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

Kate Nambiar, Harald Seifert, Siegbert Riert, Winfried V Kern, Matt Scarborough, N Claire Gordon, Hong Bin Kim, Kyoung-Ho Song, Robert Tilley, Hannah Gott, Chun Hsing Liao, Jonathan Edgeworth, Emmanuel Nsutebu, Luis Eduardo López-Cortés, Laura Morata, A Sarah Walker, Guy Thwaites, Martin Llewelyn, Achim J Kaasch, International *Staphylococcus aureus* collaboration study group, ESCMID Study Group for Bloodstream Infections and Sepsis

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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 different across these categories.

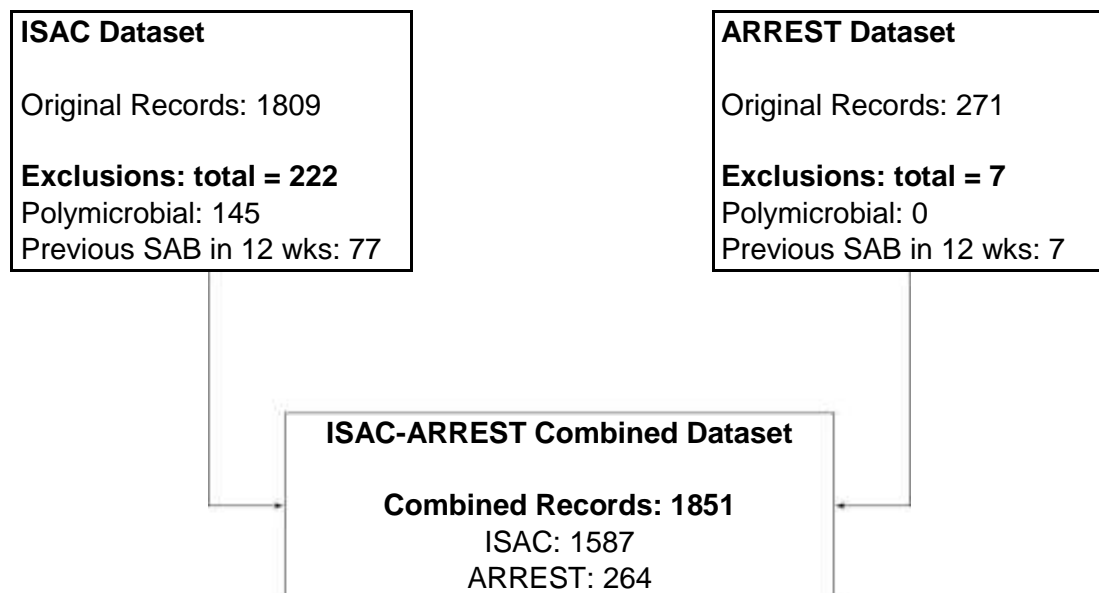


Figure 1: Flowchart showing datasets contributing to final analysis

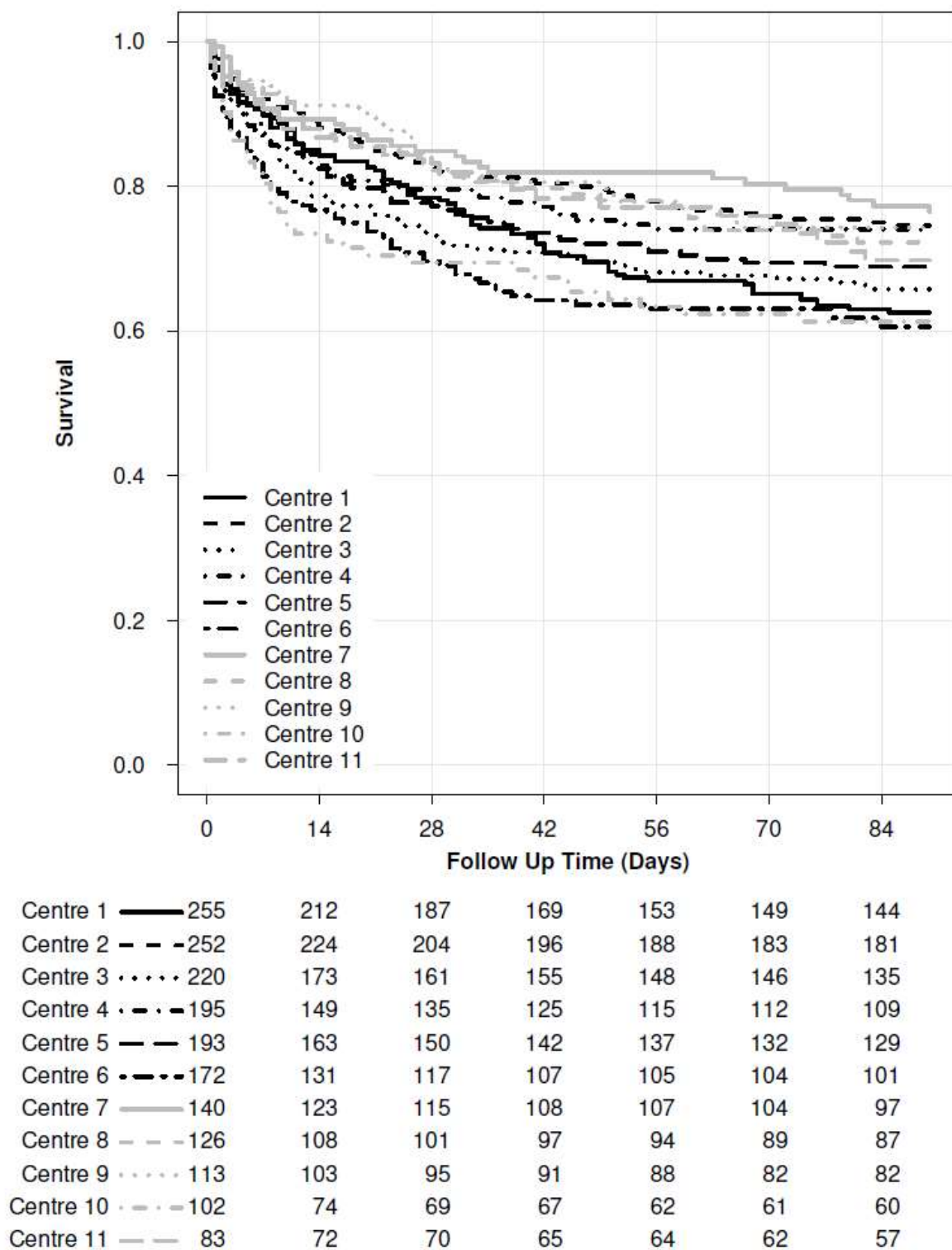
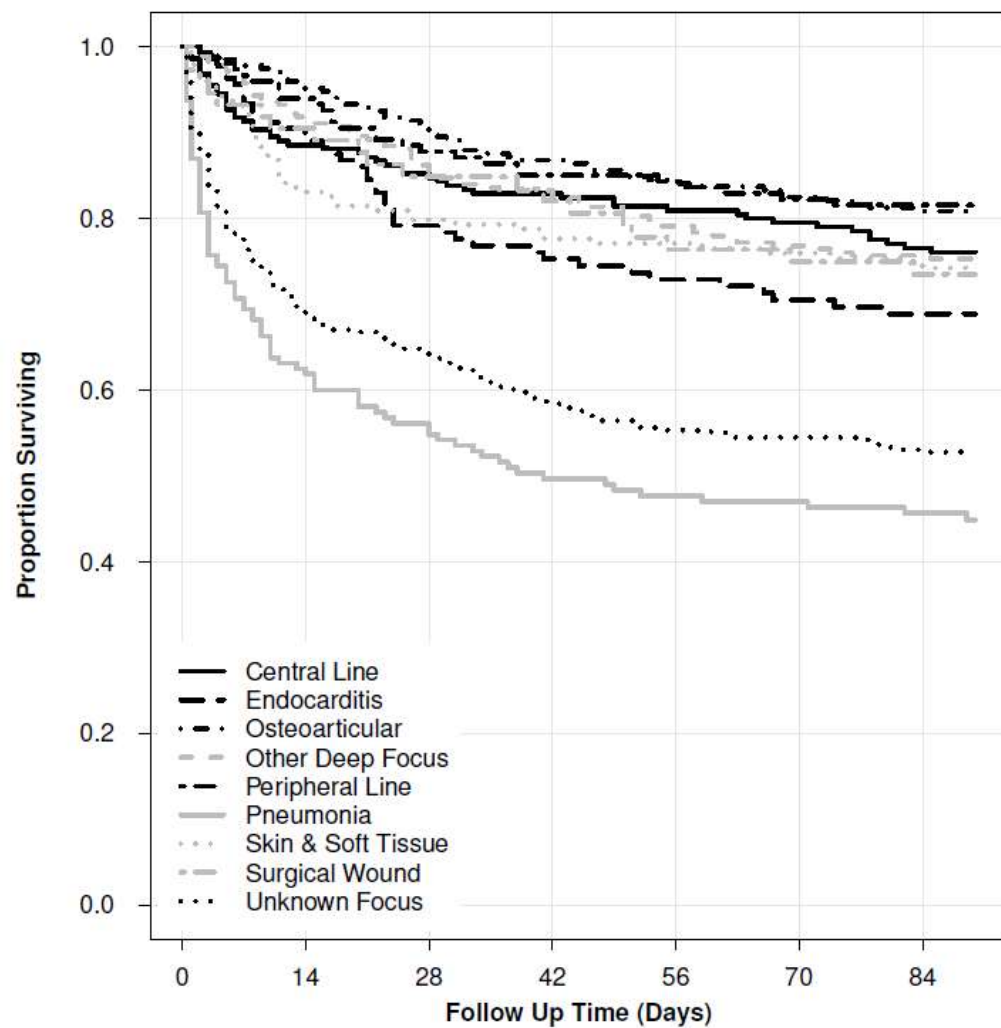


Figure 2(a) Survival through 90 days by