

	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
<b>Mode of Acquisition</b>													<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)	
<b>Charlson Comorbidity Index (CCI)</b>													
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
<b>SOFA Score</b>													
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
<b>Dominant focus</b>													<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
<b>Outcome</b>													
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.

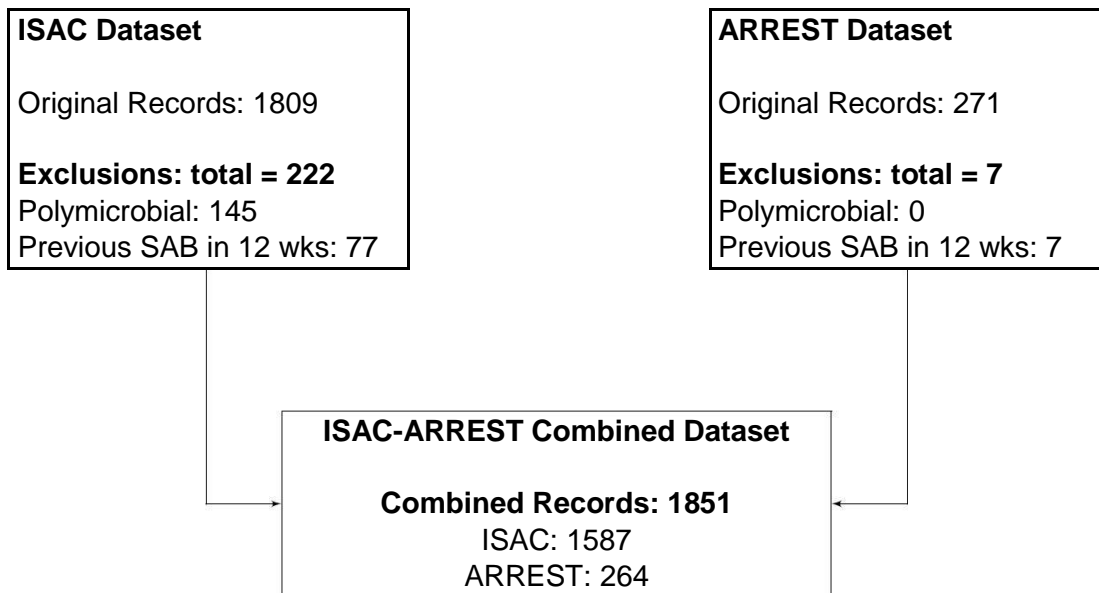
	Univariable Cox model			Multivariable Cox model, main effects only			Multivariable Cox model, main effects and interactions*			Multivariable flexible model, main effects and interactions		
	Hazard Ratio (95% CI)	p-value		Hazard Ratio (95% CI)	p-value		Hazard Ratio (95% CI)	p-value		Hazard Ratio (95% 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	
<b>Mode of acquisition</b>												
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	
<b>Dominant Focus</b>												
