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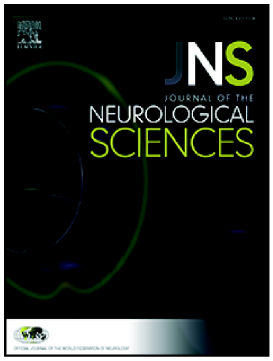

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Sulfonylurea Drug Pretreatment and Functional Outcome in Diabetic Patients with Acute Intracerebral Hemorrhage

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Abstract

Purpose: Intracerebral hemorrhage (ICH) is associated with poor clinical outcome and high mortality. Sulfonylurea (SFU) use may be a viable therapy for inhibiting sulfonylurea receptor-1 and $NC_{Ca\text{-}ATP}$ channels and reducing perihematomal edema and blood-brain barrier disruption. We sought to evaluate the effects of prehospital SFU use with outcomes in diabetic patients with acute ICH.

Methods: We retrospectively analyzed a cohort of diabetic patients presenting with acute ICH at a tertiary care center. Study inclusion criteria included spontaneous ICH etiology and age >18 years. Baseline clinical severity was documented using ICH-score. Hematoma volumes (HV) on admission were calculated using ABC/2 formula. Unfavorable functional outcome was documented as discharge modified Rankin Scale scores 2-6.

Results: 230 diabetic patients with acute ICH fulfilled inclusion criteria (mean age 64±13 years, men 53%). SFU pretreatment was documented in 16% of the study population. Patients with SFU pretreatment had significantly (p<0.05) lower median ICH-scores (0, IQR:0-2) and median admission HV (4cm^3, IQR:1-12) compared to controls [ICH-score: 1 (IQR:0-3); HV: 9cm^3 (IQR:3-20)]. SFU pretreatment was independently (p=0.033) and negatively associated with the cubed root of admission HV (linear regression coefficient: -0.208; 95%CI:-0.398−-0.017) in multiple linear regression analyses adjusting for potential confounders. Pretreatment with SFU was also independently (p=0.033) associated with lower likelihood of unfavorable functional outcome (OR=0.19; 95%CI:0.04–0.88) in multivariable logistic regression models adjusting for potential confounders.

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Conclusion: SFU pretreatment may be an independent predictor for improved functional outcome in diabetic patients with acute ICH. This association requires independent confirmation in a large prospective cohort study.

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Introduction

Intracerebral hemorrhage (ICH) accounts for 10% of 795,000 yearly new strokes [1] and is associated with poor clinical outcome and unimproved mortality rates [2]. ICH consists of a primary phase marked by hematoma volume (HV) expansion and a slower, subacute secondary phase marked by perihematomal edema. Major ICH trials of the past decade have largely targeted HV (STICH II [3], FAST [4], INTERACT 2 [5], and ATACH II [6]), but have failed to improve clinical outcomes in randomized-controlled settings. Greater focus on secondary mechanisms of injury and attenuation of subacute perihematomal edema [7] may play a role in improving clinical outcome after ICH.

One potential pathophysiological mechanism for cerebral edema lies with sulfonylurea receptor 1 (SUR1). SUR1 is transcriptionally upregulated in focal cerebral ischemia, which triggers upregulation of $NC_{Ca\text{-}ATP}$ channels and allows for passive diffusion of Na^+ and vasogenic edema formation [8]. $NC_{Ca\text{-}ATP}$ channel inhibition by sulfonylureas (SFU) may lead to decreased cerebral edema and hemorrhagic transformation, which may consequently improve functional outcomes. These findings were suggested in the GAMES-pilot trial, which showed a trend toward lower mortality and improved functional outcome in patients with malignant ischemic stroke who were treated with intravenous glyburide [9]. Although the GAMES phase 2 trial failed to show improved clinical outcome, thirty-day mortality was significantly reduced, and improvement in cerebral edema was suggested by the significant reduction in subacute midline shift present in the glyburide group [10].

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As the subacute progression of perihematomal edema may play a role in ICH, we sought to evaluate the effects of prehospital SFU use in clinical outcomes of patients with acute ICH and diabetes.

