

Supplemental Digital Content

A comparison of mortality from sepsis in Brazil and England: the impact of heterogeneity in general and sepsis-specific patient characteristics

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eTable1: Comorbidity definitions for Brazil (Charlson comorbidities) and England (APACHE II definitions) (green stands for full match / salmon for partial match / red for poor match)

Comorbidities	Brazil	England
Severe cardiovascular disease	NYHA IV	NYHA IV
Severe respiratory disease	Severe COPD	Severe respiratory disease (Chronic restrictive, obstructive or vascular disease with severe exercise restriction); Respiratory dependency
Renal disease (chronic renal failure under RRT)	Chronic dialysis	Chronic dialysis
Chronic liver disease	Cirrhosis Child AB; Child C; Hepatic failure	Bx-proven cirrhosis and documented hypertension; GI bleeding due to portal hypertension; Hepatic failure/encephalopathy/coma
Immunocompromised		
Haematological malignancy	Haematological malignancy	Haematological malignancy
AIDS	AIDS	AIDS
Metastatic disease (solid neoplasia)	Metastatic disease	Metastatic disease
Steroid use	Steroid use	Steroid use
Functional status		
Independent*	Fully active, able to carry on all activities without restriction	No assistance to carry out activities of daily living
Partially or fully dependent*	From restriction in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary to completely disabled; not carrying on any selfcare; totally confined to bed or chair	Partial or total assistance to carry out activities of daily living

NYHA IV – New York Heart Association (NYHA) Functional Classification

COPD: Chronic Obstructive Pulmonary Disease

AIDS – Acquired immune deficiency syndrome

* Both definitions have full match for the “independent” category, thus the complement of it “non-independent” (partially or fully dependent) have also full match. This variable was entered as a binary variable (independent x non-independent).

eTable2: Modified SOFA score definitions: calculated with the worst values within first 24h of admission (green stands for full match / salmon for partial match / red for poor match)

admission: green status for full match / caution for partial match / red for poor match				
		Brazil	England	
	Points	Definition by: PaO ₂ /FiO ₂ (mmHg)	Definition by: PaO ₂ /FiO ₂ (kPa)	
Respiratory	0	≥400	≥53.4	
	1	300-399	40-53.33	
	2	200-299	26.7-39.9	
	3	100-199 and Respiratory support	13.3-26.6 and Respiratory support	
	4	<100 and Respiratory Support	<13.3 and Respiratory support	
		Brazil	England	
	Points	Definition by: MAP or vasoactive drugs*	Definition by: Use of advanced cardiovascular support [#]	
Cardiovascular	0	Without drugs or hypotension		
	1	MAP < 70 mmHg		
	2	Dopamine ≤5 or Dobutamine (any dose)	X	
	3	Dopamine >5 or Epinephrine ≤0.1 or Norepinephrine ≤0.1	X	
	4	Dopamine >15 or Epinephrine >0.1 or Norepinephrine >0.1	X	
*Vasoactive drugs administrated at least for one hour. In µg/kg-min				
		Brazil	England	
	Points	Definition by: Platelets count (x10 ⁹ /L)	Definition by: Platelets count (x10 ⁹ /L)	
Haematological	0	≥150	≥150	
	1	100-149	100-149	
	2	50-99	50-99	
	3	20-49	20-49	
	4	<20	<20	
		Brazil	England	
	Points	Definition by: Creatinine (mg/dL) or Urinary Output (mL)	Definition by: Creatinine (µmol/L) or Urinary Output (mL)	
Renal	0	sCr <1.2	sCr <110	
	1	sCr 1.2-1.9	sCr 110-170	
	2	sCr 2.0-3.4	sCr 171-299	
	3	sCr 3.5-4.9 or UO<500 ml/24h	sCr 300-440 or UO<500 ml/24h	
	4	sCr ≥5.0 or UO≤ 200ml/24h	sCr >440 or UO≤ 200ml/24h	
		Brazil	England	
	Points	Definition by: Glasgow Coma Scale	Definition by: Glasgow Coma Scale	Or Sedated/paralyzed
Neurological	0	15	15	
	1	13-14	13-14	
	2	10-12	10-12	X
	3	6-9	6-9	X
	4	<6	<6	X

For those sedated/mechanically ventilated, the GCS calculated was the GCS immediately before sedation/intubation

