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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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Abstract

Objective: To test whether differences in both general and sepsis-specific patient characteristics explain the observed differences in sepsis mortality between countries, using two national critical care (ICU) databases.

Design: Cohort study.

Setting: We analyzed 62 and 164 ICUs in Brazil and England, respectively.

Patients: 22,426 adult ICU admissions from January 2013 to December 2013.

Interventions: None.

Measurements and Main Results: After harmonizing relevant variables, we merged the first ICU episode of adult medical admissions from Brazil (ORCHESTRA study) and England (ICNARC Case Mix Programme). Sepsis-3 definition was used and the primary outcome was hospital mortality. We used multilevel logistic regression models to evaluate the impact of country (Brazil versus England) on mortality, after adjustment for general (age, sex, comorbidities, functional status, admission source, time to admission) and sepsis-specific (site of infection, organ dysfunction (OD) type and number) patient characteristics. Of medical ICU admissions, 13.2% (4,505/34,150) in Brazil and 30.7% (17,921/58,316) in England met the sepsis definition. The Brazil cohort was older, had greater prevalence of severe comorbidities and dependency compared with England. Respiratory was the most common infection site in both countries. The most common OD was cardiovascular in Brazil (41.2%) and respiratory in England (85.8%). Crude hospital mortality was similar (Brazil 41.4% versus England 39.3%, OR=1.12 [0.98-1.30]). After adjusting for general patient characteristics, there was an important change in the point-estimate of the odds ratio (OR=0.88 [0.75-1.02]). However, after adjusting for sepsis-specific patient characteristics, the direction of effect reversed again with Brazil having higher risk-adjusted mortality (OR=1.22 [1.05-1.43]).

Conclusions Patients with sepsis admitted to ICUs in Brazil and England have important differences in general and sepsis-specific characteristics, from source of admission to organ dysfunctions. We show that comparing crude mortality from sepsis patients admitted to the ICU between countries, as currently performed, is not reliable and that the adjustment for both general and sepsis-specific patient characteristics is essential for valid international comparisons of mortality amongst sepsis patients admitted to critical care units.

Keywords: sepsis; intensive care; epidemiology; outcomes; international; heterogeneity

Introduction

Sepsis is defined as life-threatening organ dysfunction due to dysregulated host response to infection(1, 2). Recently, the World Health Organization (WHO) recognized sepsis as a global health priority, highlighting the importance of accurate international benchmarking to inform regional health policy(3). The key drivers for this WHO resolution include a high extrapolated global sepsis burden of 15 to 20 million cases per annum(4, 5) and the 26% average hospital mortality with sepsis-related critical illness(5). There are several global initiatives to address the high mortality from sepsis(6, 7), but little consensus on how best to do international comparisons.

The crude hospital mortality from sepsis varies significantly between countries in prevalence studies(5, 8-10). This variation in mortality has been linked to differences in critical care (ICU) provision(11, 12), case definition(13), sepsis incidence(9), economic region(8) and to differences in guideline compliance(10, 14-16). In this scenario, Brazil and England have important differences, such as higher critical care bed availability per population in Brazil (13 per 100,000 inhabitants) compared with England (3.5–7.4 per 100,000 inhabitants)(17). These between countries differences highlight the need for standardized benchmarking to compare sepsis mortality, because crude mortality comparisons would be not accurate(5, 17).

At the patient level, both general **patients characteristics** (such as age, sex, presence of comorbidities) and sepsis-specific **characteristics** (such as site of infection and number and type of organ dysfunction) are important determinants of mortality in septic

patients(17-19). However, lack of readily available calibrated risk prediction models and agreed risk adjustment methods that are easy to implement across countries, precludes risk-adjusted mortality comparisons between countries. Added to this is the heterogeneity observed among patients with sepsis, which presents a further challenge in designing risk-adjusted mortality comparisons(17, 20). Together with incorporating new biomarkers and deriving phenotypes(20), another approach uses main determinants of the syndrome sepsis, such as site of infection and associated organ dysfunction, to account for sepsis heterogeneity(17).