Methods

Patient Selection and Study Protocol

Institutional review board approval was obtained for the conduct of a prospective cohort study evaluating functional outcomes in adult non-traumatic ICH patients at a tertiary-level hospital. All data was prospectively collected for acute (< 24 hours) ICH and retrospectively reviewed for accuracy by blinded neurologists (YK and AK). Consecutive patients with ICH meeting inclusion criteria were initially identified by ICD code during the period January 2011 to December 2015.

Study inclusion criteria included history of diabetes mellitus (DM) as documented by past medical history or hemoglobin A1c levels > 7.0 [11], spontaneous ICH etiology, and age > 18 years old. Exclusion criteria included structural etiology for ICH (attributable to trauma or underlying vascular lesions such as cavernous malformation, arteriovenous malformation, or arterial-venous fistula), coagulopathy (INR > 1.7), and thrombocytopenia (platelets < 50,000/mm^3). As per hospital protocol, all oral diabetic medications (including SFUs) were stopped on admission and replaced with sliding scale insulin and long-acting insulin. Pretreatment SFUs included glipizide, glyburide, and glimepiride.

Demographics and vascular risk factors were documented at hospital admission as previously described [12]. Baseline clinical severity was documented using ICH-score [13] and National Institutes of Health Stroke Scale (NIHSS) score [12]. Clinical outcome endpoints

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included modified Rankin Scale score (mRS) at discharge, hospital length of stay, disposition, and in-hospital mortality. ICH-score, NIHSS scores, and mRS-scores were documented by certified vascular neurologists (YK and AK) blinded to SFU pretreatment. Admission HV was calculated using the ABC/2 formula [14]. Significant hematoma expansion was defined as a proportional increase of greater than 33% or an absolute increase greater than 12.5 mL from the initial ICH volume [15,16]. HV at admission, follow-up neuroimaging, and hematoma expansion were evaluated by neuroradiologists blinded to SFU pretreatment. The following in-hospital complications were prospectively recorded: decompressive hemicraniectomy, vasopressor use, respiratory failure, and external ventricular drain placement.

Statistical analysis

Initial demographic differences, neuroimaging features, in-hospital complications, and outcomes between the pretreated SFU and non-pretreated SFU groups were evaluated with independent samples t-test, χ^2 test, Mann-Whitney U test, and Cochran-Mantel-Haenszel shift test as appropriate. Kolmogorov-Smirnov goodness-of-fit test was used to evaluate for normal distribution of continuous variables.

HV was not found to have a normal distribution ($p< 0.001$ by Kolmogorov-Smirnov test) and was cube root transformed for each patient to satisfy Kolmogorov-Smirnov goodness-of-fit test ($p= 0.200$) regarding normality [17]. The cubed root of HV (CRHV) was utilized as the dependent variable in simple and multiple linear regression models evaluating independent associations between baseline characteristics and admission HV. A p value of < 0.1 was selected as a cut-off in simple linear regression analyses for inclusion of candidate variables in the multiple linear regression model. Predictor variables that were significant at $p< 0.05$ were

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retained in the multiple linear regression model. Associations are presented as unstandardized linear regression coefficients with corresponding 95% CIs.

Univariable and backward selection multivariable logistic regression analyses were used to determine independent predictors of dichotomized baseline ICH-score and functional outcome at discharge. ICH-score was dichotomized to "mild" (ICH-score 0-1) or "severe" (ICH-score 2-6) based on the median ICH score of the study population (1 point). Functional outcome at discharge was dichotomized into "favorable" [modified Rankin score (mRS) of 0-2] and "unfavorable" (mRS score of 3-6) as previously described [12]. A p value of < 0.1 was selected as a cut-off in univariable logistic regression analyses for inclusion of candidate variables in the multivariable logistic regression models. Predictor variables that were significant at $p< 0.05$ were retained in the multivariable model. Associations are presented as OR with corresponding 95% CIs. The Statistical Package for Social Science (version 17.0 for Windows; SPSS Inc., Chicago, IL) was used for statistical analyses.

