

Survival following Staphylococcus aureus bloodstream infection; a prospective multinational cohort study assessing the impact of place of care

Article (Supplemental Material)

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| | Centre 1 n = 255 | Centre 2 n = 252 | Centre 3 n = 220 | Centre 4 n = 195 | Centre 5 n = 193 | Centre 6 n = 172 | Centre 7 n = 140 | Centre 8 n = 126 | Centre 9 n = 113 | Centre 10 n = 102 | Centre 11 n = 83 | Total n = 1851 | p-value |
|---|---------------------|---------------------|---------------------|---------------------|---------------------|---------------------|---------------------|---------------------|---------------------|----------------------|---------------------|-------------------|---------|
| Age, years (median, IQR) | 66 (53-76) | 65 (52-76) | 71 (57-80) | 67 (55-77) | 66 (53-78) | 65 (55-79) | 56 (43-72) | 68 (51-79) | 63 (45-74) | 66 (55-77) | 67 (53-78) | 66 (52-77) | 0.0001 |
| Male gender | 164 (64) | 151 (60) | 140 (64) | 126 (65) | 121 (63) | 110 (64) | 95 (68) | 77 (61) | 69 (61) | 71 (70) | 57 (69) | 1181 (64) | 0.82 |
| MRSA | 23 (9) | 14 (6) | 17 (8) | 100 (51) | 4 (2) | 69 (40) | 9 (6) | 13 (10) | 14 (12) | 19 (19) | 20 (24) | 302 (16) | <0.0001 |
| Injecting drug use | 4 (2) | 13 (5) | 5 (2) | 2 (1) | 11 (6) | 10 (6) | 29 (21) | 13 (10) | 13 (12) | 2 (2) | 2 (2) | 104 (6) | <0.0001 |
| Mode of Acquisition | | | | | | | | | | | | | <0.0001 |
| Community | 50 (20) | 66 (26) | 152 (69) | 33 (17) | 70 (36) | 59 (34) | 77 (55) | 60 (48) | 66 (58) | 26 (25) | 26 (31) | 685 (37) | |
| Healthcare associated | 51 (20) | 83 (33) | 17 (8) | 88 (45) | 57 (30) | 81 (47) | 23 (16) | 29 (23) | 23 (20) | 27 (26) | 14 (17) | 493 (27) | |
| Nosocomial | 154 (60) | 103 (41) | 51 (23) | 74 (38) | 66 (34) | 32 (19) | 40 (29) | 37 (29) | 24 (21) | 49 (48) | 43 (52) | 673 (36) | |
| Charlson Comorbidity Index (CCI) | | | | | | | | | | | | | |
| Median (IQR) | 3 (1-5) | 3 (2-6) | 1 (0-3) | 3 (1-5) | 2 (1-4) | 4 (2-6) | 2 (0-3) | 2 (0-3) | 2 (1-3) | 2 (1-3) | 3 (1-5) | 2 (1-4) | 0.0001 |
| SOFA Score | | | | | | | | | | | | | |
| Median (IQR) | 3 (1-6) | 3 (2-6) | 3 (1-4) | 5 (2-9) | 3 (1-5) | 5 (2-8) | 3 (1-5) | 3 (1-5) | 2 (1-5) | 2 (0-4) | 2 (1-5) | 3 (1-6) | 0.0001 |
| Dominant focus | | | | | | | | | | | | | <0.0001 |
| Central line | 40 (16) | 23 (9) | 13 (6) | 27 (14) | 18 (9) | 29 (17) | 18 (13) | 7 (6) | 14 (12) | 15 (15) | 14 (17) | 218 (12) | 0.003 |
| Peripheral line | 33 (13) | 36 (14) | 8 (4) | 4 (2) | 15 (8) | 0 (0) | 4 (3) | 7 (6) | 1 (1) | 22 (22) | 21 (25) | 151 (8) | <0.0001 |
| Skin / soft tissue | 15 (6) | 19 (8) | 29 (13) | 19 (10) | 11 (6) | 22 (13) | 10 (7) | 22 (17) | 21 (19) | 14 (14) | 8 (10) | 190 (10) | <0.0001 |
| Surgical wound | 17 (7) | 6 (2) | 10 (5) | 5 (3) | 3 (2) | 7 (4) | 6 (4) | 5 (4) | 8 (7) | 5 (5) | 2 (2) | 74 (4) | 0.16 |
| Endocarditis | 18 (7) | 24 (10) | 8 (4) | 17 (9) | 17 (9) | 14 (8) | 14 (10) | 11 (9) | 3 (3) | 6 (6) | 4 (5) | 136 (7) | 0.17 |
| Osteoarticular | 19 (7) | 49 (19) | 32 (15) | 37 (19) | 38 (20) | 12 (7) | 26 (19) | 26 (21) | 10 (9) | 4 (4) | 16 (19) | 269 (15) | <0.0001 |
| Pneumonia | 11 (4) | 17 (7) | 16 (7) | 28 (14) | 9 (5) | 25 (15) | 2 (1) | 17 (13) | 18 (16) | 10 (10) | 8 (10) | 161 (9) | <0.0001 |
| Other deep focus | 35 (14) | 48 (19) | 31 (14) | 29 (15) | 38 (20) | 25 (15) | 30 (21) | 8 (6) | 21 (19) | 14 (14) | 3 (4) | 282 (15) | 0.002 |
| Unknown focus | 67 (26) | 30 (12) | 73 (33) | 29 (15) | 44 (23) | 38 (22) | 30 (21) | 23 (18) | 17 (15) | 12 (12) | 7 (8) | 370 (20) | <0.0001 |
| Outcome | | | | | | | | | | | | | |
| Length of hospital stay | 20 (12-33) | 18 (10-30) | 16 (9-29) | 18 (8-34) | 16 (9-31) | 16 (8-31) | 19 (10-31) | 17 (9-29) | 21 (12-36) | 12 (7-22) | 18 (9-34) | 18 (9-31) | <0.0001 |
| Death within 72 hours | 17 (7) | 13 (5) | 18 (8) | 15 (8) | 12 (6) | 21 (12) | 5 (4) | 7 (6) | 6 (5) | 14 (14) | 4 (5) | 132 (7) | 0.03 |
| Death within 7 days | 26 (10) | 20 (8) | 28 (13) | 25 (13) | 19 (10) | 32 (19) | 13 (9) | 11 (9) | 7 (6) | 20 (20) | 6 (7) | 207 (11) | 0.003 |
| Death within 30 days | 56 (22) | 46 (18) | 62 (28) | 38 (19) | 45 (23) | 53 (31) | 21 (15) | 23 (18) | 20 (18) | 31 (30) | 15 (18) | 410 (22) | 0.003 |
| Death within 90 days | 91 (36) | 63 (25) | 75 (34) | 48 (25) | 60 (31) | 67 (39) | 32 (23) | 34 (27) | 29 (26) | 39 (38) | 25 (30) | 563 (30) | 0.004 |

Table 1: Patient characteristics of the combined ISAC and ARREST datasets by centre.