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	
<b>Centre</b>												
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	
<b>Interactions</b>												
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

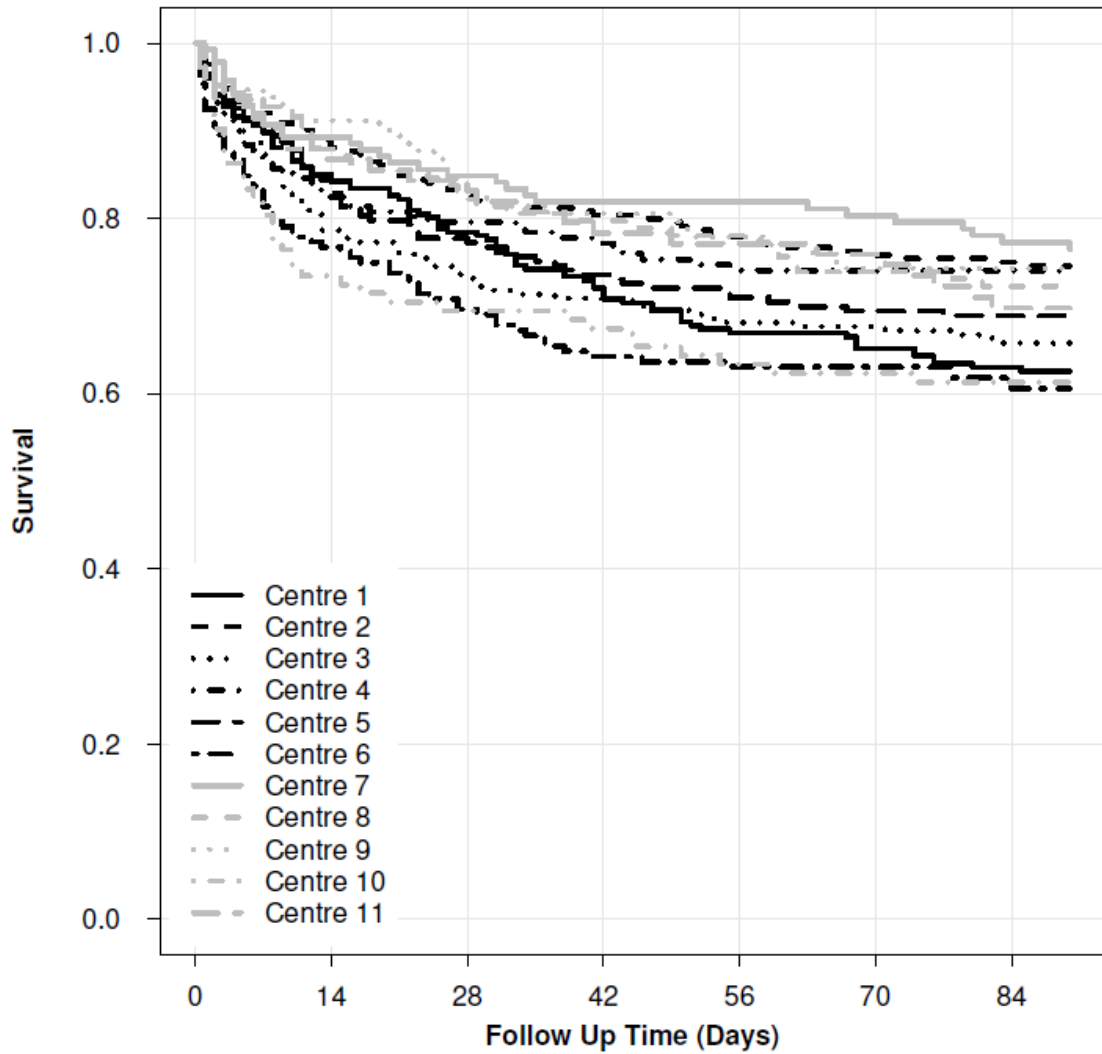
**Table 2:** Univariable and multivariable associations with 90-day mortality (Cox proportional hazards regression).

\* 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 different across these categories.

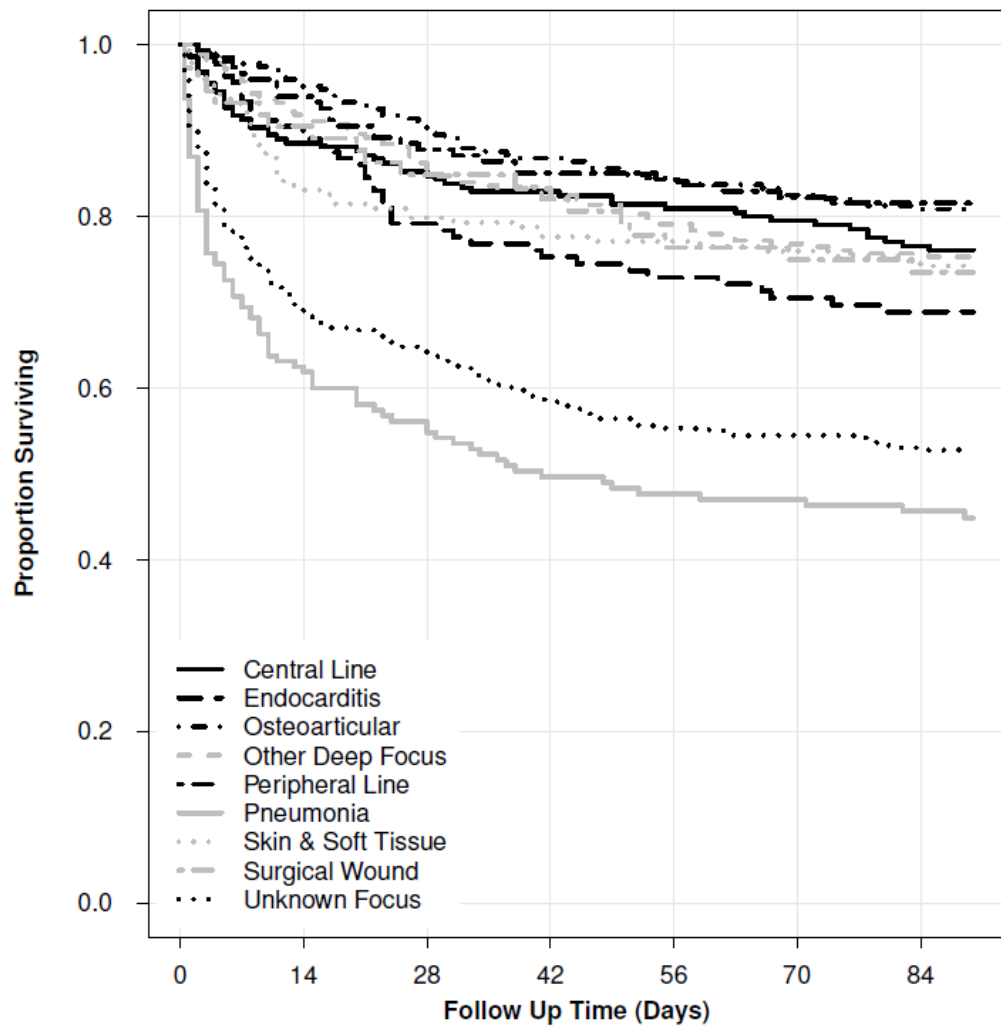