Results

A total of 790 patients were identified by ICD code and confirmed by chart review as ICH patients in this time span. We excluded 118 ICH patients because of coagulopathy, thrombocytopenia, or underlying structural lesions. The remaining 672 patients had spontaneous ICH, of which 230 patients had spontaneous ICH, a past history of DM, and fulfilled the remaining inclusion criteria (supplemental Figure I). Study population mean age was 64±13 years (53% men). We identified 37 patients with SFU pretreatment (mean age 67±10 years, 41% men) vs. 193 patients without SFU pretreatment (mean age 63±13 years, 55% men). Baseline characteristics are shown in Table 1. The two groups did not differ in baseline characteristics

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including demographics, vascular risk factors, pre-hospital use of antiplatelets, anticoagulants or statins, admission blood pressure values, serum creatinine, and glucose levels. The two groups had similar coagulation profiles in terms of baseline platelet number and international normalized ratio.

Table 2 summarizes clinical and radiological outcomes as well as in-hospital complications between the two groups. Patients with SFU pretreatment had significantly lower median ICH-score [0 points (interquartile range (IQR): 0-2) vs. 1 point (IQR:0-3); p= 0.021] and lower median HV [4cm^3 (IQR:1-12) vs. 9cm^3 (IQR: 3-20) p=0.026]. Mild ICH severity (ICH score of 0-1) was documented more frequently in patients pretreated with SFU (75% vs. 54%; p= 0.019). The rates of hematoma expansion did not differ (p= 0.184) in the two groups. In-hospital complications favored the group with SFU pretreatment with lower rates of external ventricular drain placement (5% vs. 20%; p= 0.034) and respiratory failure (19% vs. 40%; p= 0.015). The median duration of hospitalization was significantly shorter in the pretreated SFU group [median duration 5 (IQR:3-7) days vs. 7 (IQR:4-15) days; p= 0.012]. Functional improvement at hospital discharge was greater in the group of patients pretreated with SFU [median mRS-score 3 (IQR:1-5) vs. 4 (IQR:2-5); p= 0.034 by Cochran Mantel Haenszel shift test]. Unfavorable functional outcome at discharge was less prevalent in the SFU group (54% vs. 72%; p= 0.028). The rates of in-hospital mortality were similar (p= 0.771) in the two groups.

Table 3 depicts associations between baseline characteristics and CRHV in simple and multiple linear regression models. CRHV was associated (p< 0.1) with the following variables in simple linear regression analyses: NIHSS-score at admission (p< 0.001), prior stroke (p= 0.025), hyperlipidemia (p= 0.057), prehospital antiplatelet use (p= 0.083), prehospital SFU use (p= 0.044), and platelets at admission (p= 0.076). In multiple linear regression analysis, SFU

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pretreatment (p= 0.033) was independently and negatively associated with CRHV (linear regression coefficient -0.208, 95%CI: -0.398− -0.017). Higher baseline NIHSS-scores and prior antiplatelet use remained independently (p< 0.05) associated with larger CRHV in multiple linear regression models.

Table 4 depicts associations between baseline characteristics and mild ICH-score (0-1) in univariable and multivariable logistic regression models. The following variables were associated (p< 0.1) with mild ICH-score in univariable analyses: age (p= 0.008), body mass index (BMI; p= 0.042), NIHSS-score at admission (p< 0.001), hypertension (p= 0.019), prior stroke (p= 0.042), hyperlipidemia (p= 0.093), prehospital SFU use (p= 0.022), admission glucose (p= 0.028), systolic blood pressure at admission (p= 0.004), and diastolic blood pressure at admission (p= 0.036). Admission NIHSS-score, age and prehospital SFU use remained independently (p< 0.05) associated with ICH-score in the final multivariable logistic regression model. More specifically, SFU pretreatment was independently related to higher odds of mild ICH-score (OR: 11.91, 95%CI 2.74–51.80; p=0.001), while increasing age and increasing admission NIHSS-scores were associated with a lower likelihood of mild ICH-score at baseline.

