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ORIGINAL ARTICLE

Intensive Care Unit Admission for Patients in the INTERACT2 ICH Blood Pressure Treatment Trial: Characteristics, Predictors, and Outcomes

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Abstract

Background Wide variation exists in criteria for accessing intensive care unit (ICU) facilities for managing patients with critical illnesses such as acute intracerebral hemorrhage (ICH). We aimed to determine the predictors of admission, length of stay, and outcome for ICU among participants of the main Intensive Blood Pressure Reduction in Acute Cerebral Hemorrhage Trial (INTERACT2).

Methods INTERACT2 was an international, open, blinded endpoint, randomized controlled trial of 2839 ICH patients (<6 h) and elevated systolic blood pressure (SBP) allocated to receive intensive (target SBP <140 mmHg within 1 h) or guideline-recommended (target SBP <180 mmHg) BP-lowering treatment. The primary outcome was death or major disability, defined by modified Rankin scale scores 3–6 at 90 days. Logistic regression and propensity score analyses were used to determine independent associations.

Main Results Predictors of ICU admission included younger age, recruitment in China, prior ischemic/undetermined stroke, high SBP, severe stroke [National Institute of Health stroke scale (NIHSS) score ≥15], large ICH volume (≥15 mL), intraventricular hemorrhage (IVH) extension, early neurological deterioration, intubation and surgery. Determinants of prolonged ICU stay (≥5 days) were prior antihypertensive use, NIHSS ≥15, large ICH volume, lobar ICH location, IVH, early neurological deterioration, intubation and surgery. ICU admission was associated with higher-risk major disability at 90-day assessment compared to those without ICU admission.

Conclusions This study presents prognostic variables for ICU management and outcome of ICH patients included in a large international cohort. These data may assist in the selection and counseling of patients and families concerning ICU admission.

Keywords Intracranial hemorrhage · Intensive care unit · Outcome predictors · Mortality · Duration of stay

Katja E. Wartenberg and Xia Wang are joint primary authors.

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Introduction

Acute spontaneous intracerebral hemorrhage (ICH) is the most devastating and least treatable form of stroke that affects several million people in the world each year [1].

Though prognosis is strongly linked to initial clinical severity, and the size, location and growth of the hematoma [2–5], intensive care unit (ICU) admission and the associated expertise can improve outcome in certain types of ICH patients [6–10]. However, ICU access is variable both within and between countries, and increasingly limited with increasing demands in aging populations. In addition, compared to acute ischemic stroke, few critical care pathways or protocols exist and/or are routinely applied in the management of ICH patients; further exacerbating inequalities in treatment [11]. We aimed to determine the predictors of admission, length of stay, and outcome for ICU among participants with ICH in the large-scale, international, Intensive Blood Pressure Reduction in Acute Cerebral Hemorrhage Trial (INTERACT2).

Methods

Study Design and Participants

This is a post hoc analysis of the INTERACT2 trial, the design and main results of which are described in detail elsewhere [12, 13]. Briefly, the study included 2839 adult patients with acute spontaneous CT-confirmed ICH within 6 h of onset and sustained elevated systolic blood pressure (SBP 150–220 mmHg), who were eligible to receive active management. Exclusion criteria encompassed having: (a) a clear indication for, or contraindication to, intensive BP lowering; (b) definite evidence that ICH was secondary to a structural brain abnormality; (c) severe condition defined by coma (scores 3–5 on the Glasgow coma scale (GCS) [14]), concurrent medical illness, a high likelihood of early death, or massive ICH; (d) patients with known pre-stroke advanced dementia or disability [e.g., modified Rankin scale (mRS) score of 3–5] and (e) where early surgery was planned. All relevant ethics committees approved the study, and informed consent was obtained from all patients or relevant surrogates. The study is registered with ClinicalTrials.gov (NCT00716079).