**Figure 1:** Flowchart showing datasets contributing to final analysis



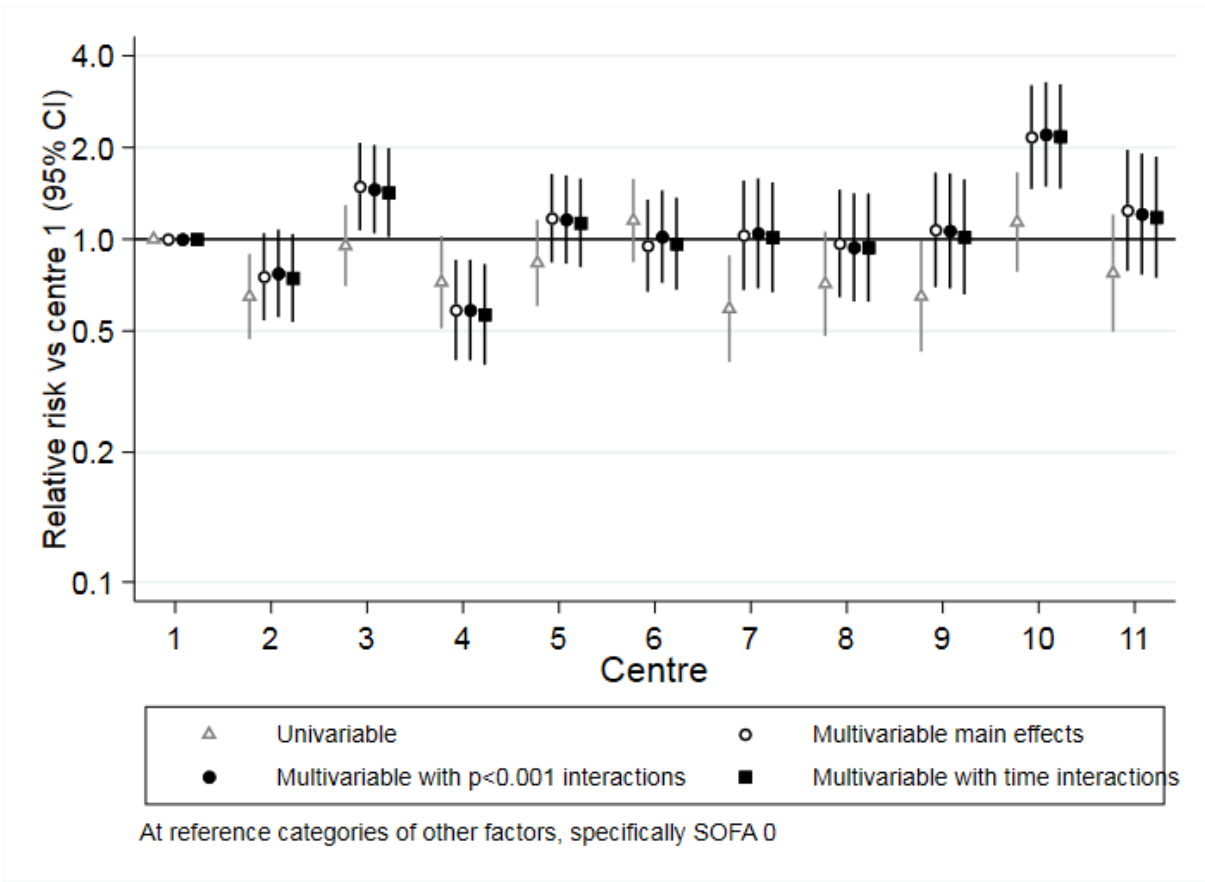
Centre 1	255	212	187	169	153	149	144
Centre 2	252	224	204	196	188	183	181
Centre 3	220	173	161	155	148	146	135
Centre 4	195	149	135	125	115	112	109
Centre 5	193	163	150	142	137	132	129
Centre 6	172	131	117	107	105	104	101
Centre 7	140	123	115	108	107	104	97
Centre 8	126	108	101	97	94	89	87
Centre 9	113	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)

