NEUROCRITICAL CARE SOCIETY

ORIGINAL WORK

Global Survey of Outcomes of Neurocritical Care Patients: Analysis of the PRINCE Study Part 2

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Abstract

Background: Neurocritical care is devoted to the care of critically ill patients with acute neurological or neurosurgical emergencies. There is limited information regarding epidemiological data, disease characteristics, variability of clinical care, and in-hospital mortality of neurocritically ill patients worldwide. We addressed these issues in the **P**oint P**R**evalence **I**n **N**eurocritical **C**ar**E** (PRINCE) study, a prospective, cross-sectional, observational study.

Methods: We recruited patients from various intensive care units (ICUs) admitted on a pre-specified date, and the investigators recorded specific clinical care activities they performed on the subjects during their first 7 days of admission or discharge (whichever came first) from their ICUs and at hospital discharge. In this manuscript, we analyzed the final data set of the study that included patient admission characteristics, disease type and severity, ICU resources, ICU and hospital length of stay, and in-hospital mortality. We present descriptive statistics to summarize data from the case report form. We tested differences between geographically grouped data using parametric and nonparametric testing as appropriate. We used a multivariable logistic regression model to evaluate factors associated with in-hospital mortality.

Results: We analyzed data from 1545 patients admitted to 147 participating sites from 31 countries of which most were from North America (69%, $N = 1063$). Globally, there was variability in patient characteristics, admission diagnosis, ICU treatment team and resource allocation, and in-hospital mortality. Seventy-three percent of the participating centers were academic, and the most common admitting diagnosis was subarachnoid hemorrhage (13%). The majority of patients were male (59%), a half of whom had at least two comorbidities, and median Glasgow Coma Scale (GCS) of 13. Factors associated with in-hospital mortality included age (OR 1.03; 95% CI, 1.02 to 1.04); lower GCS (OR 1.20; 95% CI, 1.14 to 1.16 for every point reduction in GCS); pupillary reactivity (OR 1.8; 95% CI, 1.09 to 3.23 for bilateral unreactive pupils); admission source (emergency room versus direct admission [OR 2.2; 95% CI, 1.3 to 3.75]; admission from a general ward versus direct admission [OR 5.85; 95% CI, 2.75 to 12.45; and admission from another ICU versus

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See complete listing of the PRINCE Study Investigators in Appendix.

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direct admission [OR 3.34; 95% CI, 1.27 to 8.8]); and the absence of a dedicated neurocritical care unit (NCCU) (OR 1.7; 95% CI, 1.04 to 2.47).

Conclusion: PRINCE is the first study to evaluate care patterns of neurocritical patients worldwide. The data suggest that there is a wide variability in clinical care resources and patient characteristics. Neurological severity of illness and the absence of a dedicated NCCU are independent predictors of in-patient mortality.

Keywords: Neurocritical care, Observational study, Outcomes, Critical care, Prospective

Background and Significance

Neurocritical care (NCC) is dedicated to the treatment of patients who are critically ill with neurological or neurosurgical diseases. The practice of NCC aims to treat the primary insult to the nervous system and prevent or ameliorate secondary neurological injuries. Patients admitted to a neurocritical care unit (NCCU) benefit from care by a specialized multidisciplinary team comprised of physicians, nurses, respiratory therapists, physical and occupational therapists, pharmacists, nutritionists, social workers, and spiritual care providers. Provision of such care has been associated with reduced mortality, duration of hospitalization, and cost of care [1, 2]. Consequently, The Leapfrog Group, a premier nonprofit organization that promotes transparency in healthcare provision and advocates for patient outcomes in the USA, recognized neurointensivists as vital critical care providers in 2008; this helped establish NCC as an integral part of healthcare systems [3].

Patients admitted to NCCUs usually have diagnoses such as acute ischemic stroke (AIS), intracerebral hemorrhage (ICH), subarachnoid hemorrhage (SAH), traumatic brain and spinal cord injuries (TBI and TSI), neuromuscular weakness, status epilepticus, and hypoxic–ischemic injury that may require targeted temperature management. These diseases frequently are associated with significant morbidity. Clinical outcomes of neurocritically ill patients have mainly been documented in the setting of clinical trials or institutional databases. Recently, there have been attempts to collect patient characteristics and outcomes prospectively for several common disorders such as the Get With The Guidelines database from the American Heart Association for AIS [4], Transforming Research and Clinical Knowledge in TBI (TRACK-TBI) [5], and Collaborative European Neuro Trauma Effectiveness Research in TBI (CENTER-TBI) [6].

Despite management advances and long-term follow-up of NCC patients, the overall impact of NCCU care on patient outcomes is difficult to define for multiple reasons. First, outcome reporting varies across studies as the differences in the definition of the variables and the timeline of collection can vary. Second, a majority of single-center studies tend to be descriptive and hence report outcomes of several pathologies while clinical trials report outcomes for a single disorder. Third, multicenter studies may not truly represent global data since there are geographical limitations in enrollment and are concentrated in developed countries from large urban academic centers. For example, AIS is the leading cause of morbidity in the USA and about 1 in 8 thrombolysis patients require intensive care therapy [7]. However, it is not known whether the same applies to other geographic areas. Finally, availability and composition of NCCUs vary. NCCUs attached to trauma programs may treat severe TBI and TSI, while non-affiliated NCCUs may not.

It is important, therefore, to evaluate global patterns of care of neurocritically ill patients to help elucidate some areas for potential research: ascertain the global burden of neurocritical illnesses; delineate resource availability; and identify care patterns with potential global application to mitigate primary and secondary neurological injuries. We therefore designed a multicenter, international, point-prevalence, cross-sectional, prospective, observational study in NCC (PRINCE [**P**oint P**R**evalence **I**n **N**eurocritical **C**ar**E**] Study). We hypothesized that there is geographic variability in the scope of practice of neurointensivists and NCC delivery. In addition, we wanted to determine whether factors related to difference in care were associated with patient outcome.

Methods

Study Design

The PRINCE Study design has been described in detail in an accompanying manuscript, and we summarize it below [8]. The Institutional Review Board (IRB) of the Baylor College of Medicine (BCM) approved the study with a waiver of consent.

