Title
Shock Index Predicts Patient-Related Clinical Outcomes in Stroke

Journal
Journal of the American Heart Association, 7(18)

ISSN
2047-9980

Authors
Myint, Phyo Kyaw
Sheng, Shubin
Xian, Ying
et al.

Publication Date
2018-09-18

DOI
10.1161/jaha.117.007581

Peer reviewed

ORIGINAL RESEARCH

Shock Index Predicts Patient-Related Clinical Outcomes in Stroke

Phyo Kyaw Myint, MD; Shubin Sheng, PhD; Ying Xian, MD, PhD; Roland A. Matsouaka, PhD; Mathew J. Reeves, PhD; Jeffrey L. Saver, MD; Deepak L. Bhatt, MD, MPH; Gregg C. Fonarow, MD; Lee H. Schwamm, MD; Eric E. Smith, MD, MPH

Background—The prognostic value of shock index (SI), heart rate divided by systolic blood pressure, in stroke for clinical outcomes other than mortality is not well understood.

Methods and Results—We examined the Get With The Guidelines–Stroke (GWTG-Stroke) data to explore the usefulness of SI in predicting in-hospital outcomes in 425 808 acute stroke cases (mean age: 71.0±14.5 years; 48.8% male; 89.7% ischemic stroke and 10.3% intracerebral hemorrhage) admitted between October 2012 and March 2015. Compared with patients with SI of 0.5 to 0.7, patients with SI >0.7 (13.6% of the sample) had worse outcomes, with adjusted odds ratios of 2.00 (95% confidence interval [CI], 1.92–2.08) for in-hospital mortality, 1.46 (95% CI, 1.43–1.49) for longer length of hospital stay >4 days, 1.50 (95% CI, 1.47–1.54) for discharge destination other than home, 1.41 (95% CI, 1.38–1.45) for inability to ambulate independently at discharge, and 1.52 (95% CI, 1.47–1.57) for modified Rankin Scale score of 3 to 6 at discharge. Results were similar when analyses were confined to those with available National Institutes of Health Stroke Scale (NIHSS) or within individual stroke subtypes or when SI was additionally included in the models with or without blood pressure components. Every 0.1 increase in SI >0.5 was associated with significantly worse outcomes in linear spline models. The addition of SI to existing GWTG-Stroke mortality prediction models without NIHSS demonstrated modest improvement, but little to no improvement was noted in models with NIHSS.

Conclusions—SI calculated at the point of care may be a useful prognostic indicator to identify those with high risk of poor outcomes in acute stroke, especially in hospitals with limited experience with NIHSS assessment. **(*J Am Heart Assoc*. 2018;7: e007581. DOI: 10.1161/JAHA.117.007581.)**

Key Words: length of stay • mortality • prognosis • shock index

The shock index (SI), expressed as a ratio of heart rate to systolic blood pressure (BP), was used initially to detect hypovolemia in patients with septic or hypovolemic shock, indicated by a SI value of >0.7.[1,2] In addition, high SI has been reported to have prognostic significance in trauma[3] and acute cardiovascular events such as acute myocardial infarction and stroke.[4–6] Although heart rate and BP are important variables in predicting acute stroke outcome, physiologically they are linked to each other. Thus SI, which considers the ratio of these variables, could perform better in predicting outcomes. The SI may also reflect the development of Cushing reflex, which is seen with ischemic brain injury caused by any stroke subtypes. In addition to identifying patients at higher risk of mortality, SI may also predict functional outcomes depicted by discharge modified Rankin Scale and ambulatory status in acute stroke.

McCall et al[6] were the first to report the relationship between this simple and readily available physiological index

From the Institute of Applied Health Sciences, School of Medicine, Medical Sciences & Nutrition, University of Aberdeen, United Kingdom (P.K.M.); Duke Clinical Research Institute, Duke University School of Medicine, Durham, NC (S.S., Y.X., R.A.M.); Department of Neurology, Duke University Medical Center, Durham, NC (Y.X.); Department of Biostatistics and Bioinformatics, Duke University, Durham, NC (R.A.M.); Department of Epidemiology and Biostatistics, Michigan State University, Michigan, MI (M.J.R.); Stroke Program, Department of Neurology (J.L.S.) and Division of Cardiology (G.C.F.), David Geffen School of Medicine at UCLA, Los Angeles, CA; Brigham and Women's Hospital Heart & Vascular Center, Harvard Medical School, Harvard University, Boston, MA (D.L.B.); Department of Neurology, Stroke Service, Massachusetts General Hospital, Boston, MA (L.H.S.); Calgary Stroke Programme & Department of Clinical Neurosciences, University of Calgary, Calgary, Canada (E.E.S.).

Accompanying Tables S1 through S3 and Figures S1 through S6 are available at https://www.ahajournals.org/doi/suppl/10.1161/JAHA.117.007581

Correspondence to: Phyo Kyaw Myint, MD, Room 4:013 Polwarth Building, Institute of Applied Health Sciences, School of Medicine, Medical Sciences & Nutrition, University of Aberdeen, Foresterhill, Aberdeen AB25 2ZD, United Kingdom. E-mail: phyo.myint@abdn.ac.uk

Received March 28, 2018; accepted July 20, 2018.

Clinical Perspective

What Is New?

- Shock index (heart rate divided by systolic blood pressure) at presentation to the emergency department predicts patient-related clinical outcomes in ischemic and hemorrhagic stroke.

What Are the Clinical Implications?

- Shock index may be useful in providing prognostic information to patients and relatives.
- Shock index may also serve as an easily available bedside assessment tool to identify high-risk individuals and to guide clinicians in providing appropriate management for these patients.
- Shock index may be particularly useful in low-resource settings or in hospitals with limited experience with stroke-specific assessments such as the National Institutes of Health Stroke Scale.

and acute stroke mortality. In their UK-based multicenter study (N=2121), the authors demonstrated that whereas the higher SI is associated with increased risk of in-hospital mortality, both low and high SIs (low SI indicating presence of Cushing reflex) were associated with early mortality within 3 and 7 days, albeit with higher odds associated with high SI compared with low SI. Although a clear plausible link exists between high or low SI and stroke mortality outcome, no study to date has examined the link between admission SI and other important stroke outcomes such as length of hospital stay and disability.

Using the Get With The Guidelines–Stroke (GWTG-Stroke) data, we aimed to examine admission SI as a prognostic marker not just for in-hospital mortality but also for other important stroke outcomes (ie, in-hospital mortality, discharge destination, discharge ambulatory status, length of stay, and discharge modified Rankin score) controlling for multiple potential confounders in a large cohort of stroke patients. We were also interested in exploring whether adding SI to existing mortality prediction scores would improve the scores' discriminative ability significantly if SI were an independent predictor of in-hospital mortality outcome. Therefore, we also aimed to examine the added value of inclusion of SI in existing GWTG-Stroke mortality prediction models.

Methods

The American Heart Association (AHA) and American Stroke Association GWTG-Stroke database data collection methods have been described previously.[7–10] In brief, participating hospitals used the AHA's Internet-based Patient Management Tool (Quintiles) to enter data, receive decision support, and obtain feedback via on demand reports of performance on quality measures and recorded data from consecutive admissions for acute ischemic stroke.

Trained hospital personnel abstracted data using the Internet-based Patient Management Tool with standardized data definitions and detailed coding instructions. The Internet-based system performs checks to ensure that the reported data are complete and internally consistent. In addition, data quality is monitored for both completeness and accuracy. Hospitals that participate must receive approval through their local institutional review boards or a waiver of individual consent under the common rule. Quintiles is the data collection coordination center for the GWTG-Stroke program.[11]

The Duke Clinical Research Institute serves as the data analysis center. Hospital characteristics (ie, academic teaching status, bed size) were based on American Hospital Association data.[10] Past medical history was defined on the basis of preexisting conditions, with the exclusion of conditions that were newly diagnosed during the hospital stay.