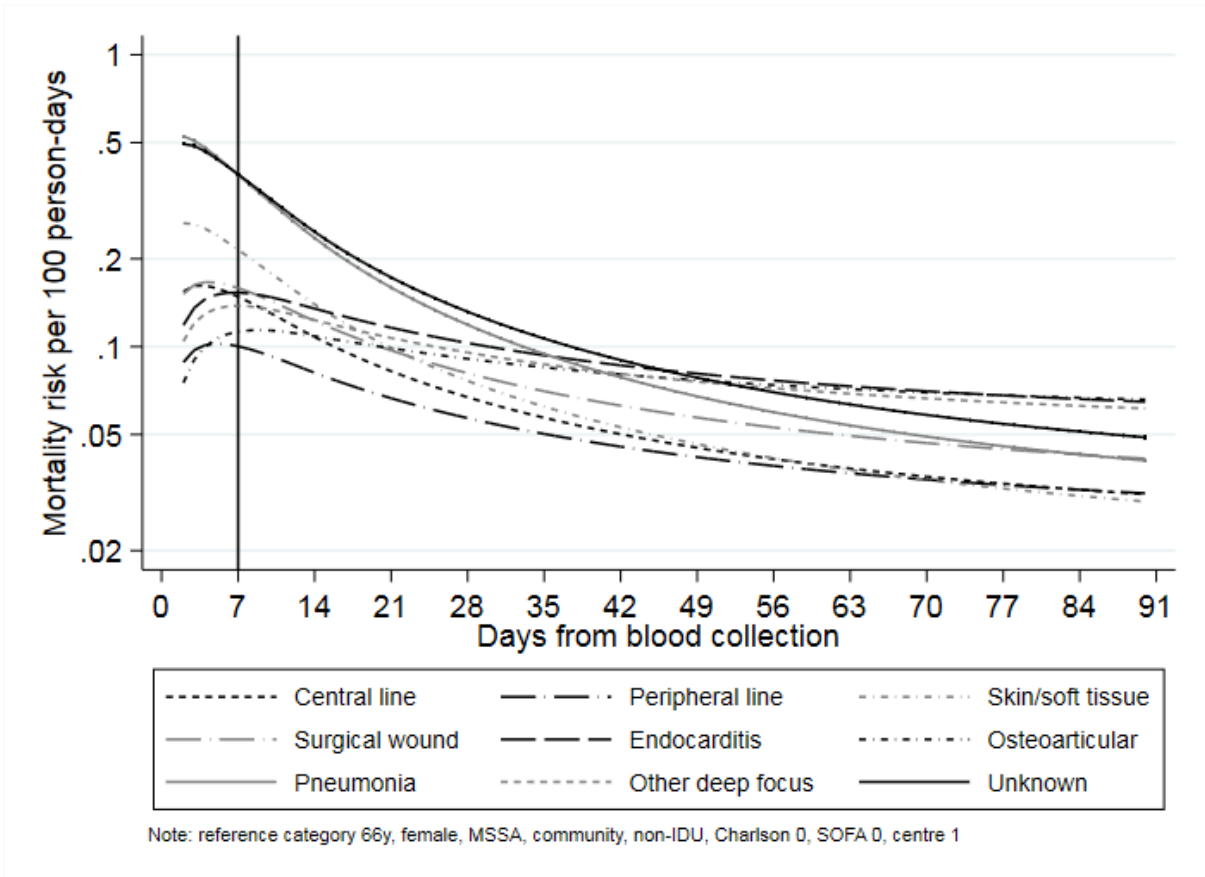


Central Line	218	192	180	174	168	163	155
Endocarditis	136	122	102	96	92	87	84
Osteoarticular	269	254	238	224	212	206	197
Other Deep Focus	282	253	231	222	210	202	196
Peripheral Line	151	138	128	122	121	118	116
Pneumonia	161	99	87	76	71	70	66
Skin & Soft Tissue	190	156	147	140	136	134	131
Surgical Wound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



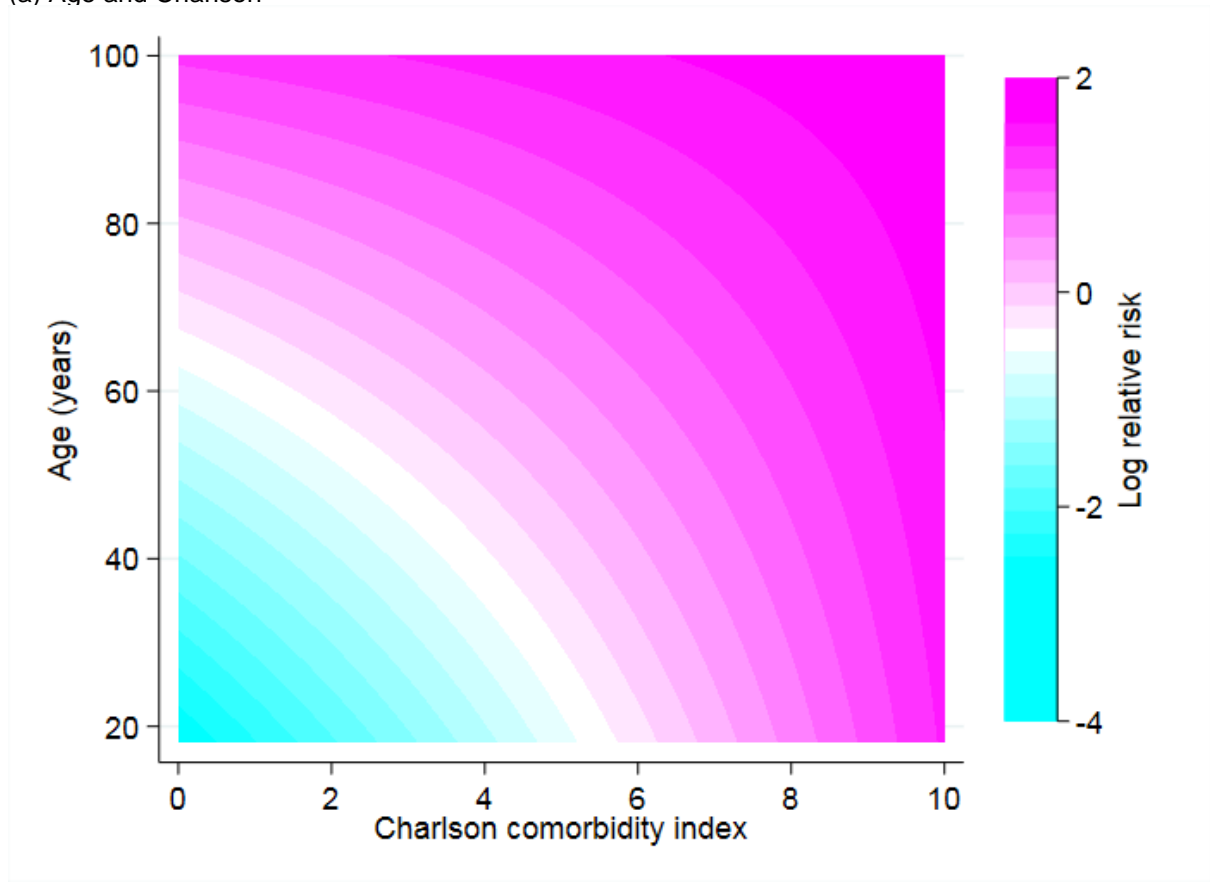
**Figure 3:** Crude and adjusted estimates of effect of centre on 90-day mortality



