**Effects of hyperoxemia in patients with sepsis – a post-hoc analysis of a multicentre randomized clinical trial**

**Supplementary material**

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|  | Total ALBIOS N=1810 | Included pzN=1632 | Excluded patients N=178 | P\* |
| Treatment | Albumin | N (%) | 898(49.6) |  |  |  |
| Sex | Female | N (%) | 717(39.6) | 625(38.3) | 92(51.7%) | 0.0005 |
| Age | year | Mean (SD) | 66.3(14.6) | 66(15) | 67.4(15) | 0.254 |
| BMI | kg/m2 | Mean (SD) | 26.6(5.9) | 26.6(6) | 26.1(6) | 0.245 |
| Reason for admission | Medical | N (%) | 1029(56.8) | 914(56.0) | 115(64.6) | 0.027 |
| Elective  | N (%) | 127(7.02) | 116(7.1) | 11(6.2) | 0.645 |
| Emergency | N (%) | 654(36.1) | 602(36.9) | 52(29.2) | 0.043 |
| MAP | mmHg | Median[IQR] | 72[62-83] | 73.3[63.3-83.3] | 65[55-73] | <.0001 |
| Heart Rate | bpm | Median[IQR]) | 105[92-120] | 105[91-120] | 114[100-128] | <.0001 |
| Haemoglobin | g/dL | Median[IQR] | 10.8[9.5-12.3] | 11[9-12] | 10[9-12] | 0.046 |
| SAPS II score | Median [IQR] | 48[37-60] | 46[36-56] | 69[59-82] | <.0001 |
| Arterial oxygen saturation | % | Median[IQR] | 97[95-99] | 97[95-99] | 96[91-98] | <.0001 |
| Central Venous oxygen saturation | % | Median[IQR | 73[67-79] | 73[67-79] | 68[65-71] | 0.165 |
| Central venous pressure | mmHg | Median[IQR] | 10[7-13] | 10[9-13] | 11[6-13] | 0.350 |
| Mechanical ventilation | N (%) | 1446(79.8) | 1289(79.0) | 157(88.2) | 0.004 |
| FiO2 % | Median[IQR] | 55[50-70] | 50[50-70] | 68[50-90] | <.0001 |
| Congestive/ischemic heart disease | N (%) | 314(17.4) | 283(17.4) | 31(17.4) | 0.980 |
| Liver disease | N (%) | 27(1.5) | 23(1.4) | 4(2.3) | 0.381 |
| Immunodeficiency | N (%) | 243(13.4) | 204(12.5) | 39(21.9) | 0.0005 |
| Chronic renal failure | N (%) | 76(4.2) | 63(3.8) | 13(7.3) | 0.029 |
| COPD | N (%) | 221(12.2) | 194(11.9) | 27(15.2) | 0.204 |
| AIDS | N (%) | 18(0.99) | 15(0.9) | 3(1.7) | 0.327 |
| Primary site of infection | Lung | N (%) | 728(40.2) | 663(40.6) | 65(36.5) | 0.288 |
| Abdomen | N (%) | 716(39.5) | 644(39.5) | 72(40.5) | 0.797 |
| Urinary tract  | N (%) | 238(13.2) | 222(13.6) | 16(9.0) | 0.083 |
| Other site  | N (%) | 339(18.7) | 297(18.2) | 42(23.6) | 0.079 |
| Baseline lactate | mmol/L | Median[IQR] | 2.5[1.5-4.2] | 2.3[1.5-3.9] | 5[2.5-8.7] | <.0001 |
| Baseline albumin  | g/L | Median[IQR] | 24[20-28] | 24[20-29] | 23[19-27] | 0.007 |
| White blood cells | baseline | Median[IQR] | 12[5.4-18.6] | 12[6-19] | 11[2.6-18.4] | 0.020 |
| day 1 | Median[IQR] | 12.3[7.5-18.7] | 12.3[7.8-18.6] | 9.8[2.7-18.7] | 0.027 |
| day 2 | Median[IQR] | 12.3[8.4-18.3] | 12.3[8.4-18.2] | 15.0[8.3-22] | 0.853 |
| day 7 | Median[IQR] | 12.7[9-18] | 12.7[9-18] | - | - |
| SOFA score | baseline | Median [IQR] | 8[6-10] | 8[5-10] | 11[9-13] | <.0001 |
| Septic shock | N (%) | 1135(62.7) | 990(60.7) | 145(81.5) | <.0001 |
| Supplementary Table 1 – assessment of in- and excluded patients. \* P value for Mann-Whitney or Chi2 test, as appropriate. AIDS - Acquired Immune Deficiency Syndrome, BMI – Body Mass Index, MAP – Mean Arterial Pressure, COPD – Chronic Obstructive Pulmonary Disease, FiO2 – Fraction of Inspired O2, SOFA score - Sequential Organ Failure Assessment score. |