The predictor variable was SI, which is calculated as heart rate divided by systolic BP. These variables were abstracted by trained hospital personnel from the first values recorded in the emergency department record. For descriptive purposes, 3 categories of SI were defined: SI <0.50, SI 0.50 to 0.70 as the normal range, and SI >0.70. The outcomes of interest are patient-relevant outcomes of in-hospital mortality; poor discharge outcome, defined as discharge other than home; poor functional status at discharge, defined as inability to ambulate independently; disability at the time of discharged, defined as modified Rankin Scale (mRS) 3 to 6; and acute hospital length of stay (LOS). For this study purpose, only intracerebral hemorrhages were included as hemorrhagic stroke, and other hemorrhages presenting with stroke symptoms such as subarachnoid hemorrhages or subdural hematoma were excluded.

Patient Inclusion and Exclusion

A total of 694 623 ischemic stroke patients were admitted between October 2012 to April 1, 2015, at 1732 sites after excluding hospitals with >25% missing medical history. Further exclusions included patients with missing admission heart rate or missing admission systolic BP (206 sites, n=232 475); patients who transferred out, who left against medical advice, or whose discharge disposition was missing, not determined, or unable to be determined (8 sites, n=13 618); and patients who were transferred in (4 sites, n=66 658). Consequently, a total of 381 872 ischemic stroke patients from 1514 sites were included in the current study (Figure S1A). Similar inclusion and exclusion criteria were

applied for hemorrhagic stroke (intracerebral hemorrhage) over the same study period (Figure S1B). Comparison of patients who were included and excluded showed that a majority of the characteristics are not significantly different between the 2 groups (data not shown).

Statistical Analysis

Patient characteristics are summarized and compared by SI groups. To examine the association of SI and study outcomes, adjusted multivariable logistic regression models with generalized estimating equations to account for in-hospital clustering were created for each binary outcome. Multiple imputation with 25-fold imputations were used to impute missing data for covariates (see Table S1 for missing data) to account for possible confounders. If a patient had missing medical history, it was assumed that the medical condition did not occur. National Institutes of Health Stroke Scale (NIHSS) score and hospital characteristics were not imputed.

Regression models controlled for various important confounders that are known or likely to influence the relationship between predictor and outcome. We adjusted demographic characteristics such as age, sex, race, insurance, and comorbidities (prosthetic heart valve, previous stroke, coronary artery disease or prior myocardial infarction, diabetes mellitus, peripheral vascular disease, hypertension, heart failure). Other covariates included risk factors such as body mass index (kg/m^2), smoking status, and ambulatory status before the current event, and whether the patient arrived at the hospital during off-hours (regular hours defined as 7 AM to 6 PM Monday–Friday). We also adjusted for other relevant biochemical and physiological markers at the time of admission: glucose (mg/dL), creatinine (mg/dL), diastolic BP (mm Hg), international normalized ratio, total cholesterol, HDL (high-density lipoprotein), LDL (low-density lipoprotein), and triglycerides. Other clinical factors included presence or absence of thrombotic complications of deep venous thrombosis and pulmonary embolism. We also controlled for the following hospital characteristics: region, hospital type, number of beds, rural versus urban location, annual volume of respective ischemic/hemorrhagic stroke admissions, annual volume of tissue plasminogen activator administration (ischemic stroke patients only), and primary stroke center. For those with NIHSS data (n=344 100), we also adjusted for NIHSS, and analyses were conducted as subanalyses.

We repeated the analysis by including SI along with systolic BP instead of diastolic BP. Given high collinearity, heart rate was not included in the model. We also examined the associations by including SI alone without BP components or heart rate. We further assessed the association between both systolic BP and heart rate on all outcomes using multivariable logistic regression models.

To better understand the observed associations between SI and outcomes examined within each SI category, we also fitted both linear and nonlinear models. The latter was done by way of linear splines. First, restricted cubic spline models were used (data not shown) as inference to help us to see the shape of the curves and choose the knots (or cut points) for linear splines.[12] SI was modeled as cubic splines with knots at 5th, 50th and 95th percentiles of SI. Based on the results from cubic spline, SI was modeled by using linear splines with knots at 0.5 and 1.5.

Finally, we examined the usefulness of adding the SI to existing GWTG-Stroke in-hospital mortality risk scores[9,13] by calculating C-index with or without SI in the original GWTG-Stroke models with or without NIHSS (categorical as well as every 0.1 increase in SI). Estimates of reclassification were also assessed using net reclassification index analysis. Calibration plots were also constructed using the continuous SI models.

Results

The study cohort consisted of 425 808 patients with a mean±SD age of 71.04±14.53 years (48.8% male), of whom 89.7% had ischemic stroke and 10.3% had intracerebral hemorrhage. The mean±SD ages were 70.4±14.6 and 69.5±14.8 years for patients ischemic and hemorrhagic stroke, respectively. The majority of patients were white; black patients represented ≈18% and 20% of the sample with ischemic and hemorrhagic stroke subtypes, respectively (versus 69% and 63% white, respectively).

Table 1 shows the total sample characteristics for selected variables (overall and by SI categories). Statistically significant differences were noted among the 3 SI groups. Those with higher SIs (>0.70) were more likely to be younger, and fewer were male. They were more likely to arrive during off-hours and tended to have more severe stroke, depicted by NIHSS (median NIHSS values for SI of <0.5, 0.5–0.7, and >0.7 were 3, 4, and 6, respectively), and were less likely to be independently ambulatory. Notable differences in cardiovascular comorbidities included significantly higher prevalence of peripheral vascular disease and heart failure with significantly lower prevalence of hypertension compared with the other 2 categories. They had significantly higher heart rate and lower systolic BP on admission and were associated with significantly higher rates of poor outcomes for all outcomes examined.

Tables S1 through S3 show the characteristics of all variables included in the models and the outcomes of the overall sample and the ischemic and hemorrhagic stroke groups in detail. Figures S2A through S2C demonstrate the sample's SI distribution for the total sample and for the ischemic and hemorrhagic stroke groups. With large numbers,

Table 1. Characteristics and Outcomes for the Study Population and by SI Categories for Selected Variables

Variable	Overall (N=425 808)	SI <0.50 (n=203 807)	SI 0.50–0.70 (n=163 980)	SI >0.70 (n=58 021)	*P* Value
Characteristics					
Age, y	71.04±14.53	72.39±13.57	70.01±15.01	69.21±15.88	<0.0001
Sex (male)	207 763 (48.79)	101 863 (49.98)	79 539 (48.51)	26 361 (45.43)	<0.0001
Stroke type					<0.0001
Ischemic	381 872 (89.68)	180 229 (88.43)	149 002 (90.87)	52 641 (90.73)	
Hemorrhagic	43 936 (10.32)	23 578 (11.57)	14 978 (9.13)	5380 (9.27)	
Race/ethnicity					<0.0001
Other	13 629 (3.20)	6424 (3.15)	5321 (3.25)	1884 (3.25)	
Asian	13 134 (3.09)	6705 (3.29)	4848 (2.96)	1581 (2.73)	
Hispanic (any race)	30 802 (7.24)	14 502 (7.12)	12 187 (7.44)	4113 (7.09)	
Black	79 285 (18.63)	38 601 (18.95)	30 139 (18.39)	10 545 (18.18)	
White	288 753 (67.85)	137 491 (67.49)	111 397 (67.97)	39 865 (68.75)	
Missing	205 (0.05)	84 (0.04)	88 (0.05)	33 (0.06)	
Arrived during off-hours (yes)*	188 736 (44.32)	89 970 (44.14)	72 638 (44.30)	26 128 (45.03)	0.0007
Initial NIHSS (missing, 19.19%), median (IQR)	4 (1–10)	3 (1–9)	4 (1–10)	6 (2–14)	<0.0001
Ambulatory status independent	127 089 (31.60)	63 606 (33.06)	49 701 (32.10)	13 782 (25.08)	<0.0001
Medical history (yes)					
Previous stroke/TIA	134 334 (31.56)	63 784 (31.30)	52 209 (31.85)	18 342 (31.62)	0.0019
CAD/prior MI	104 509 (24.55)	51 914 (25.48)	38 659 (23.58)	13 936 (24.03)	<0.0001
Diabetes mellitus	144 248 (33.88)	69 071 (33.90)	55 983 (34.15)	19 194 (33.09)	<0.0001
PVD	20 170 (4.74)	9479 (4.65)	7662 (4.67)	3029 (5.22)	<0.0001
Hypertension	330 174 (77.56)	167 235 (82.07)	122 128 (74.50)	40 811 (70.36)	<0.0001
Heart failure	39 167 (9.20)	16 217 (7.96)	15 526 (9.47)	7424 (12.80)	<0.0001
Smoker (yes)	73 445 (17.25)	32 259 (15.83)	30 084 (18.35)	11 102 (19.14)	<0.0001
BMI, kg/m^2	28.07±6.78	28.16±6.56	28.14±6.89	27.50±7.18	<0.0001
Heart rate, beats/min	82±18	71±12	86±14	105±20	<0.0001
Systolic BP, mm Hg	160±31	177±27	149±23	126±23	<0.0001
Glucose, mg/dL	145±72	141±67	146±75	153±82	<0.0001
Cholesterol, mg/dL	170±48	173±48	167±48	158±48	<0.0001
Hospital characteristics					
Primary stroke center (yes)	186 487 (43.80)	89 369 (43.85)	71 698 (43.72)	25 420 (43.81)	0.74
Region					<0.0001
West	77 212 (18.15)	36 559 (17.95)	29 849 (18.22)	10 804 (18.64)	
South	150 665 (35.41)	73 109 (35.90)	57 350 (35.00)	20 206 (34.86)	
Midwest	77 841 (18.30)	37 440 (18.39)	29 773 (18.17)	10 628 (18.33)	
Northeast	119 722 (28.14)	56 514 (27.75)	46 879 (28.61)	16 329 (28.17)	
Missing	368 (0.09)	185 (0.09)	129 (0.08)	54 (0.09)	
Outcomes					
In-hospital mortality	27 903 (6.55)	11 895 (5.84)	9601 (5.85)	6407 (11.04)	<0.0001
Died as inpatient					
LOS >4 d (missing, n=12 884)	164 760 (39.90)	75 788 (37.96)	62 682 (39.42)	26 290 (48.43)	<0.0001

