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ORIGINAL WORK

The Magnitude of Blood Pressure Reduction Predicts Poor In-Hospital Outcome in Acute Intracerebral Hemorrhage

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Abstract

Background: Early systolic blood pressure (SBP) reduction is believed to improve outcome after spontaneous intracerebral hemorrhage (ICH), but there has been a limited assessment of SBP trajectories in individual patients. We aimed to determine the prognostic significance of SBP trajectories in ICH.

Methods: We collected routine data on spontaneous ICH patients from two healthcare systems over 10 years. Unsupervised functional principal components analysis (FPCA) was used to characterize SBP trajectories over first 24 h and their relationship to the primary outcome of unfavorable shift on modified Rankin scale (mRS) at hospital discharge, categorized as an ordinal trichotomous variable (mRS 0–2, 3–4, and 5–6 defined as good, poor, and severe, respectively). Ordinal logistic regression models adjusted for baseline SBP and ICH volume were used to determine the prognostic significance of SBP trajectories.

Results: The 757 patients included in the study were 65 ± 23 years old, 56% were men, with a median (IQR) Glasgow come scale of 14 (8). FPCA revealed that mean SBP over 24 h and SBP reduction within the first 6 h accounted for 76.8% of the variation in SBP trajectories. An increase in SBP reduction (per 10 mmHg) was significantly associated with unfavorable outcomes defined as mRS > 2 (adjusted-OR = 1.134; 95% CI 1.044–1.233, $P = 0.003$). Compared with SBP reduction < 20 mmHg, worse outcomes were observed for SBP reduction = 40–60 mmHg (adjusted-OR = 1.940, 95% CI 1.129–3.353, $P = 0.017$) and > 60 mmHg, (adjusted-OR = 1.965, 95% CI 1.011, 3.846, $P = 0.047$). Furthermore, the association of SBP reduction and outcome varied according to initial hematoma volume. Smaller SBP reduction was associated with good outcome (mRS 0–2) in small (< 7.42 mL) and medium-size (≥ 7.42 and < 30.47 mL) hematomas. Furthermore, while the likelihood of good outcome was low in those with large hematomas (≥ 30.47 mL), smaller SBP reduction was associated with decreasing probability of severe outcome (mRS 5–6).

Conclusion: Our analyses suggest that in the first 6 h SBP reduction is significantly associated with the in-hospital outcome that varies with initial hematoma volume, and early SBP reduction > 40 mmHg may be harmful in ICH patients. For early SBP reduction to have an effective therapeutic effect, both target levels and optimum SBP reduction goals vis-à-vis hematoma volume should be considered.

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Introduction

Chronic hypertension is the most significant modifiable risk factor for spontaneous intracerebral hemorrhage (ICH), and elevated systolic blood pressure (SBP) after onset is associated with hematoma expansion (HE), early neurological deterioration, and poor functional outcome [1, 2]. Optimal management of SBP in the acute phase of ICH remains controversial, specifically regarding potential harm associated with intensive BP reduction [3]. In two large randomized trials comparing intensive (< 140 mmHg) versus conservative (< 180 mmHg) SBP-lowering strategies, early intensive SBP reduction did not clearly improve 90-day functional outcome [4, 5]. However, the relationship between SBP-lowering and ICH outcome is complex, and SBP parameters beyond the level of achieved SBP reduction may influence outcome [6]. We aimed to determine the temporal evolution of SBP levels in ICH patients and explore whether magnitude of acute SBP reduction might influence in-hospital functional outcome.

Methods

The data that support the findings of this study are available from the corresponding author upon reasonable request. Prior to conducting the study, approval was obtained from the Institutional Review Boards at Hennepin County Medical Center and Fairview Health Services in Minneapolis, MN. All the hospitals included in the study were covered by the faculties from the University of Minnesota (Neurology and Neurosurgery Departments). Therefore, all the included hospitals practiced similar ICH management protocols. The data collection protocol has been described previously [7, 8]. Briefly, we included 10 years consecutive admission data of spontaneous ICH patients between January 2008 and December 2017 from the two healthcare systems in the Twin Cities, MN. Subjects were identified by using the International Classification of Diseases (ICD) coding system with the primary or secondary diagnosis codes of 431, 432, and 432.9 for the 9th Revision (ICD-9) and I61.0-I61.9 and I62.9 diagnosis codes for the ICD-10 (when applicable). We excluded primary or secondary hemorrhage due to other etiologies.

BP Recording

BP recordings were extracted on admission, every hour for the first 6 h post-admission, and every two hours from 8 to 24 h post-admission for a total of 16 BP readings. As a routine practice, all BP measurements were recorded using an automated cuff at mid-biceps level [9]. Sequences of SBP constitute the focal independent variables of this study.