Procedures

Demographic and clinical characteristics of patients were captured upon enrollment. Scores on the GCS [14] and National Institutes for Health Stroke Scale (NIHSS) [15] were recorded by appropriately qualified personnel to measure neurological status and stroke severity immediately prior to randomization and 24 h later. Patients were randomly assigned to receive early intensive BP-lowering treatment (according to a standardized protocol to achieve a SBP goal of <140 mmHg within 1 h, commencing with an intravenous agent and changed to oral agents when feasible to maintain the SBP goal for at least 7 days) or guideline-recommended best practice BP control (SBP <180 mmHg). Clinical and management data were recorded upon enrollment and over the next 7 days of hospital admission (or until death/discharge, whichever occurred soonest). These data included any ICU admission during first 7 days, key management procedures, and duration of ICU, as well as overall hospital stay. Patients admitted to ICU following local protocols according to the attending clinician, since this pragmatic study did not provide particular criteria for ICU admission. Date of ICU admission was not recorded. Brain imaging was performed according to standardized techniques and analyzed centrally by trained staff blinded to clinical data, treatment and sequence of scan. ICH volume and growth were calculated using computer-assisted multi-slice planimetric and voxel threshold techniques. Trained local staff unaware of group assignment or treatments followed up patients in person or by telephone at 90 days. Clinical outcomes were the combined and separate endpoints of death and major disability (mRS [16, 17] scores 3–6, 6, and 3–5, respectively).

Statistical Analysis

A logistic regression model was used to identify baseline, clinical, and neuroradiological variables associated with admission to ICU and subsequent duration of stay ≥ 5 days (based on a median ICU stay of 5 days). Significant univariate variables and others considered clinically important, including gender and randomization to intensive BP-lowering treatment, were entered into the first model. A second model was created that included all previous parameters, important management variables of intubation or neurosurgical intervention, as well as neurological deterioration within the first 24-h post-randomization, defined as an increase in NIHSS of ≥ 4 points or a decline of ≥ 2 in GCS from baseline to 24 h. The full model was reduced by successively removing nonsignificant covariates until all remaining predictors remained statistically significant.

A logistic regression model that included all the significant covariates, plus gender, is outlined in Supplemental Table 1 and was constructed to estimate the propensity score (PS) for ICU admission. We used optimal matching 1:1 without replacement, and an initial caliper width matching algorithm that equates to 0.17 (20% of the SD of the logit of the PS) [18]. Generalized estimating equations were used to test the effect of ICU admission on the primary and secondary outcomes, accounting for matching in the PS-matched subpopulation [19]. Pre- and post-matching balance of covariates between the ICU admission groups was assessed by using standardized difference, with values closer to zero indicating better balance

[20]. After PS matching, all the covariates were <0.05, which indicated good balance between ICU admission groups (Supplementary Table 2). We also conducted an analysis that was stratified across fifths of the PS. A summary estimate was calculated using unadjusted logistic regression stratified by PS strata as previous stated [21]. Finally, PS was used as a covariate in the logistic model to assess the impact of ICU admission.

Data are reported with odds ratios (OR) and 95% confidence intervals (CI). A two sided P value <0.05 was set as the level for statistical significance. All statistical analyses were performed using SAS version 9.3 (SAS Institute, Cary, NC, USA).

Results

Of 2779 patients with available data, 1061 (38%) were admitted to ICU; all other patients were managed in an acute stroke unit. Table 1 describes the baseline patient characteristics and their management over the first 7 days of hospital admission according to ICU admission. Multivariate regression analysis shows that ICU admission was associated with younger age, China region of recruitment, prior history of ischemic/undifferentiated stroke, increased stroke severity (NIHSS $\geq$15), higher SBP, left hemisphere location, larger hematoma volume, and IVH extension (Table 1). After adjusting for management factors (neurological decline in first 24 h, intubation, and any surgical intervention), only China region and SBP were predictors of ICU admission (Model 2, Table 1). With respect to differences in management over the first 7 days of hospital admission, ICU-treated patients were more likely to have experienced early neurological deterioration, to have received intravenous mannitol, intubation, and mechanical ventilation, and to have undergone hematoma evacuation or other neurosurgical intervention, including ventricular drain insertion.

Median duration of ICU stay was five days (interquartile range 3–7), and this figure did not differ significantly between high- and middle-income countries (Supplementary Table 3). Independent predictors of longer ICU admission, defined as a median of or greater than five days, were determined (Table 2). After multivariable analysis, adjusting for pre-specified baseline and management factors, only prior antihypertensive therapy use, lobar ICH location, IVH, and intubation and surgical intervention were the significant predictors of prolonged ICU admission (Table 2).

