Association between critical care admission and 6-month functional outcome after spontaneous intracerebral haemorrhage

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ABSTRACT

Background. There is uncertainty about the clinical benefit of admission to critical care after spontaneous intracerebral haemorrhage (ICH).

Purpose. We investigated factors associated with critical care admission after spontaneous ICH and evaluated associations between critical care and 6-month functional outcome.

Methods. We included 825 patients with acute spontaneous non-traumatic ICH, recruited to a prospective multicenter observational study. We evaluated the characteristics associated with critical care admission and poor 6-month functional outcome (modified Rankin Scale, mRS > 3) using univariable (chi-square test and Wilcoxon rank-sum test, as appropriate) and multivariable analysis.

Results. 286 patients (38.2%) had poor 6-month functional outcome. Seventy-seven (9.3%) patients were admitted to critical care. Patients admitted to critical care were younger (p<0.001), had lower GCS score (p<0.001), larger ICH volume (p<0.001), more often had intraventricular extension (p = 0.008) and underwent neurosurgery (p<0.001). Critical care admission was associated with poor functional outcome at 6 months (39/77 [50.7%] vs 286/748 [38.2%]; p = 0.034); adjusted OR 2.43 [95%CI 1.36-4.35], p=0.003), but not with death (OR 1.29 [95%CI 0.71 – 2.35; p = 0.4). In ordinal logistic regression, patients admitted to critical care showed an OR 1.47 (95% CI 0.98 – 2.20; p = 0.07) for a shift in the 6-month modified Rankin Scale.

Conclusions. Admission to critical care is associated with poor 6-month functional outcome after spontaneous ICH but not with death. Patients admitted to critical care were *a priori* more severely affected. Although adjusted for main known predictors of poor outcome, our findings could still be confounded by unmeasured factors. Establishing the true effectiveness of critical care after ICH requires a randomized trial with clinical outcomes and quality of life assessments.

INTRODUCTION

Acute spontaneous intracerebral haemorrhage (ICH) accounts for about 15% of all strokes, affecting approximately 2 million people worldwide each year[1]. ICH remains the deadliest and least treatable form of stroke; almost half of patients die within the first month, and 80% of survivors are dependent on a caregiver[2].

The term “critical care” refers to care in a high-dependency unit (HDU) and/or Intensive Care Unit (ICU)[3] and provides specialized, continuous, multidisciplinary care for patients with a life-threatening, but treatable, condition. Projections show that the overall stroke burden in Europe will further increase by 35% by 2050[4]. This, combined with changing population demographics and improved chronic disease management, may potentially lead to more patients being considered for critical care treatment. Given the healthcare costs of acute care and for survivors that extend beyond admission, this trend might be unsustainable[5].

Currently, decisions about access to critical care for ICH patients are variably decided on by local preferences and bed availability, with few standardised care pathways or protocols. This has resulted in a lack of clear guidance on which patients might benefit. Some clinicians consider critical care to have little value for ICH[6, 7], yet clinical nihilism (including early DNAR [do not attempt resuscitation] orders) is independently associated with a poor outcome after ICH.[8, 9, 10]

We aimed (1) to investigate factors associated with critical care admission after spontaneous ICH and (2) to evaluate the association between critical care admission and 6-month functional outcome in a UK prospective, multicentre, hospital-based observational study.

MATERIALS AND METHODS

Patient Selection

This is a post hoc analysis of The Clinical Relevance of Microbleeds In Stroke Study, (CROMIS-2 ICH), a prospective multicentre observational cohort study of patients with acute spontaneous ICH. Full details of the study protocol are described in detail elsewhere[11]. The study included adult patients with neuroimaging-confirmed ICH from 79 centres in the UK (and 1 in the Netherlands) between August 2011 and July 2015. The study protocol excluded secondary causes for ICH, such as major head trauma in previous 24 hours, vascular malformations, tumours, cavernomas, intracranial aneurysms, other known coagulopathy, or haemorrhagic transformation of an infarction. The study was approved by the National Research Ethics Service (IRAS reference 10/HO716/61). Written informed consent was obtained from all patients (or a relevant consultee or legal representative per local legislation).