Table 5 depicts associations between baseline characteristics and unfavorable functional outcome (mRS-score of 3-6) at discharge in univariable and multivariable logistic regression models. The following variables were associated (p< 0.1) with unfavorable functional outcome in univariable analyses: age (p= 0.091), BMI (p= 0.063), NIHSS-score at admission (p< 0.001), subcortical location (p= 0.056), HV at admission (p< 0.001), intraventricular hemorrhage (p< 0.001), history of hypertension (p= 0.091), prehospital antiplatelet use (p= 0.037), prehospital SFU use (p= 0.031), admission systolic blood pressure (p= 0.006), and admission diastolic blood pressure (p= 0.028). Admission NIHSS-score, age, admission HV and prehospital SFU use

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remained independently ($p< 0.05$) associated with unfavorable functional outcome in the final multivariable logistic regression model. SFU pretreatment was independently related to lower odds of unfavorable functional outcome (OR: 0.19; 95%CI: 0.04-0.88; $p= 0.033$), while increasing age and increasing admission NIHSS-scores were associated with a higher likelihood of unfavorable functional outcome at discharge.

We also repeated our multivariable logistic regression analyses using forward selection procedure. The association between SFU pretreatment and lower likelihood of unfavorable functional outcome was almost identical (OR: 0.12; 95%CI: 0.020-0.64; $p= 0.013$). Additionally, when we used a different cut-off for discharge mRS-score (0-1 vs. 2-6), SFU pretreatment remained independently associated with a lower likelihood of unfavorable functional outcome (mRS-score 2-6) at discharge in multivariable logistic regression models adjusting for potential confounders (OR: 0.12; 95%CI: 0.023-0.059; $p= 0.010$; Supplemental Table I).

Discussion

Our study is the first to report a potential beneficial effect of SFU pretreatment in the outcomes of diabetic patients with acute ICH. We documented that patients pretreated with SFU had lower ICH-scores and smaller HV at hospital admission compared to patients without SFU pretreatment. Moreover, prehospital SFU use was associated with lower likelihood of unfavorable functional outcome at hospital discharge, which remained consistent regardless of mRS dichotomization of "unfavorable outcome". The former three associations persisted after multivariable adjustment for potential confounders including demographics, vascular risk factors, coagulation parameters, admission blood pressure values, serum blood glucose, and creatinine levels.

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SUR1 is transcriptionally upregulated in focal cerebral ischemia [18] via the transcription factor Sp1 [8]. The activation of SUR1-$NC_{Ca\text{-}ATP}$ channels leads to an initial cytotoxic edema, which is then followed by passive influx of chloride ions and water, resulting in a subsequent vasogenic "malignant" cerebral edema [8,19] and poor clinical outcomes. In addition, SFUs have been suggested as potential matrix metalloproteinases-9 (MMP-9) inhibitors [10,20,21], which leads to decreased blood-brain barrier disruption and hemorrhagic transformation [22,23]. Finally, rat models for ischemic stroke have suggested that SFU inhibition of SUR1-$NC_{Ca\text{-}ATP}$ channels may also reduce apoptosis [24].

SFUs potentially inhibit progression of vasogenic edema by directly inhibiting SUR1-$NC_{Ca\text{-}ATP}$ channels. Animal models have demonstrated SFUs improving clinical outcome after ischemic stroke [9,25], subarachnoid hemorrhage [26], and brain metastases [27]. The role of SFUs in decreasing vasogenic edema and improving cognitive deficits has also been demonstrated in rat models of ICH [28].

However, to date, no study has evaluated the association of SFU pretreatment with imaging and clinical outcomes in humans with ICH. Our findings indicate that the potential beneficial effect of SFU pretreatment in early functional outcomes of patients with acute ICH is not be solely attributed to attenuation of admission HV, since in our multivariable analyses SFU pre-hospital use was related to greater functional improvement at discharge even after adjustment for baseline HV, stroke severity, and ICH location. Notably, this association was independent of the selected mRS cut-offs (0-2 vs. 3-6 or 0-1 vs. 2-6) and persisted across the whole distribution mRS-scores (Cochran-Mantel-Haenszel test). Further research is required to elucidate the underlying mechanisms that may account for the beneficial impact of SFU pretreatment on functional outcomes in patients with spontaneous ICH.