**Supplementary Figure 1 -** Flow chart of the inclusion/exclusion process of patients

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|  | **HR** | **CI [95%]** | **P\*** |
| UNADJUSTED ANALYSIS | Log transformed PaO2 continuous | 1.21 | 0.74-1.96 | 0.454 |
| ADJUSTED ANALYSIS | Log transformed PaO2 continuous | 0.85 | 0.53-1.37 | 0.509 |
| Type of admission: surgical (elective + emergency)[ref=medical] | 0.88 | 0.74-1.04 | 0.123 |
| Mechanical ventilation (ref=0) | 1.80 | 1.40-2.33 | 6.0x10-6 |
| Shock(ref=0) | 1.03 | 0.86-1.23 | 0.770 |
| SAPS II | 1.03 | 1.02-1.04 | 3.8x10-26 |
| Chronic kidney failure (ref=0) | 1.35 | 0.95-1.92 | 0.098 |

**Supplementary table 2** – Survival analyses for 90- day mortality by continuous PaO2

\* P value for Cox proportional hazards model. SAPS II – Simplified Acute Physiology Score II. HR – Hazard ratio, CI – Confidence interval.

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|  | **HR** | **CI [95%]** | **P\*** |
| UNADJUSTED ANALYSIS | Log transformed PaO2 continuous | 1.25 | 0.73-2.13 | 0.420 |
| ADJUSTED ANALYSIS | Log transformed PaO2 continuous | 0.86 | 0.51-1.44 | 0.558 |
| Type of admission: surgical (elective + emergency)[ref=medical] | 0.90 | 0.75-1.06 | 0.208 |
| Mechanical ventilation (ref=0) | 1.64 | 1.26-2.13 | 2.6x10-4 |
| Shock(ref=0)  | 1.04 | 0.87-1.25 | 0.674 |
| SAPS II | 1.03 | 1.02-1.04 | 3.4x10-25 |
| Chronic kidney failure (ref=0) | 1.26 | 0.87-1.81 | 0.217 |
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**Supplementary table 3** – Survival analyses for 90-day mortality by continuous PaO2 for patients with PaO2>60 mmHg at admission. (n=1520)

\*P value for Cox proportional hazard regression analysis. SAPS II – Simplified Acute Physiology Score II. HR – Hazard ratio, CI – Confidence interval.

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|  | **HR** | **CI [95%]** | **P\*** |
| UNADJUSTED ANALYSIS | PaO2 above 100 mmHg (reference category PaO20-48h≤100 ) | 1.11 | 0.85-1.44 | 0.450 |
| ADJUSTED ANALYSIS | PaO2 above 100 mmHg (reference category PaO20-48h≤100 ) | 1.03 | 0.79-1.33 | 0.845 |
| Mechanical ventilation (ref=0) | 1.73 | 1.04-2.86 | 0.035 |
| Shock(ref=0)  | 0.96 | 0.73-1.28 | 0.799 |
| SAPS II | 1.03 | 1.02-1.04 | 7.2x10-13 |
| Chronic kidney failure (ref=0) | 1.36 | 0.77-2.39 | 0.287 |
| **Supplementary table 4A** – Survival analyses for 90-day mortality for post-surgical patients only. (n=718) \*P value for Cox proportional hazard regression analysis. SAPS II – Simplified Acute Physiology Score II. HR – Hazard ratio, CI – Confidence interval |