Participating Sites

Participating centers were identified through the Neurocritical Care Research Network [9]. In addition, sites were recruited by emailing members of the neurointensive care section of the European Society of Intensive Care Medicine [10], the Latin American Brain Injury Consortium [11], the Clinical Trials Group of the Australian and New Zealand Intensive Care Society [12], the Canadian Critical Care Trials Group [13], Initiative of German Neurointensive Trial Engagement of the

German Neurointensive Care Society [14], the Chinese University of Hong Kong [15], and the Neurocritical Care Middle East and North Africa chapter of the International Pan Arab Critical Care Medicine Society [16]. Four months before study launch, participating sites registered and obtained IRB/ethics board clearance. The study day was set as 7/21/2014 when all patients admitted to registered intensive care units (ICUs) were enrolled in the study. Data were collected from patient care activities from enrollment day up to 7 days or ICU discharge (whichever came first). All data collected adhered to the National Institute of Neurological Disorders and Stroke (NINDS) Common Data Elements (CDE) project [17].

Data Definition and Collection

PRINCE Study data were collected and managed using Research Electronic Data Capture (REDCap) [18] tools hosted at the BCM. The PRINCE database had a built-in audit trail that automatically logged all user activities and logged all pages viewed by every user, including contextual information (e.g., the project or record being accessed). In addition, the database implemented authentication to validate the identity of end users that logged into the system. We created six case report forms (CRFs) for investigators to fill out (See Appendix B—Part 1) [8]. CRF1 was completed upon registration. CRFs 2–5 were completed between days 1 and 7 of the data collection period. CRF 6 was completed at the time of hospital discharge. For the purpose of our study, we defined ICU resources as the work force required for patient care inclusive of physicians, nursing staff, dedicated pharmacists, respiratory therapists as well as physiotherapists. We also defined clinical care variability as the variability in the care providers (e.g., availability of dedicated NCC, availability and type of intensivist, nurse-to-patient ratios) and availability of components of ICU resources. We defined the need for monitoring as any monitoring that is required for the patient that pertains to that particular organ system that is not possible to perform in a regular floor or ward. For example, the use of pulse oximetry, mechanical ventilation, frequent pulmonary function status for respiratory system, continuous heart rate and/or frequent arterial blood pressure monitoring with pressure support for cardiac system, frequent clinical neurological monitoring, or the use of invasive monitoring devices for intracranial pressure for neurological system are some examples. In this manuscript, we describe data from the second part of the PRINCE Study, which included patient characteristics, ICU resources, disease type and severity, ICU and hospital length of stay, and in-hospital mortality.

Training and Monitoring

PRINCE specific training videos and PowerPoint presentations were submitted electronically to all participating investigators. In addition, we held weekly teleconferences with participating sites in the month before the data collection start date. During these teleconferences, we reviewed the study protocol and addressed specific instructions for data collection and entry and concerns raised by the participating sites. We did not monitor data collection and entry. However, we evaluated incongruous data and outlier values and reconciled those with site investigators.

Statistical Analysis

Investigators at the Department of Public Health Sciences at the Medical University of South Carolina (Charleston, SC) performed the data analysis. For the purpose of this study, we analyzed variables by grouping the participating centers into six geographic regions: North America, Latin America (including Mexico, Central, and South America), Europe, the Middle East and Africa, Asia, and Oceania. Since a majority of the patients in our study were from the USA, we also analyzed variables grouping those from the US sites and those from the remainder of the world. Variables also were analyzed according to each country's income in accordance with their 2013 gross national income (GNI) per person, using thresholds defined by the World Bank Atlas method. Individual countries were classified into three income groups: low and lower-middle income (GNI less than US$4035); upper-middle income (GNI of $4036–$12, 475); and high income (GNI greater than $12, 476) [19]. Data are summarized with means and SDs, medians and interquartile ranges (IQRs), or numbers and percentages as appropriate. Crude in-hospital mortality is presented as a percentage. Normality for continuous variables was assessed using statistical and graphical methods. Differences in practices among world regions were tested using ANOVA, Kruskal–Wallis test, Student's t test, Mann–Whitney test, χ^2 test, or Fisher's exact test, as appropriate. We used independent samples t test, Mann–Whitney test, χ^2 test, and Fisher's exact test to determine if there were differences in practice between the US sites and the remainder of the world.

To determine the variables that were independently associated with in-hospital mortality, we built a multivariable logistic regression model with data from the patient/subject, hospital, and region of origin. A variable was considered as potential risk factor for in-hospital mortality if it was significant at the $\alpha = 0.10$ level. Backward selection using likelihood ratio test was used to obtain the final models that included significant risk

factors. Furthermore, age, Glasgow Coma Scale (GCS) at admission, history of comorbidities, pupillary reactivity at admission, admission source of the patient, geographical region, and the presence of dedicated NCC were included in the model. We report the fixed effects (measure of association) as odds ratio (OR) with their 95% confidence intervals (CI). Statistical covariates were calculated using the Wald test, defined P-values as 2-tailed, and deemed $P < 0.05$ statistically significant. Statistical analyses were performed using SAS version 9.4.

Results

Investigators from 257 institutions located in 47 countries registered for participation and completed Part 1 of PRINCE (Appendix). However, 147 institutions from 31 countries provided patient-level data (Table 1). Most participating institutions were in the USA (68; 46%), followed by Australia (9; 6%), India (8; 5%), and Belgium (6; 4%). According to geographic location, 71 (48%) sites were in North America, 30 (20%) in Europe, 16 (11%) in Asia, 4 (2.7%) in the Middle East, 16 (11%) in Latin America, and 10 (7%) in Oceania. In total, we collected data from 1545 patients and the level of missing data varied by variable but was < 5% overall.

Patient Characteristics

Most patients (59%) were male, with a mean age of 56 years ± 0.5, and the majority were admitted to ICUs in North America (69%) (Table 1). Overall, the patients presented with a median admission GCS of 13 (IQR 7 to 15). Collectively, 7% of patients had no pupillary reactivity bilaterally, while 5% had unilateral and 88% had bilateral pupil reaction at admission. The most common primary reason for ICU admission was neurological monitoring (88%), and the majority of patients (42.6%) were admitted from the emergency department. The most frequent primary neurological diagnosis was SAH followed by ICH, subdural hematoma, and severe TBI. About a third of all patients had chronic hypertension at the time of diagnosis, and 14% of patients had more than four comorbidities. The median time for patients to be admitted to the ICU after hospital arrival was 2 h (IQR 0 to 7). Variation between the patient characteristics between the patients in the USA and the rest of the world is shown in Table 2.

Patients in the US centers who comprised the majority of our study population had several differences as compared to the rest of the world: The US patients tended to have lesser severity of illness as determined by GCS (median 14, IQR 8 to 15 versus median 10, IQR 5 to 14); lower proportion of the US patients had absent bilateral and unilateral pupillary reactivity (5% and 4%, 10% and 9%, respectively, $p < 0.001$) upon admission; the US patients also tended to have more than 4 comorbidities

(17% vs. 7%, $p < 0.0001$) and shorter admission time to the ICU (median 2 h, IQR 0 to 6 versus median 3 h, IQR 1 to 8, $p > 0.0001$). Patients from the non-US sites required more respiratory and hemodynamic monitoring (63.9% vs. 44.9%, 69.3% vs. 51.1%, respectively, $p < 0.0001$).