At 90 days after ICH, 1454/2779 (53%) patients were dead or had residual major disability (mRS 3–6); 286 (10%) deaths and 1168 (48%) with major disability (mRS scores 3–5). Sixty percent (632/1061) of ICU patients were dead or remained with residual major disability at 90 days, with higher rates of death or major disability (mRS 3–5) compared to those managed on an acute stroke unit: 13 versus 9 and 54 versus 44%, respectively ($P < 0.001$). In the PS matching population, ICU admission was significantly associated with higher risk of death or major disability (OR 1.22, 95% CI 1.01–1.48; $P = 0.040$), but this was driven by major disability (OR 1.28, 95% 1.05–1.57; $P = 0.017$) and not death (OR 0.86, 95% CI 0.62–1.20; $P = 0.377$). PS stratification and adjusted models showed consistent results (Table 3).

Discussion

Acute ICH is a condition that is associated with significant morbidity and mortality, and patients often require ICU admission—nearly 40% in this trial clinical cohort. Nonetheless, there is significant inequity in ICU access, both within and between countries, which may in part reflect limited critical care pathways and protocols for this patient group. Although ICU care and monitoring may improve a patient's chances of survival and reduce the duration of hospital stay and costs [6–9], access and utilization of this resource is limited in many parts of the world. This is an increasingly important issue as more patients are requiring critical care as a consequence of an aging population, but with limited numbers of intensivists [22]. In the face of limited capacity and expertise, risk stratification for requiring ICU care may be one approach to improve consistency and efficiency in the use of this resource. Our analysis has identified a set of clinical variables that predict management and outcomes for ICU, which could be considered as a guide to triaging decisions.

It seems plausible to consider ICU admission for ICH patients on the basis of age, stroke severity defined by clinical grade (hematoma location and volume, and the presence of IVH), vital signs, particularly of SBP level, and history of previous stroke. [23, 24], The finding of a greater likelihood of ICU admission for patients in China is less generalizable and most likely reflects the service and cultural aspects of care in this country, as well as the large volume of recruitment of patients from large Chinese academic centers in this study.

In regard to duration of ICU stay, and thus resource use, this was significantly related to prior antihypertensive therapy use, lobar ICH location, IVH, intubation and surgical intervention. It is possible that prior antihypertensive use identified a selected patient subgroup, perhaps who had end organ damage from chronic hypertension, who required more intensive BP treatment and monitoring, which led to a longer ICU stay. Some of the therapeutic interventions in the ICU observed in this study deserve