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|  | **HR** | **CI [95%]** | **P\*** |
| UNADJUSTED ANALYSIS | Log transformed PaO2 continuous | 2.07 | 0.84-5.09 | 0.113 |
| ADJUSTED ANALYSIS | Log transformed PaO2 continuous | 1.36 | 0.55-3.34 | 0.504 |
| Mechanical ventilation (ref=0) | 1.71 | 1.03-2.84 | 0.038 |
| Shock(ref=0)  | 0.96 | 0.72-1.28 | 0.782 |
| SAPS II | 1.03 | 1.02-1.04 | 1.0x10-12 |
| Chronic kidney failure(ref=0) | 1.35 | 0.77-2.38 | 0.294 |
| **Supplementary table 4B** – Survival analyses for 90-day mortality for post-surgical patients only. (n=718)\*P value for Cox proportional hazard regression analysis. SAPS II – Simplified Acute Physiology Score II. HR – Hazard ratio, CI – Confidence interval |

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|  |  | Total N=718 | PaO2 0-48h≤100 mmHgN=273 | PaO2 0-48h>100 mmHg N=445 | **P\*** |
| Death at 90 days | n (%) | 246(34.3%) | 88(35.7%) | 158(64.2%) | 0.369 |
| Death at 28 days | n (%) | 160(22.3%) | 63(39.4%) | 97(60.6%) | 0.689 |
| Renal-replacement therapy | n (%) | 146(20.3%) | 51(34.9%) | 95(65.1%) | 0.388 |
| Acute kidney injury | n (%) | 111(15.7%) | 43(38.7%) | 68(61.3%) | 0.689 |
| Duration of mechanical ventilation in days | Median [IQR] | 7[2-15] | 6[2-17] | 7[3-14] | 0.383 |
| Days to suspension of vasopressor or inotropic agents | Median [IQR] | 2[1-4] | 2[0-5] | 2[1-4] | 0.909 |
| Length of stay – days in ICU | Median [IQR] | 10[6-20] | 10[5-21] | 10[6-20] | 0.402 |
| Resolution primary infection | n (%) | 387(53.9%) | 144(37.2%) | 243(62.8%) | 0.627 |
| Secondary infection  | n (%) | 191(26.6%) | 70(36.7%) | 121(63.4%) | 0.648 |
| **Supplementary table 5 –** Association of Normoxemia (PaO2 0-48h≤100mmHg) with outcome measures for post-surgical patients only.\* P value for Mann-Whitney or Chi2 test, as appropriate. ICU – Intensive Care Unit; SOFA - Sequential Organ Failure Assessment |

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|  | **HR** | **CI [95%]** | **P\*** |
| UNADJUSTED ANALYSIS | PaO2 above 100 mmHg (reference category PaO20-48h<100) | 1.226 | 0.970-1.549 | 0.088 |
| ADJUSTED ANALYSIS | PaO2 above 100 mmHg (reference category PaO20-48h<100) | 1.07 | 0.845-1.355 | 0.575 |
| Mechanical ventilation (ref=0) | 1.877 | 1.342-2.626 | 0.0002 |
| Shock(ref=0)  | 1.023 | 0.791-1.321 | 0.864 |
| SAPS II | 1.034 | 1.026-1.041 | <.0001 |
| Chronic kidney failure(ref=0) | 1.563 | 1.010-2.419 | 0.044 |

**Supplementary table 6A** – Survival analyses for 90- day mortality excluding patients with lung as primary site of infection (PaO2 above or below 100 mmHg) (n=969)

\*P value for Cox proportional hazard regression analysis. SAPS II – Simplified Acute Physiology Score II. HR – Hazard ratio, CI – Confidence interval