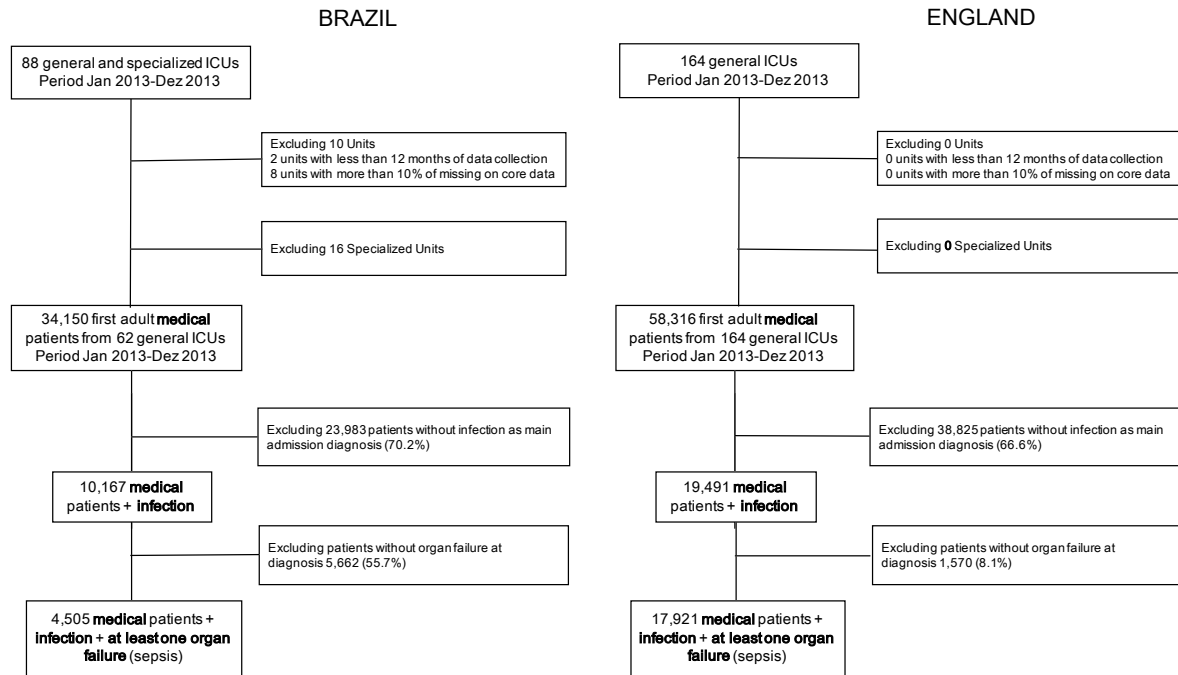
Note: Hepatic organ dysfunction was not available in both cohorts.

Advanced cardiovascular support is used as part of the critical care minimum dataset collection in ICUs in England. Advanced cardiovascular support is indicated by one or more of the following: Multiple intravenous vasoactive and/or rhythm controlling drugs when used simultaneously to support or control arterial pressure, cardiac output or organ / tissue perfusion, (e.g. inotropes, amiodarone, nitrates); Continuous observation of cardiac output and derived indices (e.g. pulmonary artery catheter, lithium dilution, pulse contour analyses, oesophageal Doppler, impedance and conductance methods); Intra-aortic balloon pumping and other assist devices and/or Insertion of a temporary cardiac pacemaker (criteria valid for each day of therapeutic connection to a functioning external pacemaker unit). Importantly, to qualify for advanced support status, at least one drug needs to be vasoactive. In our cohort 98% of patients had vasoactive drugs meeting the cardiovascular SOFA criteria.

eTable3: Site of infection definition in Brazil and England

	Brazil	England
Database	ORCHESTRA study / Epimed system	ICNARC
Coding	<p>The site of infection was determined clinically at the moment of ICU admission, following hierarchical codes(1). The hierarchy starts by classifying the admission as (a) medical, elective surgery or emergency/urgent surgery. Based on the initial classification, a list of (b) main reasons for admission is available, comprising several categories, including infection. Within each main category (e.g. infection), (c) there is a list of pre-specified diagnoses which for infection refers to sites of infection (e.g., pneumonia, meningitis, etc).</p>	<p>Diagnostic data are determined clinically at admission and coded using the hierarchical ICNARC Coding Method(2). The hierarchy has 5 tiers: (a) surgical status (coded as surgical versus non-surgical); (b) organ system (coded as respiratory, cardiovascular, neurological, genitourinary, endocrine/metabolic, haematological, musculoskeletal, dermatologic); (c) anatomical site (such as lung, bronchi for respiratory system); (d) process leading to admission (such as infection, trauma) and (e) clinical condition (such as bacterial pneumonia). A code is automatically generated that represents a patient's clinical diagnosis route through this hierarchy. All patients registered in ICNARC database participating ICU's are mandated to provide at least one coded reason for each hierarchy.</p>