It is feasible to do comparisons between countries using national level databases(21) and it is also feasible to collect general and sepsis-specific patient characteristics accurately across countries(8, 9). In this context, we hypothesized that a sequential adjustment for general and for sepsis-specific patient characteristics would illustrate the limitations of comparing crude mortality rates. To test this hypothesis, we harmonized two ICU databases from Brazil and England, with the first ICU episode for adult medical admissions with sepsis in 2013. We report crude, stratified and adjusted hospital mortality comparisons between the two countries, incrementally adjusting for general, and then for sepsis-specific, patient characteristics.

Methods

Data sources and funding

We used two national ICU databases to identify sepsis cohorts from Brazil and England admitted in 2013. The ORCHESTRA (ORganizational CHaractEeriSTics in cRitcal cAre)

study was a multicenter retrospective cohort study of critical care organization in 11 Brazilian states coordinated by the Department of Critical Care at the D'Or Institute for Research and Education. The data was collected by dedicated and trained staff through the Epimed Monitor System® (Epimed Solutions®, Rio de Janeiro, Brazil)(22). During selection of ICUs for ORCHESTRA, six ICUs with >10% of missing data on core variables (age, ICU admission diagnosis, ICU and hospital length of stay (LOS) and hospital mortality) and two ICUs with <12 months of patient data were excluded, resulting in 78 ICUs at 51 hospitals (46 private and 5 public) with available data. For this study, we excluded 16 specialized ICUs (e.g., cardiothoracic, neurological, etc) resulting in 62 general ICUs in Brazil sepsis cohort. The Intensive Care National Audit & Research Centre Case Mix Programme database (ICNARC-CMPD) is the national clinical audit for adult general ICUs in England. This database includes data from 164 ICUs in England. The data are collected by dedicated and trained staff to a defined dataset specification including the hierarchical ICNARC Coding Method(23). All 164 ICUs in England had $\leq 10\%$ of missing data on core variables and contributed ≥ 12 months of patient data. Both these high-quality ICU databases collect sociodemographic, comorbidity, physiological and outcomes data for consecutive ICU admissions to precise rules and definitions. Both databases undergo extensive data validation; the details of which have been reported previously(22, 23). Local Ethics Committee at the Instituto D'Or de Pesquisa (Parecer: 334.835) and the Brazilian National Ethics Committee (CAAE: 19687113.8.1001.5249) approved the ORCHESTRA study. Support for the collection and use of the ICNARC-CPMD data has been obtained under Section 251 of the National Health Service Act 2006 (approval number: PIAG 2–

10(f)/2005).

Harmonization of datasets

We used a flexible harmonization method(24). First, we defined, *a priori*, the target variables necessary to test our hypothesis. The data collection forms and data dictionaries from ORCHESTRA and the ICNARC-CMPD datasets were then assessed and consensus achieved on the target variables that could be reliably determined and mapped in both datasets. Both datasets were separately prepared, quality checked and anonymized using the same algorithm to generate the harmonized variables and a merged dataset that included **country** as a categorical variable. Harmonization steps were conducted before any statistical analysis.

Patients and variables in the harmonized dataset

We included the first ICU admission for adult (≥ 16 years) medical (non-surgical) **patients** with sepsis to adult general ICUs between 1 January and 31 December 2013. We excluded patients transferred in from other hospitals, and patients admitted to specialized ICUs (e.g. cardiothoracic, neurological/neurosurgical and stand-alone high dependency units).

General patient characteristics included age, sex, comorbidities, **functional status**, source of admission and time from hospital to ICU admission. Comorbidities were based on the APACHE II definitions in the ICNARC-CMPD and the Charlson comorbidity index in the ORCHESTRA study. We classified patients' **functional status** in two categories: independent and partially or fully dependent (eTable-1). Sepsis-specific patient characteristics included site of infection, number and type of organ

dysfunction(17). Sepsis was defined as infection and ≥ 2 points in any individual domain of the Sequential Organ Failure Assessment (SOFA) score using data from the first 24h of ICU admission (eTable-2). Site of infection was determined at ICU admission and coded using hierarchical codes in both datasets (eTable-3).

Statistical analysis

The primary exposure was country (Brazil or England) and the primary outcome was hospital mortality. The analysis plan was finalized prior to any analysis.