Note: figures are median (interquartile range) or number (percentage). *P* values calculated by Kruskal-Wallis (continuous) or chi-squared (categorical) tests.

| | Univariable Cox model | | | Multivariable Cox model, main effects only | | | Multivariable Cox model, main effects and interactions* | | | Multivariable flexible model, main effects and interactions | | |
|-----------------------------------|-----------------------|-----------------------|---------|--|-------------|-----------------------|---|-----------------------|---------|---|-------------|---------|
| | | Hazard Ratio (95% CI) | p-value | Hazard Ratio (95% CI) | p-value | Hazard Ratio (95% CI) | p-value | Hazard Ratio (95% CI) | p-value | | | |
| Age at onset (per 10 years older) | 1.40 | (1.32-1.49) | <0.0001 | 1.39 | (1.30-1.48) | <0.0001 | 1.60 | (1.44-1.78) | <0.0001 | 1.62 | (1.46-1.81) | <0.0001 |
| Male gender (vs female) | 0.97 | (0.82-1.15) | 0.72 | 0.86 | (0.72-1.02) | 0.08 | 0.88 | (0.73-1.05) | 0.14 | 0.88 | (0.74-1.05) | 0.16 |
| MRSA | 1.23 | (0.99-1.53) | 0.06 | 0.84 | (0.65-1.08) | 0.17 | 0.84 | (0.66-1.08) | 0.17 | 0.5 | (0.66-1.09) | 0.19 |
| Injecting drug use | 0.43 | (0.26-0.72) | 0.001 | 1.28 | (0.74-2.24) | 0.38 | 1.66 | (0.94-2.93) | 0.08 | 1.65 | (0.93-2.90) | 0.08 |
| SOFA (per unit higher) | 1.18 | (1.16-1.20) | <0.0001 | 1.19 | (1.16-1.21) | <0.0001 | 1.25 | (1.20-1.29) | <0.0001 | 1.25 | (1.21-1.29) | <0.0001 |
| Charlson (per unit higher) | 1.16 | (1.12-1.19) | <0.0001 | 1.11 | (1.07-1.15) | <0.0001 | 1.23 | (1.16-1.30) | <0.0001 | 1.23 | (1.16-1.30) | <0.0001 |
| Mode of acquisition | | | | | | | | | | | | |
| Community-acquired | 1.00 | | 0.04 | 1.00 | | 0.005 | 1.00 | | 0.002 | 1.00 | | 0.01 |
| Community-onset healthcare-assoc. | 1.27 | (1.03-1.57) | 0.03 | 1.10 | (0.86-1.39) | 0.45 | 1.12 | (0.88-1.42) | 0.35 | 1.10 | (0.87-1.40) | 0.42 |
| Nosocomial | 1.25 | (1.02-1.52) | 0.03 | 1.42 | (1.13-1.78) | 0.003 | 1.47 | (1.17-1.84) | 0.001 | 1.43 | (1.14-1.80) | 0.002 |
| Dominant Focus | | | | | | | | | | | | |
| Central line | 1.00 | | <0.0001 | 1.00 | | <0.0001 | 1.00 | | <0.0001 | 1.00 | | <0.0001 |
| Peripheral line | 0.74 | (0.46-1.18) | 0.21 | 0.81 | (0.50-1.31) | 0.39 | 0.81 | (0.50-1.32) | 0.40 | 0.75 | (0.45-1.23) | 0.26 |
| Skin / soft tissue | 1.12 | (0.76-1.66) | 0.57 | 1.27 | (0.85-1.91) | 0.25 | 1.31 | (0.87-1.97) | 0.19 | 1.33 | (0.88-2.01) | 0.17 |
| Surgical wound | 1.11 | (0.66-1.88) | 0.69 | 1.17 | (0.69-1.99) | 0.57 | 1.17 | (0.68-1.99) | 0.57 | 1.13 | (0.65-1.95) | 0.67 |
| Endocarditis | 1.33 | (0.88-2.01) | 0.17 | 1.31 | (0.85-2.02) | 0.22 | 1.34 | (0.87-2.06) | 0.19 | 1.25 | (0.80-1.94) | 0.33 |
| Osteoarticular | 0.77 | (0.52-1.14) | 0.19 | 1.15 | (0.77-1.73) | 0.49 | 1.22 | (0.81-1.83) | 0.34 | 1.02 | (0.67-1.57) | 0.93 |
| Pneumonia | 3.21 | (2.27-4.53) | <0.0001 | 2.21 | (1.53-3.18) | <0.0001 | 2.28 | (1.58-3.29) | <0.0001 | 2.31 | (1.59-3.34) | <0.0001 |
| Other deep focus | 1.01 | (0.70-1.45) | 0.95 | 1.26 | (0.87-1.83) | 0.22 | 1.28 | (0.88-1.85) | 0.20 | 1.14 | (0.78-1.68) | 0.50 |
| Unknown | 2.47 | (1.81-3.38) | <0.0001 | 2.36 | (1.70-3.27) | <0.0001 | 2.36 | (1.70-3.27) | <0.0001 | 2.38 | (1.71-3.31) | <0.0001 |
| Centre | | | | | | | | | | | | |
| Centre 1 | 1.00 | | 0.003 | 1.00 | | <0.0001 | 1.00 | | <0.0001 | 1.00 | | <0.0001 |
| Centre 2 | 0.65 | (0.47-0.89) | 0.008 | 0.75 | (0.54-1.05) | 0.09 | 0.77 | (0.55-1.08) | 0.13 | 0.75 | (0.54-1.04) | 0.09 |
| Centre 3 | 0.95 | (0.70-1.29) | 0.75 | 1.49 | (1.07-2.07) | 0.02 | 1.46 | (1.04-2.04) | 0.03 | 1.42 | (1.02-1.99) | 0.04 |
| Centre 4 | 0.72 | (0.51-1.03) | 0.07 | 0.59 | (0.40-0.86) | 0.006 | 0.59 | (0.40-0.86) | 0.006 | 0.57 | (0.39-0.83) | 0.003 |
| Centre 5 | 0.84 | (0.60-1.16) | 0.28 | 1.17 | (0.84-1.64) | 0.35 | 1.16 | (0.83-1.62) | 0.38 | 1.13 | (0.81-1.58) | 0.47 |
| Centre 6 | 1.15 | (0.84-1.58) | 0.38 | 0.95 | (0.67-1.35) | 0.78 | 1.02 | (0.72-1.45) | 0.91 | 0.97 | (0.68-1.37) | 0.85 |
| Centre 7 | 0.59 | (0.40-0.89) | 0.01 | 1.03 | (0.68-1.56) | 0.89 | 1.05 | (0.69-1.58) | 0.84 | 1.01 | (0.67-1.54) | 0.95 |
| Centre 8 | 0.71 | (0.48-1.06) | 0.09 | 0.97 | (0.64-1.46) | 0.88 | 0.94 | (0.62-1.41) | 0.77 | 0.94 | (0.62-1.41) | 0.76 |
| Centre 9 | 0.65 | (0.43-0.99) | 0.04 | 1.07 | (0.70-1.66) | 0.75 | 1.06 | (0.69-1.64) | 0.78 | 1.02 | (0.66-1.57) | 0.94 |
| Centre 10 | 1.14 | (0.78-1.66) | 0.50 | 2.16 | (1.46-3.20) | 0.0001 | 2.21 | (1.49-3.27) | 0.0001 | 2.17 | (1.47-3.23) | 0.0001 |
| Centre 11 | 0.77 | (0.50-1.21) | 0.26 | 1.24 | (0.79-1.96) | 0.35 | 1.21 | (0.76-1.91) | 0.42 | 1.18 | (0.75-1.87) | 0.48 |
| Interactions | | | | | | | | | | | | |
| Age # Charlson | - | | | - | | | | Supp Fig 1(a) | 0.0006 | | | 0.0005 |
| SOFA # Charlson | - | | | - | | | | Supp Fig 1(b) | 0.0003 | | | 0.0003 |