eFigure1. Study flowchart for the Brazil and England cohorts



eTable4: Sepsis-specific patient characteristics and length of stay stratified by ICU and hospital mortality.

	England (n=17,921)	Brazil (n=4,505)
Sepsis-specific patient characteristics		
Number of organ dysfunctions within first 24h		
Median number (IQR)	2 (1-3)	1 (1-2)
1	5881 (32.8%)	2474 (54.9%)
2	5852 (32.6%)	1205 (26.8%)
3	3935 (22.0%)	577 (12.8%)
4	1856 (10.4%)	220 (4.9%)
5	397 (2.2%)	29 (0.6%)
Type of organ dysfunction and combinations¹		
Respiratory (only)	4317 (24.1%)	449 (10.0%)
Cardiovascular (only)	185 (1.0%)	419 (9.3%)
Renal (only)	749 (4.2%)	598 (13.3%)
Hematological (only)	281 (1.6%)	356 (7.9%)
Neurological (only)	349 (2.0%)	652 (14.5%)
Respiratory + Cardiovascular	1089 (6.1%)	294 (6.5%)
Respiratory + Neurological	1686 (9.4%)	200 (4.4%)
Cardiovascular + Renal	217 (1.2%)	157 (3.5%)
Respiratory + Cardiovascular + Neurological	998 (5.6%)	210 (4.7%)
Respiratory + Cardiovascular + Renal	989 (5.5%)	153 (3.4%)
Respiratory + Cardiovascular + Renal + Neurological	991 (5.5%)	123 (2.7%)
ICU mortality	5496 (30.7%)	1431 (31.8%)
ICU Length of stay, days		
Overall		
Mean (SD)	8.2 (10)	10.5 (13)
Median (IQR)	5 (3-10)	6 (4-12)
ICU survivors		
Mean (SD)	9.1 (11)	9.8 (11)
Median (IQR)	6 (3-10)	6 (4-11)
ICU non-survivors		
Mean (SD)	6.3 (9)	12.1 (16)
Median (IQR)	3 (2-8)	7 (3-15)
Hospital mortality	7045 (39.3%)	1867 (41.4%)
Hospital Length of stay, days		
Overall		
Mean (SD)	23.6 (30)	26.8 (38)
Median (IQR)	15 (8-29)	16 (8-31)
ICU survivors		
Mean (SD)	29.1 (33)	26.2 (33)
Median (IQR)	19 (11-36)	16 (9-30)
ICU non-survivors		
Mean (SD)	15.2 (20)	27.7 (44)
Median (IQR)	9 (3-19)	15 (6-32)

¹Organ dysfunction combinations with at least 100 occurrences in both datasets in the first 24 hours following ICU admission (Totals were 11,851 (66%) patients from England and 3,611 (80%) patients from Brazil)

eTable 5: Adjusted multilevel logistic regression models for the country effect (Brazil versus England) on sepsis hospital mortality (sensitivity analysis)