Characteristics of Participating Institutions

Most participating sites were academic institutions and were located in large urban centers regardless of geographic region (Table 3). Participating institutions had a median overall ICU bed capacity of 54 (IQR 26 to 100). Two-thirds of facilities worldwide had dedicated NCCUs; this proportion was the highest in North America (83%) and lowest in Oceania (15%). The median NCCU bed capacity was 15 (IQR 10 to 20). The distribution of academic versus non-academic centers was uniform across the geographic distribution and more so when compared between the US and the non-US sites. The US sites, however, had a higher number of ICU beds (median 8, IQR 48 to 120 vs. median 32, IQR 18 to 78, $p < 0.0001$) and a higher proportion of dedicated NCC (83% vs. 56%, $p < 0.0001$) compared to the remainder of the world (see Table 2b).

ICU Treatment Teams and Resource Allocation (Variability in Clinical Care)

The most common specialty of physicians working in the ICUs was pulmonary and critical care medicine (38%) (Tables 3, 4). However, on the day of patient data entry, in North America the most common specialty was NCC (29%), whereas in Europe it was anesthesiology and critical care (44%). ICU physicians were available on site or through telecommunication 24 h a day in most institutions (85%). Dedicated physiotherapists, pharmacists, and respiratory therapists were available in 62%, 68%, and 66% of participating centers, respectively. However, there were notable differences in the allocation of these healthcare professionals: Dedicated physiotherapists were available in all of ICUs in Oceania, compared to 50% in North America ($p = 0.01$); dedicated pharmacists were available in 88% of North American ICUs compared to 30% in Latin America ($p < 0.001$); dedicated respiratory therapists were available in more than 80% of North American ICUs, the Middle East, and Latin America, compared to none in Oceania ($p < 0.001$); and advanced practice providers were mostly available in North America (72%) ($p < 0.001$). Overall nurse-to-patient ratios were 1:2 in most ICUs during day and night shifts (75% and 69%, respectively). Nurse-to-patient ratios were 1:1 in all ICUs in Oceania compared to only 31% in North America and 10% in Latin America ($p = 0.008$). North American sites had the highest proportion of 1:2

Table 1 Baseline characteristics of the study cohort on admission to the ICU by geographic location

	ALL patients (n = 1545)	North America (n = 1063)	Europe (n = 182)	Asia (n = 121)	Middle East (n = 25)	Latin America (n = 104)	Oceania (n = 50)	p-value
Severity scores on ICU admission (median, IQR)								
Glasgow Coma Score	13 (7,15)	14 (8, 15)	8 (3, 14)	10 (6.5, 14)	11 (8, 12)	11 (6, 15)	9 (3, 14)	< 0.0001
Pupillary reactivity, n (%)								< 0.0001
Both reactive	1300 (87.8)	921 (91.0)	144 (83.7)	92 (76.7)	18 (72.0)	85 (83.3)	40 (81.6)	
One reactive	79 (5.3)	38 (3.8)	14 (8.1)	15 (12.5)	4 (16.0)	5 (4.9)	3 (6.1)	
None	101 (6.8)	53 (5.2)	14 (8.1)	13 (10.8)	3 (12.0)	12 (11.8)	6 (12.2)	
ICU monitoring requirements[a] (% of patients)								
Neurological	1382 (87.8)	962 (90.5)	138 (75.8)	117 (96.7)	23 (92.0)	97 (93.3)	45 (90.0)	< 0.0001
Hemodynamic	883 (89.5)	547 (51.5)	124 (68.1)	88 (72.7)	21 (84.0)	67 (64.4)	36 (72.0)	< 0.0001
Respiratory	791 (51.2)	481 (45.3)	120 (65.9)	70 (58.9)	14 (56.0)	66 (63.5)	40 (80.0)	< 0.0001
Source of admission, n (%)								< 0.0001
Direct	352 (23.1)	286 (27.3)	27 (14.8)	20 (16.7)	3 (12.0)	5 (4.9)	11 (22.5)	
ED	650 (42.6)	438 (41.9)	69 (37.9)	61 (50.8)	11 (44.0)	49 (47.6)	22 (44.9)	
PACU	86 (5.6)	68 (6.5)	2 (1.1)	5 (4.2)	0 (0.0)	6 (5.8)	5 (10.2)	
OR	218 (14.3)	122 (11.7)	32 (17.6)	21 (17.5)	4 (16.0)	30 (29.1)	9 (18.4)	
Hospital ward	86 (5.6)	44 (4.2)	21 (11.5)	10 (8.3)	2 (8.0)	8 (7.8)	1 (2.0)	
Other ICU	37 (2.4)	21 (2.0)	13 (7.1)	1 (0.8)	0 (0.0)	2 (1.9)	0 (0.0)	
Other	96 (6.3)	67 (6.4)	18 (9.9)	2 (1.7)	5 (20.0)	3 (2.9)	1 (2.0)	
Primary diagnosis (5 most common), n (%)								< 0.0001
	SAH: 178 (12.8)	Other: 146 (15.1)	SAH: 23 (14.0)	Severe TBI: 13 (12.6)	Severe TBI: 3 (18.8)	SAH: 13 (13.4)	SAH: 7 (15.9)	
	Other: 169 (12.1)	SAH: 125 (12.9)	ICH spontaneous: 22 (13.4)	ICH spontaneous: 12 (11.7)	AIS: 3 (18.8)	Severe TBI: 12 (12.4)	ICH spontaneous: 5 (11.4)	
	ICH spontaneous: 163 (11.7)	ICH spontaneous: 116 (12.0)	Severe TBI: 15 (9.2)	SAH: 9 (8.7)	SDH: 2 (12.5)	Other: 10 (10.3)	Other: 3 (6.8)	
	SDH: 93 (6.7)	SDH: 75 (7.8)	Cardiac arrest 8 (4.9)	Severe TBI: 7 (6.8)	ICH spontaneous: 2 (12.5)	ICH spontaneous: 6 (6.2)	Head injury severe: 2 (4.6)	
	Severe TBI: 79 (5.7) = 294	AIS: 34 (3.5)	SDH: 7 (4.3)	AIS: 5 (4.9)	SAH: 1 (6.3)	Malignant brain tumor: 6 (6.2)	AIS: 2 (4.6)	
Comorbidities [Five most common, (n, %)]								< 0.0001
	HTN (501, 32.8%)	HTN (369, 34.8%)	HTN (47, 25.8%)	HTN (23, 19%)	HTN (5, 20%)	HTN (34, 32.7%)	HTN (22, 44%)	
	Other (378, 24.5%)	Other (316, 29.8%)	Other (22, 11.5%)	DM (14, 8.3%)	DM (3, 12%)	Other (19, 18.3%)	Other (13, 26%)	
	DM (191, 12.4%)	HChol (147, 13.9%)	HChol (18, 10.4%)	Other (7, 5.8%)	Other (2, 8%)	DM (11, 10.6%)	DM (10, 20%)	
	HChol (181, 11.7%)	DM (144, 13.6%)	DM (14, 7.7%)	AFib (5, 4.1%)	Systemic hemorrhage (2, 8%)	Smoking (7, 6.7%)	HChol (6, 12%)	
	CAD (82, 5.3%)	AFib (65, 6.1%)	AFib (10, 6%)	HChol (5, 4.1%)	HChol (1, 4%)	CAD (6, 6.1%)	CAD (5, 10%)	
Number of comorbidities, n (%)								< 0.0001
None	504	306 (28.8)	72 (40.0)	61 (50.4)	13 (52.0)	35 (33.7)	17 (34.0)	
1	366	244 (23.0)	42 (23.1)	33 (27.3)	8 (32.0)	29 (27.9)	10 (20.0)	
2	273	187 (17.6)	35 (19.2)	15 (12.4)	1 (4.0)	27 (26.0)	8 (16.0)	
3	189	145 (13.6)	14 (7.7)	12 (9.9)	2 (8.0)	7 (6.7)	9 (18.0)	
≥ 4	213	181 (17.0)	19 (10.4)	0 (0.0)	1 (4.0)	6 (5.8)	6 (12.0)	
Time from hospital arrival to ICU admission, in hours (median, IQR)	2 (0, 7)	2 (0, 7)	8 (3, 14)	2 (0, 7)	4.5 (0.5, 9)	6 (3, 12)	3 (1, 8)	< 0.0001