| | | | | |
|--------------|---|---|---|---------|
| SOFA # time | - | - | - | 0.0001 |
| Focus # time | - | - | - | <0.0001 |

Table 2: Univariable and multivariable associations with 90-day mortality (Cox proportional hazards regression).

* effects presented at the reference category of other factors, namely age 66 years, female, MSSA, no injecting drug use, SOFA 0, Charlson 0, true community-acquired bloodstream infection, central line, centre 1.

Note: p-values presented against the reference categories for acquisition, focus and centre are the global tests of any difference across these categories.

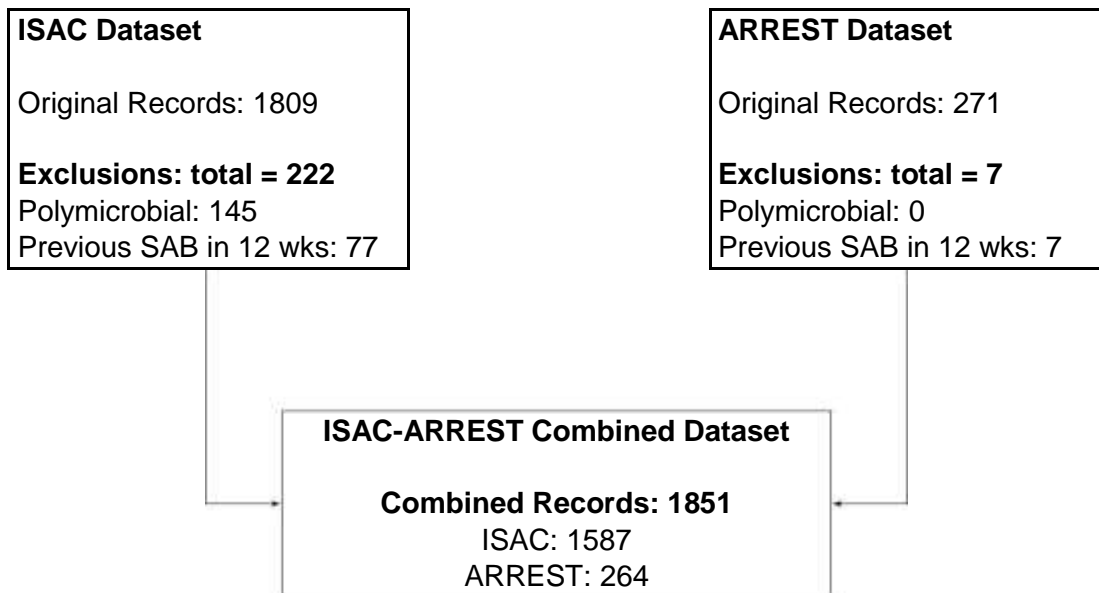
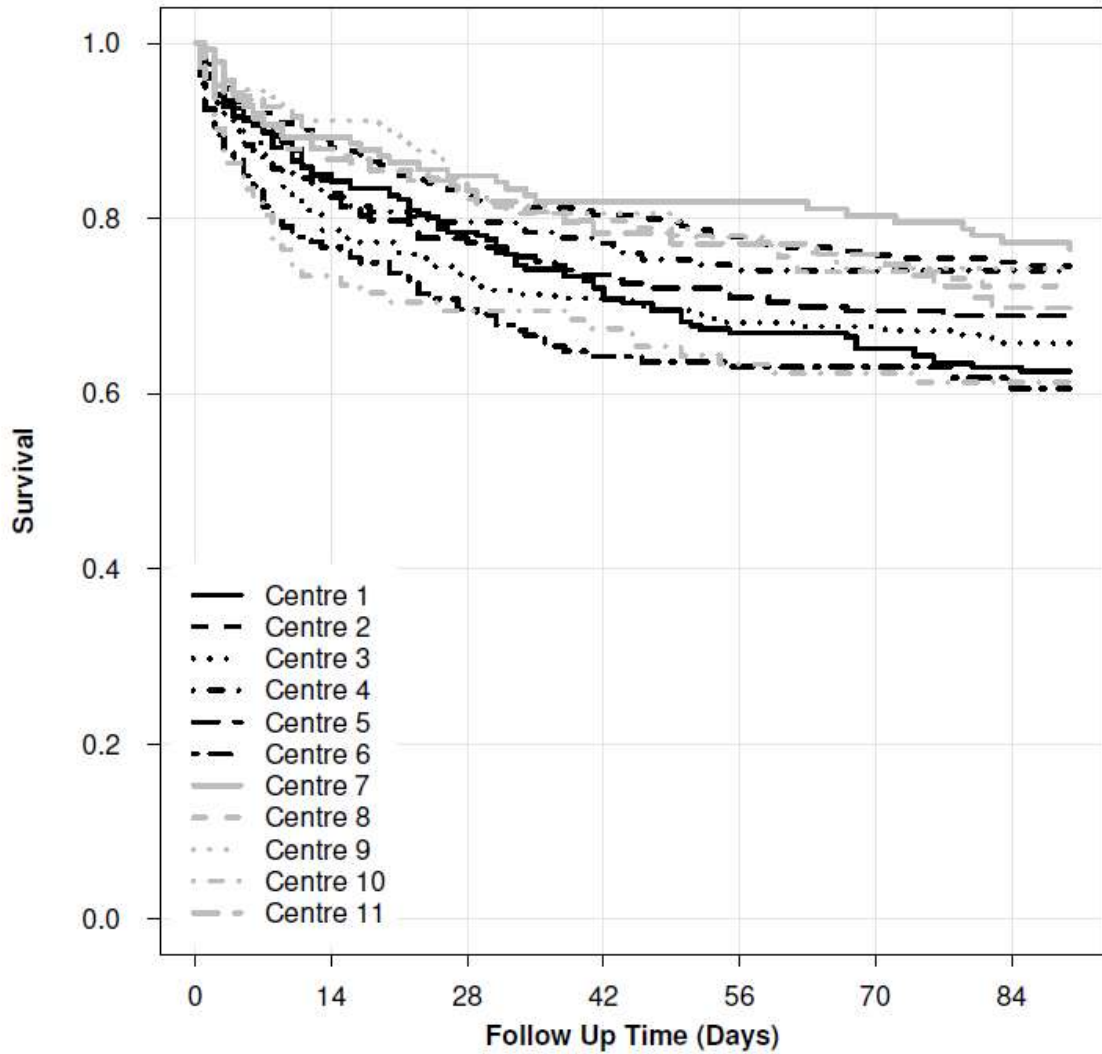
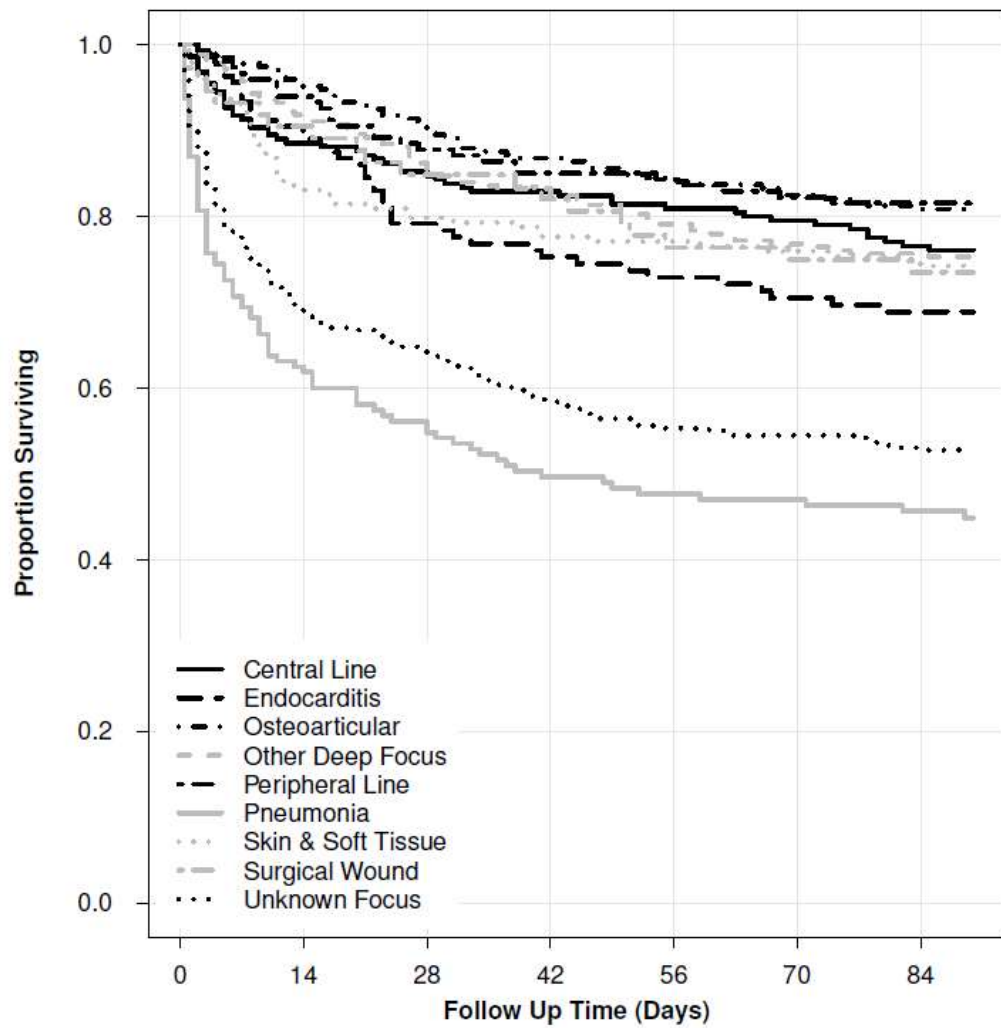


Figure 1: Flowchart showing datasets contributing to final analysis



| | | | | | | | |
|-----------|-----|-----|-----|-----|-----|-----|-----|
| Centre 1 | 255 | 212 | 187 | 169 | 153 | 149 | 144 |
| Centre 2 | 252 | 224 | 204 | 196 | 188 | 183 | 181 |
| Centre 3 | 220 | 173 | 161 | 155 | 148 | 146 | 135 |
| Centre 4 | 195 | 149 | 135 | 125 | 115 | 112 | 109 |