We used three sequential random effects, multilevel logistic regression models to evaluate the impact of country on hospital mortality. First, we fitted a baseline model with the country (Brazil/England) as a fixed effect and ICU as random effect (model-1). Second, to model-1, we added all general patient characteristics (age, sex, comorbidities, functional status, source of ICU admission, and time from hospital admission to ICU admission) (model-2). Third, to model-2, we added sepsis-specific patient characteristics (site of infection and organ dysfunctions representing acute illness severity) (model-3). We ran the same three sequential models in two sensitivity analyses: 1) in the subpopulation of patients without chronic comorbidities, to evaluate the potential impact of SOFA definition in patients with chronic organ dysfunction; 2) handling the immunosuppression category as originally entered in the database, to evaluate the potential different prognostic impact of each immunosuppressed category. Because of the multicollinearity between type and number of organ dysfunctions, we assessed the impact of organ dysfunction in two different ways: first, in model-3A we adjusted only for the types of organ dysfunctions and their first order interactions and second, in model-3B, we adjusted only for the number of organ dysfunctions. Age and

time from hospital admission to ICU admission were fitted using restricted cubic splines to deal with non-linear associations in all models. The potential for effect modification of the effect of country on outcome was explored by adding interaction terms between country and the following pre-specified covariates in model-3: source of admission (emergency department versus other), time from hospital admission to ICU admission (<1 day, 1-2 days, 3-7 days, ≥8 days) and site of infection, type of organ dysfunction (model-3A) or number of organ dysfunctions (model-3B). Finally, we explored the interaction between country effect and baseline predicted risk of hospital mortality using the linear predictor of fixed effects from model-3.

We used Wald tests for all hypothesis testing. As the amount of missing data at individual patient level for all non-core variables was expected to be low (<5%), the primary analysis was complete case analysis. Continuous variables are presented as mean (SD) for those that were not skewed and median [IQR] for those skewed. Categorical variables are presented as counts and percentages. All analyses were performed using Stata/SE Version 13.0 (StataCorp LP, College Station, TX).

Results

Patient selection

Over the study period, amongst the 34,150 and 58,316 adult medical ICU admissions, 10,167 (29.8%) and 19,491 (33.4%) patients had infection as the main reason for admission to ICUs in Brazil and England, respectively. From these cohorts, we included 4,505/10,167 (44.3%) patients with sepsis from Brazil and 17,921/19,491 (92.0%) from

England **who had organ failure and met the sepsis criteria** (eFigure1). There were 22,061 (98.4%) sepsis patients for complete case analysis.

General characteristics

Sepsis admissions to ICUs in Brazil were older, with greater prevalence of comorbidities and impaired **functional status**. The **most common** source of admission to ICU in Brazil was the emergency department (ED) (N=3,250; 72.1%) and the general ward (N=11,023; 61.5%) in England. Sepsis patients admitted to ICUs in Brazil spent a longer pre-ICU admission period either in the ED or on the ward compared with sepsis admissions to ICUs in England (Table1).

Sepsis specific characteristics

The **most common** infection source amongst ICU admissions with sepsis was respiratory for both countries. Genitourinary as an infection source was 3.5 times more common in Brazil and gastrointestinal was twice as common in England. The percentage of sepsis admissions with single organ dysfunction was higher in Brazil (54.9% versus 32.8%), whilst those with two, three, four and five organ dysfunctions were higher in England. Cardiovascular was the most common organ dysfunction in Brazil (41.2%) and respiratory was the most common organ dysfunction in England (85.8%) (Table1, eTable3).

Mortality

The crude hospital mortality for all medical ICU patients and for infected ICU patients was lower for Brazil compared to England (18.6% vs. 30.6% for medical; 27.1% vs.

37.2% for infected patients). In contrast, the crude hospital mortality for ICU sepsis admissions was comparable between Brazil (41.4%) and England (39.3%). However, when stratified by source of admission, site of infection, type, number and combinations of organ dysfunction, sepsis admissions to ICUs in Brazil had higher crude mortality (Table2, Figure1). Overall, ICU and hospital LOS were similar between countries, however, non-survivors had greater ICU and hospital LOS in Brazil compared with England (eTable3).