Demographic, clinical and radiological characteristics of patients were collected. Patients were admitted to critical care following local standard clinical practice according to the attending clinician. Brain imaging was performed at each study centre per standardised techniques and analysed centrally by trained staff. ICH location was defined according to The Cerebral Hemorrhage Anatomical RaTing inStrument (CHARTS)[12]. Intraventricular extension was rated by experienced raters. Haematoma volume was calculated using a previously described validated semi-automated planimetric method[13]. Long-term functional outcome was measured at 6 months through modified Rankin scale (mRS)[14]. mRS was dichotomized as good (0-3) and poor (4-6). We undertook follow-up by postal questionnaire at 6 months using a validated outcome self-reporting questionnaire[15]. For non-responders, we checked that they were still alive with their General Practitioner (GP) and re-sent the questionnaire. In the event that data were still not obtained, follow-up was then obtained by standardised telephone interview using a validated patient follow-up questionnaire[15]. Only patients with complete follow-up and all clinical and radiological variables of interest were included in the analysis.

Statistical analysis

We described continuous and categorical variables using mean and standard deviation (SD), median and interquartile range (IQR), or as number and percentage, as appropriate. In univariable analysis, we used chi-square and Wilcoxon/Mann–Whitney tests as appropriate.

Univariate comparisons between critical care vs non-critical patients were used to identify differences in the groups and predictors of critical care admission. Widely accepted clinical and radiological variables considered to be relevant [16, 17, 18, 19, 20, 21] were used for the comparison. Similarly, univariable comparison between good vs poor long-term functional outcome was performed (chi-square and Wilcoxon/Mann–Whitney tests as appropriate). After checking for multicollinearity (Pearson r correlation, cut-off 0.5), variables found to be statistically significant in univariate models ($p < 0.1$) were included in multivariable logistic regression model with mRS at 6-months (dichotomized: good [mRS 0-3] vs poor [mRS 4-6]). We did sensitivity analyses for: (1) outcome good mRS defined as mRS 0-2; (2) using ordinal logistic regression for a shift in the mRS at 6 months and (3) death. Results are reported as odds ratios (OR) with 95% confidence intervals (CI). The significance level was set at p=0.05. Statistical analysis was performed using STATA 16 (StataCorp. 2011. *Stata Statistical Software: Release 16*. College Station, TX: StataCorp LP).

RESULTS

Of the original cohort of patients included in the CROMIS-2 (ICH) study (n=1037), we excluded 131 (12.6%) patients without 6-month follow-up data, and 81 (7.8%) patients with missing essential clinical or radiological variables (Figure 1). Included and excluded patients were similar in terms of clinical and radiological characteristics.

The final cohort consisted of 825 patients; Table 1 shows baseline clinical characteristics, radiological variables and outcome in the entire cohort, critical care and non-critical care admitted patients. Median age was 75.7 years (IQR 16.6), 352 patients were female (42.7%), 555 (67.3%) suffered from hypertension and 151 (18.3%) from diabetes mellitus. Median GCS at presentation was 15 (IQR 1). Three hundred and forty-one patients (41.3%) were on anticoagulant drugs at the time of index event; 118 (14.3%) had a pre-ICH mRS > 2. In the entire cohort, 409 patients (49.6%) experienced deep ICH, 348 (42.2%) lobar ICH and 68 (8.2%) infratentorial. Median ICH volume was 7 ml (IQR 15.2); intraventricular extension was present in 245 patients (29.7%).