| Centre 5 | 193 | 163 | 150 | 142 | 137 | 132 | 129 |
| Centre 6 | 172 | 131 | 117 | 107 | 105 | 104 | 101 |
| Centre 7 | 140 | 123 | 115 | 108 | 107 | 104 | 97 |
| Centre 8 | 126 | 108 | 101 | 97 | 94 | 89 | 87 |
| Centre 9 | 113 | 103 | 95 | 91 | 88 | 82 | 82 |
| Centre 10 | 102 | 74 | 69 | 67 | 62 | 61 | 60 |
| Centre 11 | 83 | 72 | 70 | 65 | 64 | 62 | 57 |

Figure 2(a) Survival through 90 days by centre. $p = 0.003$, log-rank test)



| | | | | | | | |
|--------------------|-----|-----|-----|-----|-----|-----|-----|
| Central Line | 218 | 192 | 180 | 174 | 168 | 163 | 155 |
| Endocarditis | 136 | 122 | 102 | 96 | 92 | 87 | 84 |
| Osteoarticular | 269 | 254 | 238 | 224 | 212 | 206 | 197 |
| Other Deep Focus | 282 | 253 | 231 | 222 | 210 | 202 | 196 |
| Peripheral Line | 151 | 138 | 128 | 122 | 121 | 118 | 116 |
| Pneumonia | 161 | 99 | 87 | 76 | 71 | 70 | 66 |
| Skin & Soft Tissue | 190 | 156 | 147 | 140 | 136 | 134 | 131 |
| Surgical Wound | 74 | 66 | 60 | 58 | 54 | 52 | 51 |
| Unknown Focus | 370 | 252 | 231 | 210 | 197 | 192 | 186 |

Figure 2(b): Survival through 90 days by dominant infective focus ($p < 0.0001$, log-rank test).