Continued

Table 1. Continued

Variable	Overall (N=425 808)	SI <0.50 (n=203 807)	SI 0.50–0.70 (n=163 980)	SI >0.70 (n=58 021)	*P* Value
Independent ambulatory status					
No (missing, n=42 454)	188 221 (49.10)	88 897 (48.07)	71 606 (48.16)	27 718 (55.70)	<0.0001
mRS >2	146 562 (61.34)	68 182 (60.03)	55 344 (60.05)	23 036 (69.42)	<0.0001

Values presented are mean±SD for continuous data and n (%) for categorical data, except as noted. BMI indicates body mass index; BP, blood pressure; CAD, coronary artery disease; IQR, interquartile range; LOS, length of stay; MI, myocardial infarction; mRS, modified Rankin Scale; NIHSS, National Institute of Health Stroke Scale; PVD, peripheral vascular disease; SI, stroke index; TIA, transient ischemic attack.
*Daytime regular hours were defined as 7 AM to 6 PM Monday to Friday; all other times (including all day Saturday and Sunday) were considered off-hours.

the overall *P* values for trends are significant, although the material differences between groups are relatively minor. Those with higher SI in both stroke types were more likely to be younger, female, prior anticoagulant users with higher international normalized ratios, and current smokers and to have higher prevalence of heart failure, lower cholesterol, and higher glucose levels on admission. Not surprisingly, history of hypertension and higher systolic BP and lower levels of heart rate were less likely to be associated with higher SI. Higher NIHSS was associated with higher SI in ischemic stroke, but the trend appeared to be U shaped in hemorrhagic stroke; high NIHSS was associated with both low and high SI.

Higher SI is also associated with poor outcomes of mortality, ambulatory status at discharge, and disability outcome (mRS >2) when crude comparisons were made. In-hospital mortality for those with SI >0.7 was almost double that of the other SI categories (11.0% versus ≈5.9%, respectively). Also in this category, 55.7% patients were not

Table 2. ORs and Corresponding 95% CIs for Those With Admission SI <0.5 and >0.7 Compared With SI 0.5–0.7 for Study Outcomes for All Participants and by Ischemic and Hemorrhagic Stroke in GWTG-Stroke October 2012 to March 2015

Outcomes	SI <0.5 vs 0.5–0.7 OR (95% CI)	*P* Value	SI >0.7 vs 0.5–0.7 OR (95% CI)	*P* Value
In-hospital mortality				
All	0.86 (0.83–0.89)	<0.0001	2.00 (1.92–2.08)	<0.0001
Ischemic stroke	0.79 (0.76–0.82)	<0.0001	1.97 (1.87–2.06)	<0.0001
Hemorrhagic stroke	1.01 (0.96–1.08)	0.64	1.85 (1.69–2.02)	<0.0001
LOS (>4 vs 0–4 d)				
All	0.87 (0.86–0.89)	<0.0001	1.46 (1.43–1.49)	<0.0001
Ischemic stroke	0.86 (0.84–0.87)	<0.0001	1.53 (1.49–1.56)	<0.0001
Hemorrhagic stroke	0.97 (0.92–1.02)	0.21	0.95 (0.89–1.02)	0.14
Discharge destination other than home				
All	0.89 (0.87–0.90)	<0.001	1.50 (1.47–1.54)	<0.001
Ischemic stroke	0.88 (0.86–0.90)	<0.001	1.49 (1.45–1.53)	<0.001
Hemorrhagic stroke	0.97 (0.91–1.03)	0.32	1.53 (1.38–1.68)	<0.001
Independent ambulatory status at discharge (no vs yes)				
All	0.89 (0.87–0.91)	<0.0001	1.41 (1.38–1.45)	<0.0001
Ischemic stroke	0.89 (0.87–0.91)	<0.0001	1.40 (1.36–1.44)	<0.0001
Hemorrhagic stroke	0.89 (0.83–0.96)	0.0011	1.46 (1.32–1.62)	<0.0001
Disability (mRS 3–6 vs 0–2)				
All	0.88 (0.86–0.90)	<0.0001	1.52 (1.47–1.57)	<0.0001
Ischemic stroke	0.88 (0.86–0.90)	<0.0001	1.49 (1.45–1.54)	<0.0001
Hemorrhagic stroke	0.99 (0.90–1.08)	0.81	1.83 (1.59–2.09)	<0.0001

Models adjusted for patient and hospital characteristics including systolic and diastolic blood pressure (see Methods for details). CI indicates confidence interval; GWTG-Stroke, Get With The Guidelines–Stroke; LOS, length of stay; mRS, modified Rankin Scale; OR, odds ratio; SI, stroke index.

Table 3. ORs and Corresponding 95% CIs for Those With Admission SI <0.5 and >0.7 Compared With SI 0.5–0.7 for Study Outcomes for All Participants (N=344 100) and by Ischemic Stroke (n=315 612) and Hemorrhagic Stroke (n=28 488) in GWTG-Stroke October 2012 to March 2015 for Those With NIHSS Data