Post-Processing of Hematoma from CT Scans

We used a semi-automated planimetry technique to measure hematoma volumes observed on CT scans, as previously described [8, 10]. We also collected information on hematoma characteristics such as presence of intraventricular hemorrhage (IVH), midline shift (MLS), hydrocephalus, herniation, multisite hemorrhage, and irregularity of hematoma shape. HE was defined as an absolute increase of ≥ 6 ml or relative increase of ≥ 33% between hematoma volume observed on the initial and follow up CT scans at 24 h or the closest one [11]. The hematoma shape was categorized as regular or irregular using a binary scoring system, where regular represented a relatively round hematoma with smooth margin and irregular represented a pleomorphic contour of hematoma [12].

Primary and Secondary Outcomes

The primary outcome was the score on the modified Rankin Scale (mRS) at discharge, categorized as an ordinal trichotomous variable (mRS: 0–2, 3–4, and 5–6). Secondary outcomes were in-hospital death (mRS 6) and HE. Corresponding analyses with binary mRS at discharge (mRS: 0–3 and 4–6) are also provided in the Supplement.

Statistical Analysis

Functional principal component analysis (FPCA) [13] was applied to the SBP trajectories, resulting in a set of five subject-specific numerical features that can be interpreted with respect to corresponding eigenfunctions (see the Supplement for formulas). FPCA is an unsupervised statistical method for discovering the dominant modes of variation present in longitudinal data such as SBP recordings, and was chosen for this study because it is able to produce data-driven summary statistics (principal component features) of SBP that most efficiently account for heterogeneity within the cohort. Median and interquartile range (IQR) values were computed for variables. Significance of each variable was assessed in univariate logistic regression analysis, under the proportional odds assumption for ordinal primary outcome. Details of how missing data were handled are given in the Supplement.

A linear regression model was used to convert the second SBP feature from FPCA into the variable SBP

reduction, interpreted as the magnitude of SBP reduction (in mmHg) in the first 6 h. Tertile cutoffs for initial SBP and hematoma volume were used to characterize the cohort (small, medium, and large volume and low, medium, and high initial SBP). Differences in mean SBP reduction across initial hematoma volume (Model 1a) and initial SBP (Model 1b) strata were assessed by analysis of variance. History of hypertension was quantified as normotensive, treated-hypertension, or untreated-hypertension.[7] One-sided permutation tests (Models 1c–1e) assessed the hypothesis of increasing mean SBP reduction by hypertension status (i.e., normotensive < treated-hypertension < untreated-hypertension).

Associations between SBP reduction (continuous) and the primary outcome were assessed in multivariate logistic regression models under the proportional odds assumption. Model 2a controlled for initial hematoma volume and initial SBP as categorical variables, with interactions between SBP reduction and each of initial SBP and initial hematoma volume added using Akaike's Information Criterion (AIC) [14]. Model 3a controlled for initial SBP (continuous), logarithm of initial hematoma volume (continuous), and additional variables selected by the Bayesian Information Criterion (BIC) [15]. Model 4a controlled for the same variables as Model 3a, while treated SBP reduction as a categorical rather than continuous variable. Similarly, Models 2b-c, 3b-c, and 4b-c were fit for secondary outcomes, according to the above procedure. Results are reported as adjusted odds ratios (OR) and 95% confidence intervals (CI), and a standard significance level (two tailed P value < 0.05). All analyses were undertaken using the R software environment for statistical computing (Version 3.2.0, R Core Team, Vienna, Austria).

Results

Of 1119 consecutive ICH patients identified, those who died < 24 h of admission ($n = 112$) or had > 10 missing SBP readings ($n = 221$) or had 'do not resuscitate' care directives upon admission ($n = 29$) were excluded. Thus, 757 patients were included in these analyses, of whom 83.6% ($n = 633$) had 14–16, 12.3% ($n = 93$) 10–13, and 4.1% ($n = 31$) 6–10, SBP readings. Sensitivity analyses comparing included versus excluded patients are reported in Supplemental Table I. After correcting for multiple comparisons, these groups differed significantly in mean for the quantitative variables age, admission Glasgow coma scale (GCS), admission glucose levels, and initial hematoma volume, as well as in proportion for the binary variables representing sex, history of coagulopathy, history of cerebrovascular disease, intraventricular hemorrhage (IVH), midline shift, presence of hydrocephalus, herniation, multisite hemorrhage, and irregularity of hematoma shape. To avoid bias related to the time from onset to initial CT, a smaller cohort of 316 patients presenting within three hours of symptom onset was used in analyses of HE.