Model	Exposure	OR (95% CI)	P value	AUROC	Brier score
Main analysis					
All patients (n=22061)					
Model 1 – Baseline model	Brazil/England	1.12 (0.98-1.30)	0.105	0.608 (0.600-0.615)	0.2303
Model 2 – Adjusted for general characteristics ¹	Brazil/England	0.88 (0.75-1.02)	0.089	0.712 (0.705-0.719)	0.2082
Model 3A – Adjusted for general + sepsis-specific characteristics (site of infection and type of organ dysfunction) ²	Brazil/England	1.22 (1.05-1.43)	0.010	0.784 (0.778-0.790)	0.1838
Model 3B – Adjusted for general + sepsis-specific characteristics (site of infection and number of organ dysfunction) ³	Brazil/England	1.40 (1.22-1.62)	<0.001	0.777 (0.771-0.783)	0.1864
Sensitivity analysis					
Without chronic comorbidities (n=17368)					
Model 1 – Baseline model	Brazil/England	1.01 (0.87-1.18)	0.853	0.602 (0.595-0.610)	0.2326
Model 4 – Adjusted for general characteristics ⁴	Brazil/England	0.77 (0.65-0.91)	0.002	0.711 (0.704-0.719)	0.2022
Model 5A – Adjusted for general + sepsis-specific characteristics (site of infection and type of organ dysfunction) ⁵	Brazil/England	1.11 (0.93-1.32)	0.239	0.788 (0.781-0.795)	0.1773
Model 5B – Adjusted for general + sepsis-specific characteristics (site of infection and number of organ dysfunction) ⁶	Brazil/England	1.29 (1.10-1.51)	0.002	0.780 (0.773-0.787)	0.1801
With immunocompromised comorbidities not grouped (n=22061)					
Model 1 – Baseline model	Brazil/England	1.12 (0.98-1.30)	0.105	0.608 (0.600-0.615)	0.2303
Model 6 – Adjusted for general characteristics ⁷	Brazil/England	0.84 (0.73-0.98)	0.029	0.714 (0.707-0.721)	0.2077
Model 7A – Adjusted for general + sepsis-specific characteristics (site of infection and type of organ dysfunction) ⁸	Brazil/England	1.18 (1.01-1.37)	0.037	0.785 (0.779-0.791)	0.1834
Model 7B – Adjusted for general + sepsis-specific characteristics (site of infection and number of organ dysfunction) ⁹	Brazil/England	1.35 (1.17-1.56)	<0.001	0.778 (0.772-0.784)	0.1859

¹ Adjusted for age (restricted cubic spline), sex, cardiovascular, respiratory, renal, hepatic comorbidities, immunocompromised, functional status and, admission source and time from hospitalization to ICU admission (restricted cubic spline)

² Adjusted for characteristics in model 2 + site of infection and type of organ dysfunction and first-order interaction between each organ dysfunction system

³ Adjusted for characteristics in model 2 + site of infection and number of organ dysfunctions (Number of organ failures entered as factors)

⁴ Adjusted for age (restricted cubic spline), sex, functional status and, admission source and time from hospitalization to ICU admission (restricted cubic spline)

⁵ Adjusted for characteristics in model 4 + site of infection and type of organ dysfunction and first-order interaction between each organ dysfunction system