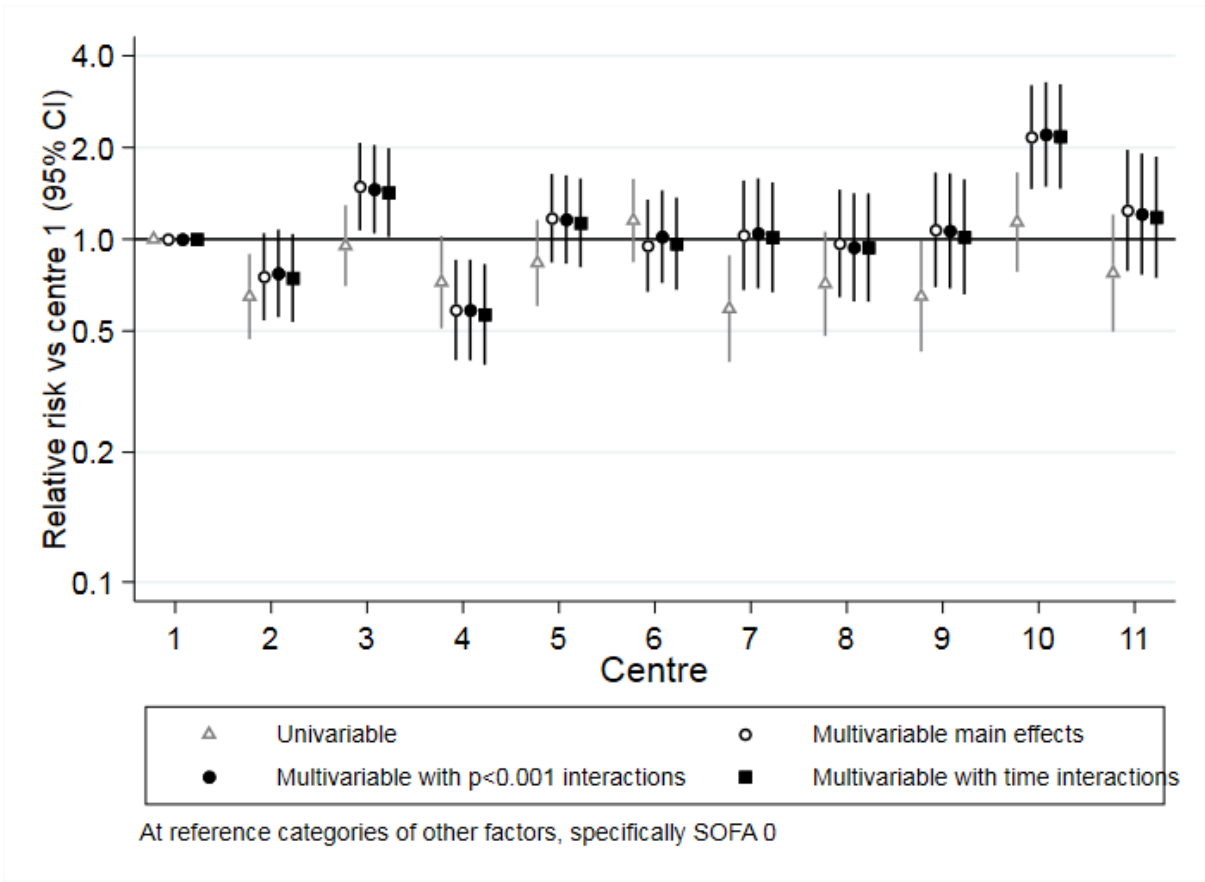


Figure 3: Crude and adjusted estimates of effect of centre on 90-day mortality