Models	SI <0.5 OR (95% CI)	*P* Value	SI >0.7 OR (95% CI)	*P* Value
In-hospital mortality				
All	0.91 (0.88–0.94)	<0.0001	1.53 (1.46–1.61)	<0.0001
Ischemic stroke	0.89 (0.85–0.92)	<0.0001	1.54 (1.46–1.62)	<0.0001
Hemorrhagic stroke	0.98 (0.90–1.07)	0.70	1.39 (1.23–1.58)	<0.0001
Length of stay (>4 vs 0–4 d)				
All	0.90 (0.88–0.92)	<0.0001	1.39 (1.36–1.43)	<0.0001
Ischemic stroke	0.89 (0.88–0.91)	<0.0001	1.42 (1.38–1.46)	<0.0001
Hemorrhagic stroke	0.99 (0.93–1.05)	0.64	1.07 (0.98–1.17)	0.16
Discharge destination other than home				
All	0.94 (0.92–0.95)	<0.001	1.28 (1.24–1.31)	<0.001
Ischemic stroke	0.93 (0.92–0.95)	<0.001	1.28 (1.24–1.32)	<0.001
Hemorrhagic stroke	0.95 (0.88–1.03)	0.18	1.23 (1.07–1.42)	0.004
Independent ambulatory status at discharge (no vs yes)				
All	0.94 (0.92–0.97)	<0.0001	1.25 (1.21–1.29)	<0.0001
Ischemic stroke	0.95 (0.93–0.97)	<0.0001	1.25 (1.21–1.28)	<0.0001
Hemorrhagic stroke	0.89 (0.81–0.97)	0.0081	1.29 (1.12–1.49)	<0.0001
Disability (mRS 3–6 vs 0–2)				
All	0.94 (0.91–0.97)	<0.0001	1.28 (1.23–1.33)	<0.0001
Ischemic stroke	0.93 (0.91–0.96)	<0.0001	1.27 (1.21–1.33)	<0.0001
Hemorrhagic stroke	1.01 (0.91–1.13)	0.83	1.39 (1.15–1.69)	0.0007

Models were adjusted for patient and hospital characteristics, including systolic blood pressure, diastolic blood pressure, and NIHSS. See Methods for details. CI indicates confidence interval; GWTG-Stroke, Get With The Guidelines–Stroke; mRS, modified Rankin Scale; NIHSS, National Institute of Health Stroke Scale; OR, odds ratio; SI, stroke index.

able to ambulate independently compared with ≈48% in other 2 categories. The crude rate of mRS >2 outcome also increased ≈10% in those with SI >0.7 compared with the other categories. LOS (>4 days) appears to be differently associated with SI depending on stroke type; a higher proportion of ischemic stroke patients with longer LOS had higher SI (35.9% with SI <0.5, 38.1% with SI 0.5–0.7, and 48.3% with SI >0.7), whereas the reverse was true for hemorrhagic stroke (53.9%, 52.2%, and 49.9%, respectively).

As expected, the individual components of SI, heart rate and systolic BP, are also independent predictors of outcomes. Both lower heart rate and higher systolic BP are also independently associated with outcomes. Repeating the analyses including SI or replacing diastolic BP with systolic BP did not alter the results (data not shown).

Table 2 shows the odds ratios and corresponding 95% confidence intervals for the relationship between low (<0.5) and high (>0.7) SI compared with normal SI (0.5–0.7) for each selected outcome in the whole sample and separately for ischemic and hemorrhagic stroke subtypes after controlling for potential confounders listed in the study methods. The results consistently showed the higher SI group (SI >0.7) associated with worse outcomes including in-hospital mortality, longer LOS, likelihood of being discharged to a destination other than home, inability to ambulate independently at the time of hospital discharge, and association with higher likelihood of disability defined as mRS >2 (ie, discharge mRS 3–6).

Table 3 shows the results for those with NIHSS data available (n=344 100) with additional adjustment for NIHSS score. Results were broadly similar to the whole sample except for the nonsignificant association of the hemorrhagic stroke subtype with longer LOS, although a point estimate showed a similar direction (odds ratio: 1.07). Based on cubic spline results, linear spline models were constructed for these outcomes using knots at 0.5 and 0.7 to better understand the dose-response relationship within each SI category. Odds ratios and their corresponding 95% confidence intervals were calculated by incremental 0.1-U increase in SI, and results are presented in Table 4. Consistent with earlier results, an

Table 4. ORs and Corresponding 95% CIs for Every Incremental Increase in SI 0.1 Within Each SI Category (Coded as Linear Spline With Knots at 0.5 and 0.7) for Study Outcomes for All Patients and by Ischemic and Hemorrhagic Stroke Patients Separately in GWTG-Stroke (October 2012–March 2015)

Outcomes	SI 0.0–0.5 OR (95% CI)	SI 0.5–0.7 OR (95% CI)	SI >0.7 OR (95% CI)
In-hospital mortality			
All	0.91 (0.89–0.94)	1.35 (1.26–1.45)	1.22 (1.10–1.35)
Ischemic stroke	1.00 (0.97–1.04)	1.37 (1.26–1.50)	1.20 (1.07–1.35)
Hemorrhagic stroke	0.83 (0.79–0.87)	1.22 (1.08–1.38)	1.26 (1.04–1.52)
LOS (>4 vs 0–4 d)			
All	1.02 (1.00–1.03)	1.20 (1.16–1.25)	1.10 (1.04–1.17)
Ischemic stroke	1.01 (1.00–1.03)	1.22 (1.18–1.27)	1.13 (1.06–1.20)
Hemorrhagic stroke	1.07 (1.03–1.11)	1.00 (0.91–1.10)	0.96 (0.83–1.12)
Discharge destination other than home			
All	1.01 (1.00–1.03)	1.18 (1.13–1.22)	1.16 (1.09–1.23)
Ischemic stroke	1.02 (1.01–1.04)	1.18 (1.13–1.23)	1.16 (1.09–1.23)
Hemorrhagic stroke	0.96 (0.91–1.01)	1.14 (1.00–1.30)	1.19 (0.97–1.46)
Independent ambulatory status at discharge (no vs yes)			
All	1.02 (1.01–1.04)	1.17 (1.12–1.21)	1.12 (1.05–1.19)
Ischemic stroke	1.03 (1.01–1.04)	1.16 (1.12–1.21)	1.12 (1.05–1.19)
Hemorrhagic stroke	1.00 (0.95–1.06)	1.18 (1.02–1.35)	1.11 (0.89–1.39)
Disability (mRS 3–6 vs 0–2)			
All	1.00 (0.98–1.02)	1.20 (1.14–1.26)	1.17 (1.08–1.26)
Ischemic stroke	1.01 (0.99–1.04)	1.19 (1.13–1.26)	1.16 (1.07–1.26)
Hemorrhagic stroke	0.94 (0.87–1.01)	1.15 (0.95–1.40)	1.29 (0.93–1.79)

Models were adjusted for baseline patient and hospital characteristics, including systolic and diastolic blood pressure. CI indicates confidence interval; GWTG-Stroke, Get With The Guidelines–Stroke; LOS, length of stay; mRS, modified Rankin Scale; OR, odds ratio; SI, stroke index.

incremental increase of 0.1 U of SI in a linear fashion was associated with worse outcomes for SI >0.5. With a lower number of events, the results appeared to be less consistent for hemorrhagic stroke. The cubic splines, which were constructed for inference purposes of finding relevant knots for linear spline models, are shown as Figures S4A–S4C to S5A–S5C.

Table 5 shows the comparison of C-indexes calculated with or without inclusion of SI for the original GWTG-Stroke models with or without NIHSS for mortality outcome. There were modest improvements in C-statistics by adding SI (categorically or every 0.1-U incremental increase in SI) to the original model without stroke severity,[9] but little to no improvement when SI was added to the model that also included NIHSS.[13] However, in the subsample with available NIHSS data, exclusion of NIHSS from the model performed less well. Table 5 also shows the results of the net reclassification index with values >0 for the model with SI, confirming the reclassification improvement of the new model (with SI) compared with the model without SI.

Figure shows the calibration plots for overall population (Figure 1A), and then for ischemic stroke and intracerebral hemorrhage cohorts separately (Figure 1B and 1C, respectively) using the continuous SI models (ie, the last 3 models in Table 5). This demonstrates the good fit of model prediction from the observed data.

Discussion

To our knowledge, this study is the first to examine the association between the SI and relevant clinical outcomes of acute hospital LOS, discharge destination, ambulatory status at the time of discharge, and disability outcome. We are the first to examine this association for specific stroke subtypes, ischemic and hemorrhagic stroke, using the largest sample to date, with >420 000 patients with unselected consecutively admitted strokes to stroke services across the United States.