Figure 1a shows the five SBP eigenfunctions produced by FPCA. The first eigenfunction (F1) is roughly flat and constant over the 24-hour time period and accounts for 55.8% of variation in the SBP trajectories (see Equation II in Supplement). Moreover, F1 was highly correlated with actual mean SBP over 24 h ($r = 0.988$) and thus interpreted as equivalent to actual mean SBP. The second eigenfunction (F2) reflects a sharp initial decrease, then becoming constant after 6 h, and accounted for 21.0% of variation. This feature was highly correlated ($r = 0.813$) with the change in SBP during the first 6 h (initial SBP minus SBP at 6 h). To enhance interpretability of these

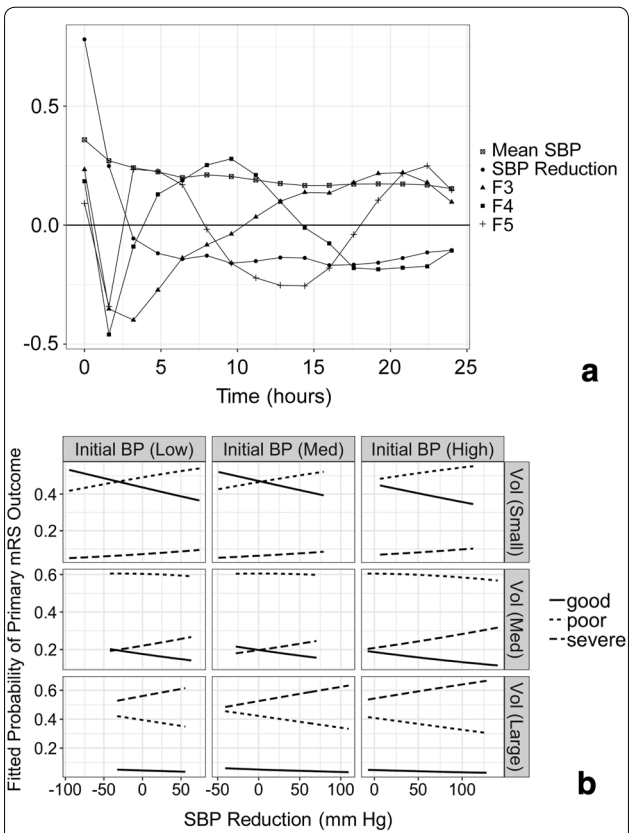

Fig. 1 **a** SBP eigenfunctions from functional principal components analysis. **b** Probabilities of different primary ordinal mRS outcome (good: mRS 0–2, poor: mRS 3–4, severe: mRS 5–6) by initial SBP/Volume grouping, where Volume referes to intitial hematoma volume. Horizontal axes correspond to SBP reduction, meaning the magnitude of SBP reduction within the first 6 h. Vertical axes correspond to the estimated probability of primary mRS outcome obtained from ordinal logistic regression Model 2a, which controlled for initial hematoma volume and initial SBP as categorical variables

first two FPCA features, simple linear regression analyses produced the following adjustments:

$$\text{Mean SBP} = 135.583 + 0.229 * \text{F1}$$

$$\text{SBPreduction} = 36.903 + 0.997 * \text{F2}$$

These variables derived from FPCA are highly correlated with actual mean SBP and change in SBP during the first 6 h, respectively, and can thus be interpreted in a similar way. Positive values of SBP reduction indicate a decrease in SBP over the first 6 h, while negative values indicate an increase. The other eigenfunctions and corresponding features (denoted F3, F4, and F5) are less clinically meaningful and represent different patterns of short-term SBP fluctuations, accounting for smaller (11.4%, 6.0%, and 2.8%, respectively) portions of total variation. Table 1 summarizes associations between all variables, including SBP features, and the primary outcome. Univariate regression analyses demonstrated that age, admission GCS, history of coagulopathy, cardiovascular disease/stroke, admission glucose, comfort care

Table 1 Summary statistics of all considered variables for full cohort, by modified Rankin scale (mRS) scores at discharge