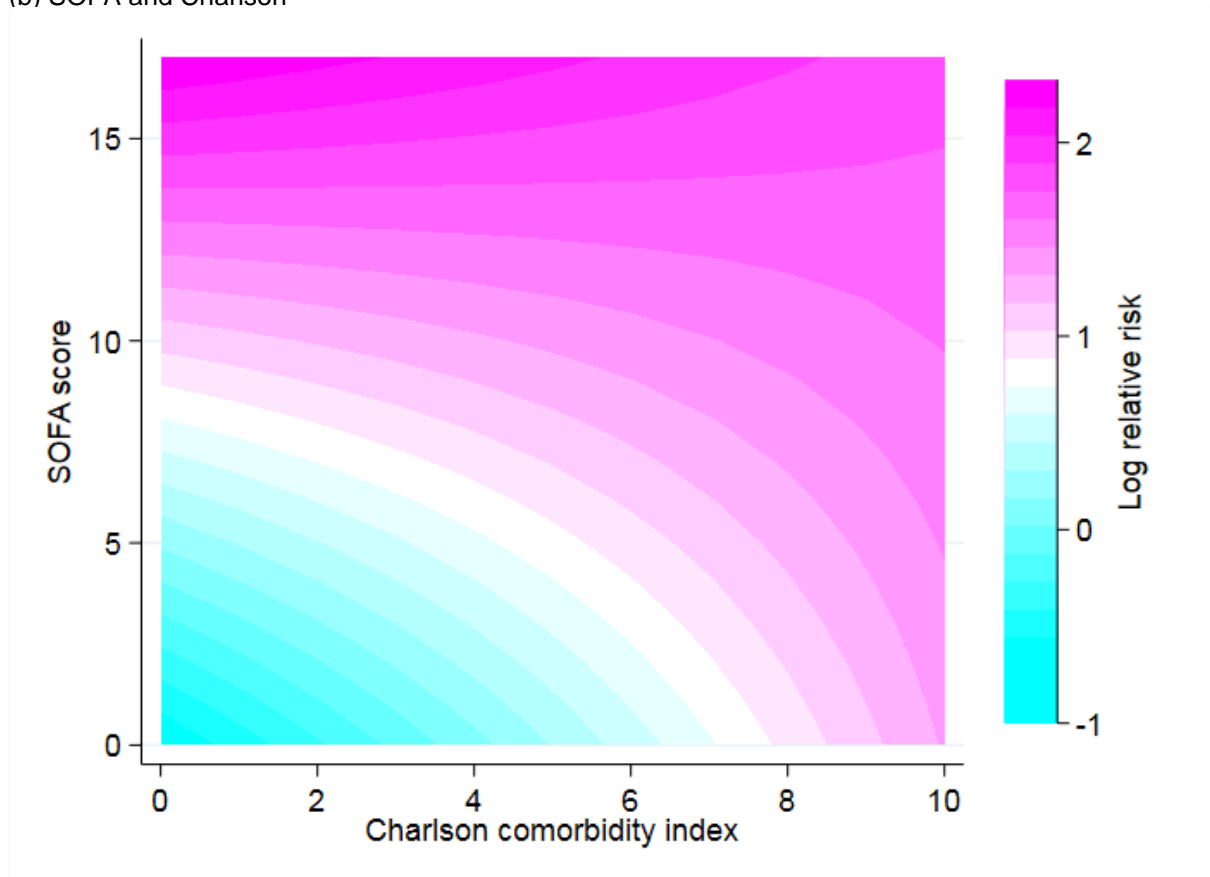
**Figure 4:** Daily mortality risk (hazard) over 90 days of follow-up by dominant focus of infection.



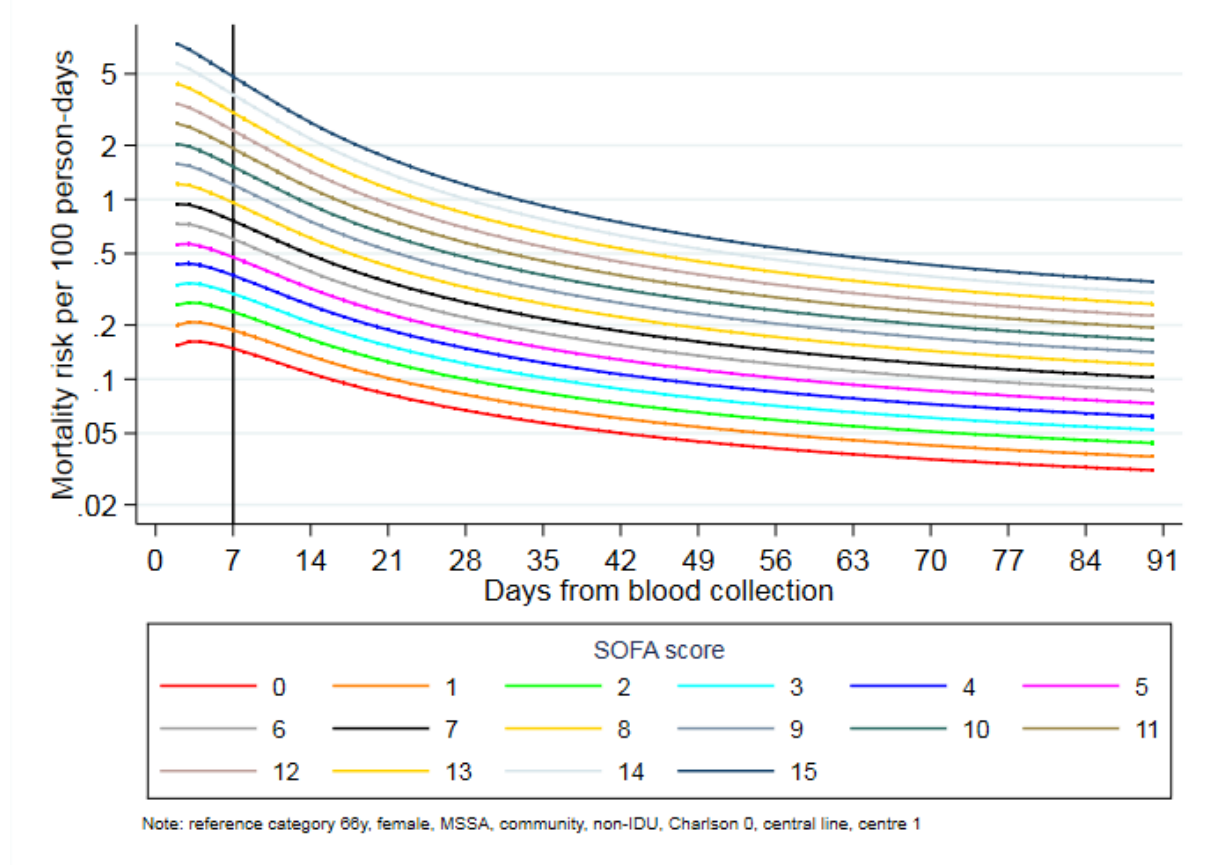