Critical care and non-critical care

Seventy-seven patients (9.3%) were admitted in critical care and 748 (90.7%) in non-critical care units (including any other ward other than intensive care and/or a high dependency unit [HDU]). Patients admitted to critical care were significantly younger than those not admitted (median age: 65.0 years [IQR 13.1] vs 76.3 years [IQR 15.6]; $p < 0.001$) and had lower GCS scores (median GCS: 14 [IQR 3] vs 15 [IQR 1]; $p < 0.001$), more frequently underwent neurosurgery (21/77 [27.3%] vs 4/748 [0.43%]; $p < 0.001$) and received blood pressure lowering treatment (38/77 [49.4%] vs 136/748 [18.2%]; $p < 0.001$). Neuroimaging findings showed that critical care admitted patients had larger ICH volumes (median volume: 14.0 ml [IQR 25.8] vs 6.9 ml [IQR 14.2]; $p < 0.001$) and were more likely to have intraventricular extension (33/77 [42.9%] vs 212/748 [28.3%]; $p = 0.008$). Critical care patients had poorer long-term mRS than non-critical care patients (mRS > 3 in 39/77 [50.7%] vs 286/748 [38.2%]; $p = 0.034$).

Outcome at 6-months

Clinical and radiological variables associated with poor (mRS > 3) 6-months functional outcome are reported in Table 2 (univariable analysis). Critical care admission (OR 1.66 [95%CI 1.04-2.65]; $p = 0.035$), age (OR 1.06 per year increase [95%CI 1.05-1.08]; $p < 0.001$), female gender (OR 2.17 [1.64-2.89]; $p < 0.001$), baseline GCS (OR 0.66 per point [95%CI 0.60-0.73]; $p < 0.001$), arterial hypertension (OR 1.62 [95%CI 1.19-2.20]; $p = 0.002$), diabetes mellitus (OR 1.91 [95%CI 1.34-2.72]; $p < 0.001$), anticoagulant therapy at the time of index event (OR 1.42 [95%CI 1.07-1.88]; $p = 0.016$) and pre-ICH mRS > 2 (OR 1.44 [95%CI 0.65-3.19]; $p < 0.001$) were all associated with poor 6-month functional outcome.

Regarding radiological variables, poor outcome was associated with larger ICH volume (OR 1.02 per ml increase [95%CI 1.01-1.03]; p < 0.001) and intraventricular extension (OR 2.46 [95%CI 1.81-3.34]; p < 0.001). No collinearity was found between any of the variables significantly associated with poor functional outcome (not shown).

In the multivariable model (Table 3) critical care admission maintained a significant association with poor 6-month functional outcome (OR 2.43 [95%CI 1.36-4.35]; p = 0.003). Other variables associated with poor outcome in a multivariable model were: age (OR 1.06 per year increase [95%CI 1.36-4.35]; p < 0.001), GCS (OR 0.72 per point [95%CI 0.65-0.81]; p < 0.001), ICH volume (OR 1.01 per ml increase [95%CI 1.00-1.02]; p = 0.033), IV extension (OR 1.83 [95%CI 1.27-2.62]; p = 0.001), female gender (OR 1.65 [95%CI 1.18-2.31]; p = 0.003), diabetes mellitus (OR 2.15 [95%CI 1.40-3.30]; p < 0.001) and pre-ICH mRS >2 (OR 2.95 [95%CI 1.84- 4.74]; p < 0.001).