Variable	Primary outcome (mRS scores)				
	All	0–2	3–4	5–6	*P*-value
Sample size	757	160	377	220	
Demographics					
Age	65 (23)	62 (17.5)	65 (22)	69 (21)	< 0.001
Male	426 (56.3%)	101 (63.1%)	204 (54.1%)	121 (55%)	0.169
Beds (small, medium, large)	46, 593, 118	9, 126, 25	18, 293, 66	19, 174, 27	0.223
Clinical Features (History and on Admission)					
Admission GCS	14 (8)	15 (1)	14 (4)	6 (7)	< 0.001
History of stroke	88 (12%)	11 (7%)	51 (13.7%)	26 (13%)	0.132
History of coagulopathy	137 (18.1%)	22 (13.8%)	62 (16.5%)	53 (24.1%)	0.006
History of cardiovascular disease	168 (22.9%)	34 (21.5%)	74 (19.8%)	60 (29.7%)	0.035
History of cerebrovascular disease	160 (21.9%)	26 (16.5%)	86 (23.1%)	48 (24%)	0.112
Anti-platelet use	240 (33.1%)	56 (35.2%)	116 (31.4%)	68 (34.7%)	0.997
Admission platelet count (10^9/L)	213 (88)	212.5 (83.5)	215 (82)	212 (102)	0.773
Admission glucose (mg/dL)	130 (58.5)	117.5 (42.2)	127.5 (53.5)	149 (71)	< 0.001
Acute renal failure	51 (6.7%)	6 (3.8%)	27 (7.2%)	18 (8.2%)	0.119
Comfort care	187 (24.7%)	0 (0)	6 (1.6%)	181 (82.3%)	< 0.001
Imaging Characteristics					
IVH	328 (43.3%)	33 (20.6%)	146 (38.7%)	149 (67.7%)	< 0.001
MLS	241 (31.8%)	22 (13.8%)	98 (26%)	121 (55%)	< 0.001
Hydrocephalus	118 (15.6%)	9 (5.6%)	44 (11.7%)	65 (29.5%)	< 0.001
Herniation	82 (10.8%)	1 (0.6%)	27 (7.2%)	54 (24.5%)	< 0.001
Multisite hemorrhage	54 (7.2%)	5 (3.1%)	24 (6.5%)	25 (11.5%)	0.002
Irregular hematoma shape	338 (45.4%)	36 (22.6%)	143 (38.9%)	159 (72.9%)	< 0.001
Initial hematoma volume (mL)	16.4 (36.4)	5 (9.9)	13.1 (25.7)	49.6 (54.3)	< 0.001
HE (> 33% or > 6 mL)	114 (18.4%)	11 (8.1%)	53 (15.8%)	50 (33.6%)	< 0.001
Infratentorial hemorrhage	116 (15.3%)	23 (14.4%)	54 (14.3%)	39 (17.7%)	0.311
SBP Features					
Mean SBP	135.3 (16.0)	137.7 (17.5)	135.7 (17.1)	133.7 (13.8)	0.002
SBP reduction	35.0 (43.0)	28.3 (38.7)	37.8 (41.4)	38.7 (46.4)	0.048
F3	1.9 (34.7)	3.3 (35)	− 1.1 (34.9)	4.2 (35.8)	0.924
F4	− 0.7 (21)	− 2.1 (18.7)	0.7 (21.2)	0.5 (21.9)	0.017
F5	− 0.4 (12.4)	− 0.5 (10.9)	− 0.4 (12.6)	− 0.2 (12.9)	0.928

Note: Numeric variables are reported as median (IQR), and binary variables are reported as count (% of total). P-values correspond to univariate ordinal regression for primary outcome

The variable Beds is reported as the count of patients treated in small (< 100 beds), medium (100–499 beds), and large (≥ 500 beds) hospitals

GCS glasgow coma scale, *HE* hematoma expansion, *IVH* intraventricular hemorrhage, *MLS* midline shift

directive, intraventricular hemorrhage, hydrocephalus, midline shift, multisite hemorrhage, irregular hematoma shape, initial hematoma volume, HE, and SBP features (Mean SBP, SBP Reduction, and F4) were all significantly associated with discharge mRS. Supplemental Tables II and III contain corresponding results for the secondary outcomes.

Initial SBP was categorized by tertile cutoffs of <140, ≥ 140 and <180, and ≥ 180 mmHg, corresponded to low, medium, and high levels, respectively. Hematoma volume (mL) was categorized as <7.42 (small), ≥ 7.42 and <30.47 (medium), and ≥ 30.47 (large). Mean reduction in SBP values over first 6 h was significantly greater with higher initial SBP strata ($P<0.001$, Table 2, Model 1a). Differences in mean SBP reduction values across strata of initial hematoma volume were not significant ($P=0.057$ Model 1b). The analysis of the history of hypertension revealed that mean SBP reduction was significantly larger for untreated-hypertension patients compared to treated-hypertension ($P=0.026$) and normotensive ($P=0.002$), see Table 3. No significant difference in mean SBP reduction was found between treated-hypertension and normotensive patients.