centre. $p = 0.003$, log-rank test)



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).

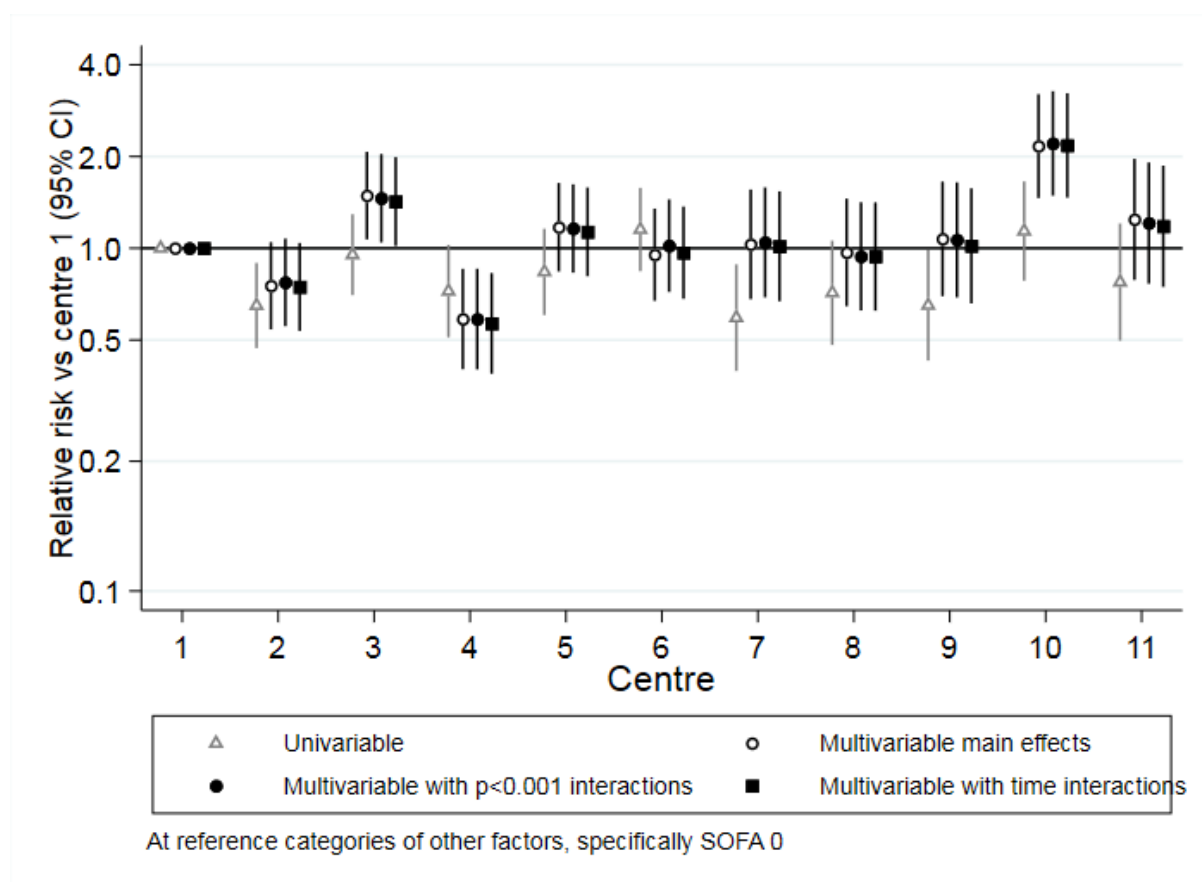


Figure 3: Crude and adjusted estimates of effect of centre on 90-day mortality