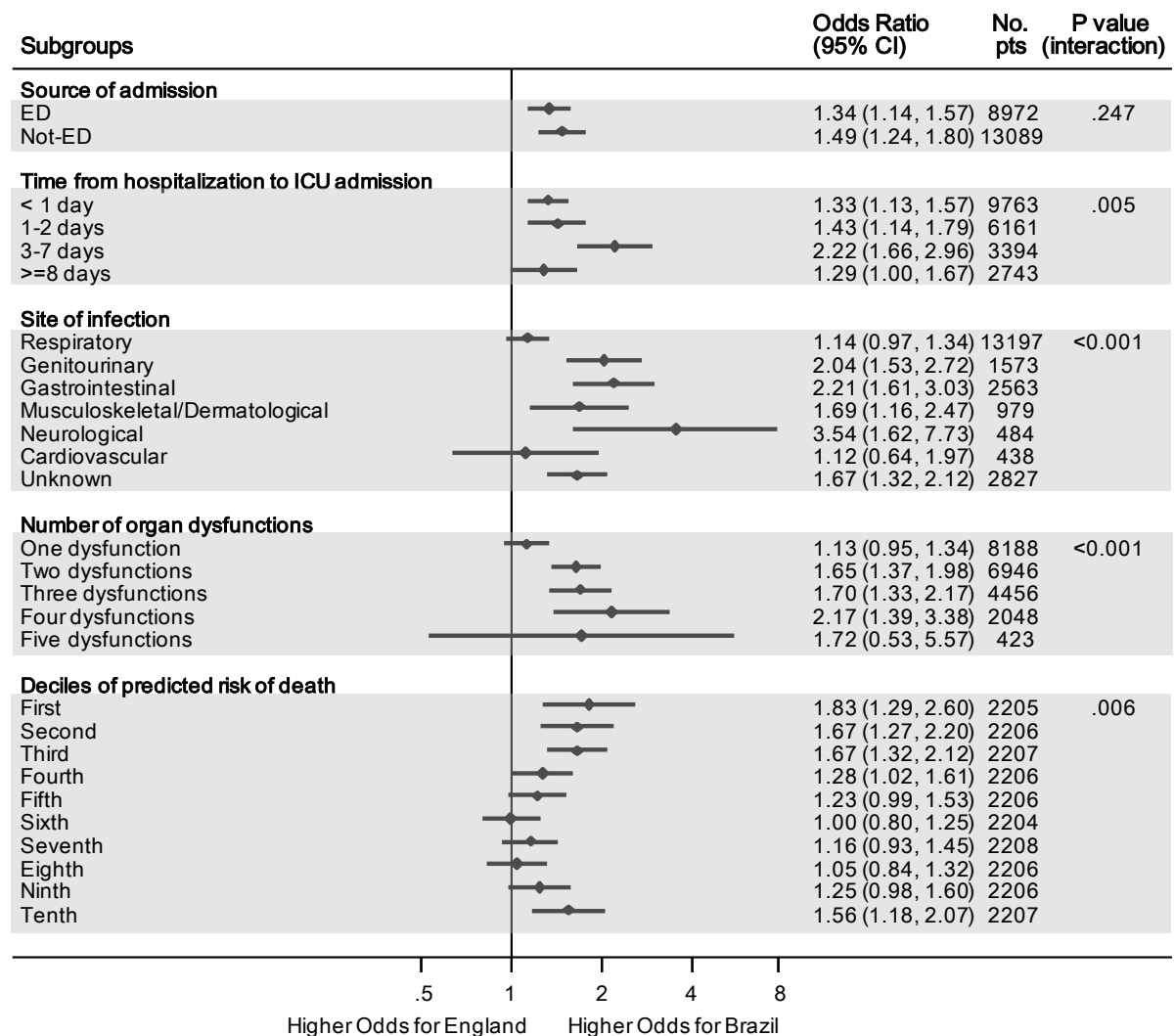
⁶ Adjusted for characteristics in model 4 + site of infection and number of organ dysfunctions (Number of organ failures entered as factors)

⁷ Adjusted for age (restricted cubic spline), sex, cardiovascular, respiratory, renal, hepatic comorbidities, haematological malignancy, AIDS, metastatic disease (solid neoplasia), steroid use, functional status and, admission source and time from hospitalization to ICU admission (restricted cubic spline)

⁸ Adjusted for characteristics in model 6 + site of infection and type of organ dysfunction and first-order interaction between each organ dysfunction system

⁹ Adjusted for characteristics in model 6 + site of infection and number of organ dysfunctions (Number of organ failures entered as factors)

eFigure2: Effect modification of country effect on hospital mortality and by pre-specified subgroups and deciles of the predicted risk from the Model 3-B



eTable6: Effect modification of country effect on hospital mortality and by pre-specified subgroups in the Model 3-A

Stratified by	Country	Events/ subtotal (%)	Stratum-specific adjusted OR (95%CI)	P value for interaction
Source of Admission				
Emergency department	England	2038/5874 (34.7%)	1 (Reference)	0.176
	Brazil	1099/3098 (35.5%)	1.17 (0.99-1.38)	
Not emergency department	England	4966/11963 (41.5%)	1 (Reference)	
	Brazil	647/1126 (57.5%)	1.34 (1.09-1.63)	
Time from hospitalization to ICU admission				
<1 day	England	2451/7195 (34.1%)	1 (Reference)	0.003
	Brazil	833/2568 (32.4%)	1.16 (0.98-1.37)	
1-2 days	England	2021/5407 (37.4%)	1 (Reference)	
	Brazil	318/754 (42.2%)	1.23 (0.98-1.55)	
3-7 days	England	1318/3032 (43.5%)	1 (Reference)	
	Brazil	241/362 (66.6%)	1.96 (1.46-2.64)	
≥8 days	England	1214/2203 (55.1%)	1 (Reference)	
	Brazil	354/540 (65.6%)	1.07 (0.82-1.40)	
Site of infection				
Respiratory	England	4457/11025 (40.4%)	1 (Reference)	<0.001
	Brazil	956/2172 (44.0%)	0.98 (0.83-1.16)	
Genitourinary	England	191/863 (22.1%)	1 (Reference)	
	Brazil	204/710 (28.7%)	1.76 (1.32-2.36)	
Gastrointestinal	England	878/2290 (38.3%)	1 (Reference)	
	Brazil	121/273 (44.3%)	1.89 (1.36-2.61)	
Musculoskeletal/Dermatological	England	259/738 (35.1%)	1 (Reference)	
	Brazil	81/241 (33.6%)	1.64 (1.11-2.43)	
Neurological	England	77/444 (17.3%)	1 (Reference)	
	Brazil	17/40 (42.5%)	3.18 (1.46-6.94)	
Cardiovascular	England	147/347 (42.4%)	1 (Reference)	
	Brazil	40/91 (44.0%)	1.02 (0.57-1.82)	
Unknown	England	995/2130 (46.7%)	1 (Reference)	
	Brazil	327/697 (46.9%)	1.42 (1.12-1.82)	