Impact of sequential risk factor adjustment with multilevel logistic regression models

There was no statistically significant difference in the crude mortality between the two countries (crude OR 1.12 [0.98-1.30] for Brazil versus England, $p=0.11$, model-1). After adjusting for general patient characteristics, there was a change in the point estimate of the OR, which highlighted that the general patient characteristics confounded the sepsis-mortality relationship (adjusted OR 0.88 [0.75-1.02] for Brazil versus England, $p=0.09$, model-2). When we adjusted for general and for sepsis-specific patient characteristics, the point estimate reversed, with sepsis admissions in Brazil having significantly greater odds of hospital death compared with England (model-3A: adjusted OR 1.22 [1.05-1.43], $p=0.01$; model-3B: adjusted OR 1.40 [1.22-1.62], $p<0.01$; Table3). The two sensitivity analyses showed similar phenomena in the reversal of the point-estimate of the association when adjusting for general and sepsis-specific characteristics (eTable5).

Effect modifiers of the country effect on mortality

The country effect also varied with time from hospitalization to ICU admission, site of infection, type and number of organ dysfunctions strata, implying effect modification of these variables in the sepsis-mortality relationship (Figure2 and eFigure2; eTable6; eTable7). Brazil had worse outcomes for those with very low- and very-high predicted risk of hospital death, which implies interaction between country effect and baseline predicted risk of death (Figure3, eFigure2, eTable8; eTable9).

Discussion

We report the first study testing the impact of general and sepsis-specific patient characteristics, whilst accounting for country effect, in the sepsis-mortality relationship, using harmonized raw patient-level clinical data from two high quality ICU databases. Brazil had a greater prevalence of patients with sepsis-specific characteristics associated with lower risk of death such as genitourinary infection and single organ dysfunction and a greater prevalence of patients with general patient characteristics associated with higher risk of death such as older age, comorbidities and impaired functional status. Although the overall crude hospital mortality was similar between Brazil and England, there were major differences in the stratified hospital mortality. Brazil had a significantly higher adjusted risk of death from sepsis when general and sepsis-specific patient characteristics were accounted for.

The framework for international comparisons of sepsis cohorts presented in this study addresses the challenges highlighted with crude comparisons(17) and provides novel

data towards 2017 WHO agenda(3, 25) - *on the need for better evaluation tools for global sepsis epidemiology*. As illustrated in our two national cohorts, sepsis-specific patient characteristics such as site of infection, the number and types of organ dysfunctions are likely to vary between health care systems/countries. Therefore, it is expected that general prognostic models such as APACHE II, where sepsis might be a single category weighted by a single coefficient, **are** not enough to capture the impact of the variation of sepsis-specific patient characteristics on mortality. Our model accounted for those important variables, used commonly collected variables and used two accessible modelling strategies to enhance the adjustments: (1) for sepsis-specific patient characteristics, by including a first order interaction between organ dysfunctions and (2) for unmeasured variability at the health unit level, by including random intercepts for each unit(17). Nevertheless, it is possible that a more complex model, allowing for other acute physiological derangements, could improve the adjustments between cohorts.

The strong impact of sepsis-specific characteristics on the country-associated hospital mortality also must be highlighted. Indeed, sepsis from neurological infections and those patients with increasing number of organ dysfunctions seem to drive the change on the direction of the OR after adjusting for general and sepsis-specific characteristics. This should be further evaluated, but it might represent differences in health practices within each country, such as clinical suspicion and organ support indications. Moreover, it might be informative for international benchmarking, highlighting room for improvement in specific sepsis diagnosis and care areas.

Our study has strengths. We harmonized data variables between two representative national ICU databases(22, 23), using similar definitions(24), over the same period and explicitly tested for country effect after adjusting for key confounders(26). We developed our statistical analysis plans blinded to country level outcome data. The harmonization of data variables and application of hierarchical multilevel regression analysis, allowing for random effects, is methodologically robust for testing our research question(27). We used previously reported sepsis-specific patient characteristics and current knowledge from sepsis epidemiology for adjustment and comparison between cohorts(17). Importantly, the proposed adjustment based on target variables for general and for sepsis-specific patient characteristics are feasible and reproducible, both fundamental features for international comparisons, and for informed benchmarking.