Table 1 Characteristics and predictors of admission to intensive care unit

Variable	Admission to ICU				Predictors of admission to ICU			
	No	Yes	OR (95% CI)	*P* value	Model 1		Model 2	
	(*N* = 1718)	(*N* = 1061)			aOR (95% CI)*	*P* value	aOR (95% CI)[a]	*P* value
Demographic								
Age, per 10-year increase	64 (13.0)	63 (12.6)	0.92 (0.87–0.98)	0.006	0.92 (0.86–0.99)	0.016	0.96 (0.89–1.03)	0.217
Male	1059 (62)	681 (64)	1.12 (0.95–1.31)	0.178				
China region	1128 (66)	757 (71)	1.30 (1.10–1.54)	0.002	1.45 (1.21–1.74)	0.01	1.79 (1.47–2.19)	<0.0001
Medical history								
Prior ICH	139 (8)	83 (8)	0.96 (0.73–1.28)	0.794				
Prior ischemic/UND stroke	179 (10)	138 (13)	1.28 (1.01–1.63)	0.039	1.31 (1.01–1.69)	<0.0001	1.24 (0.95–1.62)	0.122
Heart disease	182 (11)	114 (11)	1.02 (0.79–1.30)	0.908				
Diabetes mellitus	186 (11)	114 (11)	0.99 (0.77–1.27)	0.938				
History of hypertension	1224 (71)	789 (74)	1.17 (0.98–1.39)	0.082				
Current antihypertensive use	805 (47)	453 (43)	0.84 (0.72–0.98)	0.030				
Warfarin use	49 (3)	30 (3)	0.99 (0.62–1.57)	0.966				
Antiplatelet agent use	172 (10)	89 (8)	0.82 (0.63–1.08)	0.152				
Clinical features								
Time to randomization, h	3.7 (2.8–4.7)	3.8 (2.8–4.8)	1.01 (0.95–1.08)	0.694				
NIHSS ≥15	428 (25)	349 (33)	1.48 (1.25–1.76)	<0.001	1.38 (1.14–1.68)	0.001	1.22 (1.00–1.51)	0.056
SBP, per 10 mmHg increase	178 (17)	181 (17)	1.13 (1.08–1.18)	<0.001	1.12 (1.07–1.17)	<0.001	1.12 (1.07–1.18)	<0.0001
DBP, mmHg	100 (15)	102 (15)						
Deep hematoma[b]	1349 (85)	801 (82)	0.85 (0.69–1.05)	0.129				
Left hemisphere hematoma	776 (47)	518 (53)	1.20 (1.02–1.41)	0.025				
Hematoma volume, mL	9.9 (5.4–17.5)	12.3 (6.3–21.5)	1.26 (1.16–1.37)	<0.001	1.01 (1.01–1.02)	0.0004	1.00 (1.00–1.01)	0.753
Intraventricular extension	403 (25)	315 (32)	1.42 (1.19–1.69)	0.001	1.36 (1.13–1.63)	0.001	1.20 (0.99–1.46)	0.064
Intensive BP treatment	847 (49)	532 (50)	1.03 (0.89–1.21)	0.667				
Management after randomization								
Early neurological decline[c]	198 (11.6)	211 (20.1)	1.92 (1.55–2.37)	<0.001			1.17 (0.90–1.52)	0.244
Intubation	28 (1.6)	161 (15.2)	10.80 (7.17–16.26)	<0.001			9.77 (6.05–15.78)	<0.001
VTE prophylaxis	391 (22.8)	219 (20.6)	0.88 (0.73–1.06)	0.190				
Compression stockings	163 (10)	130 (12)						
Subcutaneous heparin	332 (19)	161 (15)						
Intravenous mannitol	978 (57)	741 (70)	1.75 (1.49–2.06)	<0.001				
Hemostatic therapy	56 (3.3)	41 (3.9)	1.19 (0.79–1.80)	0.399				

Table 1 continued

Variable	Admission to ICU				Predictors of admission to ICU			
	No	Yes	OR (95% CI)	*P* value	Model 1		Model 2	
	($N = 1718$)	($N = 1061$)			aOR (95% CI)*	*P* value	aOR (95% CI)[a]	*P* value
Any surgical intervention	31 (1.8)	123 (11.6)	7.14 (4.77–10.67)	<0.001			3.62 (2.29–5.70)	<0.001
Evacuation of hematoma	20 (1)	61 (6)						
Ventricular drain insertion	12 (1)	73 (7)						
Decision to withdrawal active care	76 (4.4)	45 (4.2)	0.96 (0.66–1.40)	0.820				

Data are shown in *n* (%), mean (SD), or median (IQR)

BP blood pressure, *CI* confidence interval, *CT* computerized tomography, *DBP* diastolic blood pressure, *GCS* Glasgow coma scale, *ICU* intensive care unit, *NIHSS* National Institutes of Health Stroke Scale, *SBP* systolic blood pressure, *UND* undetermined stroke, *VTE* venous thromboembolism

[a] Model 2 includes variables from Model 1 plus neurological deterioration in first 24-h post-randomization, and intubation and any surgical intervention

[b] Refers to location of hematoma in the basal ganglia or thalamus

[c] Defined as an increase of ≥4 on the NIHSS or a decline of ≥2 on the GCS from baseline to 24 h

* Model 1 includes all baseline significant variables in the univariate analysis, plus gender and intensive BP treatment. We reduced the full model by successively removing the nonsignificant covariates until all the remaining predictors remained statistically significant ($P < 0.05$)

clarification. Intravenous mannitol infusion was administered in China as routine therapy within a standardized protocol for treatment of ICH regardless of whether there was suspected or confirmed raised intracranial pressure. The preference for the use of compression stockings rather than prophylactic heparin for venous thromboembolism prophylaxis likely reflects clinicians' concerns about the potential for hematoma expansion or hemostatic problems should surgical evacuation be required [25].