[Abbreviations: n=number; % –percentage; 95% CI: 95% Confidence intervals]

eTable7: Effect modification of country effect on hospital mortality and by pre-specified subgroups for hospital mortality in the Model 3-B

Stratified by	Country	No. events/subtotal (%)	Stratum-specific adjusted OR (95% CI)	P value for interaction
Source of Admission				
Emergency department	England	2038/5874 (34.7%)	1 (Reference)	0.247
	Brazil	1099/3098 (35.5%)	1.34 (1.14-1.57)	
Not emergency department	England	4966/11963 (41.5%)	1 (Reference)	
	Brazil	647/1126 (57.5%)	1.49 (1.24-1.80)	
Time from hospitalization to ICU admission				
<1 day	England	2451/7195 (34.1%)	1 (Reference)	0.005
	Brazil	833/2568 (32.4%)	1.33 (1.13-1.57)	
1-2 days	England	2021/5407 (37.4%)	1 (Reference)	
	Brazil	318/754 (42.2%)	1.43 (1.14-1.78)	
3-7 days	England	1318/3032 (43.5%)	1 (Reference)	
	Brazil	241/362 (66.6%)	2.22 (1.66-2.96)	
≥8 days	England	1214/2203 (55.1%)	1 (Reference)	
	Brazil	354/540 (65.6%)	1.29 (1.00-1.67)	
Site of infection				
Respiratory	England	4457/11025 (40.4%)	1 (Reference)	<0.001
	Brazil	956/2172 (44.0%)	1.14 (0.97-1.34)	
Genitourinary	England	191/863 (22.1%)	1 (Reference)	
	Brazil	204/710 (28.7%)	2.04 (1.53-2.72)	
Gastrointestinal	England	878/2290 (38.3%)	1 (Reference)	
	Brazil	121/273 (44.3%)	2.21 (1.61-3.03)	
Musculoskeletal/Dermatological	England	259/738 (35.1%)	1 (Reference)	
	Brazil	81/241 (33.6%)	1.69 (1.16-2.47)	
Neurological	England	77/444 (17.3%)	1 (Reference)	
	Brazil	17/40 (42.5%)	3.54 (1.62-7.73)	
Cardiovascular	England	147/347 (42.4%)	1 (Reference)	
	Brazil	40/91 (44.0%)	1.12 (0.64-1.98)	
Unknown	England	995/2130 (46.7%)	1 (Reference)	
	Brazil	327/697 (46.9%)	1.67 (1.32-2.12)	
Number of organ dysfunctions				
1	England	1373/5855 (23.5%)	1 (Reference)	<0.001
	Brazil	597/2333 (25.6%)	1.13 (0.95-1.34)	
2	England	2080/5830 (35.7%)	1 (Reference)	
	Brazil	577/1116 (51.7%)	1.65 (1.37-1.98)	
3	England	2001/3911 (51.2%)	1 (Reference)	
	Brazil	377/545 (69.2%)	1.70 (1.33-2.17)	
4	England	1247/1846 (67.6%)	1 (Reference)	
	Brazil	171/202 (84.7%)	2.17 (1.39-3.37)	
5	England	303/395 (76.7%)	1 (Reference)	
	Brazil	24/28 (85.7%)	1.72 (0.53-5.56)	

[Abbreviations: n=number; % –percentage; 95% CI: 95% Confidence intervals]

eTable8: Effect modification of country effect on hospital mortality and by deciles of the predicted risk from the Model 3-A