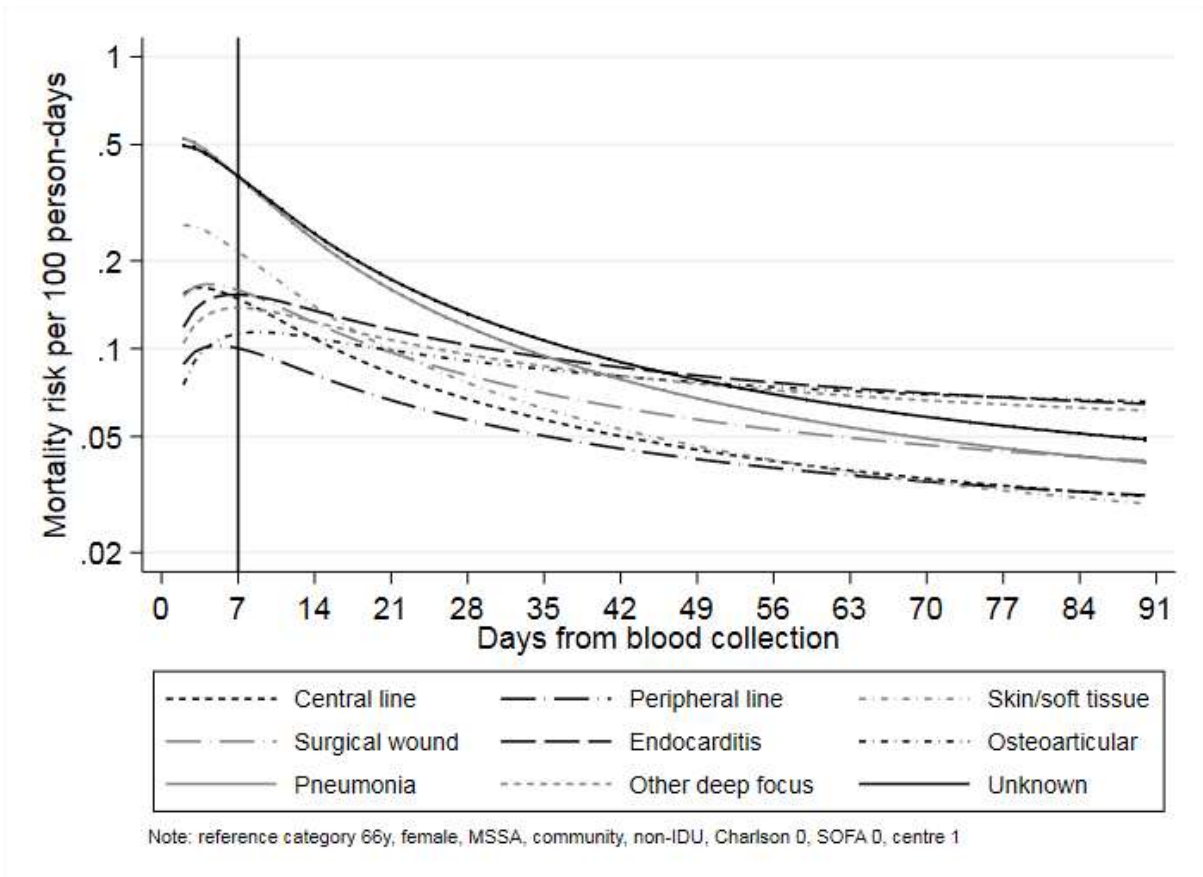
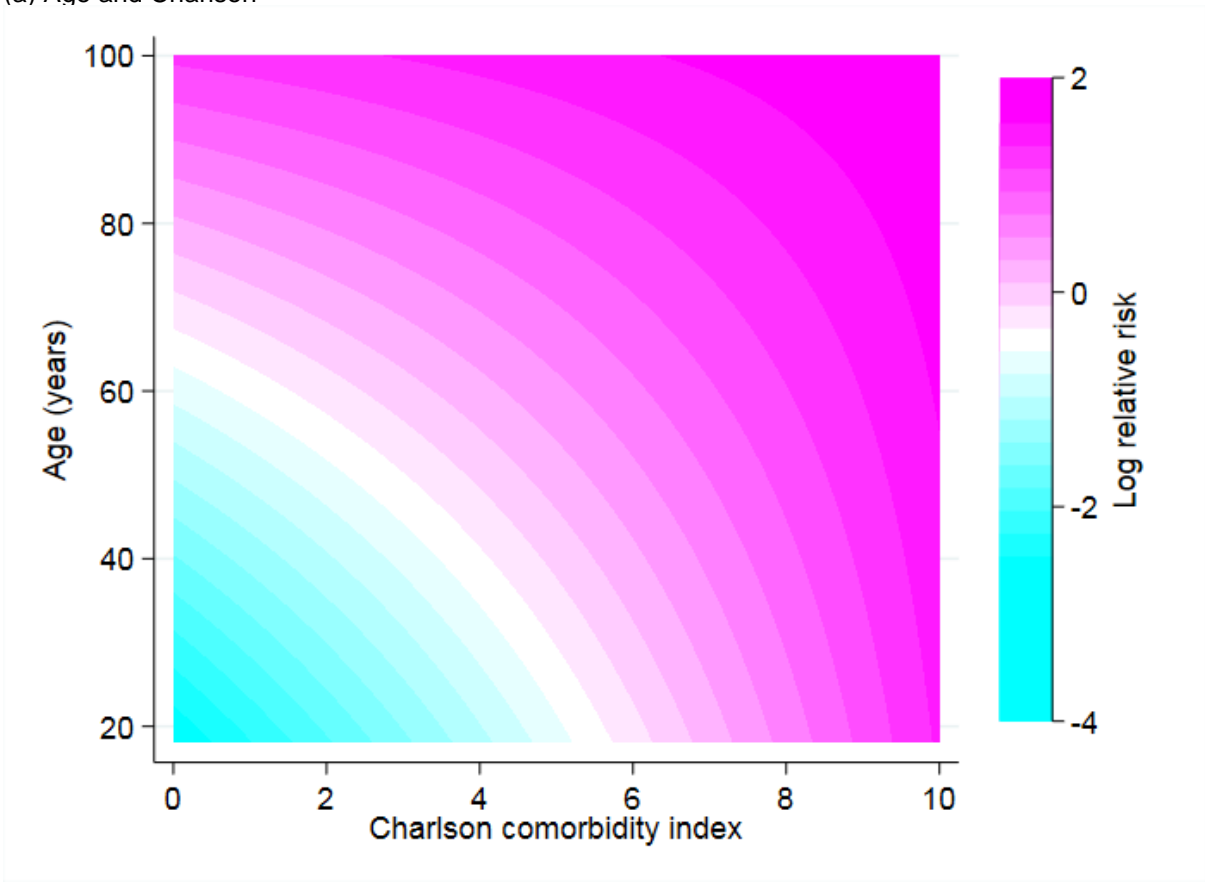
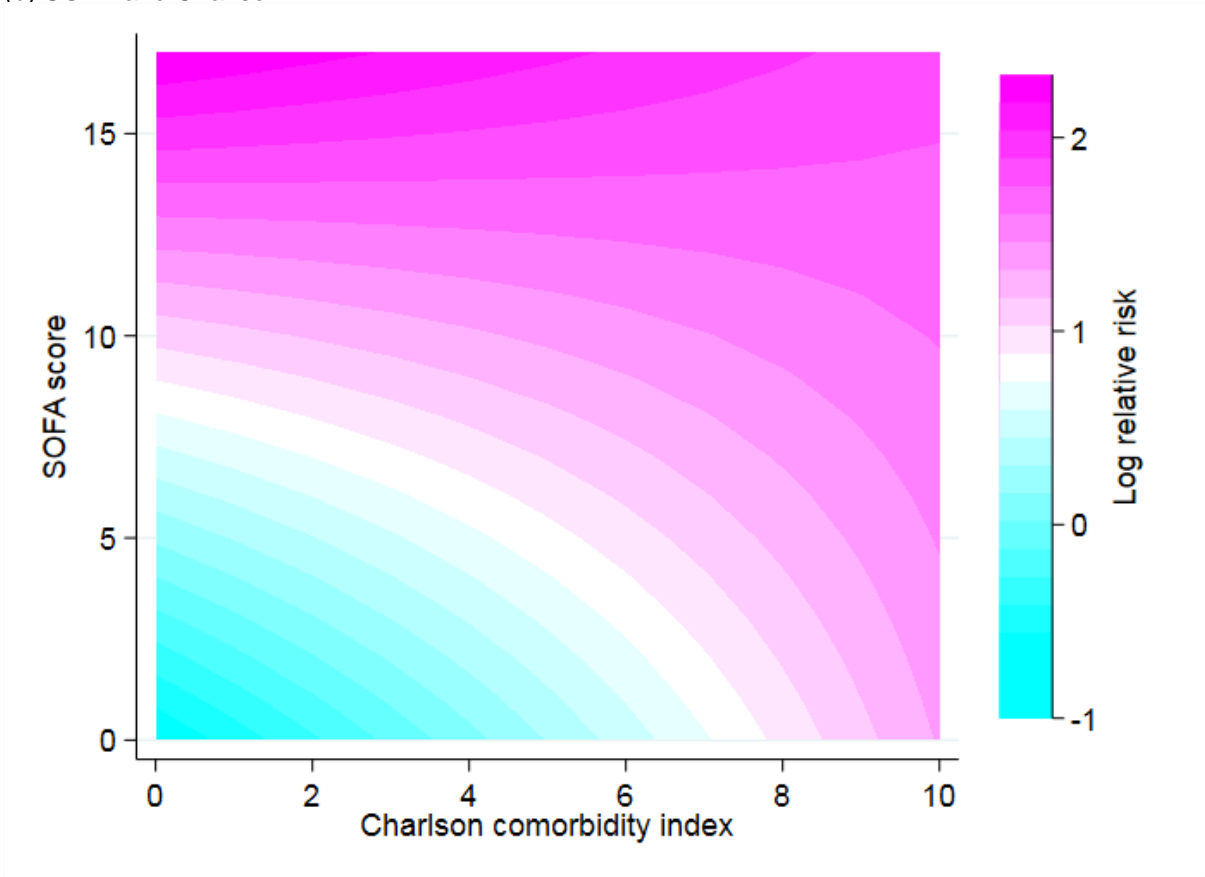