The combined poor 90-day outcome of death and major disability was higher in ICH patients admitted to ICU than those managed on acute stroke units, was driven by the latter component, and may relate to an early survivor bias and the effects of larger hematoma volume and initial clinical severity after ICH [2–5, 23, 24]. It is likely, though, that patients with these factors were more likely to be treated in an ICU setting as part of active therapy through participation in a clinical trial of intensive BP lowering. Nevertheless, while PS matching and complementary analyses produced consistent results, the outcome of major disability might have been related to unmeasured variables that were not accounted for in the PS model, such as re-bleeding, later neurological deterioration, or other complications such as ventriculitis. Ninety-day outcomes, whether assessed by combined death and major disability or the separate components, were worse in those participants who required ICU care. The association between shorter time from onset to randomization and worse outcomes can be explained by the finding that patients randomized earlier had larger hematoma volumes and higher rates of hematoma expansion, factors known to be associated with worse functional outcome [26–30].

Strengths of this study include the large heterogeneous sample of patients recruited from a diverse range of hospitals and health-care settings, who were assessed according to a standardized protocol and objective outcome measures. The limitations include the limited range of variables that were assessed mainly at the time of hospital presentation as part of a large-scale pragmatic clinical trial. Factors that determine ICU admission, such as advance directives, change in physiological parameters and comorbid variables, and of adverse events, were not predefined or adjudicated and thus could not be included in analyses. ICU admission was decided by the treating teams, and local preferences and service availability would also influence decisions about care. As these analyses were not pre-specified, they are prone to random error and residual confounding. Finally, as this study was based on a clinical trial population, which excluded patients with profound coma (GCS score 3–5), significant previous disability, and those for whom early surgery was planned, the findings may not be readily applied to severe cases of ICH.

Table 2 Predictors of long duration of stay (≥5 days) in an ICU

Variable	Duration of ICU stay				Multivariable			
	<5 days ($n = 458$)	≥5 days ($n = 602$)	OR (95% CI)	*P* value	Model 1		Model 2	
					aOR (95% CI)[a]	*P* value	aOR (95% CI)[b]	*P* value
Demographic								
Age, per 10-year increase	62 (12)	63 (13)	1.05 (0.95–1.15)	0.345				
Male	284 (62)	396 (66)	1.18 (0.92–1.52)	0.205				
Chinese region	338 (74)	418 (69)	0.81 (0.62–1.06)	0.120				
Medical history								
Prior ICH	30 (7)	53 (9)	1.38 (0.87–2.19)	0.178				
Prior ischemic or UND stroke	58 (13)	80 (13)	1.06 (0.74–1.52)	0.765				
Heart disease	51 (11)	63 (11)	0.93 (0.63–1.38)	0.726				
Diabetes mellitus	49 (11)	65 (11)	1.01 (0.68–1.50)	0.959				
History of hypertension	342 (75)	446 (74)	0.97 (0.73–1.28)	0.829				
Antihypertensive use	177 (39)	276 (46)	1.34 (1.05–1.72)	0.019	1.36 (1.04–1.78)	0.023	1.33 (1.01–1.75)	0.042
Use of warfarin anticoagulation	16 (4)	14 (2)	0.66 (0.32–1.36)	0.259				
Use of an antiplatelet agent	36 (8)	53 (9)	1.13 (0.73–1.76)	0.583				
Clinical features								
Time to randomization, h	3.7 (2.8–4.8)	3.8 (2.9–4.8)	1.05 (0.95–1.16)	0.343				
NIHSS ≥15	122 (27)	227 (38)	1.67 (1.28–2.18)	0.002	1.44 (1.07–1.93)	0.015	1.31 (0.96–1.77)	0.085
Systolic BP, per 10 mmHg increase	180 (17)	182 (16)	1.05 (0.98–1.13)	0.157				
Deep location of hematoma[c]	361 (86)	439 (80)	0.65 (0.46–0.91)	0.012	0.63 (0.44–0.89)	0.010	0.65 (0.46–0.94)	0.020
Left hemisphere site of hematoma	224 (53)	293 (53)	1.00 (0.77–1.28)	0.969				
Hematoma volume ≥15, mL	146 (35)	242 (44)	1.47 (1.13–1.91)	0.004	1.36 (1.03–1.81)	0.032	1.19 (0.89–1.59)	0.253
Intraventricular extension	116 (28)	199 (36)	1.48 (1.13–1.95)	0.005	1.51 (1.14–2.01)	0.004	1.43 (1.07–1.91)	0.015
Management post-randomization								
Intensive BP lowering	230 (50)	302 (50)	1.00 (0.78–1.27)	0.987				
Neurological deterioration[d]	70 (15)	141 (24)	1.70 (1.24–2.33)	0.001			1.25 (0.87–1.79)	0.236
Intubation	38 (8)	123 (20)	2.84 (1.93–4.18)	<0.001			1.60 (1.03–2.49)	0.038
Any surgical intervention	28 (6)	95 (16)	2.88 (1.85–4.47)	<0.001			1.85 (1.14–3.02)	0.014