We found consistent predictive value of admission SI by clear demonstration of significantly worse outcomes with higher levels of SI, including mortality. This association

Table 5. Mortality Outcome Prediction by Including SI in the Original GWTG-Stroke and GWTG-Stroke NIHSS Indexes in This Cohort

Model	C-Index Comparison		Model With SI, NRI (95% CI)
	With SI	Without SI	
GWTG-Stroke without NIHSS*			
In-hospital mortality (overall population)	0.816	0.809	0.250 (0.238–0.262)*
In-hospital mortality (ischemic stroke subgroup)	0.767	0.757	0.192 (0.163–0.222)*
In-hospital mortality (hemorrhagic stroke)	0.744	0.741	0.232 (0.218–0.246)*
Available NIHSS Data GWTG-Stroke With NIHSS Model†			
In-hospital mortality (overall population)	0.875	0.873	0.802
In-hospital mortality (ischemic stroke subgroup)	0.855	0.852	0.767
In-hospital mortality (hemorrhagic stroke)	0.852	0.852	0.734
SI as 0.1 Increment			
In-hospital mortality (overall population)	0.818	0.809	. . .
In-hospital mortality (ischemic stroke subgroup)	0.771	0.757	. . .
In-hospital mortality (hemorrhagic stroke)	0.748	0.741	. . .

CI indicates confidence interval; GWTG-Stroke, Get With The Guidelines–Stroke; mRS, modified Rankin Scale; NIHSS, National Institute of Health Stroke Scale; NRI, net reclassification improvement; SI, shock index.

*NRI >0 means reclassification improvement of the new model with SI compared with the model without SI.

†NRI is for model with SI without NIHSS.

appears to be linear; every incremental increase in SI of 0.1 above an SI value of 0.5 appears to be an important prognostic factor after taking into account individual prognostic factors and clinical and hospital characteristics. McCall and colleagues previously examined the link between SI and acute stroke mortality in a much smaller sample (n=2121). They found similar results demonstrating that high SI value was associated with increased inpatient mortality (odds ratio: 1.85; 95% confidence interval, 1.17–2.92).[6] Of note, their population was predominantly white (>95%), and they were not able to control for some key variables of initial stroke severity, such as NIHSS or poststroke complications. Our results are broadly similar, with an overall estimated odds ratio of 2.0 for mortality. We were able to examine the stroke type–specific in-hospital mortality outcome, and the results appeared to be consistent for both stroke subtypes.

Acute stroke causes an increase in sympathetic outflow to the heart in an attempt to increase arterial BP and total peripheral resistance to maintain cerebral blood flow, accompanied by bradycardia known as Cushing reflex. Although Cushing reflex is noticeable only with more severe ischemic injury (direct effect of ischemic injury or secondary to hemorrhagic stroke with resultant edema), the subtle physiological changes may have already been occurring in any ischemic stroke depending on the severity of ischemic injury. Kalmer et al[14] showed that the Cushing reflex indicated by higher systolic BP and bradycardia predicted poor intracranial perfusion and high intracranial pressure even with minimally invasive procedures. Furthermore, mortality after a subarachnoid hemorrhage was predicted by high intracranial pressure, which demonstrated poor intracranial perfusion.[15]

A lower SI may also have prognostic significance in stroke, serving as an early marker of the Cushing reflex. Conversely, large strokes with dysphagia or posterior circulation strokes presenting with vomiting present a high risk of aspiration pneumonia and may be associated with higher SI, as they are more likely to cause higher heart rate and lower systolic BP. Consequently, a potential U- or J-shaped relationship was expected between SI and selected outcomes; however, we did not find the U-shaped relationship that was observed in the study by McCall et al.[6] Of note, McCall and colleagues did not adjust for poststroke complications, which could influence the outcomes examined.

The prognostic value of high SI has been previously reported in conditions such as sepsis and severe volume depletion.[1,16] Previous studies have used SI to assess outcomes in patients with community-acquired pneumonia and acute circulatory failure and to predict those who would require immediate intensive therapy.[1,16–18] Moreover, a recent study that used prospectively collected audit data showed that an SI >1.0 was predictive of inpatient mortality in individuals aged >90 years.[19] It should be noted that SI can vary during the process of care, as BP management in stroke may influence its values, and thus it is expected that SI would fluctuate during the course of admission. This may have attenuated the observed relationships.

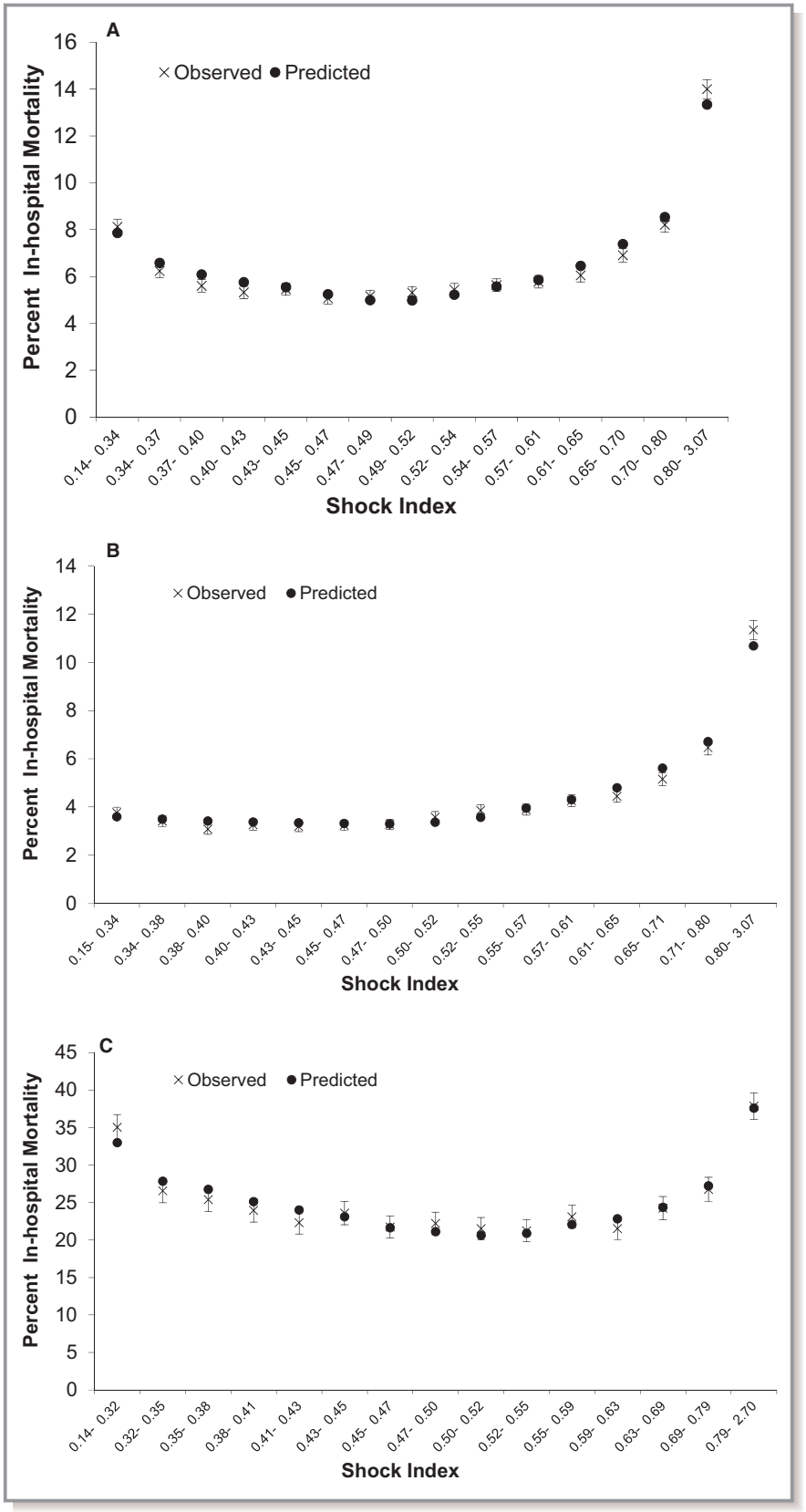


Figure. Calibration plots for (A) the overall population, (B) the ischemic stroke cohort, and (C) the intracerebral hemorrhage cohort.