Sensitivity analysis

In a sensitivity analysis, we evaluated alternative approaches to assessment of poor outcome. We considered 1) mRS>2 as poor functional outcome, 2) ordinal regression analysis of full range of mRS scores and 3) death. The univariable odds ratio for critical care for outcome mRS>2 was very similar to that for mRS>3 (OR 1.69 [95% CI 1.00-2.85; p = 0.047] and OR 1.66 [95%CI 1.04-2.65; p = 0.034], respectively. In multivariable analysis, given critical care admission the odds ratio for mRS>2 (OR 1.95 [95%CI 1.06-3.58; p = 0.032]) ant the OR for death (OR 2.14 [95%CI 1.03-4.43; p = 0.041]) are slightly lower than the one for mRS>3 (OR 2.43 [95%CI 1.36-4.35; p = 0.003), but the association is still consistent (Appendix e-2 and Appendix e-3). In ordinal logistic regression analysis, patients admitted to critical care showed an OR 1.47 (95% CI 0.98 – 2.20; p = 0.07) for a shift in the 6-month modified Rankin Scale score. Univariate associations between clinical and radiological characteristics and outcome mRS>2 (e-1). The distribution of mRS scores at 6-months are reported in Figure 2. The univariable odds ratio for critical care for death at 6-months is 1.29 (95%CI 0.71 – 2.35; p = 0.4).

DISCUSSION

We found that critical care admission is strongly associated with poor 6-month functional outcome after spontaneous ICH (both in univariable and multivariable analysis). However, as expected, patients who require critical care have more severe ICH and ICU admission is not associated with higher rate of death. Despite adjustment for markers of ICH severity and poor prognosis (including lower GCS scores, large ICH volume, intraventricular extension and surgery), we cannot fully exclude unmeasured confounding factors, so residual confounding exists.

The characteristics we found to be associated with critical care admission are consistent with previous data. A *post hoc* analysis of The Intensive Blood Pressure Reduction in Acute Cerebral Hemorrhage Trial 2 (INTERACT2) study found that predictors of ICU admission included (among others) younger age, clinically severe ICH (NIHSS > 14), large ICH volumes, intraventricular extension and surgery[22]. There are few formal critical care pathways or protocols to guide the management of ICH patients. Without a standardized approach, critical care admission is decided by treating physician, per local preferences and availability. The lack of critical care pathways is also reflected in the different proportion of patients admitted to critical care across studies and countries. In our study, only a small proportion of patients (9.3%) were admitted to critical care, confirming that only the most severely affected patients are referred. However, in INTERACT2 study, up to 40% of patients required intensive care unit (ICU) admission. This major difference may be due to the higher proportion of ICU admission in Chinese hospitals (71% of ICU patients were admitted in Chinese ICUs) and most likely reflects service and cultural differences[23].

Regarding outcome after critical care admission, one might expect that continuous intensive care and multidisciplinary expertise can improve outcome. However, our findings are in line with existing evidence that suggests that admission to critical care after ICH is associated with a higher risk of major disability[22, 24, 25, 26, 27, 28] even after adjusting for baseline ICH severity. However, when considering differences in death between admitted and non-admitted patients to critical care we did not find any relevant differences (OR for death after critical care admission: 1.29 [95%CI 0.71 – 2.35; p = 0.4]). Given that the aim of ICU admission could be to prevent death, and considering that more severe patients are generally those admitted to critical care units, our results can be interpreted as a relative success of critical care unit in ICH management (despite a larger proportion of disabled patients at 6 months). Further evaluation, with randomised trials, is needed to evaluate the true effectiveness of critical care in optimising long-term functional outcome after ICH.

Beside critical care admission (and clinical/radiological severity-related variables), we found that increasing age and female gender are significantly associated with a poor outcome after ICH; this is again consistent with existing evidence.[21, 29]

We measured 6-month outcome using the mRS, which is heavily weighted towards motor disability and does not fully reflect health-related quality of life (HRQol) measures. The score implies that death (mRS 6) is worse than severe disability (mRS 5), whereas the opposite view could be argued.[30] More qualitative research on the lived experiences of stroke survivors (and their carers and family members) is required to fully elucidate the true effectiveness of critical care.

Due to severity of ICH we used mRS>3 to define poor functional outcome, but many studies on cerebrovascular disease use a cutoff of mRS>2 or ordinal regression analysis. In our sensitivity analysis, we found that univariable and multivariable odds ratio (for critical care) for mRS>2 and death are lower but still coherent to that for the mRS>3. However, using ordinal regression analysis we found a slightly lower odds ratio for a shift in scores on the modified Rankin Scale. Other independent studies are needed to elucidate the role of critical care admission in optimizing outcome after ICH.