Our study has several limitations. Although neither ICU database was set up for exploring sepsis epidemiology, they are appropriate to inform how adjustment for both general and sepsis-specific patient characteristics could improve upon the crude mortality comparisons often reported. There is no “gold-standard” for international comparisons of sepsis epidemiology(17). However, we illustrate that outcome variability is partially related to differences in type of sepsis patients cared between Brazil and England. Thus, such comparisons are feasible, and our hypothesis driven risk-adjustment proposal provides a valid starting point to generate between country estimates for external benchmarking. We used our previously published feasible risk adjustment methods(17), including variables commonly measured in the ICUs that are

well-known risk factors for sepsis mortality, and illustrate the impact of sequential adjustment for general and for sepsis-specific patient characteristics. Nevertheless, we made minor adaptations in the comorbidities and SOFA definitions to harmonize both datasets. We believe these adaptations might have introduced some degree of non-differential misclassification, according to the flexible harmonization approach(24). We could not measure access to the health system, the ICU capacity strain during the period, do-not resuscitate practices, refused admissions to critical care and discharge practices. The finding that lower- and higher-risk patients have worse outcomes in the Brazilian cohort might reflect differences in these factors. Restricted by available data in the ICU databases, we could not generalize our findings to sepsis patients treated outside the ICU, however we applied a standardized sepsis definition in patients admitted to general ICUs, strengthening our internal validity. We applied a modified version of the SOFA score, missing the liver domain. However, the expected incidence of liver dysfunction is low in adult general ICUs and commonly occurs simultaneously with other organ dysfunctions, such that we anticipate that we may have missed only very small differences between the cohorts. Finally, we compared two countries for this case-study and explored the **country variable** as a fixed effect. If more countries were to be evaluated, it may be advisable to consider a random effects approach.

Our study informs future research. First, our study highlights an approach for international comparisons of sepsis mortality that requires replication. Our approach is very similar to the cancer literature, where international differences in stage-specific cancer survival between countries could be explained by differences in general patient

characteristics such as comorbidities and cancer-specific patient characteristics such as cancer stage(28, 29). Second, the process of care improvement strategies for sepsis is likely to vary by country(14) which requires formal testing. For example, the impact of pre-ICU time: we observed that patients in Brazil were commonly referred direct to ICU, whilst higher proportions of patients in England were transferred to general wards prior to ICU admission. Additionally, the country effect on sepsis hospital mortality varied with time from hospitalization to ICU admission. This could also imply differences in the magnitude of strain(30, 31) operating on the general wards and in the ICUs between countries. The treatment these patients received pre-ICU admission is also of paramount importance, because of the importance of early treatment for sepsis patients(32). We observed that, despite similar proportions of patients with infection at ICU admission, the proportion of admissions with sepsis was lower in Brazil compared with England, potentially explained by the lower admission threshold of private ICUs contributing to the ORCHESTRA database. Third, international harmonization of ICU clinical trials and large global adaptive platform trials are being considered(33). Our study highlights the need to have stratification by country to account for the differences in crude mortality and to explore biological differences in treatment response in sepsis populations between countries.

Conclusion

Our study highlights that crude mortality comparison of sepsis patients admitted to critical care units is of limited value in understanding reasons for differences in outcome between countries. Both general and sepsis-specific patient characteristics influence

mortality of sepsis patients admitted to the ICU and are distributed differently between cohorts from the two countries. We provide a template for studies attempting international benchmarking of ICU sepsis mortality.

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Contributors All authors conceptualized and designed the study, interpreted data, and critically revised the manuscript. DAH, LSR, JIFS, KMR and MS led data collection. OTR did data analyses. OTR and MSH wrote the first draft of the manuscript.

Lígia S. Rabello died during the peer-review process of this manuscript. All authors unanimously agreed on her fundamental contribution for this study.