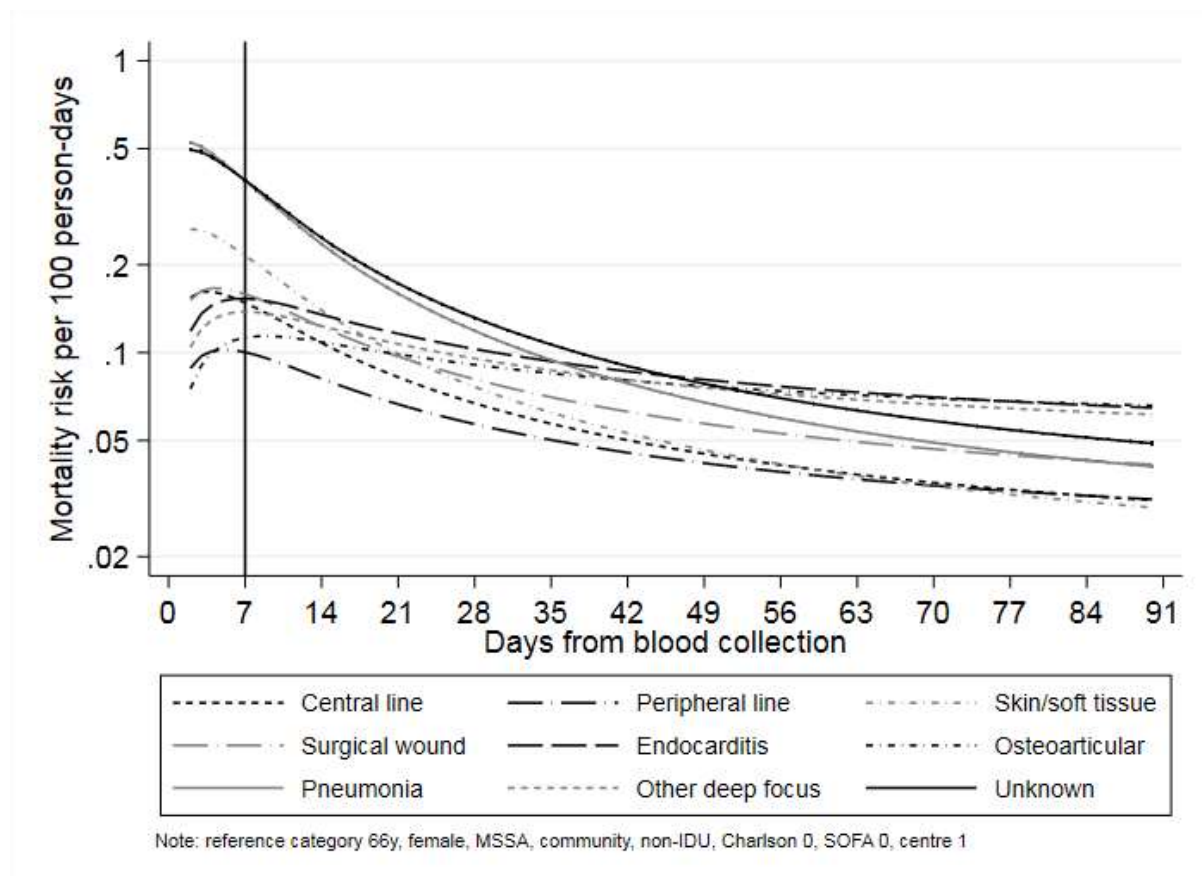
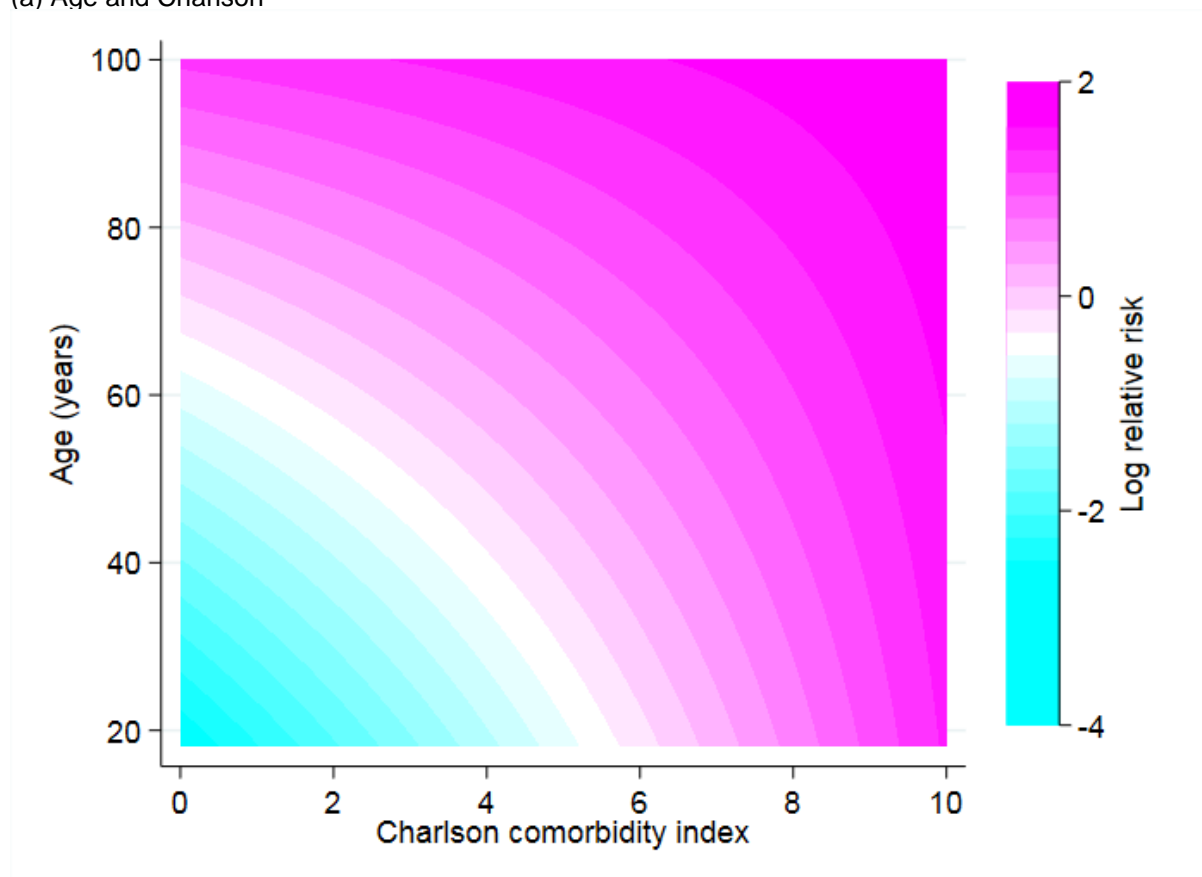
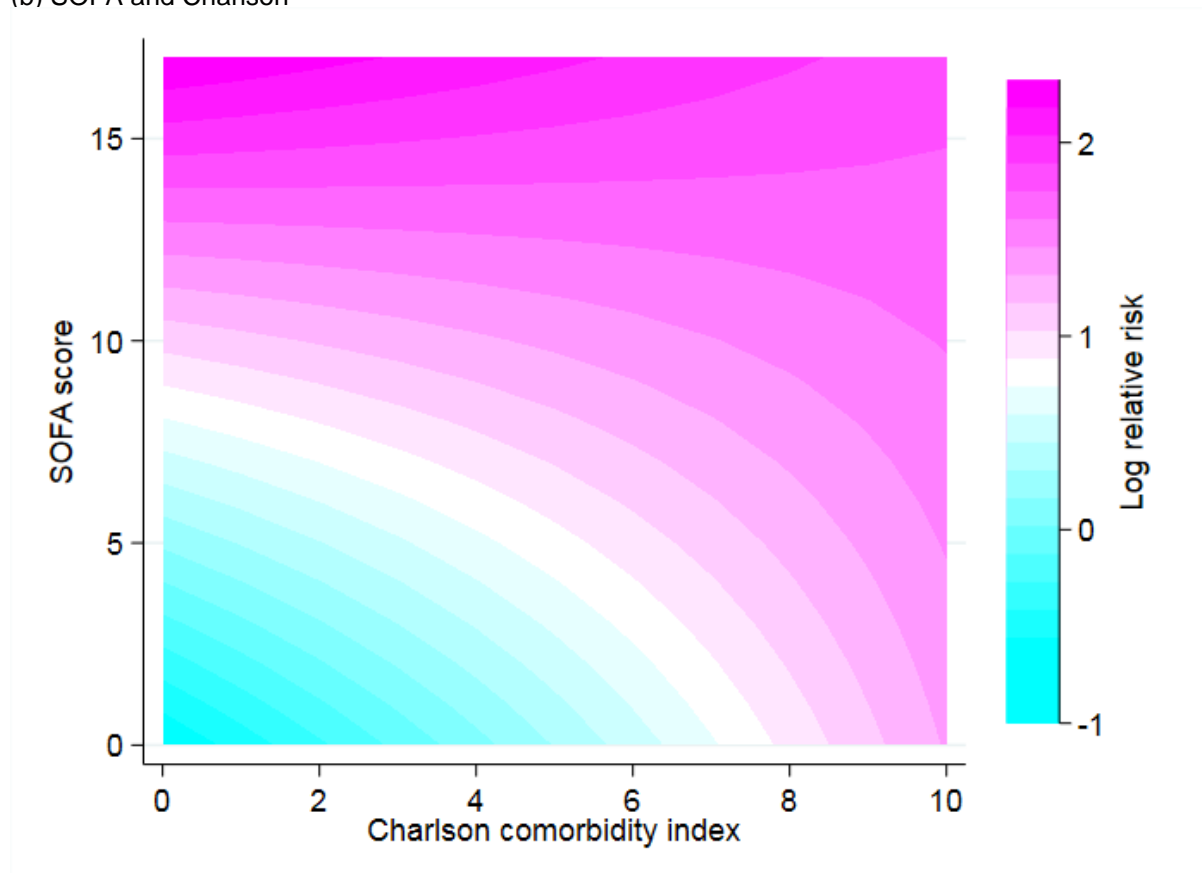


Figure 4: Daily mortality risk (hazard) over 90 days of follow-up by dominant focus of infection.