Figure 4: Daily mortality risk (hazard) over 90 days of follow-up by dominant focus of infection.

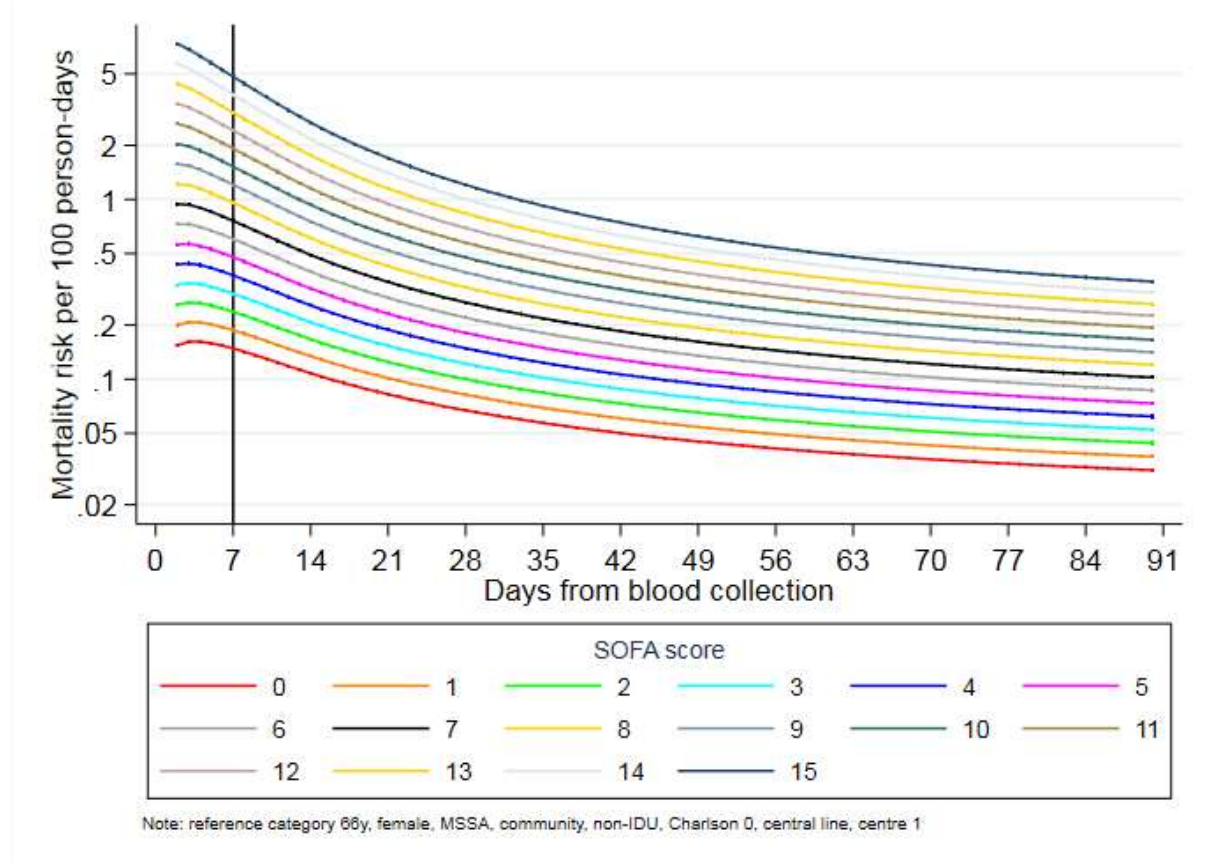
Supplementary Figure 1: Interactions in the proportional hazards model
(a) Age and Charlson