AIC selected an interaction between SBP reduction and hematoma volume in Model 2b but did not select any interactions for Models 2a or 2c. Figure 1b depicts the relationship between SBP reduction and risk of the different primary ordinal outcomes in Model 2a, after controlling for initial SBP and hematoma volume as categorical variables. The risks of poor in-hospital outcome varied according to initial hematoma volume and magnitude of SBP reduction. Smaller SBP reduction increased the probability of good outcome (mRS: 0–2) in small and medium hematomas (<30.47 mL) and decreased the probability of severe outcome (mRS 5–6) in large hematomas.

Similar results for Models 2b and 2c with in-hospital death and HE as outcomes are shown in Supplemental Figures I and II, respectively. Higher SBP reduction was associated with decreased risk of death for small and medium size hematomas, but increased risk of death for large hematomas. Higher SBP reduction was also associated with decreased risk of HE regardless of initial SBP or hematoma volume.

Table 3 Tests for differences in mean SBP reduction between hypertension groups

History of hypertension	Mean SBP reduction (mmHg)
Normotensive	33.6
Treated-hypertension	35.8
Untreated-hypertension	42.5
Group Comparison	*P*-value*
Untreated-hypertension > Normotensive (Model 1c)	0.002
Untreated-hypertension > Treated-hypertension (Model 1d)	0.026
Treated-hypertension > Normotensive (Model 1e)	0.182

*One-sided permutation *P*-values for testing equality of mean SBP reduction

Results for multivariate regression Models 3a-c and 4a-c are shown in Table 4. Model 3a suggested that higher SBP reduction (OR = 1.134, 95% CI 1.044–1.233 per 10 mmHg increase in SBP reduction in the first 6 h) and larger initial hematoma volume (OR = 1.032, 95% CI 1.019–1.046 per 10% increase) were significantly associaOR with respect to 10% increase in hematomated with a shift toward worse (good to poor or poor to severe) outcome. Figure 2 shows fitted probability contours of severe (mRS 5–6) and poor (mRS 3–6) outcome from Model 3a for different values of initial hematoma volume and SBP reduction, with other covariates fixed at the median for numeric variables or the most common value for binary variables. Subjects having SBP reduction between 40 and 60 mmHg (OR 1.940, 95% CI 1.129–3.353) or >60 mmHg (OR = 1.965, 95% CI 1.011–3.846) had increased risk of poor outcome compared with the reference group of SBP reduction <20 mmHg (Model 4a). Only patients with SBP reduction >60 mmHg (OR = 4.175, 95% CI 1.063–17.802) showed increased risk of death compared to subjects with SBP reduction <20 mmHg (Model 4b).

Table 2 Mean (SD) reduction in systolic blood pressure (SBP reduction) over first 6 h from baseline, by initial SBP and hematoma volume

Grouping Variable	Level			*P*-value*
Initial SBP (Model 1a)	Low (<140 mmHg)	Med (≥ 140 and <180 mmHg)	High (≥ 180 mmHg)	
Mean (SD)	10.19 (25.06)	29.99 (23.45)	61.69 (25.79)	<0.001
Initial Volume (Model 1b)	Small (<7.42 mL)	Medium (≥ 7.42 and <30.47 mL)	Large (≥ 30.47 mL)	
Mean (SD)	33.38 (31.95)	40.14 (30.81)	37.5 (32.08)	0.057

*Two-sided ANOVA P-value for testing equality of mean SBP reduction

Table 4 Results for multivariate Models 3a–3c for SBP reduction, initial SBP, and initial hematoma volume as continuous predictors and Models 4a–4c for categorized SBP reduction