AFib atrial fibrillation, *AIS* acute ischemic stroke, *CAD* coronary artery disease, *DM* diabetes mellitus type II, *ED* emergency department, *HChol* hypercholesterolemia/hyperlipidemia, *Hemodyn* hemodynamic, *HTN* chronic hypertension, *ICH* spontaneous intracerebral hemorrhage, *ICU* intensive care unit, *IQR* interquartile range, *OR* operating room, *PACU* post-anesthesia care unit, *SAH* subarachnoid hemorrhage, *SDH* subdural hematoma, *TBI* traumatic brain injury

[a] Could have multiple options chosen. Monitoring is defined as any monitoring that is required for the patient that pertains to that particular organ system that is not possible to perform in a regular floor or ward

Table 2 Baseline characteristics of the study cohort on admission to the ICU: the USA versus remainder of the world

	USA (*n* = 1033)	Remainder of the world (*n* = 512)	*p*-value
Severity scores on ICU admission (median ± IQR)			
Glasgow Coma Score	14 (8, 15)	10 (5, 14)	< 0.0001
Pupillary reactivity, *n* (%)			< 0.0001
Both reactive	894 (91.0)	406 (81.5)	
One reactive	36 (3.7)	43 (8.6)	
None	52 (5.3)	49 (9.8)	
ICU monitoring requirements[a] (% of patients)			
Neurological	933 (90.3)	449 (87.7)	0.1140
Hemodyn	528 (51.1)	355 (69.3)	< 0.0001
Respiratory	464 (44.9)	327 (63.9)	< 0.0001
Source of admission, *n* (%)			< 0.0001
Direct	284 (28.0)	68 (13.4)	
ED	428 (42.1)	222 (43.6)	
PACU	64 (6.3)	22 (4.3)	
OR	120 (11.8)	98 (19.3)	
Hospital floor	43 (4.2)	43 (8.5)	
Other ICU	14 (1.4)	23 (4.5)	
Other	63 (6.2)	33 (6.5)	
Primary diagnosis (5 most common), *n* (%)			< 0.0001
	Other 144 (15.3)	SAH 58 (12.8)	
	SAH 120 (12.8)	ICH spontaneous 53 (11.7)	
	ICH spontaneous 110 (11.7)	Severe TBI 38 (8.4)	
	SDH 73 (7.8)	Other 25 (5.5)	
	Stroke/AIS 50 (5.3)	SDH 20 (4.4)	
Number of comorbidities, *n* (%)			< 0.0001
None	299 (28.9)	205 (40.0)	
1	238 (23.0)	128 (25.0)	
2	187 (17.8)	89 (17.4)	
3	137 (13.3)	52 (10.2)	
≥ 4	175 (16.9)	38 (7.4)	
Time from hospital arrival to ICU admission, in hours (median, IQR)	2 (0, 6)	3 (1, 8)	< 0.0001

USA included Puerto Rico

AIS acute ischemic stroke, *ED* emergency department, *Hemodyn* hemodynamic, *ICH* spontaneous intracerebral hemorrhage, *ICU* intensive care unit, *IQR* interquartile range, *PACU* post-anesthesia care unit, *OR* operating room, *SAH* subarachnoid hemorrhage, *SDH* subdural hematoma, *SOFA* sequential organ failure assessment, *USA* The United States of America

[a] Could have multiple options chosen

nurse-to-patient staffing (89%, $p < 0.0001$), while Latin America had highest proportion of 1:3 nurse-to-patient staffing ($p < 0.0001$ for both). The US patients are generally treated in dedicated NCC (83% vs. 56%, $p < 0.001$) by a higher proportion of pulmonary and critical care intensivists (38%, $p = 0.002$) and receive a higher complement of physiotherapists, pharmacists, respiratory therapists and, advanced practice providers ($p < 0.001$ for all) (Table 4).