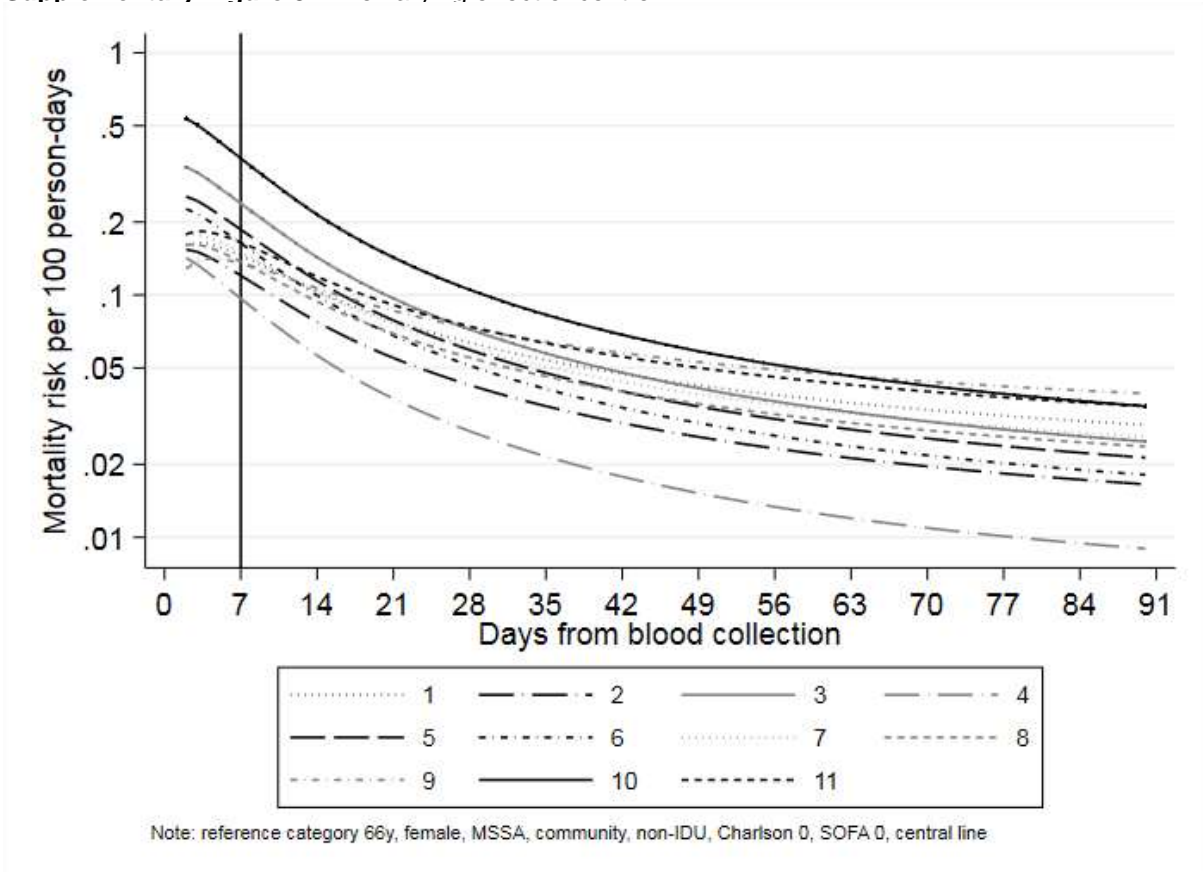
(b) SOFA and Charlson



Supplementary Figure 2: Time-varying effect of SOFA score



Supplementary Figure 3 Time varying effect of centre



| | Multivariable Cox model, main effects and interactions, all deaths through 90 days | | | Multivariable Cox model, main effects and interactions, excluding deaths in the first 3 days | | |
|-----------------------------------|--|---------|--|--|---------|--|
| | Hazard Ratio (95% CI) | p-value | | Hazard Ratio (95% CI) | p-value | |
| Age at onset (per 10 years older) | 1.60 (1.44-1.78) | <0.0001 | | 1.56 (1.38-1.76) | <0.0001 | |
| Male gender (vs female) | 0.88 (0.73-1.05) | 0.14 | | 0.89 (0.72-1.09) | 0.24 | |
| MRSA | 0.84 (0.66-1.08) | 0.17 | | 0.84 (0.63-1.12) | 0.22 | |
| Injecting drug use | 1.66 (0.94-2.93) | 0.08 | | 1.30 (0.64-2.68) | 0.47 | |
| SOFA (per unit higher) | 1.25 (1.20-1.29) | <0.0001 | | 1.22 (1.17-1.28) | <0.0001 | |
| Charlson (per unit higher) | 1.23 (1.16-1.30) | <0.0001 | | 1.24 (1.16-1.32) | <0.0001 | |
| Mode of acquisition | | | | | | |
| Community-acquired | 1.00 | 0.002 | | 1.00 | 0.0008 | |
| Community onset healthcare-assoc. | 1.12 (0.88-1.42) | 0.35 | | 1.15 (0.87-1.52) | 0.32 | |
| Nosocomial | 1.47 (1.17-1.84) | 0.001 | | 1.63 (1.24-2.13) | 0.0004 | |
| Dominant Focus | | | | | | |
| Central line | 1.00 | <0.0001 | | 1.00 | 0.002 | |
| Peripheral line | 0.81 (0.50-1.32) | 0.40 | | 0.91 (0.55-1.51) | 0.72 | |
| Skin / soft tissue | 1.31 (0.87-1.97) | 0.19 | | 1.39 (0.89-2.19) | 0.15 | |
| Surgical wound | 1.17 (0.68-1.99) | 0.57 | | 1.10 (0.61-2.01) | 0.75 | |
| Endocarditis | 1.34 (0.87-2.06) | 0.19 | | 1.85 (1.16-2.95) | 0.01 | |
| Osteoarticular | 1.22 (0.81-1.83) | 0.34 | | 1.46 (0.94-2.27) | 0.09 | |
| Pneumonia | 2.28 (1.58-3.29) | <0.0001 | | 1.88 (1.21-2.92) | 0.005 | |
| Other deep focus | 1.28 (0.88-1.85) | 0.20 | | 1.47 (0.99-2.21) | 0.06 | |
| Unknown | 2.36 (1.70-3.27) | <0.0001 | | 2.06 (1.42-2.99) | 0.0002 | |
| Centre | | | | | | |
| Centre 1 | 1.00 | <0.0001 | | 1.00 | 0.0008 | |
| Centre 2 | 0.77 (0.55-1.08) | 0.13 | | 0.67 (0.46-0.97) | 0.04 | |
| Centre 3 | 1.46 (1.04-2.04) | 0.03 | | 1.39 (0.95-2.02) | 0.09 | |
| Centre 4 | 0.59 (0.40-0.86) | 0.006 | | 0.51 (0.33-0.80) | 0.003 | |
| Centre 5 | 1.16 (0.83-1.62) | 0.38 | | 0.99 (0.68-1.45) | 0.96 | |
| Centre 6 | 1.02 (0.72-1.45) | 0.91 | | 0.88 (0.58-1.32) | 0.53 | |
| Centre 7 | 1.05 (0.69-1.58) | 0.84 | | 1.00 (0.63-1.58) | 0.99 | |
| Centre 8 | 0.94 (0.62-1.41) | 0.77 | | 0.89 (0.57-1.41) | 0.63 | |
| Centre 9 | 1.06 (0.69-1.64) | 0.78 | | 1.07 (0.66-1.75) | 0.78 | |
| Centre 10 | 2.21 (1.49-3.27) | 0.0001 | | 1.68 (1.04-1.69) | 0.03 | |
| Centre 11 | 1.21 (0.76-1.91) | 0.42 | | 1.08 (0.65-1.78) | 0.76 | |

Supplementary Table 1: Multivariable associations with 90-day mortality (Cox proportional hazards regression) overall and excluding deaths in the first 3 days.

Note: p-values presented against the reference categories for acquisition, focus and centre are the global tests of any different across these categories. Effects presented at the reference category of other factors, namely age 66 years, female, MSSA, no injecting drug use, SOFA 0, Charlson 0, true community-acquired bloodstream infection, central line, centre 1.