Our study has strengths as it included a large population cohort with a multicentre design therefore our results should be generalizable to western populations. Some limitations deserve comment. The CROMIS-2 study required signed informed consent. This could have created a selection bias towards non-extremely severe ICH. Although we adjusted for factors known to influence outcome after ICH, only a small proportion of patients (9.3%) were admitted to critical care, limiting statistical power and precision. Additionally our sample lacked detailed data on care pathways therefore residual confounding could still be a factor. We could not adjust our models for advanced directives, frailty, or unrecorded changes in physiological parameters.

CONCLUSION

Our study suggests that, after spontaneous ICH, admission to critical care is associated with poor functional outcome at 6-months but not with death. However, patients admitted to critical care were generally more severely affected, with higher *a priori* potential to suffer neurological deterioration and poor outcome. Despite adjustment for main known available markers of ICH severity and poor prognosis we cannot exclude unmeasured confounding. Further evaluation, ideally in randomised trials, is needed to elucidate the true effectiveness of critical care in optimising long-term outcome for ICH patients.

CONFLICT OF INTEREST: There are no conflicts of interest.

DISCLOSURES: None

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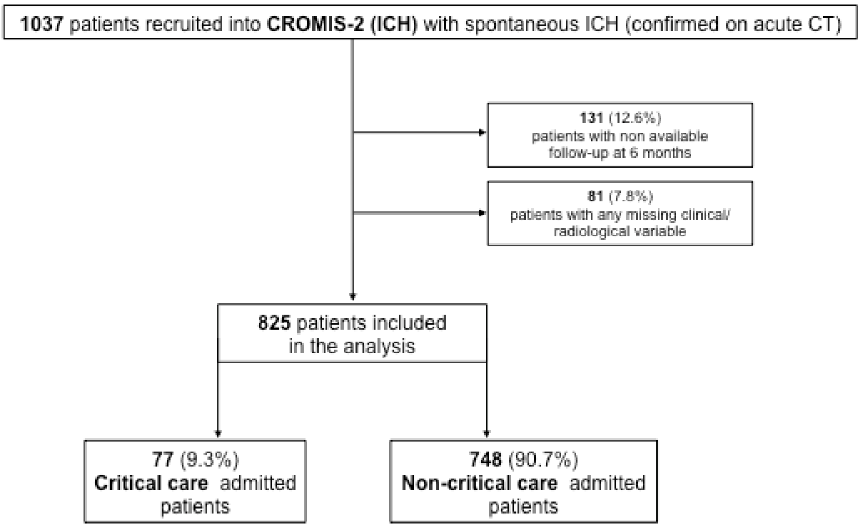
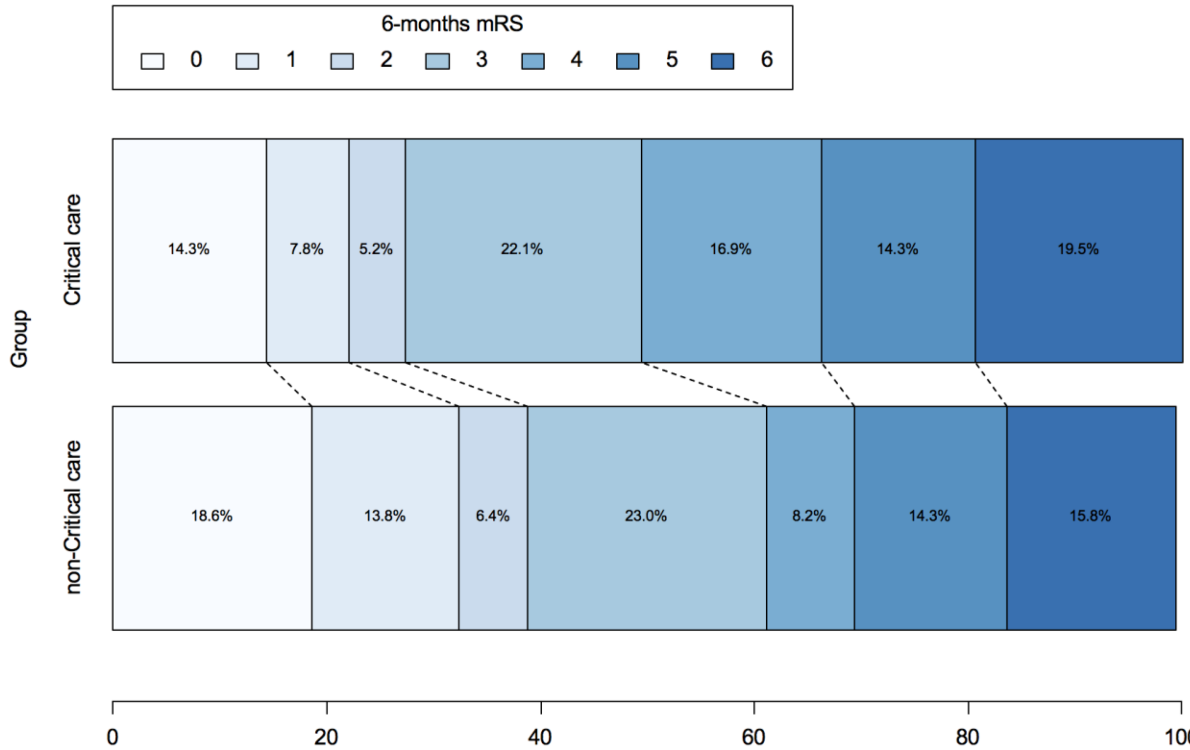