ICU Procedures

We collected data on ICU procedures, including mechanical ventilation, at the time of study entry. In addition, we identified procedures that were performed up to the time of hospital discharge. The procedures performed included: external ventricular drains (116 patients, 7.5%); other intracranial pressure monitors (28 patients, 1.8%); brain tissue oxygen monitoring (10 patients, 0.6%); jugular vein oxygen saturation monitors (1 patient, 0.1%); cerebral microdialysis (2 patients, 0.1%); arterial line (337 patients, 22%); central venous catheter (63 patients,

Table 3 Characteristics of hospitals and ICUs by geographic location

	ALL sites	North America	Europe	Asia	Middle East	Latin America	Oceania	*p*-value
Number of countries	31	2	10	7	1	9	2	
Type of hospital (% of sites)								0.0511
Academic Center	107 (72.6)	48 (70.2)	19 (77.8)	10 (67.7)	4 (100.0)	10 (67.6)	8 (85.7)	
Private, non-academic	20 (13.7)	13 (18.6)	0 (0.0)	3 (20.6)	0 (0.0)	2 (13.5)	1 (7.1)	
Public, non-academic	11 (7.6)	4 (6.5)	5 (15.6)	1 (2.9)	0 (0.0)	1 (8.1)	1 (7.1)	
Other	9 (6.1)	3 (4.8)	3 (6.7)	1 (2.9)	0 (0.0)	2 (10.8)	0 (0.0)	
City population (% sites responding)								0.0217
< 100,000	6 (4.2)	4 (6.5)	1 (2.2)	1 (6.3)	0 (0.0)	0 (0.0)	0 (0.0)	
100,000–250,000	17 (11.5)	7 (9.7)	7 (24.4)	3 (12.5)	0 (0.0)	2 (8.1)	0 (0.0)	
250,000–500,000	23 (15.7)	10 (15.3)	5 (20.0)	1 (9.4)	0 (0.0)	3 (21.6)	0 (0.0)	
500,000–750,000	16 (10.7)	9 (12.9)	5 (17.8)	0 (0.0)	0 (0.0)	1 (2.7)	2 (14.3)	
750,000–1,000,000	21 (14.2)	12 (17.7)	3 (13.3)	3 (12.5)	0 (0.0)	2 (8.1)	2 (14.3)	
> 1,000,000	64 (43.7)	26 (37.9)	6 (22.2)	7 (56.3)	4 (100.0)	7 (59.5)	6 (64.3)	
Number of ICU beds (median, IQR)	54 (26, 100)	77 (48, 120)	40 (21, 90)	39 (20, 96)	35 (22, 60)	20 (12, 44)	24 (21.5, 53)	< 0.0001
Presence of dedicated neuroICU, (% of sites responding)								< 0.0001
Yes	99 (67.4)	56 (83.1)	17 (64.4)	7 (57.6)	1 (37.5)	8 (54.1)	1 (14.3)	
Number of neuroICU beds (median ± IQR)	15 (10, 20)	18 (12.5, 22.5)	10 (8, 16)	17 (10, 26)	8 (7, 15)	8 (6, 10)	11.5 (10, 13)	< 0.0001
Specialty of physician caring for patients (%)[b]								0.0023
NCC	17 (19.8)	6 (28.6)	2 (12.5)	3 (20.0)	1 (20.0)	4 (23.5)	1 (8.3)	
PCCM	31 (38.4)	4 (19.1)	5 (37.5)	3 (20.0)	3 (60.0)	10 (58.8)	6 (58.3)	
ACC	13 (16.3)	0 (0.0)	7 (43.8)	5 (40.0)	0 (0.0)	1 (5.9)	0 (0.0)	
SCC	4 (4.7)	4 (19.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	
Neurosurgery	2 (3.5)	2 (9.5)	0 (0.0)	1 (6.7)	0 (0.0)	0 (0.0)	0 (0.0)	
Other	14 (17.4)	5 (23.8)	1 (6.3)	2 (13.3)	1 (20.0)	2 (11.8)	4 (33.3)	
ICU physician availability 24 h (% of ICUs)								0.0243
Yes	127 (86.8)	53 (78.1)	26 (97.7)	14 (93.9)	4 (100.0)	13 (91.9)	9 (92.9)	
Dedicated physiotherapist availability (% of ICUs)								0.0128
Yes	91 (62.0)	34 (50.1)	20 (75.0)	10 (69.7)	4 (100.0)	10 (70.0)	9 (92.9)	
Dedicated pharmacist available (% of ICUs) †								< 0.001
Yes	100 (68.1)	60 (88.4)	13 (48.8)	7 (45.5)	3 (66.7)	6 (37.8)	8 (85.7)	
Dedicated respiratory therapists availability (% of ICUs)								< 0.001
Yes	96 (65.4)	58 (85.1)	7 (25.6)	6 (42.4)	3 (85.7)	312 (83.8)	1 (7.7)	
Dedicated advanced practice providers availability (% of ICUs)								< 0.001
Yes	61 (41.7)	49 (72.7)	3 (11.7)	3 (18.2)	0 (0.0)	2 (16.2)	1 (7.7)	
Daytime nurse-to-patient ratio (% of ICUS)[a]								
1:1	31 (21.1)	7 (10.7)	5 (18.2)	6 (39.4)	2 (57.1)	1 (8.1)	9 (92.9)	0.0081
1:2	98 (66.8)	59 (87.6)	17 (63.6)	7 (54.5)	2 (42.9)	6 (43.2)	0 (0.0)	< 0.0001
1:3	12 (8.6)	1 (0.8)	4 (13.6)	1 (3.0)	0 (0.0)	5 (35.1)	1 (7.1)	< 0.0001
1:4	3 (2.0)	0 (0.0)	1 (2.3)	1 (3.0)	0 (0.0)	2 (8.1)	0 (0.0)	0.1276
Other	2 (1.6)	0 (0.0)	1 (2.3)	0 (0.0)	0 (0.0)	1 (5.4)	0 (0.0)	0.3759
Nighttime nurse-to-patient ratio (% of ICUs)								
1:1	24 (16.7)	7 (9.2)	4 (13.6)	3 (21.2)	2 (57.1)	1 (5.6)	10 (100.0)	0.0037
1:2	90 (61)	58 (85.0)	11 (38.6)	10 (66.7)	1 (14.3)	6 (36.1)	0 (0.0)	< 0.0001
1:3	22 (15)	2 (3.0)	9 (36.7)	2 (9.1)	1 (14.3)	5 (30)	0 (0.0)	< 0.0001
1:4	10 (6.3)	0 (0.0)	3 (11.4)	0 (0.0)	0 (0.0)	3 (25)	0 (0.0)	0.0029
Other	1 (0.8)	1 (0.8)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	N/A

ACC anesthesiology and critical care, *ICU* intensive care unit, *IQR* interquartile range, *NCC* neurocritical care, *PCCM* pulmonary critical care medicine, *SCC* surgical critical care

[a] May have more than one response per site

[b] Physicians caring for patients whose data were entered into the study

Table 4 Characteristics of hospitals and ICUs by geographic location: the USA versus remainder of the world