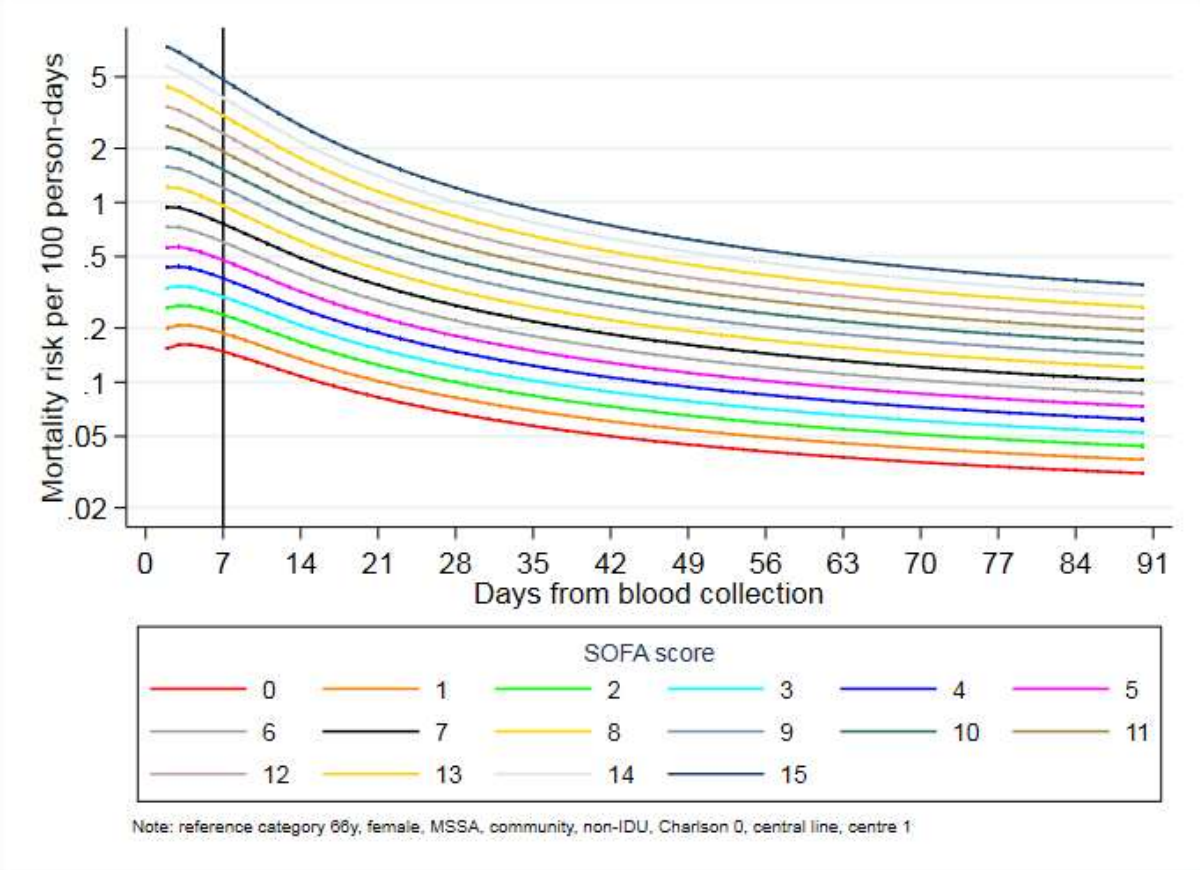
Supplementary Figure 1: Interactions in the proportional hazards model
(a) Age and Charlson