It was unknown whether incorporating SI into prognostic scoring systems to improve existing scoring systems such as GWTG-Stroke,[9,13] iScore,[20] SOAR (Stroke Subtype, Oxford Community Stroke Project Classification, Age, Prestroke Modified Rankin) score,[21] and mSOAR (modified SOAR)[22] would improve the clinical prediction rules in stroke. We extended our study aims to examine the usefulness of adding SI to existing GWTG-Stroke scores.[9,13] The addition of SI in the absence of NIHSS data appeared to improve the prediction of the GWTG-Stroke prognosis scoring system. Indeed, both heart rate and systolic BP can be accurately measured and recorded in any hospital setting without special training. Furthermore, McCall et al already demonstrated that using SI has greater predictive ability than systolic BP with regard to short-term mortality.[6] In clinical practice, information on vital signs can be readily abstracted from routine examination; therefore, SI can be easily calculated, and using SI could improve prediction of outcomes for individual patients as well as risk adjustment. Consequently, SI is particularly useful in jurisdictions where standardized stroke scales that require training (eg, NIHSS) are difficult to implement in the emergency setting.

SI is a very simple index derived from 2 readily available vital signs—heart rate and systolic BP—and its value at the point of care can provide valuable prognostic information. Indeed, Lee et al demonstrated in the GUSTO-I (Global Utilization of Streptokinase and Tissue Plasminogen Activator for Occluded Coronary Arteries-I) that both heart rate and BP are among 5 predictors of 30-day mortality after acute myocardial infarction.[23] Contemporary findings in the field of cardiology showed similar results; in a cohort of 7187 patients with ST-segment elevation–myocardial infarction, admission SI $\geq$0.7 was also associated with 1.6- and 1.5-fold increased risk of 7- and 30-day major adverse cardiovascular events, respectively.[5]

The key strengths of our work include the large sample size and prospective data collection. We were able to conduct robust statistical analysis with control for potential confounders including poststroke complications. We were able to examine the outcomes by specific stroke subtypes and robustly control for initial stroke severity in those with NIHSS data available. Furthermore, our study has good ethnic mix and thus is potentially applicable to other populations including black, Asian, and Hispanic ethnic groups. The net reclassification index confirms the reclassification improvement of SI, and calibration plots demonstrate the model's fitness. This shows the usefulness of SI in a clinical setting because SI is an easily obtainable physiological parameter. Moreover, as a physiological index, the relationship between SI and outcome is unlikely to be different between different races or sexes; therefore, the results are generalizable.

Our study has some limitations. Hospital-based study outcomes are confined to in-hospital outcomes (ie, up to the time of hospital discharge); however, the outcomes assessed are important for stroke patients and their significant others. Moreover, prediction of LOS and discharge destination forms an important aspect of service provision and assessment of social care needs. We acknowledge large amounts of missing data for some variables; however, we have used multiple imputation to account for this. As an observational study, causality between SI and poor stroke outcomes cannot be drawn. Nevertheless, the observed associations have plausible explanations, observed prospectively and consistent with the wider literature of cardiovascular outcome epidemiology. Because data were from a hospital-based registry, some stroke patients might not have been included, such as those who died before admission. Patients and hospitals may not be entirely representative of the US population, but the sample population is comparable to all US patients hospitalized with stroke.[24]

We were not able to assess the effect of unmeasured or residual confounders; however, we were able to control for a comprehensive list of potential confounding variables. A substantial proportion of patients had missing NIHSS data; however, that was because of nonrandom missingness, and repeating the analyses in those who had NIHSS data showed similar results. About of a third of patients were excluded for various reasons including missing data, and this could potentially limit generalizability; however, we were able to impute for missing variables, and the percentage of missing values is generally low or very low. As a physiological parameter, the relationship between SI and outcome is unlikely to be influenced by population characteristics; therefore, the findings are generalizable and applicable to any stroke patient in predicting likely outcome at the point of care.

In summary, our study shows that SI is a significant predictor of important patient-related acute stroke outcomes including mortality, acute hospital LOS, discharge destination, ambulatory status at the time of discharge, and poststroke disability. Our robust statistical analysis, taking into account multiple confounding variables, showed a relationship between SI and clinical outcomes; however, further studies are required to demonstrate prognostic utility before it could be widely adopted as a clinical tool. This information may be useful in clinical practice for managing stroke patients, to identify those with high risk of poor outcomes from the point of contact, particularly if NIHSS is not available, and to better inform patients and their significant others about the prognosis of these important outcomes.

Acknowledgments

We gratefully acknowledge the contribution of Get With The Guidelines–Stroke (GWTG-Stroke) study sites and the American

Heart Association and American Stroke Association GWTG-Stroke team.

Author Contributions

Myint and Smith conceived the idea and developed the analysis plan with critical input from the coauthors. Sheng analyzed the data. Myint and Smith drafted the article with input from all coauthors. All authors contributed to interpretation of the results and made important intellectual contributions to the article.

Sources of Funding

The Get With The Guidelines–Stroke (GWTG-Stroke) program is currently supported in part by a charitable contribution from Bristol-Myers Squibb/Sanofi Pharmaceutical Partnership and the American Heart Association Pharmaceutical Roundtable. GWTG-Stroke has been funded in the past through support from Boehringer-Ingelheim and Merck. These funding agencies did not participate in the design or analysis, article preparation, or approval of this study.

Disclosures

Dr Bhatt discloses the following relationships—Advisory Board: Cardax, Elsevier Practice Update Cardiology, Medscape Cardiology, Regado Biosciences; Board of Directors: Boston VA Research Institute, Society of Cardiovascular Patient Care, TobeSoft; Chair: American Heart Association Quality Oversight Committee; Data Monitoring Committees: Baim Institute for Clinical Research (formerly Harvard Clinical Research Institute, for the PORTICO trial, funded by St. Jude Medical, now Abbott), Cleveland Clinic, Duke Clinical Research Institute, Mayo Clinic, Mount Sinai School of Medicine, Population Health Research Institute; Honoraria: American College of Cardiology (Senior Associate Editor, Clinical Trials and News, ACC.org; Vice-Chair, ACC Accreditation Committee), Baim Institute for Clinical Research (formerly Harvard Clinical Research Institute; RE-DUAL PCI clinical trial steering committee funded by Boehringer Ingelheim), Belvoir Publications (Editor in Chief, Harvard Heart Letter), Duke Clinical Research Institute (clinical trial steering committees), HMP Global (Editor in Chief, Journal of Invasive Cardiology), Journal of the American College of Cardiology (Guest Editor; Associate Editor), Population Health Research Institute (for the COMPASS operations committee, publications committee, steering committee, and USA national coleader, funded by Bayer), Slack Publications (Chief Medical Editor, Cardiology Today's Intervention), Society of Cardiovascular Patient Care (Secretary/Treasurer), WebMD (CME steering committees); Other: Clinical Cardiology (Deputy Editor), NCDR-ACTION Registry Steering Committee (Chair), VA CART Research and Publications Committee (Chair); Research Funding: Abbott, Amarin, Amgen, AstraZeneca, Bayer, Boehringer Ingelheim, Bristol-Myers Squibb, Chiesi, Eisai, Ethicon, Forest Laboratories, Idorsia, Ironwood, Ischemix, Lilly, Medtronic, PhaseBio, Pfizer, Regeneron, Roche, Sanofi Aventis, Synaptic, The Medicines Company; Royalties: Elsevier (Editor, Cardiovascular Intervention: A Companion to Braunwald's Heart Disease); Site Co-Investigator: Biotronik, Boston Scientific, St. Jude Medical (now Abbott), Svelte; Trustee: American College of Cardiology; Unfunded Research: FlowCo, Merck, PLx Pharma, Takeda. Dr Fonarow is a member of the GWTG Executive Committee; has served as a consultant to Janssen (modest), receives research support from PCORI (significant), and is an employee of UCLA, which holds a patent on retriever devices for stroke. Dr Myint has received support from Viforpharma to attend an advisory meeting. Dr Reeves has received salary support from the Michigan Stroke GWTG Registry Dr Saver is an employee of the University of California. Dr Saver has served as an unpaid site investigator in multicenter trials run by Medtronic and Stryker for which the UC Regents received payments on the basis of clinical trial contracts for the number of subjects enrolled. Dr Saver receives funding for services as a scientific consultant regarding trial design and conduct to Medtronic/Covidien, Stryker, Neuravi, BrainsGate, Pfizer, Squibb, Boehringer Ingelheim (prevention only), ZZ Biotech, and St. Jude Medical. Dr Saver serves as an unpaid consultant to Genentech advising on the design and conduct of the PRISMS trial; neither the University of California nor Dr Saver received any payments for this voluntary service. The University of California has patent rights in retrieval devices for stroke. Dr Schwamm reports being the principal investigator of an investigator-initiated study of extended-window intravenous thrombolysis funded by the National Institutes of Neurological Disorders and Stroke (clinicaltrials.gov/show/NCT01282242) for which Genentech provided alteplase free of charge to Massachusetts General Hospital as well as supplemental per-patient payments to participating sites; serving as chair of the AHA/ASA GWTG stroke clinical work group and hospital accreditation Science Committee and Quality Oversight Committees, co-chair of Mission-Lifeline: Stroke; serving as a stroke systems consultant to the Massachusetts Department of Public Health; and serving as a scientific consultant to LifeImage regarding user interface design and usability, and regarding trial design and conduct to Lundbeck (international steering committee, DIAS3, 4 trial), Penumbra (data and safety monitoring committee, Separator 3D and MIND trials) and Medtronic (Victory AF and Stroke AF trials). Dr Smith is a member of the American Heart Association Get With The Guidelines Steering Committee; has received research support from the Canadian Institutes for Health Research, Brain