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|  | **HR** | **CI [95%]** | **P\*** |
| UNADJUSTED ANALYSIS | Log transformed PaO2 continuous | 1.542 | 1.101-2.159 | 0.011 |
| ADJUSTED ANALYSIS | Log transformed PaO2 continuous | 1.288 | 0.931-1.782 | 0.126 |
| Mechanical ventilation (ref=0) | 1.838 | 1.314-2.570 | 0.0004 |
| Shock(ref=0)  | 1.018 | 0.788-1.315 | 0.836 |
| SAPS II | 1.034 | 1.026-1.042 | <.0001 |
| Chronic kidney failure(ref=0) | 1.534 | 0.991-2.375 | 0.054 |

**Supplementary table 6B** – Survival analyses for 90- day mortality excluding patients with lung as primary site of infection (n=969)

\*P value for Cox proportional hazard regression analysis. SAPS II – Simplified Acute Physiology Score II. HR – Hazard ratio, CI – Confidence interval

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|  | **HR** | **CI [95%]** | **P** |
| UNADJUSTED ANALYSIS | PaO2 above 100 mmHg (reference category PaO2 0-48h≤100 ) | 0.778 | 0.612-0.989 | 0.040 |
| ADJUSTED ANALYSIS | PaO2 above 100 mmHg (reference category PaO2 0-48h≤100 ) | 0.720 | 0.565-0.918 | 0.008 |
| Mechanical ventilation (ref=0) | 1.377 | 0.933-2.031 | 0.107 |
| Shock(ref=0)  | 1.106 | 0.859-1.425 | 0.433 |
| SAPS II | 1.026 | 1.018-1.034 | <.0001 |
| Chronic kidney failure(ref=0) | 1.199 | 0.651-2.206 | 0.560 |

**Supplementary table 7A –** Survival analyses for 90-day mortality in patients with lung as primary site of infection (PaO2 above or below 100 mmHg). (n=663)

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|  | **HR** | **CI [95%]** | **P** |
| UNADJUSTED ANALYSIS | Log transformed PaO2 continuous | 0.824 | 0.634-1.071 | 0.148 |
| ADJUSTED ANALYSIS | Log transformed PaO2 continuous | 0.699 | 0.534-0.916 | 0.009 |
| Mechanical ventilation (ref=0) | 1.373 | 0.930-2.025 | 0.110 |
| Shock(ref=0)  | 1.100 | 0.855-1.416 | 0.457 |
| SAPS II | 1.027 | 1.019-1.034 | <.0001 |
| Chronic kidney failure(ref=0) | 1.154 | 0.629-2.120 | 0.643 |

**Supplementary table 7B –** Survival analyses for 90-day mortality in patients with lung as primary site of infection (n=663)

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|  | **HR** | **CI [95%]** | **P** |
| UNADJUSTED ANALYSIS | PaO2 ABOVE 100 mmHg (reference category PaO2 0-48h≤100 ) | 0.866 | 0.725-1.035 | 0.114 |
| ADJUSTED ANALYSIS | PaO2 ABOVE 100 mmHg (reference category PaO2 0-48h≤100 ) | 0.840 | 0.702-1.004 | 0.055 |
| Shock(ref=0)  | 1.048 | 0.863-1.271 | 0.637 |
| SAPS II | 1.029 | 1.023-1.035 | <.0001 |
| Chronic kidney failure(ref=0) | 1.241 | 0.833-1.848 | 0.287 |

**Supplementary table 8A –** Survival analyses for 90-day mortality in patients mechanically ventilated (above or below 100 mmHg). (n=1290)

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|  | **HR** | **CI [95%]** | **P** |
| UNADJUSTED ANALYSIS | Log transformed PaO2 continuous | 0.938 | 0.746-1.180 | 0.586 |
| ADJUSTED ANALYSIS | Log transformed PaO2 continuous | 0.890 | 0.709-1.118 | 0.317 |
| Shock(ref=0)  | 1.043 | 0.859-1.265 | 0.671 |
| SAPS II | 1.029 | 1.023-1.035 | <.0001 |
| Chronic kidney failure(ref=0) | 1.223 | 0.821-1.821 | 0.322 |

**Supplementary table 8B –** Survival analyses for 90-day mortality in patients with mechanically ventilated (n=1290)