.02 | -0.6 | -0.1 |
| D14 | Day1 | 1.3 | 0.8 | timeDay1 | -0.4 | 0.0 | <0.01 | -0.4 | -0.3 |
| D14W | Pre | 1.0 | 0.5 |  |  |  |  |  |  |
| D14W | Post | 1.5 | 0.3 |  |  |  |  |  |  |
| D14W | Day1 | 0.9 | 0.4 |  |  |  |  |  |  |
| D14R | Pre | 1.0 | 0.2 |  |  |  |  |  |  |
| D14R | Post | 1.2 | 0.2 |  |  |  |  |  |  |
| D14R | Day1 | 0.8 | 0.1 |  |  |  |  |  |  |
| PVRI | Sham | Pre | 158.7 | 67.1 | (Intercept) | 5.7 | 0.2 | <0.01 | 5.3 | 6.0 |
| Sham | Post | 174.5 | 47.7 | Baseline | 0.2 | 0.2 | 0.25 | -0.2 | 0.6 |
| Sham | Day1 | 111.7 | 50.4 | GroupD14R | -0.4 | 0.2 | 0.03 | -0.8 | 0.0 |
| D14 | Pre | 146.2 | 64.9 | GroupD14W | -0.2 | 0.2 | 0.47 | -0.6 | 0.3 |
| D14 | Post | 352.3 | 170.5 | GroupSham | -0.6 | 0.2 | <0.01 | -1.0 | -0.2 |
| D14 | Day1 | 165.5 | 21.2 | TimeDay1 | -0.4 | 0.1 | <0.01 | -0.6 | -0.2 |
| D14W | Pre | 173.8 | 54.6 |  |  |  |  |  |  |
| D14W | Post | 302.0 | 115.1 |  |  |  |  |  |  |
| D14W | Day1 | 175.0 | 58.5 |  |  |  |  |  |  |
| D14R | Pre | 117.8 | 28.6 |  |  |  |  |  |  |
| D14R | Post | 169.6 | 54.1 |  |  |  |  |  |  |
| D14R | Day1 | 150.5 | 47.6 |  |  |  |  |  |  |
| Serum creatinine | Sham | Pre | 121.2 | 12.4 | (Intercept) | 123.8 | 4.2 | <0.01 | 115.1 | 132.6 |
| Sham | Post | 113.3 | 10.4 | Baseline | 0.7 | 0.1 | <0.01 | 0.5 | 1.0 |
| Sham | Day1 | 124.3 | 16.3 | GroupD14R | -13.1 | 5.2 | 0.02 | -23.8 | -2.4 |
| D14 | Pre | 115.2 | 5.0 | GroupD14W | 7.5 | 5.2 | 0.16 | -3.2 | 18.3 |
| D14 | Post | 120.8 | 10.8 | GroupSham | -5.4 | 5.3 | 0.32 | -16.5 | 5.6 |
| D14 | Day1 | 157.7 | 70.7 |  |  |  |  |  |  |
| D14W | Pre | 126.1 | 9.3 |  |  |  |  |  |  |
| D14W | Post | 136.9 | 17.2 |  |  |  |  |  |  |
| D14W | Day1 | 133.9 | 15.6 |  |  |  |  |  |  |
| D14R | Pre | 120.0 | 19.4 |  |  |  |  |  |  |
| D14R | Post | 107.6 | 13.9 |  |  |  |  |  |  |
| D14R | Day1 | 107.3 | 14.3 |  |  |  |  |  |  |
| Creatinine clearance | Sham | Pre | 157.7 | 29.0 | (Intercept) | 124.6 | 17.4 | <0.01 | 88.7 | 160.5 |
| Sham | Post | 146.0 | 45.7 | Baseline | 0.5 | 0.2 | 0.05 | 0.0 | 1.0 |
| Sham | Day1 | 106.6 | 71.3 | TimeDay1 | -32.6 | 12.9 | 0.01 | -59.2 | -5.9 |
| D14 | Pre | 163.2 | 36.1 |  |  |  |  |  |  |
| D14 | Post | 128.2 | 19.6 |  |  |  |  |  |  |