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Interestingly, one shortcoming of all major ICH trials of the past decade may be their sole focus on stopping primary phase HV expansion through surgical decompression (STICH II [3]), hemostasis (FAST [4]), or intensive blood pressure control (INTERACT 2 [5] and ATACH II [6]). The failure of these trials may introduce the necessity of providing therapies to reduce secondary mechanisms of injury: blood-brain barrier destruction, vasogenic edema, and pathological MMP-9 activation. The mechanisms of action of SFUs are inherently designed to target this secondary phase of ICH. Better elucidation of these mechanisms and therapies may prove a more promising target for improving clinical outcome in the future.

Several limitations need to be acknowledged when interpreting the findings of the present study. First, the modest sample size, retrospective study design, and non-randomized patient selection was a major methodological shortcoming of this research. This may have led to smaller HVs in the SFU pretreated group, which may have affected final outcomes. However, it should be noted that data was collected prospectively, while neurologists and neuroradiologists evaluating clinical and neuroimaging outcomes were blinded to SFU pretreatment.

Second, as per policy at our hospital, all oral diabetes medications were discontinued upon hospital admission and replaced with insulin during critical care management. This may question the efficacy of SFUs in our study. However, despite being discontinued, the half-lives of glyburide (7-10 hours), glipizide (2-4 hours), and glimepiride (5-8 hours) allow for the possibility that the drugs may have still been present as short as eight hours and as long as forty hours after hospitalization. Rodent models, suggesting that SUR1 is upregulated approximately 2-3 hours in the core and 8-16 hours in the penumbra region after ischemic injury [8] allows for the possibility that the effects of the SFUs may still have been present despite being discontinued. Additionally, rat models with SFU injection twenty-four hours after induction of

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ischemia have demonstrated long-term neuroprotection associated with neuroblast migration toward the ischemic core [29].

Third, perihematomal edema volumes were not measured on admission nor were follow-up images consistently obtained. Therefore, although pretreatment with SFUs was shown to be an independent predictor of good functional outcome, with other multivariable regression analysis suggesting this was not due to admission HV or admission clinical condition, the proposed mechanism of blood-brain barrier preservation and decreased vasogenic edema could not be definitively confirmed.

Fourth, HV for our ICHs was estimated using ABC/2 formula. Slight variations may have existed, however, Kothari et al. demonstrated extremely high correlations ($R^2 = 0.96$) between planimetric measurements and ABC/2 estimation of HV [14].

And finally, functional outcomes were assessed at discharge and not at three-months and this may have confounded the reported associations. However, the improvement in functional outcome in the SFU pretreatment group was robust across several categories: significant improvement both in shift of mRS-score and in different dichotomized mRS-scores (when unfavorable outcome was delineated as mRS 3-6 or mRS 2-6), shorter length of hospitalization, and a strong trend when evaluating disposition.

Conclusion

In conclusion, this pilot, single-center study provides preliminary evidence indicating that SFU pretreatment may be an independent predictor for smaller initial HV, milder admission ICH severity, and improved functional outcome at discharge in diabetic patients with acute ICH. These intriguing observations require independent confirmation by larger, multi-center

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prospective studies with careful design taking into account specific neuroimaging (perihematomal edema volume) and biochemical (MMP-9 levels) parameters that may provide additional insight regarding the potential underlying mechanisms and establish a causal association between SFU pretreatment and improved clinical outcomes in diabetic patients with acute ICH.