Stratified by	Country	No. events/ subtotal	Stratum-specific adjusted OR (95% CI)	P value for interaction
Deciles risk				
1.9-11.3%	England	87/1667 (5.2%)	1 (Reference)	0.031
	Brazil	49/538 (9.1%)	1.82 (1.26-2.62)	
11.3-17.6%	England	215/1808 (11.9%)	1 (Reference)	
	Brazil	68/399 (17.0%)	1.52 (1.13-2.05)	
17.6-23.5%	England	374/1825 (20.5%)	1 (Reference)	
	Brazil	97/381 (25.5%)	1.33 (1.03-1.71)	
23.5-29.6%	England	508/1816 (28.0%)	1 (Reference)	
	Brazil	115/390 (29.5%)	1.08 (0.85-1.37)	
29.6-36.7%	England	646/1790 (36.1%)	1 (Reference)	
	Brazil	155/415 (37.4%)	1.06 (0.85-1.32)	
36.7-44.0%	England	739/1815 (40.7%)	1 (Reference)	
	Brazil	162/392 (41.3%)	1.03 (0.82-1.28)	
40.0-52.2%	England	883/1783 (49.5%)	1 (Reference)	
	Brazil	206/423 (48.7%)	0.97 (0.78-1.20)	
52.2-61.8%	England	1032/1815 (56.9%)	1 (Reference)	
	Brazil	217/391 (55.5%)	0.95 (0.76-1.18)	
61.8-73.3%	England	1176/1822 (64.5%)	1 (Reference)	
	Brazil	266/384 (67.3%)	1.24 (0.98-1.57)	
73.3-98.2%	England	1344/1696 (79.3%)	1 (Reference)	
	Brazil	411/511 (80.4%)	1.08 (0.84-1.38)	

[Abbreviations: n=number; % –percentage; 95% CI: 95% Confidence intervals]

eTable9: Effect modification of country effect on hospital mortality and by deciles of the predicted risk from the Model 3-B

Stratified by	Country	No. events/ subtotal	Stratum-specific adjusted OR (95% CI)	P value for interaction
Deciles risk				
2.5-12.1%	England	88/1618 (5.4%)	1 (Reference)	0.006
	Brazil	56/587 (9.5%)	1.83 (1.29-2.60)	
12.1-18.4%	England	210/1753 (12.0%)	1 (Reference)	
	Brazil	84/453 (18.5%)	1.67 (1.27-2.21)	
18.4-24.5%	England	387/1789 (21.6%)	1 (Reference)	
	Brazil	132/418 (31.6%)	1.67 (1.32-2.12)	
24.5-30.6%	England	486/1778 (27.3%)	1 (Reference)	
	Brazil	139/428 (32.5%)	1.28 (1.02-1.61)	
30.6-37.1%	England	621/1788 (34.7%)	1 (Reference)	
	Brazil	165/418 (39.5%)	1.23 (0.99-1.53)	
37.1-43.9%	England	745/1809 (41.2%)	1 (Reference)	
	Brazil	163/395 (41.3%)	1.00 (0.80-1.25)	
43.9-51.8%	England	871/1825 (47.7%)	1 (Reference)	
	Brazil	197/383 (51.4%)	1.16 (0.93-1.45)	
51.8-61.0%	England	1043/1842 (56.6%)	1 (Reference)	
	Brazil	210/364 (57.7%)	1.05 (0.83-1.31)	
61.0-72.2%	England	1178/1858 (63.4%)	1 (Reference)	
	Brazil	238/348 (68.4%)	1.25 (0.98-1.60)	
72.2-97.8%	England	1375/1777 (77.4%)	1 (Reference)	
	Brazil	362/430 (84.2%)	1.56 (1.17-2.06)	

[Abbreviations: n=number; % –percentage; 95% CI: 95% Confidence intervals]

1. Zampieri FG, Soares M, Borges LP, et al. The Epimed Monitor ICU Database(R): a cloud-based national registry for adult intensive care unit patients in Brazil. *Rev Bras Ter Intensiva* 2017;29(4):418-426.
2. Shankar-Hari M, Harrison DA, Rowan KM. Differences in Impact of Definitional Elements on Mortality Precludes International Comparisons of Sepsis Epidemiology-A Cohort Study Illustrating the Need for Standardized Reporting. *Crit Care Med* 2016;44(12):2223-2230.