| D14 | Day1 | 102.6 | 41.8 |  |  |  |  |  |  |
| D14W | Pre | 114.9 | 29.7 |  |  |  |  |  |  |
| D14W | Post | 128.0 | 36.3 |  |  |  |  |  |  |
| D14W | Day1 | 104.3 | 45.7 |  |  |  |  |  |  |
| D14R | Pre | 146.4 | 25.3 |  |  |  |  |  |  |
| D14R | Post | 184.4 | 58.8 |  |  |  |  |  |  |
| D14R | Day1 | 137.7 | 47.6 |  |  |  |  |  |  |
| NGAL | Sham | Pre |  |  | (Intercept) | 3.5 | 0.3 | <0.01 | 2.9 | 4.1 |
| Sham | Post |  |  | Baseline | 0.2 | 0.3 | 0.51 | -0.4 | 0.7 |
| Sham | Day1 |  |  | GroupD14R | -1.2 | 0.4 | 0.01 | -2.1 | -0.4 |
| D14 | Pre |  |  | GroupD14W | 0.0 | 0.4 | 0.99 | -0.8 | 0.8 |
| D14 | Post |  |  | GroupSham | -0.5 | 0.4 | 0.19 | -1.3 | 0.3 |
| D14 | Day1 |  |  | TimeDay1 | 1.9 | 0.2 | <0.01 | 1.4 | 2.3 |
| D14W | Pre |  |  |  |  |  |  |  |  |
| D14W | Post |  |  |  |  |  |  |  |  |
| D14W | Day1 |  |  |  |  |  |  |  |  |
| D14R | Pre |  |  |  |  |  |  |  |  |
| D14R | Post |  |  |  |  |  |  |  |  |
| D14R | Day1 |  |  |  |  |  |  |  |  |
| IL-6 | Sham | Pre | 19.3 | 11.0 | (Intercept) | 3.1 | 0.1 | <0.01 | 2.9 | 3.3 |
| Sham | Post | 16.7 | 4.1 | Baseline | 0.7 | 0.1 | <0.01 | 0.5 | 1.0 |
| Sham | Day1 | 20.0 | 7.5 | GroupD14R | -0.5 | 0.1 | <0.01 | -0.7 | -0.2 |
| D14 | Pre | 18.5 | 3.7 | GroupD14W | -0.5 | 0.2 | 0.01 | -0.8 | -0.2 |
| D14 | Post | 64.2 | 75.1 | GroupSham | -0.5 | 0.1 | <0.01 | -0.7 | -0.2 |
| D14 | Day1 | 21.7 | 4.0 | TimeDay1 | -0.3 | 0.1 | 0.03 | -0.5 | 0.0 |
| D14W | Pre | 12.1 | 2.9 |  |  |  |  |  |  |
| D14W | Post | 12.8 | 3.2 |  |  |  |  |  |  |
| D14W | Day1 | 15.2 | 8.7 |  |  |  |  |  |  |
| D14R | Pre | 9.1 | 0.7 |  |  |  |  |  |  |
| D14R | Post | 10.3 | 0.9 |  |  |  |  |  |  |
| D14R | Day1 | 10.9 | 1.0 |  |  |  |  |  |  |
| IL-8 | Sham | Pre | 94.0 | 36.0 | (Intercept) | 5.0 | 0.3 | <0.01 | 4.5 | 5.5 |
| Sham | Post | 121.3 | 58.1 | Baseline | 0.6 | 0.2 | 0.01 | 0.1 | 1.1 |
| Sham | Day1 | 45.3 | 11.5 | GroupD14R | -1.2 | 0.3 | <0.01 | -1.8 | -0.5 |
| D14 | Pre | 88.0 | 48.3 | GroupD14W | 0.3 | 0.3 | 0.40 | -0.4 | 0.9 |
| D14 | Post | 197.1 | 141.9 | GroupSham | -0.4 | 0.3 | 0.24 | -1.0 | 0.3 |
| D14 | Day1 | 60.2 | 25.8 | TimeDay1 | -0.7 | 0.2 | <0.01 | -1.1 | -0.3 |
| D14W | Pre | 106.0 | 37.3 |  |  |  |  |  |  |
| D14W | Post | 347.5 | 219.7 |  |  |  |  |  |  |