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Figures

Figure Legends

Figure 1 – Observed hospital mortality stratified by country, site of infection (Figure 1-A) and number of organ dysfunctions (Figure 1-B)

Figure 2 – Effect modification of country effect on hospital mortality and by pre-specified subgroups and by deciles of the predicted risk from the Model 3-A

Model 3-A was adjusted for general (age, sex, cardiovascular, respiratory, renal, hepatic comorbidities, immunocompromised, **functional status** and, admission source and time from hospitalization to ICU admission) and sepsis-specific characteristics (site of infection and type of organ dysfunction and first-order interaction between each organ dysfunction system)

Table 1. General and sepsis-specific patient characteristics of patients with sepsis

General patient characteristics	England (n=17,921)	Brazil (n=4,505)
Age, mean (SD)	64.3 (16)	68.9 (19)
Sex (male)	9992 (55.8%)	2327 (51.7%)
Predicted risk of hospital death¹ , mean (SD)	ICNARC model 38.8% (29)	SAPS 3 model 40.0% (24)
Comorbidities⁴		
Severe cardiovascular disease	340 (1.9%)	42 (0.9%)
Severe respiratory disease	676 (3.8%)	433 (9.6%) ¹
Renal disease (chronic renal failure under RRT)	433 (2.4%)	328 (7.3%)
Chronic liver disease	509 (2.8%)	109 (2.4%)
Immunocompromised	1704 (9.5%)	693 (15.4%)
Haematological malignancy	855 (4.8%)	229 (5.1%)
AIDS	29 (0.2%)	118 (2.6%)
Metastatic disease (solid neoplasia)	440 (2.5%)	259 (5.8%)
Steroid use	535 (3.0%)	164 (3.6%)
Functional status		
Independent	11922 (66.8%) ³	2247 (53.2%) ²
Partially or fully dependent	5915 (33.2%)	1978 (46.8%)
Source of admission		
Emergency department	5912 (33.0%)	3250 (72.1%)
Ward	11023 (61.5%)	990 (22.0%)
High dependency unit	824 (4.6%)	129 (2.9%)
Other	162 (0.9%)	136 (3.0%)
Time from hospital admission to ICU admission, days mean (SD) / median (p25-p75)		
Among those from emergency department	3.4 (7) / 1 (0-3)	3.7 (10) / 0 (0-2)
Among those from ward	0.3 (2) / 0 [0-0]	1.1 (5) / 0 [0-0]
	4.8 (8) / 2 [1-5]	10.6 (14) / 5 [2-13]
Sepsis-specific patient characteristics		
Site of infection		
Respiratory	11078 (61.8%)	2285 (50.7%)
Genitourinary	865 (4.8%)	748 (16.6%)
Gastrointestinal	2304 (12.9%)	296 (6.6%)
Musculoskeletal/Dermatological	739 (4.1%)	251 (5.6%)
Neurological	445 (2.5%)	43 (0.9%)
Cardiovascular	351 (2.0%)	111 (2.5%)
Unknown	2139 (11.9%)	771 (17.1%)
Type of organ dysfunctions within first 24h		
Respiratory	15371 (85.8%)	1768 (39.3%)
Cardiovascular	6137 (34.2%)	1857 (41.2%)
Renal	7324 (40.9%)	1496 (33.2%)
Hematological	3609 (20.1%)	872 (19.4%)
Neurological	6358 (35.5%)	1647 (36.6%)
Organ support during critical care stay		
Advanced respiratory support	9230 (51.5%)	1995 (44.3%)
Advanced cardiovascular support	6137 (34.2%)	1866 (41.4%)
Advanced renal support	3439 (19.2%)	647 (14.4%)

¹The risk of death was estimated based on the ICNARC model, 2015 recalibration for England cohort and based on SAPS3 model from Brazil cohort, using standard equations.