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Conflicts of Interest: none

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Tables

Table 1: Baseline characteristics in intracerebral hemorrhage patients with history of diabetes stratified by sulfonylurea pretreatment

Baseline characteristic	**SFU pretreatment (n=37)**	**No SFU pretreatment (n=193)**	**p**
Mean age, years (SD)	67 (10)	63 (13)	0.079
Male gender, %	41%	55%	0.109
African American race, %	73%	73%	0.957
Mean BMI, kg/m^2 (SD)	33.10 (6.22)	31.02 (7.72)	0.124
Hypertension, %	97%	92%	0.267
Coronary Artery Disease, %	22%	18%	0.564
Congestive Heart Failure, %	11%	10%	0.999*
Prior Stroke, %	22%	22%	0.985
Chronic Kidney Disease, %	19%	20%	0.858
Alcohol use, %	18%	20%	0.864
Smoker, %	24%	29%	0.591
Hyperlipidemia, %	49%	40%	0.314
Prehospital Antiplatelet use, %	47%	38%	0.274
Prehospital Anticoagulation use, %	8%	2%	0.090*
Prehospital Statin, %	38%	32%	0.509
Median serum glucose, mg/dl (interquartile range)	182 (148-269)	171 (133-243)	0.417
Median INR (interquartile range)	1.10 (1.00-1.10)	1.00 (1.00-1.10)	0.802
Mean number of platelets, $10^3/\mu L$(SD)	229 (66)	229 (81)	0.965
Median serum creatinine, mg/dl (interquartile range)	1.10 (0.80-1.30)	1.20 (0.90-1.80)	0.128
Mean admission systolic blood pressure, mmHg (SD)	177 (40)	187 (37)	0.138
Mean admission diastolic blood pressure, mmHg (SD)	94 (21)	103 (26)	0.057

SD: standard deviation; SFU: sulfonylurea; BMI: body mass index; INR: international normalized ratio
* p value was calculated by Fisher's exact test

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Table 2. Baseline stroke severity, neuroimaging parameters, in-hospital complications and outcomes in intracerebral hemorrhage patients with history of diabetes stratified by sulfonylurea pretreatment

Variables	**SFU pretreatment (n=37)**	**No SFU pretreatment (n=193)**	**p**
Stroke Severity			
Median NIHSS-score, points (IQR)	6 (2-17)	10 (3-18)	0.225
Median ICH score, points (IQR)	0 (0-2)	1 (0-3)	0.021
Mild ICH score (0-1), %	75%	54%	0.019
Neuroimaging Findings			
Subcortical location, %	57%	63%	0.449
Intraventricular Hemorrhage, %	35%	47%	0.170
Median ICH hematoma volume, cm^3 (IQR)	4 (1-12)	9 (3-20)	0.026
Hematoma Expansion, %	26%	14%	0.184
Complications			
Hemicraniectomy, %	0%	8%	0.138*
Vasopressor, %	0%	2%	0.999*
Respiratory Failure, %	19%	40%	0.015
External Ventricular Drain, %	5%	20%	0.034*
Outcomes			
Length of Hospitalization (days)	5 (3-7)	7 (4-15)	0.012
Median mRS-score at discharge (IQR)	3 (1-5)	4 (2-5)	0.034 [a]
Unfavorable functional Outcome [b], %	54%	72%	0.028
Poor Disposition [c], %	30%	47%	0.058
In-hospital death, %	22%	24%	0.771

NIHSS: National Institute of Health Stroke Scale; IQR: interquartile range;
mRS: modified Rankin Scale
* p value was calculated by Fisher's exact test
[a] p-value was calculated by Cochran-Mantel-Haenszel shift test
[b] unfavorable functional outcome: mRS score 3-6 at hospital discharge
[c] poor disposition: disposition to skilled nursing facility, hospice, or death

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Table 3: Simple and multiple linear regression analyses depicting associations between baseline characteristics and cubed root of admission hematoma volume