Variable	Adjusted OR*	95% CI	*P*-value
Model 3a: mRS: 0–2, 3–4, and 5–6			
SBP reduction**	1.134	(1.044, 1.233)	0.003
Initial SBP***	0.966	(0.901, 1.036)	0.339
Initial hematoma volume (log)****	1.0**32**	(1.0**19**, 1.**046**)	0.000
Model 3b: In-hospital Death			
SBP reduction**	1.105	(0.943, 1.305)	0.223
Initial SBP***	0.884	(0.764, 1.019)	0.092
Initial hematoma volume (log)****	1.028	(0.993, 1.063)	0.117
Model 3c: HE			
SBP reduction**	0.880	(0.757, 1.022)	0.093
Initial SBP***	1.007	(0.882, 1.148)	0.916
Initial hematoma volume (log)****	0.993	(0.967, 1.022)	0.639
Model 4a: mRS: 0–2, 3–4, and 5–6			
SBP reduction ≤ 20 mmHg	Reference		
20 mmHg < SBP reduction ≤ 40 mmHg	1.021	(0.629, 1.658)	0.934
40 mmHg < SBP reduction ≤ 60 mmHg	1.940	(1.129, 3.353)	0.017
SBP reduction > 60 mmHg	1.965	(1.011, 3.846)	0.047
Model 4b: In-hospital Death			
SBP reduction ≤ 20 mmHg	Reference		
20 mmHg < SBP reduction ≤ 40 mmHg	3.030	(0.998, 9.945)	0.057
40 mmHg < SBP reduction ≤ 60 mmHg	1.404	(0.455, 4.432)	0.557
SBP reduction > 60 mmHg	4.175	(1.063, 17.802)	0.046
Model 4c: HE			
SBP reduction ≤ 20 mmHg	Reference		
20 mmHg < SBP reduction ≤ 40 mmHg	0.521	(0.184, 1.406)	0.206
40 mmHg < SBP reduction ≤ 60 mmHg	0.533	(0.206, 1.363)	0.190
SBP reduction > 60 mmHg	0.346	(0.102, 1.128)	0.082

Models 3a and 4a further controlled for IVH, hydrocephalus, age, admission, GCS, history of cerebrovascular disease, and comfort care. Models 3b and 4b further controlled for IVH, hydrocephalus, admission GCS, and comfort care. Models 3c and 4c further controlled for IVH, hydrocephalus, irregular hematoma shape, midline shift, history of cerebrovascular disease, history of stroke, glucose, history of coagulopathy, comfort care, and acute renal failure

*Values > 1 indicates increased risk of worse outcome for increasing values of the variable

**Adjusted OR with respect to 10 mm-Hg increase in SBP reduction within the first 6 h after admission

***Adjusted OR with respect to10 mm-Hg increase in absolute SBP

****Adjusted OR with respect to 10% increase in hematoma size from initial volume

Discussion

In this observational study, unsupervised FPCA identified SBP reduction within the first 6 h post-ICH as the second most prominent SBP feature, after the achieved mean SBP level over 24 h. The five SBP eigenfunctions produced by FPCA were able to reflect the cohort SBP trajectories during the first 24 h post-ICH, with an accuracy of about 97%. Although the level of SBP in the first 24 h had a significant impact on outcome [5], other factors including SBP reduction can affect the prognosis of ICH. The SBP reduction pattern accounted for about 21% of the total variance, suggesting that controlling SBP reduction according to initial hematoma volume and initial SBP level may influence the outcome (Figs. 1b and 2).

In addition, we found that the association of SBP reduction with outcome varied depending on initial hematoma volume. Specifically, smaller SBP reduction was associated with increased probability of good outcome (mRS 0–2) in small (< 7.42 mL) and medium size (≥ 7.42 and < 30.47 mL) hematomas. In contrast, while the likelihood of good outcome was low in those with large hematomas (≥ 30.47 mL), smaller SBP reduction was associated with decreasing probability of severe outcome (mRS 5–6).