Figure 1. Study population

Figure 2. Modified Rankin Scale scores according to critical care admission



mRS, modified Rankin Scale

Table 1. Clinical, radiological characteristics and outcome in the entire cohort and univariate associations with critical care admission

	Entire cohort N (%)	**Critical Care N (%)**	**Non-Critical Care N (%)**	**P value**
N (%)	*825*	*77 (9.3)*	*748 (90.7)*	
Age (median; [IQR])	75.7 [16.6]	65.0 [13.1]	76.3 [15.6]	<0.001
Female gender	352 (42.7)	27 (35.1)	325 (43.5)	0.157
GCS (median; [IQR])	15 [1]	14 [3]	15 [1]	<0.001
ICH volume*(median; [IQR])	7.0 [15.2]	14.0 [25.8]	6.9 [14.2]	<0.001
Intra-ventricular extension	245 (29.7)	33 (42.9)	212 (28.3)	0.008
ICH location				0.500
Deep	409 (49.6)	41 (53.2)	368 (49.2)	
Lobar	348 (42.2)	28 (36.4)	320 (42.8)	
Infratentorial	68 (8.2)	8 (10.4)	60 (8.0)	
Arterial Hypertension	555 (67.3)	53 (68.8)	502 (67.1)	0.760
Diabetes Mellitus	151 (18.3)	18 (23.4)	133 (17.8)	0.227
Oral anticoagulant drug	341 (41.3)	26 (33.8)	315 (42.1)	0.157
Pre-ICH mRS > 2	118 (14.3)	6 (7.8)	112 (15.0)	0.087
Neurosurgery	25 (3.0)	21 (27.3)	4 (0.43)	<0.001
Blood Pressure lowering treatment	174 (21.1)	38 (49.4)	136 (18.2)	<0.001
mRS at 6 months				0.157
0	150 (18.2)	11 (14.3)	139 (18.6)	