Canada, Alberta Innnovates—Health Solutions, and the Canadian Partnership Against Cancer. The remaining authors have no disclosures to report.

References

1. Berger T, Green J, Horeczko T, Hagar Y, Garg N, Suarez A, Panacek E, Shapiro N. Shock index and early recognition of sepsis in the emergency department: pilot study. *West J Emerg Med*. 2013;14:168–174.
2. Allgöwer M, Burri C. Shock index. *Dtsch Med Wochenschr*. 1967;92:1947–1950.
3. Pandit V, Rhee P, Hashmi A, Kulvatunyou N, Tang A, Khalil M, O'Keeffe T, Green D, Friese RS, Joseph B. Shock index predicts mortality in geriatric trauma patients: an analysis of the National Trauma Data Bank. *J Trauma Acute Care Surg*. 2014;76:1111–1115.
4. Bilkova D, Motovska Z, Widimsky P, Dvorak J, Lisa L, Budesinsky T. Shock index: a simple clinical parameter for quick mortality risk assessment in acute myocardial infarction. *Can J Cardiol*. 2011;27:739–742.
5. Huang B, Yang Y, Zhu J, Liang Y, Tan H, Yu L, Gao X, Li J. Usefulness of the admission shock index for predicting short-term outcomes in patients with ST-segment elevation myocardial infarction. *Am J Cardiol*. 2014;114:1315–1321.
6. McCall SJ, Musgrave SD, Potter JF, Hale R, Clark AB, Mamas MA, Metcalf AK, Day DJ, Warburton EA, Bachmann MO, Myint PK; Anglia Stroke Clinical Network Evaluation Study (ASCNES) Group. The shock index predicts acute mortality outcomes in stroke. *Int J Cardiol*. 2015;182:523–527.
7. LaBresh KA, Reeves MJ, Frankel MR, Albright D, Schwamm LH. Hospital treatment of patients with ischemic stroke or transient ischemic attack using the "Get With The Guidelines" program. *Arch Intern Med*. 2008;168:411–417.
8. Schwamm LH, Fonarow GC, Reeves MJ, Pan W, Frankel MR, Smith EE, Ellrodt G, Cannon CP, Liang L, Peterson E, Labresh KA. Get With the Guidelines-Stroke is associated with sustained improvement in care for patients hospitalized with acute stroke or transient ischemic attack. *Circulation*. 2009;119:107–115.
9. Smith EE, Shobha N, Dai D, Olson DM, Reeves MJ, Saver JL, Hernandez AF, Peterson ED, Fonarow GC, Schwamm LH. Risk score for in-hospital ischemic stroke mortality derived and validated within the Get With the Guidelines-Stroke Program. *Circulation*. 2010;122:1496–1504.
10. *American Hospital Association Guide Book*. Chicago, IL: American Hospital Association; 2008.
11. Xian Y, Fonarow GC, Reeves MJ, Webb LE, Blevins J, Demyanenko VS, Zhao X, Olson DM, Hernandez AF, Peterson ED, Schwamm LH, Smith EE. Data quality in the American Heart Association Get With The Guidelines-Stroke (GWTG-Stroke): results from a national data validation audit. *Am Heart J*. 2012;163:392–398, 398.e1.
12. Desquilbet L, Mariotti F. Dose-response analyses using restricted cubic spline functions in public health research. *Stat Med*. 2010;29:1037–1057.
13. Smith EE, Shobha N, Dai D, Olson DM, Reeves MJ, Saver JL, Hernandez AF, Peterson ED, Fonarow GC, Schwamm LH. A risk score for in-hospital death in patients admitted with ischemic or hemorrhagic stroke. *J Am Heart Assoc*. 2013;2:e005207. DOI: 10.1161/JAHA.112.005207.
14. Kalmar AF, Van Aken J, Caemaert J, Mortier EP, Struys MMRF. Value of Cushing reflex as warning sign for brain ischaemia during neuroendoscopy. *Br J Anaesth*. 2005;94:791–799.
15. Ryttlefors M, Howells T, Nilsson P, Ronne-Engström E, Enblad P. Secondary insults in subarachnoid hemorrhage: occurrence and impact on outcome and clinical deterioration. *Neurosurgery*. 2007;61:704–714.
16. Sankaran P, Kamath AV, Tariq SM, Ruffell H, Smith AC, Prentice P, Subramanian DN, Musonda P, Myint PK. Are shock index and adjusted shock index useful in predicting mortality and length of stay in community-acquired pneumonia? *Eur J Intern Med*. 2011;22:282–285.
17. Rady MY, Smithline HA, Blake H, Nowak R, Rivers E. A comparison of the shock index and conventional vital signs to identify acute, critical illness in the emergency department. *Ann Emerg Med*. 1994;24:685–690.
18. Rady MY, Nightingale P, Little RA, Edwards JD. Shock index: a re-evaluation in acute circulatory failure. *Resuscitation*. 1992;23:227–234.
19. Wilson AH, Kidd AC, Skinner J, Musonda P, Pai Y, Lunt CJ, Butchart C, Soiza RL, Potter JF, Myint PK. A simple 5-point scoring system, NaURSE (Na+, urea, respiratory rate and shock index in the elderly), predicts in-hospital mortality in oldest old. *Age Ageing*. 2014;43:352–357.
20. Saposnik G, Kapral MK, Liu Y, Hall R, O'Donnell M, Raptis S, Tu JV, Mamdani M, Austin PC; Investigators of the Registry of the Canadian Stroke Network; Stroke Outcomes Research Canada (SORCan) Working Group. IScore: a risk score to predict death early after hospitalization for an acute ischemic stroke. *Circulation*. 2011;123:739–749.
21. Myint PK, Clark AB, Kwok CS, Davis J, Durairaj R, Dixit AK, Sharma AK, Ford GA, Potter JF. The SOAR (Stroke subtype, Oxford Community Stroke Project classification, Age, prestroke modified Rankin) score strongly predicts early outcomes in acute stroke. *Int J Stroke*. 2014;9:278–283.
22. Abdul-Rahim AH, Quinn TJ, Alder S, Clark AB, Musgrave SD, Langhorne P, Potter JF, Myint PK. Derivation and validation of a novel prognostic scale (modified-stroke subtype, Oxfordshire community stroke project classification, age, and prestroke modified rankin) to predict early mortality in acute stroke. *Stroke*. 2016;47:74–79.
23. Lee KL, Woodlief LH, Topol EJ, Weaver WD, Betriu A, Col J, Simoons M, Aylward P, Van de Werf F, Califf RM. Predictors of 30-day mortality in the era of reperfusion for acute myocardial infarction. Results from an international trial of 41,021 patients. GUSTO-I Investigators. *Circulation*. 1995;91:1659–1668.
24. Reeves MJ, Fonarow GC, Smith EE, Pan W, Olson D, Hernandez AF, Peterson ED, Schwamm LH. Representativeness of the Get With The Guidelines-Stroke Registry: comparison of patient and hospital characteristics among Medicare beneficiaries hospitalized with ischemic stroke. *Stroke*. 2012;43:44–49.