² n=280 and ³n= 84 missing values;

⁴please refer to eTable-2 for definitions of comorbid conditions used in the study;

Table 2. Hospital mortality stratified by country, by structure and by sepsis-specific patient characteristics

Outcomes	England (n=17,921)	Brazil (n=4,505)
ICU mortality	5496 (30.7%)	1431 (31.8%)
Hospital mortality	7045 (39.3%)	1867 (41.4%)
By source of admission		
Emergency department	2054/5912 (34.7%)	1152/3250 (35.5%)
Ward	4571/11023 (41.5%)	589/990 (59.5%)
HDU	360/824 (43.7%)	73/129 (56.6%)
Other	60/162 (37.0%)	53/136 (39.0%)
By functional status		
Independent	4173/11922 (35.0%)	780/2247 (34.7%)
Partially or fully dependent	2831/5915 (47.9%)	967/1978 (48.9%)
By Site of infection		
Respiratory	4480/11078 (40.4%)	1008/2285 (44.1%)
Genitourinary	192/865 (22.2%)	214/748 (28.6%)
Gastrointestinal	885/2304 (38.4%)	132/296 (44.6%)
Musculoskeletal/Dermatological	260/739 (35.2%)	87/251 (34.7%)
Neurological	77/445 (17.3%)	18/43 (41.9%)
Cardiovascular	150/351 (42.7%)	48/111 (43.2%)
Unknown	1001/2139 (46.8%)	360/771 (46.7%)
By number of organ dysfunctions within first 24h		
1	1385/5881 (23.6%)	642/2474 (26.0%)
2	2090/5852 (35.7%)	616/1205 (51.1%)
3	2015/3935 (51.2%)	400/577 (69.3%)
4	1250/1856 (67.4%)	184/220 (83.6%)
5	305/397 (76.8%)	25/29 (86.2%)
Type of organ dysfunction within first 24h		
Respiratory	6211/15371 (40.4%)	995/1768 (56.3%)
Cardiovascular	3418/6137 (55.7%)	1075/1857 (57.9%)
Renal	3646/7324 (49.8%)	669/1496 (44.7%)
Hematological	1666/3609 (46.2%)	366/872 (42.0%)
Neurological	3194/6358 (50.2%)	830/1647 (50.4%)
By type of organ dysfunction alone and in combinations¹		
Respiratory (only)	970/4317 (22.5%)	124/449 (27.6%)
Cardiovascular (only)	72/185 (38.9%)	142/419 (33.9%)
Renal (only)	201/749 (26.8%)	120/598 (20.1%)
Hematological (only)	51/281 (18.2%)	62/356 (17.4%)
Neurological (only)	91/349 (26.1%)	194/652 (29.8%)
Respiratory + Cardiovascular	497/1089 (45.6%)	178/294 (60.5%)
Respiratory + Neurological	546/1686 (32.4%)	105/200 (52.5%)
Cardiovascular + Renal	87/217 (40.1%)	71/157 (45.2%)
Respiratory + Cardiovascular + Renal	567/989 (57.3%)	112/153 (73.2%)
Respiratory + Cardiovascular + Neurological	479/998 (48.0%)	144/210 (68.6%)
Respiratory + Cardiovascular + Renal + Neurological	710/991 (71.6%)	104/123 (84.6%)
Organ support during ICU stay		
Advanced respiratory support	4482/9230 (48.6%)	1366/1995 (68.5%)
Advanced cardiovascular support	3418/6137 (55.7%)	1136/1866 (60.9%)
Advanced renal support	1897/3439 (55.2%)	428/647 (66.2%)

¹Organ dysfunctions combinations with at least 100 occurrences in both datasets (Totals 11,851 (66%) patients from England and 3,611 (80%) patients from Brazil)
ICU – intensive care unit; HDU – high dependency unit.

Table 3. Adjusted multilevel logistic regression models for the country effect (Brazil versus England) on sepsis hospital mortality

Model	Exposure	OR (95% CI)	P value	AUROC	Brier score
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

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)

A – By site of infection

B – By number of organ dysfunctions

Supplemental Digital Content

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

eTable1: Comorbidity definitions for Brazil (Charlson comorbidities) and England (APACHE II definitions)

eTable2: Modified SOFA score definitions

eTable3: Site of infection definition in Brazil and England

eFigure1. Study flowchart for the Brazil and England cohorts

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

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

eTable5: Effect modification of country effect on hospital mortality and by pre-specified subgroups in the Model 3-A

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

eTable7: Effect modification of country effect on hospital mortality and by deciles of the predicted risk from the Model 3-A

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

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]

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