	Simple Linear Regression Analysis		Multiple Linear Regression Analysis	
Variable	**Linear Regression Coefficient (95% CI)**	**p***	**Linear Regression Coefficient (95% CI)**	**p**
Age	+0.003 (-0.003–0.009)	0.357		
Gender	-0.087 (-0.246–0.071)	0.279		
African American Race	-0.084 (-0.265–0.096)	0.359		
BMI	-0.004 (-0.014–0.007)	0.484		
NIHSS-score at admission	+0.026 (0.020–0.032)	< 0.001	+0.025 (0.019–0.031)	< 0.001
Subcortical location	-0.094 (-0.260–0.073)	0.269		
Hypertension	-0.016 (-0.343–0.312)	0.925		
Coronary artery disease	+0.143 (-0.061–0.347)	0.169		
Congestive heart failure	+0.071 (-0.184–0.327)	0.583		
Prior stroke	-0.220 (-0.412–-0.027)	0.025	-0.205 (-0.381–-0.030)	0.022
Chronic kidney disease	+0.071 (-0.126–0.269)	0.477		
Alcohol use	+0.061 (-0.144–0.266)	0.559		
Smoker	-0.078 (-0.260–0.105)	0.403		
Hyperlipidemia	-0.156 (-0.317–0.004)	0.057	-0.099 (-0.249–0.050)	0.193
Prehospital Antiplatelet use	+0.147 (-0.019–0.314)	0.083	+0.237 (0.088–0.385)	0.002
Prehospital Anticoagulation use	-0.157 (-0.650–0.335)	0.529		
Prehospital Statin use	-0.128 (-0.303–0.047)	0.151		
Prehospital Sulfonylurea use	-0.223 (-0.439–-0.006)	0.044	-0.208 (-0.398–-0.017)	0.033
INR at admission	+0.079 (-0.333–0.492)	0.706		
Serum Glucose at admission	-0.000 (-0.001–0.001)	0.550		
Platelets at admission (per 1.000/μL increase)	-0.001 (-0.002–0.000)	0.076	+0.000 (-0.001–0.001)	0.449
Serum Creatinine at admission	-0.005 (-0.053–0.043)	0.845		
Systolic blood pressure at admission	+0.000 (-0.002–0.002)	0.708		
Diastolic blood pressure at admission	+0.001 (-0.002–0.004)	0.481		

NIHSS: National Institutes of Health Stroke Scale; BMI = body mass index; INR = international normalized ratio
*cutoff of p< 0.1 was used for selection of candidate variables for inclusion in multiple linear regression models

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Table 4: Univariable and multivariable logistic regression analyses depicting the associations between baseline characteristics and mild ICH score (0-1) at admission.

	Univariable Logistic Regression Analysis		Multivariable Logistic Regression Analysis	
Variable	**Odds Ratio (95% CI)**	**p***	**Odds Ratio (95% CI)**	**p**
Age	0.97 (0.95-0.99)	0.008	0.91 (0.87-0.95)	<0.001
Gender	1.01 (0.59-1.71)	0.983		
African American Race	0.80 (0.44-1.45)	0.46		
BMI	1.04 (1.00-1.08)	0.042	1.04 (0.98-1.11)	0.194
NIHSS-score at admission	0.81 (0.77-0.86)	< 0.001	0.77 (0.72-0.83)	< 0.001
Subcortical location	0.85 (0.49-1.46)	0.546		
Hypertension	0.09 (0.01-0.67)	0.019	0.03 (0.00-1.10)	0.056
Coronary artery disease	0.74 (0.38-1.46)	0.382		
Congestive heart failure	0.88 (0.36-2.14)	0.781		
Prior stroke	2.01 (1.03-3.95)	0.042	2.82 (0.85-9.45)	0.092
Chronic kidney disease	1.12 (0.57-2.21)	0.75		
Prior Alcohol use	1.31 (0.65-2.64)	0.451		
Smoker	0.71 (0.39-1.29)	0.257		
Hyperlipidemia	1.60 (0.92-2.77)	0.093	1.31 (0.51-3.33)	0.573
Prehospital antiplatelet use	0.95 (0.55-1.65)	0.851		

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Prehospital anticoagulation use	1.49 (0.27-8.32)	0.648		
Prehospital statin use	1.54 (0.86-2.77)	0.146		
Prehospital SFU use	2.56 (1.14-5.73)	0.022	11.91 (2.74-51.80)	0.001
Glucose (per 10mg/dL increase)	0.97 (0.95-1.00)	0.028	0.97 (0.93-1.01)	0.181
INR at admission	1.03 (0.42-2.50)	0.948		
Platelets at admission (per 1.000/μL increase)	1.00 (0.99-1.01)	0.28		
Creatinine at admission	0.97 (0.84-1.17)	0.917		
Systolic blood pressure at admission (per 10mmHg increase)	0.90 (0.84-0.97)	0.004	0.95 (0.79-1.15)	0.613
Diastolic blood pressure at admission (per 10mmHg increase)	0.89 (0.80-0.99)	0.036	0.97 (0.71-1.34)	0.869