**Supplementary Figure 1:** Interactions in the proportional hazards model  
(a) Age and Charlson



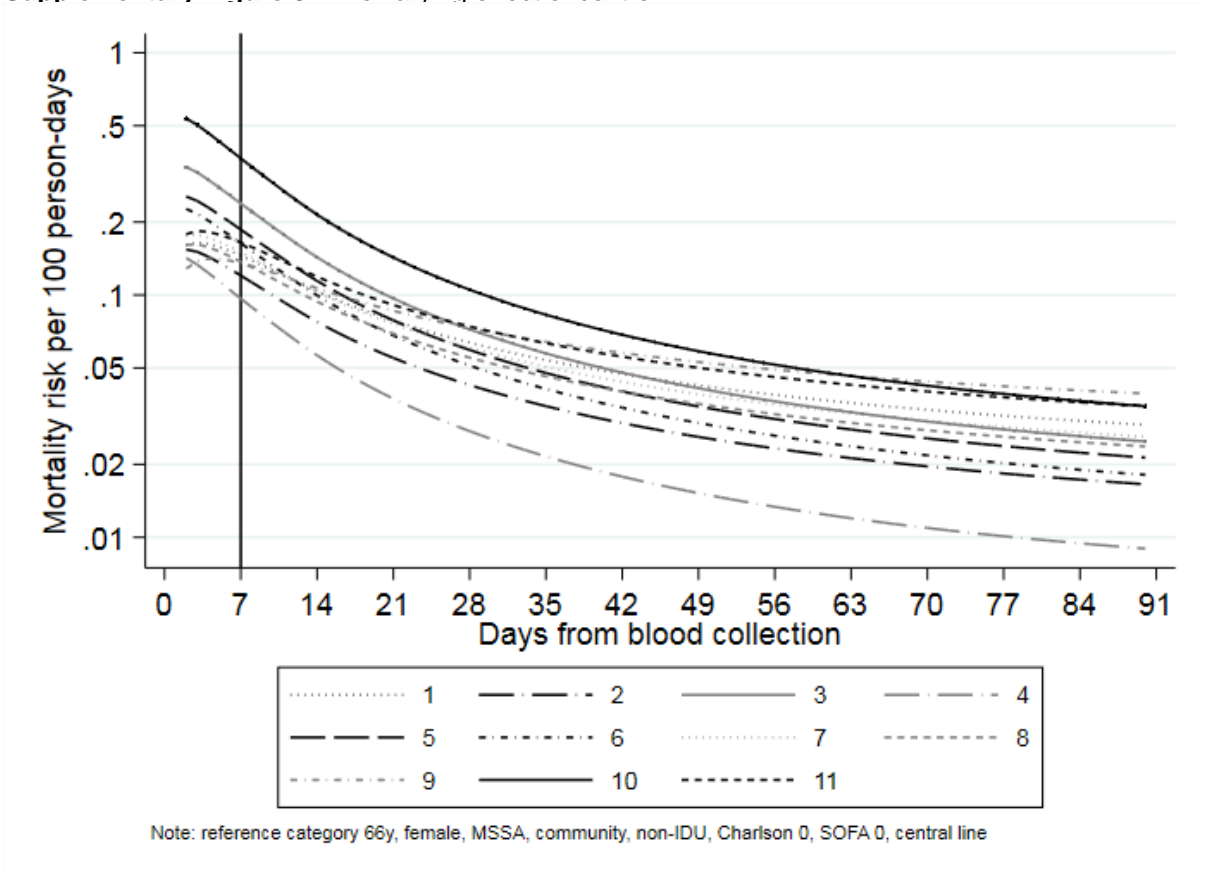
(b) SOFA and Charlson



**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	
<b>Mode of acquisition</b>						
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	
<b>Dominant Focus</b>						
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	
<b>Centre</b>						
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.