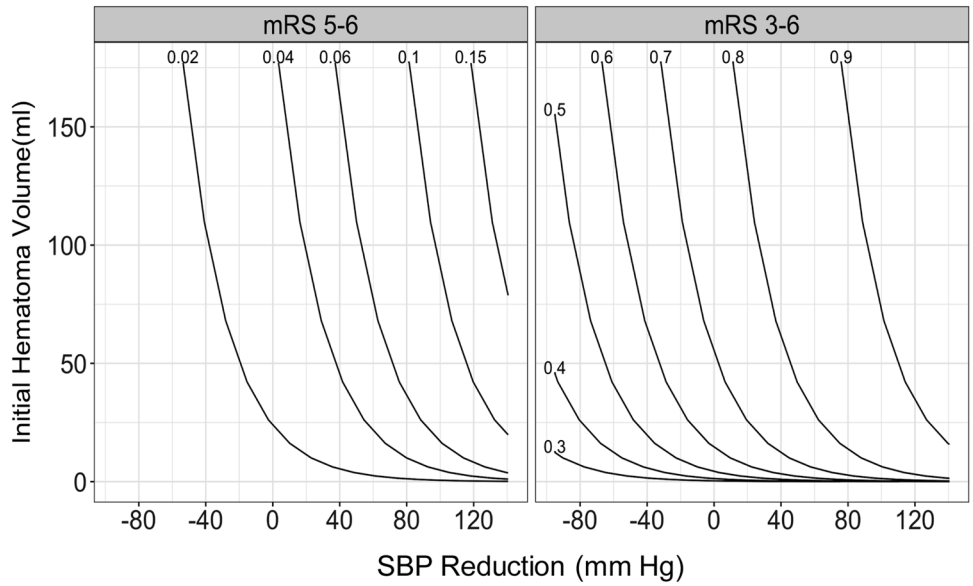

Fig. 2 Fitted probability contours for severe outcome (mRS 5–6, left) and severe or poor outcome (mRS 3–6, right) for ranges of initial volume and SBP reduction values from Model 3a. Horizontal axes correspond to SBP reduction, meaning the magnitude of BP reduction within the first 6 h. Curves correspond to estimated probability contours of primary mRS outcome (left: mRS 5–6, right: mRS 3–6) obtained from multivariate ordinal logistic regression Model 3a. Other control variables (initial SBP, IVH, hydrocephalus, age, admission GCS, history of cerebrovascular disease, and comfort care) were set to median value for quantitative variables and most common value for binary variables

Model 3b, where SBP reduction (continuous), initial SBP, and hematoma volume were included, showed no significant association with death, possibly due to confounding from the use of early withdrawal of care measures, which affected nearly all patients who died (97.5%) and only very few survivors (5.5%), as shown in Supplemental Table II.

We observed that SBP reduction ≥ 60 mmHg was significantly associated with higher probability of death (Table 4), but larger SBP reduction was associated with decreased risk of HE regardless of initial SBP or hematoma volume (Supplemental Figure II). As shown elsewhere [16], we observed an inverse relationship between SBP reduction and HE in univariate analyses (see Supplemental Table III). However, after controlling for relevant covariates, including initial hematoma volume and initial SBP, SBP reduction had a borderline significant association with HE (Table 4). While our HE rate was similar to that observed in Antihypertensive Treatment of Acute Cerebral Hemorrhage (ATACH-II) [5] and Intensive Blood Pressure Reduction in Acute Intracerebral Hemorrhage Trial (INTERACT2) [4] studies, their analyses were based on target SBP and not SBP reduction that was done in our study. Thus, although HE remains sensitive to larger reductions in SBP, this benefit is likely overwhelmed by other detriments of overly aggressive SBP reduction.

Interestingly, we observed heterogeneity in the association of SBP reduction on death between small and large hematoma volumes. The finding of a lower risk of death from large SBP reduction in small hematomas requires further investigation of the underlying mechanisms but may reflect a beneficial effect of avoidance of HE. It is plausible that a greater SBP reduction for larger hematomas in the context of increased intracranial pressure and decreased cerebral perfusion pressure (due to the Cushing reflex [17]) could influence cerebral hemodynamic to induce hypo-perfusion. One possibility is that larger hematomas have already expanded. Furthermore, we hypothesize that increased ICP due to higher static pressure from the mass-effect may reduce the expansion rate in initial large hematomas, while smaller initial hematomas have a greater possibility of expansion, in about one-third of the cases [18]. For smaller hematomas, more aggressive BP reduction may reduce the proportion of hematomas that could expand while the autoregulatory system is sustained by blood pressure manipulation. However, even though more aggressive BP reduction may be favorable in terms of minimizing HE, it may not have an optimum impact on lowering rate of death and disability as discussed above. This may be similar to the observation that made in ATACH-II that aggressive BP reduction led to reduction in HE but did not resulted in clinical benefits [5]. In short, larger hematomas do

not have enough space to expand, and smaller hematomas expansion may have potentially constrained by BP reduction. This may potentially explain the fact that we did not observe a statistically significant difference (data are not shown) in HE between smaller and larger hematomas. Consequently, the extent to which SBP reduction might influence the outcome depends heavily on the initial hematoma size. As indicated by Fig. 1b, the probability of severe outcome (mRS 5–6) is very low for small hematomas, and this probability does not change very much depending on SBP reduction. The tradeoff for small hematomas is primarily between good (mRS 0–2) and poor (mRS 3–4) outcomes, with smaller SBP reduction being associated with increased probability of good outcome. In large hematomas, although good outcome is unlikely and not much influenced by SBP reduction, SBP reduction can still influence whether the outcome is poor versus severe. Therefore, the concept of individualizing the BP reduction approach may be more appropriate than a uniform target BP level. In addition, it is suggested that chronic hypertension shifts the cerebral autoregulation curve to the right compared to untreated hypertensive patients [19], potentially raising the risk of harm in the former from relative hypo-perfusion at a lower limit of autoregulation. Our results show that SBP reduction was significantly greater in untreated-hypertension patients. Impaired autoregulation and adverse effects of acute SBP-lowering has been shown in patients with malignant hypertension [20]. Hypertension may also negatively affect brain capillary density leading to increased vascular resistance [21]. Even though preclinical studies investigating the influence of SBP-lowering on potential perihematomal ischemia showed the treatment was safe and could prevent HE [22–24], no studies have been undertaken in chronically hypertensive animals according to different hematoma volumes.