	USA	Remainder of world	*p*-value
Type of hospital (% of sites)			0.1070
Academic Center	47 (69.0)	61 (76.4)	
Private, non-academic	13 (19.8)	7 (9.3)	
Public, non-academic	5 (6.9)	6 (7.9)	
Other	3 (4.3)	5 (6.4)	
City population (% sites)			0.0766
< 100,000	4 (6.0)	2 (2.2)	
100,000–250,000	7 (10.3)	10 (13.0)	
250,000–500,000	10 (15.5)	12 (15.9)	
500,000–750,000	9 (13.8)	7 (8.7)	
750,000–1,000,000	14 (19.0)	9 (10.9)	
> 1,000,000	24 (35.3)	39 (49.3)	
Number of ICU beds (median, IQR)	80 (48, 120)	32 (18, 78)	< 0.0001
Presence of dedicated neuroICU, (% of sites)			< 0.0001
Yes	56 (82.8)	44 (55.8)	
Number of neuroICU beds (median ± IQR)	18 (13, 23.5)	10 (8, 16)	< 0.0001
Specialty of physician caring for patients (%)[b]			0.0023
NCC	14 (21.0)	22 (28.6)	
PCCM	26 (38.3)	16 (19.1)	
ACC	12 (16.1)	23.9 (19.0)	
SCC	3 (4.9)	15 (19.0)	
Neurosurgery	2 (2.5)	7 (9.5)	
Other	11 (17.3)	3 (5.0)	
ICU physician available 24 h (% of ICUs)			0.0007
Yes	51 (75.8)	75 (94.8)	
Dedicated physiotherapist available (% of ICUs)			< 0.0001
Yes	33 (48.9)	62 (79.2)	
Dedicated pharmacist available (% of ICUs)			< 0.001
Yes	61 (89.3)	32 (40.3)	
Dedicated respiratory therapist available (% of ICUs)			< 0.001
Yes	55 (81.7)	37 (47.4)	
Dedicated advanced practice providers available, (% of ICUs)			< 0.001
Yes	55 (81.7)	11 (14.5)	
Daytime nurse-to-patient ratio (% of ICUS)[a]			
1:1	20 (30.2)	20 (26.0)	0.5390
1:2	62 (90.6)	44 (55.8)	< 0.0001
1:3	1 (1.0)	13 (16.9)	0.0001
1:4	0 (0.0)	4 (5.2)	0.0375
Other	0 (0.0)	2 (2.6)	0.1967
Nighttime nurse-to-patient ratio (% of ICUs)[a]			
1:1	18 (27.1)	14 (18.2)	0.1676
1:2	60 (88.5)	35 (44.2)	< 0.0001
1:3	2 (3.1)	21 (27.3)	< 0.0001
1:4	0 (0.0)	9 (11.7)	0.0005
Other	0 (0.0)	0 (0.0)	N/A

ACC anesthesiology and critical care, *ICU* intensive care unit, *IQR* interquartile range, *NCC* neurocritical care *PCCM* pulmonary critical care medicine, *SCC* surgical critical care, *USA* The United States of America

[a] Could have multiple options chosen

[b] Specialty of physicians caring for patients not within an ICU

Table 5 Patient characteristics, length of stay, mortality rates, and interventions by region

	ALL patients	North America	Europe	Asia	Middle East	Latin America	Oceania	p-value
Age, median (IQR)	58 (44, 70)	59 (47, 70)	61 (48, 73)	46.5 (29, 60.5)	41 (26, 59)	55 (36, 69)	58 (46, 68)	< 0.0001
Gender, n (%)								0.0105
Male	908 (59.0)	596 (56.2)	119 (65.4)	78 (65.0)	17 (68.0)	72 (69.9)	26 (53.1)	
Female	632 (41.0)	465 (43.8)	63 (34.6)	42 (35.0)	8 (32.0)	31 (30.1)	23 (46.9)	
ICU LOS (in days), median (IQR)	7 (3, 16)	7 (3, 15)	11.5 (6, 25)	5 (3, 9)	16 (12, 20)	16 (12, 20)	6.5 (3, 14)	< 0.0001
Hospital LOS (in days), median (IQR)	13 (6, 24)	12 (5, 21)	25 (11, 39)	14.5 (9.5, 24.5)	25 (22, 34)	13 (7, 23)	11 (6, 23)	< 0.0001
In-hospital death rate, n (%)	192 (12.4)	111 (10.4)	31 (17.0)	12 (9.9)	3 (12.0)	28 (26.9)	7 (14.0)	< 0.0001
DNR order initiated, n (%)								0.1549
Yes	195 (14.6)	142 (15.3)	25 (15.3)	5 (5.4)	1 (11.1)	13 (13.5)	9 (20.0)	
Comfort care instituted, n (%)								0.0202
Yes	148 (11.2)	110 (11.9)	14 (8.5)	2 (2.3)	0 (0.0)	16 (17.0)	6 (13.6)	
Palliative care consultation, n (%)								0.0388
Yes	86 (6.6)	68 (7.5)	14 (8.6)	1 (1.1)	0 (0.0)	2 (2.1)	1 (2.3)	

DNR do-not-resuscitate, *ICU* intensive care unit, *IQR* interquartile range, *LOS* length of stay

Table 6 Patient characteristics, length of stay, mortality rates, and interventions by region (the USA vs. remainder of the world)

	USA	Remainder of world	p-value
Age, median (IQR)	59 (47, 70)	56 (39, 70)	0.0006
Gender, n (%)			0.0015
Male	579 (56.2)	329 (64.6)	
Female	452 (43.8)	180 (35.4)	
ICU LOS (in days), median (IQR)	7 (3, 15)	8 (4, 18)	< 0.0001
Hospital LOS (in days), median (IQR)	12 (5, 21)	17 (8, 32)	< 0.0001
In-hospital death rate, n (%)	108 (10.5)	84 (16.4)	0.0008
DNR order initiated, n (%)			0.3239
Yes	137 (15.3)	58 (13.3)	
Comfort care instituted, n (%)			0.0952
Yes	109 (12.2)	39 (9.1)	
Palliative care consultation, n (%)			0.0071
Yes	69 (7.9)	17 (3.9)	

DNR do-not-resuscitate, *ICU* intensive care unit, *IQR* interquartile range, *LOS* length of stay

4%); mechanical ventilation (288 patients, 19%); tracheostomies (288 patients, 19%); and gastrostomy tube placements (316 patients, 20.5%). There was geographic variation in the number of procedures performed with more being performed in North America including 63% of mechanical ventilation and 85% of external ventricular drains. Brain tissue oxygenation, jugular vein oxygen saturation monitoring, and cerebral microdialysis were only performed in North America and Europe.

In-Hospital Length of Stay and Mortality

Median length of ICU and hospital stay was 7 days and 13 days, respectively (Table 5). European centers

reported having the longest lengths of ICU and hospital stay (12 and 25 days, respectively) and the USA the shortest (7 and 12 days) (Table 6).