NIHSS: National Institutes of Health Stroke Scale; BMI = body mass index; INR = international normalized ratio
*cutoff of $p < 0.1$ was used for selection of candidate variables for inclusion in multiple logistic regression models

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Table 5: Univariable and multivariable logistic regression analyses depicting the associations between baseline characteristics and unfavorable functional outcome at discharge (modified Rankin Scale score of 3-6).

	Univariable Logistic Regression Analysis		Multivariable Logistic Regression Analysis	
Variable	**Odds Ratio (95% CI)**	**p***	**Odds Ratio (95% CI)**	**p**
Age	1.02 (1.00-1.04)	0.091	1.10 (1.03-1.17)	0.003
Gender	1.23 (0.70-2.16)	0.479		
African American Race	1.31 (0.71-2.43)	0.394		
BMI	0.97 (0.93-1.00)	0.063	0.99 (0.92-1.05)	0.540
NIHSS-score at admission	1.51 (1.33-1.72)	< 0.001	1.89 (1.50-2.43)	< 0.001
Subcortical location	1.76 (0.99-3.14)	0.056	0.86 (0.28-2.67)	0.797
ICH volume at admission	1.08 (1.04-1.12)	< 0.001	0.94 (0.88-0.99)	0.028
Intraventricular hemorrhage	5.07 (2.60-9.86)	< 0.001	3.34 (0.90-12.36)	0.071
Hematoma Expansion	1.18 (0.45-3.10)	0.730		
Hypertension	2.42 (0.87-6.73)	0.091	0.91 (0.15-5.63)	0.923
Coronary artery disease	0.82 (0.40-1.69)	0.598		
Congestive heart failure	2.26 (0.74-6.89)	0.154		
Prior stroke	0.93 (0.47-1.82)	0.822		
Chronic kidney disease	0.98 (0.48-1.98)	0.947		
Prior Alcohol use	0.81 (0.40-1.65)	0.560		
Smoker	1.48 (0.76-2.86)	0.248		
Hyperlipidemia	0.65 (0.36-1.16)	0.141		
Prehospital antiplatelet use	0.92 (0.51-1.66)	0.792		
Prehospital anticoagulation use	0.17 (0.03-0.90)	0.037	0.001 (0.000-7.67)	0.938
Prehospital statin use	0.99 (0.53-1.83)	0.967		
Prehospital SFU use	0.45 (0.22-0.93)	0.031	0.19 (0.04-0.88)	0.033
Glucose (per 10mg/dL increase)	1.01 (0.98-1.03)	0.626		
INR at admission	0.64 (0.26-1.60)	0.339		
Platelets at admission (per 1.000/μL increase)	1.00 (0.99-1.01)	0.650		
Creatinine at admission	1.01 (0.85-1.20)	0.943		
Systolic blood pressure at admission (per 10mmHg increase)	1.12 (1.03-1.21)	0.006	1.07 (0.86-1.32)	0.561
Diastolic blood pressure at admission (per 10mmHg increase)	1.14 (1.02-1.28)	0.028	1.22 (0.83-1.79)	0.310

ICH: intracerebral hemorrhage; NIHSS: National Institutes of Health Stroke Scale; BMI: body mass index; INR: international normalized ratio

*cutoff of $p < 0.1$ was used for selection of candidate variables for inclusion in multiple logistic regression model.

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Highlights for Review

- Intracerebral hemorrhage remains associated with poor clinical outcome
- SUR-1-$NC_{Ca\text{-}ATP}$ channels may provide a viable therapeutic target for neuroprotection
- Sulfonylurea pretreatment in diabetic patients with ICH may improve outcome

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