| D14W | Day1 | 92.6 | 37.2 |  |  |  |  |  |  |
| D14R | Pre | 112.7 | 50.6 |  |  |  |  |  |  |
| D14R | Post | 62.4 | 74.1 |  |  |  |  |  |  |
| D14R | Day1 | 35.3 | 12.9 |  |  |  |  |  |  |
| PaO2/FiO2 | Sham | Pre | 401.7 | 56.5 | (Intercept) | 13.6 | 0.7 | <0.01 | 12.1 | 15.1 |
| Sham | Post | 301.3 | 64.5 | Baseline | 0.5 | 0.2 | <0.01 | 0.2 | 0.8 |
| Sham | Day1 | 391.3 | 49.0 | TimeDay1 | 3.6 | 0.3 | <0.01 | 3.0 | 4.3 |
| D14 | Pre | 321.3 | 103.4 |  |  |  |  |  |  |
| D14 | Post | 173.5 | 20.0 |  |  |  |  |  |  |
| D14 | Day1 | 289.3 | 69.9 |  |  |  |  |  |  |
| D14W | Pre | 317.3 | 83.1 |  |  |  |  |  |  |
| D14W | Post | 207.8 | 49.1 |  |  |  |  |  |  |
| D14W | Day1 | 347.8 | 82.3 |  |  |  |  |  |  |
| D14R | Pre | 273.1 | 55.9 |  |  |  |  |  |  |
| D14R | Post | 227.0 | 62.6 |  |  |  |  |  |  |
| D14R | Day1 | 344.8 | 60.0 |  |  |  |  |  |  |
| Plasma iron levels | Sham | Pre | 0.0 | 0.0 | (Intercept) | 0.1 | 0.1 | 0.50 | -0.1 | 0.2 |
| Sham | Post | 0.0 | 0.2 | Baseline | -0.1 | 0.3 | 0.80 | -0.7 | 0.5 |
| Sham | Day1 | -0.1 | 0.2 | GroupD14R:TimeDay1 | 0.1 | 0.1 | 0.20 | -0.1 | 0.3 |
| D14 | Pre | 0.2 | 0.0 | GroupD14W:TimeDay1 | 0.2 | 0.2 | 0.40 | -0.3 | 0.6 |
| D14 | Post | 0.1 | 0.1 | GroupSham:TimeDay1 | -0.1 | 0.1 | 0.30 | -0.3 | 0.1 |
| D14 | Day1 | 0.1 | 0.2 |  |  |  |  |  |  |
| D14W | Pre | 0.1 | 0.1 |  |  |  |  |  |  |
| D14W | Post | -0.1 | 0.4 |  |  |  |  |  |  |
| D14W | Day1 | 0.1 | 0.3 |  |  |  |  |  |  |
| D14R | Pre | 0.1 | 0.2 |  |  |  |  |  |  |
| D14R | Post | -0.1 | 0.1 |  |  |  |  |  |  |
| D14R | Day1 | 0.1 | 0.1 |  |  |  |  |  |  |
| Nitric oxide bioavailability | D14 | Day1 | 254.2 | 92.5 | No significant difference |  |  |  |  |  |
| D14 | Post | 409.9 | 218.8 |  |  |  |  |  |
| D14 | Pre | 521.2 | 111.0 |  |  |  |  |  |
| D14R | Day1 | 798.0 | 212.1 |  |  |  |  |  |
| D14R | Post | 893.5 | 61.4 |  |  |  |  |  |
| D14R | Pre | 895.8 | 96.0 |  |  |  |  |  |
| D14W | Day1 | 263.6 | 276.8 |  |  |  |  |  |
| D14W | Post | 355.8 | 113.5 |  |  |  |  |  |
| D14W | Pre | 459.2 | 212.0 |  |  |  |  |  |
| Sham | Day1 | 346.5 | 306.3 |  |  |  |  |  |
| Sham | Post | 669.9 | 202.9 |  |  |  |  |  |
| Sham | Pre | 530.3 | 209.9 |  |  |  |  |  |