1	109 (13.2)	6 (7.8)	103 (13.8)	
2	52 (6.3)	4 (5.2)	48 (6.4)	
3	189 (22.9)	17 (22.1)	172 (23.0)	
4	74 (9.0)	13 (16.8)	61 (8.2)	
5	118 (14.3)	11 (14.3)	107 (14.3)	
6	133 (16.1)	15 (19.5)	118 (15.8)	
mRS >3 at 6 months	325 (39.4)	39 (50.7)	286 (38.2)	0.034
mRS >2 at 6 months	514 (62.3)	56 (72.7)	458 (61.2)	0.047

**ml*

ICH, intra-cerebral haemorrhage; GCS, Glasgow Coma Scale; mRS, modified Rankin Scale

Table 2. Clinical and radiological characteristics and univariate associations with poor functional outcome at 6 months (mRS >3)

Variable	Poor outcome	OR (95% CI)	P value
Non-critical care	286 (38.2)	REF	
Critical care	39 (50.7)	1.66 (1.04-2.65)	0.035
Age (median [IQR])	80.7 [12.8]	1.06 (1.05-1.08) *	<0.001
Female gender	176 (50.0)	2.17 (1.64-2.89)	<0.001
Male gender	149 (31.5)	REF	
GCS (median; [IQR])	14 [3]	0.66 (0.60-0.73) §	<0.001
ICH volume (ml; median; [IQR])	10.0 [23.8]	1.02 (1.01-1.03) ç	<0.001
Intra-ventricular extension			<0.001
Presence	134 (54.7)	2.46 (1.81-3.34)	
Absence	191 (32.9)	REF	
ICH location			
Deep	162 (39.6)	REF	
Lobar	132 (37.9)	0.93 (0.69-1.25)	0.637
Infratentorial	31 (45.6)	1.28 (0.76-2.14)	0.353
Arterial Hypertension			0.002
Presence	239 (43.1)	1.62 (1.19-2.20)	
Absence	86 (31.9)	REF	
Diabetes mellitus			<0.001
Presence	79 (52.3)	1.91 (1.34-2.72)	
Absence	246 (36.5)	REF	
Anticoagulant drug			0.016
Yes	151 (44.3)	1.42 (1.07-1.88)	

No	174 (36.0)	REF	
Pre-ICH mRS >2			<0.001
Yes	81 (68.6)	4.15 (2.73-6.31)	
No	244 (34.5)	REF	
Neurosurgery			0.371
Yes	12 (48.0)	1.44 (0.65-3.19)	
No	313 (39.12)	REF	
Blood Pressure lowering treatment			0.260
Yes	75 (43.1)	1.22 (0.87-1.71)	
No	250 (38.4)	REF	

[*] *per year increase*

[§] *per point decrease*

[ç] *per ml increase*

GCS, Glasgow Coma Scale; ICH, intracranial hemorrhage; ITU, intensive treatment unit; mRS, modified Rankin Scale; OR, odds ratio; CI, confidence interval

Table 3. Multivariable analysis for association between clinical and radiological variables and poor mRS (>3) at 6 months

	OR	95% Confidence Interval	P value
Critical Care	2.43	1.36-4.35	0.003
Age	1.06*	1.05-1.08	<0.001
Glasgow Coma Scale	0.72[§]	0.65-0.81	<0.001
ICH volume	1.01[ç]	1.00-1.02	0.033
Intra-ventricular extension	1.83	1.27-2.62	0.001
Female gender	1.65	1.18-2.31	0.003
Arterial hypertension	1.26	0.88-1.82	0.212
Diabetes mellitus	2.15	1.40-3.30	<0.001
Anticoagulant drug	0.94	0.67-1.33	0.739
Pre-ICH mRS >2	2.95	1.84-4.74	<0.001

[*] *per year increase*

[§] *per point decrease*

[ç] *per ml increase*

GCS, Glasgow Coma Scale; ICH, intracranial hemorrhage; mRS, modified Rankin Scale; OR, odds ratio

Appendix

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