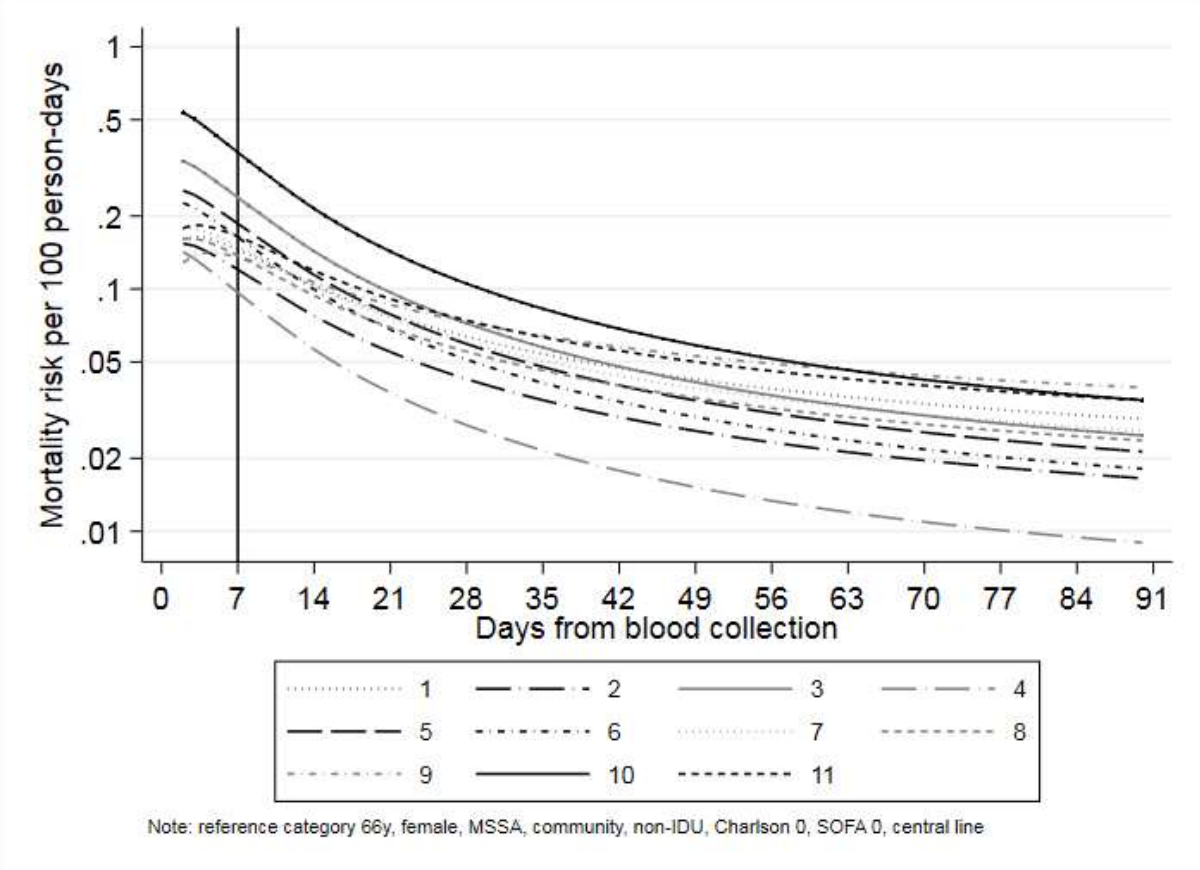
(b) SOFA and Charlson



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.