Data are shown in *n* (%), mean (SD), or median (IQR)

BP blood pressure, *CI* confidence interval, *aOR* adjusted odds ratio, *GCS* Glasgow coma scale, *ICU* intensive care unit, *NIHSS* National Institutes of Health Stroke Scale, *CT* computerized tomography, *UND* undetermined stroke

[a] Model 1 includes all baseline significant variables in the univariate analysis, plus gender and intensive BP treatment

[b] Model 2 includes variables from Model 1 plus neurological deterioration in first 24 h post-randomization, and intubation and any surgical intervention

[c] Refers to location of hematoma in the basal ganglia or thalamus

[d] Defined as an increase from baseline to 24 h of ≥4 on the NIHSS or a decline of ≥ 2 on the GCS

Table 3 Association between ICU admission and outcome

	Overall population					PS-matched population		
Analysis method		Stratification		PS adjusted		PS matching		
Admission to ICU	*n* (%)	OR (95% CI)	*P* value	OR (95% CI)	*P* value	*n* (%)	OR (95% CI)	*P* value
Death or major disability								
No	822 (48.5)	1.0		1.0		407 (50.5)	1.0	
Yes	632 (60.3)	1.40 (1.18–1.66)	0.0001	1.23 (1.03–1.46)	0.021	447 (55.5)	1.22 (1.01–1.48)	0.040
Death								
No	148 (8.7)	1.0		1.0		79 (9.8)	1.0	
Yes	138 (13.2)	1.16 (0.88–1.54)	0.285	0.87 (0.65–1.18)	0.371	69 (8.6)	0.86 (0.62–1.20)	0.377
Major disability								
No	674 (43.6)	1.0		1.0		328 (45.1)	1.0	
Yes	494 (54.2)	1.41 (1.18–1.69)	0.0002	1.29 (1.08–1.55)	0.006	378 (51.3)	1.28 (1.05–1.57)	0.017

ICU intensive care unit; PS, propensity score

In conclusion, this study presents management and prognostic issues of ICH patients admitted to ICU from a large international cohort. These findings may contribute to improve risk stratification and allow appropriate selection of ICH patients most likely to benefit from ICU admission.

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Authors' contributions KEW and PMV made substantial contribution to conception, design, acquisition and interpretation of data, drafted manuscript, and gave final approval of version to be published and agreement to be accountable for all aspects of the work; XW made substantial contribution to data analysis, drafted manuscript, and gave final approval of version to be published and agreement to be accountable for all aspects of the work; CA and TR made substantial contribution to conception, design, acquisition, analysis and interpretation of data, critical input to the final version to be published and gave final approval of version to be published and agreement to be accountable for all aspects of the work; AAR, HA, PML, RIL, and JC made substantial contribution to acquisition of data and gave critical input to the final version to be published.

Compliance with Ethical Standards

Conflicts of interest Dr. Anderson reports grants from National Health and Medical Research Council (NHMRC) of Australia, during the conduct of the study; personal fees from Takeda China, personal fees from Astra Zeneca, personal fees from Medtronic, outside the submitted work; and Member of the Editorial Committee of the journals Stroke, Cerebrovascular Diseases and International Journal of Stroke. Other authors have no conflicts to declare.

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