A secondary analysis of INTERACT2 data suggests worse outcome associated with achieved target SBP < 130 mmHg [25], and secondary analysis of the Systolic Blood Pressure Interventional Trial (SPRINT) showed that hypertensive patients (> 144 mmHg) who smoke may have a higher rate of cardiovascular and acute kidney injury from long-term intensive SBP reduction [26]. Similar concerns over low SBP have arisen from studies of elderly hypertensive patients with reduced arterial compliance [27, 28]. Thus, it is conceivable that a rapid reduction of SBP may offset any benefits derived from an achieved level of SBP. A recent combined analysis of INTERACT2 [4] and ATACH-II [5] trials suggests that in addition to level of achieved SBP, SBP variability over 24 h was also important in determining outcome, but the relationship of magnitude of SBP reduction in the first hour was not clearly defined [29]. The potential for harm from rapid large SBP reduction was shown in the Studying the Treatment of Acute hyperTension (STAT) registry [30], in which lower minimum SBP values in the first 6 h from acute brain injury, including ICH, were associated with increased mortality.

Published data suggest that hematoma volumes ≥ 30 ml are associated with poor outcome [31]. We hypothesize that an individualized approach to SBP management may be a reasonable objective in acute ICH. However, appropriate randomized clinical trials are needed to assess individualized SBP reduction paradigms as opposed to a fixed target BP for all patients. Our fitted probability contour plots can potentially help with selecting the appropriate SBP reduction values for ranges of initial ICH volumes.

We also analyzed the effect of categorized SBP on the primary and secondary outcomes, as suggested by Moullaali et al. [29]. Rather than using a predetermined time of 1-hour post-admission [29], we used changes in SBP reduction in the first 6 h. Interestingly, our results revealed a negative effect on the primary outcome for a SBP reduction of 40–60 and > 60 mmHg compared with ≤ 20 mmHg. The association between SBP reduction and death was only significant for SBP reduction > 60 mmHg, similar to the previous findings [29].

Analysis of SBP with respect to ICH outcome in this cohort was subject to large inter-subject variability of number and frequency of blood pressure recordings, as well as missing values. FPCA is a useful approach for this type of irregular longitudinal data in order to estimate outcome trends, as it compensates for both inter-subject variability and intra-subject correlation and ensures that essential trends for recovery patterns are not overlooked due to limitations of the statistical analysis. Thus, we used FPCA to assess differences in the outcomes of ICH and established which SBP variables (other than just absolute level) could be more effective for promoting standardized protocols for acute SBP treatment. Future applications of FPCA in larger samples could be helpful to determine the effectiveness of a drug therapy for ICH.

Some limitations should be considered in interpreting current findings. The retrospective study design may predispose to methodological issues such as missing data and reliability of diagnoses and medical histories. Exclusion of subjects who died during the first 24 h after admission or with comfort care directives may have also introduced selection biases. We could not gauge the true compliance rate for antihypertensive medications, and only the outcome at hospital discharge was considered. Furthermore, the observational nature of the study precluded us from performing further detailed analyses, which are possible with data collected in prospective randomized clinical trials. Also,

the current study presents an association (not effect), and thus is prone to various biases and should be considered hypothesis generating.

Although we primarily used ordinal classification for mRS at discharge [32], the results for binary mRS values (0–3 vs. 4–6) have been also presented (see Supplemental Tables IV and V and Figure V). The results obtained from binary mRS classifications for continuous SBP reduction were consistent with the ordinal mRS, although with a higher *P* value (0.044) compared with ordinal outcome (0.003). However, while for categorical SBP reduction, >40 and ≤ 60 mmHg was significant, SBP reduction >60 mmHg was not significant (see Table 4 for Models 3a and 4a and Supplemental Table V for Models 3d and 4d). It seems that the use of ordinal mRS was more appropriate as the binary mRS classification led to loss of statistical power.

In conclusion, the current study demonstrated the association between initial hematoma volume and amount of SBP reduction during the first 6 h with ICH outcome. This data provide a strong incentive for designing SBP reduction protocols that consider initial hematoma volume, baseline SBP level and magnitude of early SBP reduction, rather than solely aim for a target SBP level.

Electronic supplementary material
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Ethical approval/Informed consent
Prior to conducting the study, approval was obtained from the Institutional Review Boards at Hennepin County Medical Center and Fairview Health Services in Minneapolis, MN.

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