One hundred and ninety-two patients died before hospital discharge. Median hospital mortality (described as crude mortality rates) was 12.4% and varied by geographical regions; it was the highest in Latin America (27%) and the lowest in Oceania (11%) (Table 5). Palliative care consultation does not resuscitate (DNR) orders, and comfort care measures were most frequently reported in North American sites. Worldwide 1 in 10 patients had comfort care measures. Patients admitted in the USA had lower length

Table 7 Patient characteristics, length of stay, mortality rates, and interventions by gross national income

	Lower	Upper	High	*p*-value
Age, median (IQR)	45 (28, 60)	44 (32, 62)	59 (46, 70)	< 0.0001
Gender, *n* (%)				0.0399
Male	36 (58.1)	60 (72.3)	812 (58.2)	
Female	26 (41.9)	23 (27.7)	583 (41.8)	
ICU LOS (in days), median (IQR)	7 (3.5, 13.5)	7 (4, 17)	7 (3, 16)	0.9502
Hospital LOS (in days), median (IQR)	14 (6, 28)	15 (10, 23)	12 (6, 24)	0.2620
In-hospital death rate, *n* (%)	8 (12.7)	20 (24.1)	164 (11.7)	0.0040
DNR order initiated, *n* (%)				0.0569
Yes	2 (3.6)	9 (15.0)	184 (15.1)	
Comfort care instituted, *n* (%)				0.0613
Yes	2 (4.1)	11 (18.3)	135 (11.1)	
Palliative care consultation, *n* (%)				0.0361
Yes	0 (0.0)	1 (1.8)	85 (7.1)	

DNR do-not-resuscitate; *ICU* intensive care unit; *IQR* interquartile range; *LOS* length of stay

of ICU (median 7, IQR 3 to 15 vs. median 8, IQR 4 to 18, $p < 0.0001$) and hospital stay, (median 12, IQR 5 to 21 vs. median 17, IQR 8 to 32, $p < 0.0001$), and in-hospital deaths (10.5% vs. 16.4%, $p = 0.0008$) and received higher rates of palliative care consultations (Table 6). We noticed that patients from upper- and high-GNI nations had higher mortality and received higher proportion of comfort care measures and palliative care consultations. The proportion of patients who received DNR orders and comfort care measures did not differ ($p = 0.15$) (Table 7).

Independent predictors of increased in-hospital mortality included the following: age; admission GCS score; admission pupillary response; admission source (e.g., emergency room, transfer from another hospital or from elsewhere in the hospital); geographic location; and the absence of a dedicated NCCU (Table 8).

Discussion

The PRINCE Study is the first to evaluate the provision of NCC around the world. We demonstrate a wide variability in several aspects, including disease burden, patient characteristics, NCCU treatment teams and resource allocations, and mortality in the NCCU patient population.

Study Strengths and Limitations

The PRINCE Study has several strengths. First, PRINCE is the first study to evaluate prospectively a day in the life of a NCCU and of a neurointensivist around the world. Second, the majority of world regions, except for the African continent, are represented in the study. Third, we used NINDS-recommended CDE, when available, and

Table 8 Predictors of in-hospital mortality

Predictors	Odds ratio	95% Wald CI
Patient age	1.03	1.02, 104
Total Glasgow Coma Scale[a]	0.81	0.77, 0.85
Pupillary reactivity at admission		
One reactive vs both reactive	1.64	0.85, 3.17
None reactive vs both reactive	2.07	1.19, 3.17
Admission source of the patient		
ED versus direct	2.20	1.30, 3.75
OR (PACU and OR) versus direct	1.44	0.75, 2.76
General hospital ward versus direct	5.85	2.75, 12.35
Other ICU versus direct	3.34	1.27, 8.80
Other versus direct	1.35	0.52, 3.51
Region		
Asia versus North America	0.53	0.24, 1.16
Europe versus North America	0.79	0.47, 1.32
Latin America versus North America	2.29	1.28, 4.12
The Middle East versus North America	2.2	0.44, 11.08
Oceania versus North America	0.66	0.25, 1.69
Dedicated NeuroICU		
No versus yes	1.71	1.05, 2.45

The following variables were included in the model: patient age ($p < 0.0001$), total Glasgow Coma Scale at admission (p-value < 0.0001), history of comorbidities (p-value $= 0.1004$), pupillary reactivity at admission (p-value $= 0.0219$), admission source of the patient (p-value $= 0.0002$), region (p-value $= 0.0051$), and whether the hospital has a dedicated NCC (p-value $= 0.0311$)

ED emergency department; *ICU* intensive care unit; *PACU* post-anesthesia care unit

[a] For every unit increase in Glasgow Coma Scale, mortality decreases by 17%

trained the investigators in data collection. However, the PRINCE Study has several potential limitations. First, the study was not funded, and hence, the participation was

voluntary and uncompensated. This may have potentially limited sites from participating in PRINCE. In addition, this meant the data were only evaluated in the setting of incongruence or for outliers, since site monitoring was not feasible. Second, nearly half of the sites were from North America (comprising about two-thirds of the patients), and nearly three quarters were from academic centers in large cities. This may not completely represent neurocritical patient care in other hospital settings. Third, there were challenges associated with data user agreements and institutional board regulations, which may have limited some sites from participating. Fourth, the sample size is limited by the study design and a short collection period; this may not fully represent the actual annual disease distribution in each region. Fifth, we did not collect long-term outcomes and quality of life measures. Finally, we used multiple logistic regression modeling to evaluate mortality, which inherently cannot account for unmeasured variables. Despite these limitations, we believe PRINCE provides robust data to help define global NCC.

Implications of the PRINCE Study

There are several important observations that result from the PRINCE Study. Based on the data presented, an average NCCU patient as per our study can be described as a sexagenarian with at least one comorbidity, who presents with a GCS of 13, is likely to stay in the NCCU for about a week and has a 2 out of 3 chance for mechanical ventilation, 1 in 5 chance for gastrostomy and tracheostomy, and a 13% risk of in-hospital mortality. We observed variability in the healthcare resources available worldwide; this is similar to general critical care. Dedicated NCCUs were far more likely in North America. However, worldwide neurointensivists cared for only a fifth of NCCU patients. Furthermore, depending on the geographic area, a non-intensivist as the primary provider cared for 1 in 10 to 1 in 3 of patients. Similar observations are described in general critical care studies where about half of the patients did not have a critical care physician as the primary provider [20]. Similar to general critical care studies, the PRINCE Study also showed variability in the physical therapist [21], pharmacist [22], respiratory therapist, and advanced practice provider staffing or availability and the nurse-to-patient ratio [21]. Staffing ICUs with appropriately trained intensivists can reduce mortality and ICU length of stay in both general medical ICUs and NCCUs [23–25]. Relative to the non-US sites, we observed a higher number of ICU beds, NCC beds, in the US sites. In relation to manpower, the US sites had a lower proportion of physicians available around the clock, with a third of them representing pulmonary and critical care intensivists. In addition, the US sites were less supported by physical therapists, while had better pharmacist and respiratory therapist support.

The characteristics of NCCU patients and care have several similarities with general critical care including: median age and gender distribution [26, 27]. However, there are several differences between NCC and general critical care. First, nearly 20% of NCCU patients had a tracheostomy and gastrostomy compared to 2–11% of patients in general critical care [28, 29]. This may have to do more with airway control than respiratory function in the NCCU patients. Second, the proportion of NCCU patients with >4 comorbidities (14%) was greater than that observed in general critical care patients described in the ICON patient cohort [27]. Third, the most common diagnosis for NCCU admission was SAH, which is one of the neurological emergencies in need of further research to help improve long-term clinical outcomes [30]. Fourth, PRINCE Study patients had a longer length of ICU stay (13 days) compared to general ICU patients (4 days) [31]. Possible explanations for this difference include the underlying pathology, more comorbidities, lack of trained intensivists, and variable treatment teams.

The in-hospital mortality of PRINCE patients was 12%. Patient characteristics that were associated with higher mortality included: age, lower GCS score, and the absence of pupillary response bilaterally [32, 33]. Several hospital- and resource-associated factors also were associated with mortality. First, admission from the emergency room or from the general ward or other ICU influenced mortality. We speculate that the presence of a neurological disorder superimposed on a different illness for which the patients were treated on a regular ward may aggravate outcome. This second disorder was not present in patients who were directly admitted to the ICU. Second, the absence of a dedicated NCCU was associated with a near twofold increase in mortality. This is consistent with previous observations that suggest the presence of critical or NCC teams is associated with reduced mortality and length of ICU stay [23–25]. Together, these findings suggest that specialized NCCUs may help improve patient outcomes. Third, there were geographic differences in mortality. For example, patients admitted to ICUs in Latin America had a several-fold greater mortality than those admitted to North American ICUs. Similar observations have been made in general critical care and may be explained by availability of treatment teams and their allocations [27]. However, in the PRINCE Study patients admitted to ICUs in Latin America often appeared to be sicker than those admitted in other geographic regions and had lower median GCS and more frequently had bilateral absent pupillary reflexes and had higher rates of comfort care initiation.

The majority population in our study, from the USA, had a lower mortality relative to the rest of the world. Several factors can explain this observation. As noted earlier, the US patients had higher GCS scores, sequential organ failure assessment scores, more favorable pupillary reflexes, and lesser requirement for pulmonary and hemodynamic monitoring. Furthermore, a lower proportion of the US patients were admitted from regular hospital ward and other ICUs. Surprisingly, despite comparable use of DNR orders, the US patients had more comfort care institutions and more palliative consultations. We can only speculate that these patients might have been transferred to a hospice facility. This may have artificially reduced the ICU mortality in addition to reducing the lengths of stay in the ICU and hospital.

In general critical care, hospital mortality is reported to be 10–29% and ICU mortality about 3%, based on patients' age and underlying severity of illness [34, 35]. However, mortality varies with pathology and can be as much as 45% for sepsis [26]. In part, the in-hospital mortality observed in NCC may be explained by the more frequent use of DNR and palliative care rather than allowing patients with devastating neurological disorders survive with severe disability. In PRINCE, we observed that DNR, comfort measures, and palliative care were initiated in 15%, 11%, and 7% of patients, respectively. In a study by Hua et al. [36], evaluating patients in general ICU, DNR was initiated in 8% of adults >65 years and 4% of adults <65 years. In the same study, about 1 in 7 patients were eligible for palliative care in a general ICU. However, whether these findings can be generalizable worldwide remains to be determined. Similar to general critical care, we observed that comfort care and DNR status were more frequent in countries with higher GNI [37].

Future Directions

The PRINCE Study provides the first detailed information about the care of neurocritically ill patients worldwide. There still are several important questions that need to be addressed including: the influence on mortality relative to the percentage of a nation's gross domestic product (GDP) assigned to healthcare; the impact of protocol-based management on patient mortality; variability of care within and across regions; type of neuroimaging and whether it is available 24 h a day; patterns of care to treat individual diagnoses; and long-term mortality and quality of life of survivors. We anticipate that the PRINCE Study can create a platform and serve as the springboard to address such issues in the future.

Conclusion

The PRINCE Study provides valuable data on care for NCC patients globally. Mortality of neurocritical patients appears to be associated with the severity of neurological injury and the absence of a dedicated NCCU.

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Authors' contributions
Jose I Suarez was involved in protocol development, data collection, data analysis, and manuscript writing/editing; Renee H Martin contributed to data collection, data management, data analysis, and manuscript writing/editing; Colleen Bauza took part in data collection, data management, data analysis, and manuscript writing/editing; Alexandros Georgiadis was involved in protocol development, data collection, data analysis, and manuscript writing/editing; Chethan P Venkatasubba Rao contributed to protocol development, data collection, data analysis, and manuscript writing/editing; Eusebia Calvillo took part in protocol development, data collection, data analysis, and manuscript writing/editing; J Claude Hemphill was involved in protocol development, data collection, data analysis, and manuscript writing/editing; Mauro Oddo contributed to protocol development, and manuscript writing/editing; Fabio Silvio Taccone took part in protocol development, and manuscript writing/editing; Peter D LeRoux was involved in protocol development, and manuscript writing/editing. The corresponding author confirms that authorship requirements have been met, the final manuscript was approved by ALL authors, and that this manuscript has not been published elsewhere and is not under consideration by another journal. There was no support for this work. The PRINCE Study adhered to ethical guidelines, and the IRB at the Baylor College of Medicine approved it with a waiver of consent. We used the STROBE reporting checklist for observational studies.

Compliance with ethical standards

Conflict of interest
Dr Suarez reports being the President of the Neurocritical Care Society, a member of the Editorial Board of Stroke Journal, and Chair of the DSMB for the INTREPID Study sponsored by BARD, outside of the submitted work. Dr LeRoux, Dr Bauza, Dr Sung, Dr Hemphill, Dr Oddo, Dr Martin, Dr Taccone, Dr Georgiadis, Dr Venkatasubba Rao, and Ms Calvillo have nothing to disclose.

Appendix
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