SUPPLEMENTAL MATERIAL

Table S1. Characteristics and outcomes by shock index (all)

Variable	Level	Overall (N=425808)	Shock Index <0.5 (N=203807)	Shock Index 0.50-0.70 (N=163980)	Shock Index > 0.7 (N=58021)	P-value+
Demographics						
Age*	Mean (SD)	71.0 (14.5)	72.4 (13.6)	70.0 (15.0)	69.2 (15.9)	
		N (%)	**N (%)**	**N (%)**	**N (%)**	
Sex	Female	218045 (51.21)	101944 (50.02)	84441 (51.49)	31660 (54.57)	<0.0001
	Male	207763 (48.79)	101863 (49.98)	79539 (48.51)	26361 (45.43)	
Race	Other (includes UTD)	13629 (3.20)	6424 (3.15)	5321 (3.25)	1884 (3.25)	<0.0001
	Asian	13134 (3.09)	6705 (3.29)	4848 (2.96)	1581 (2.73)	
	Hispanic (any race)	30802 (7.24)	14502 (7.12)	12187 (7.44)	4113 (7.09)	
	Black	79285 (18.63)	38601 (18.95)	30139 (18.39)	10545 (18.18)	
	White	288753 (67.85)	137491 (67.49)	111397 (67.97)	39865 (68.75)	
	Missing	205 (0.05)	84 (0.04)	88 (0.05)	33 (0.06)	
Insurance	Not Documented	1998 (0.49)	936 (0.48)	789 (0.51)	273 (0.49)	<0.0001
	Self-Pay/No Insurance	25481 (6.28)	12140 (6.24)	9985 (6.39)	3356 (6.06)	
	Medicare	153450 (37.80)	76054 (39.12)	57154 (36.59)	20242 (36.55)	
	Medicaid	46954 (11.57)	19983 (10.28)	18948 (12.13)	8023 (14.49)	
	Private/VA/ Champus/Other	178095 (43.87)	85305 (43.88)	69305 (44.37)	23485 (42.41)	
	Missing	19830 (4.66)	9389 (4.61)	7799 (4.76)	2642 (4.55)	
Arrival and Admission Information						
Ambulatory status on Admission	ND	75542 (18.78)	35887 (18.65)	28948 (18.70)	10707 (19.49)	<0.0001
	Unable to ambulate	112865 (28.06)	49911 (25.94)	42941 (27.73)	20013 (36.42)	
	With assistance (from person)	86662 (21.55)	42969 (22.34)	33251 (21.47)	10442 (19.00)	

Variable	Level	Overall (N=425808)	Shock Index <0.5 (N=203807)	Shock Index 0.50-0.70 (N=163980)	Shock Index > 0.7 (N=58021)	P-value+
	Able to ambulate independently (no help from another person) with or without device	127089 (31.60)	63606 (33.06)	49701 (32.10)	13782 (25.08)	
	Missing	23650 (5.55)	11434 (5.61)	9139 (5.57)	3077 (5.30)	
Arrival Mode	Unknown	4164 (1.01)	1958 (0.99)	1676 (1.06)	530 (0.98)	<0.0001
	Private transport/taxi/ other from home/scene	159310 (38.76)	80496 (40.50)	61431 (38.83)	17383 (32.17)	
	EMS from home/scene	247546 (60.23)	116307 (58.52)	95115 (60.11)	36124 (66.85)	
	Missing	14788 (3.47)	5046 (2.48)	5758 (3.51)	3984 (6.87)	
Advanced notification by EMS?	N/A	7016 (2.92)	3277 (2.91)	2597 (2.81)	1142 (3.25)	<0.0001
	No	80002 (33.31)	37336 (33.12)	30766 (33.31)	11900 (33.91)	
	Yes	153168 (63.77)	72116 (63.97)	59001 (63.88)	22051 (62.84)	
	Missing	185622 (43.59)	91078 (44.69)	71616 (43.67)	22928 (39.52)	
Arrival during Off Hours (Regular hours: 7 AM - 6 PM, M-F)	Yes	188736 (44.32)	89970 (44.14)	72638 (44.30)	26128 (45.03)	0.0007
	No	237072 (55.68)	113837 (55.86)	91342 (55.70)	31893 (54.97)	
Medications Prior to Admission						
Antiplatelet or Anticoagulation medications	Yes	228103 (53.63)	110758 (54.40)	86711 (52.94)	30634 (52.86)	<0.0001
	No	197229 (46.37)	92836 (45.60)	77070 (47.06)	27323 (47.14)	
	Missing	476 (0.11)	213 (0.10)	199 (0.12)	64 (0.11)	
Medical History						
Prosthetic heart valve	Yes	5498 (1.29)	2370 (1.16)	2228 (1.36)	900 (1.55)	<0.0001

Variable	Level	Overall (N=425808)	Shock Index <0.5 (N=203807)	Shock Index 0.50-0.70 (N=163980)	Shock Index > 0.7 (N=58021)	P-value+
	No	420210 (98.71)	201396 (98.84)	161713 (98.64)	57101 (98.45)	
Previous stroke / TIA	Yes	134334 (31.56)	63784 (31.30)	52209 (31.85)	18341 (31.62)	0.0019
	No	291374 (68.44)	139982 (68.70)	111732 (68.15)	39660 (68.38)	
CAD/ prior MI	Yes	104509 (24.55)	51914 (25.48)	38659 (23.58)	13936 (24.03)	<0.0001
	No	321199 (75.45)	151852 (74.52)	125282 (76.42)	44065 (75.97)	
Diabetes (combined)	Yes	144248 (33.88)	69071 (33.90)	55983 (34.15)	19194 (33.09)	<0.0001
	No	281460 (66.12)	134695 (66.10)	107958 (65.85)	38807 (66.91)	
PVD	Yes	20170 (4.74)	9479 (4.65)	7662 (4.67)	3029 (5.22)	<0.0001
	No	405538 (95.26)	194287 (95.35)	156279 (95.33)	54972 (94.78)	
Hypertension	Yes	330174 (77.56)	167235 (82.07)	122128 (74.50)	40811 (70.36)	<0.0001
	No	95534 (22.44)	36531 (17.93)	41813 (25.50)	17190 (29.64)	
Smoker	Yes	73445 (17.25)	32259 (15.83)	30084 (18.35)	11102 (19.14)	<0.0001
	No	352263 (82.75)	171507 (84.17)	133857 (81.65)	46899 (80.86)	
Heart failure	Yes	39167 (9.20)	16217 (7.96)	15526 (9.47)	7424 (12.80)	<0.0001
	No	386541 (90.80)	187549 (92.04)	148415 (90.53)	50577 (87.20)	
Medical History Panel missing	Yes	100 (0.02)	41 (0.02)	39 (0.02)	20 (0.03)	0.14
	No	425708 (99.98)	203766 (99.98)	163941 (99.98)	58001 (99.97)	
Labs/Vitals at Admission						
Glucose (mg/dL)*	Median (IQR) Missing (%)	400601 121 (102, 159) 5.92	191827 119 (101, 155) 5.88	154374 121 (102, 161) 5.86	54400 126 (105, 169) 6.24	<0.0001
INR*	Median (IQR) Missing (%)	361907 1.0 (1.0, 1.1) 15.01	173125 1.00 (1.0, 1.1) 15.05	139194 1.00 (1.0, 1.1) 15.12	49588 1.10 (1.0, 1.2) 14.53	<0.0001
Total Cholesterol	Median	349921 165	170085 168	135408 164	44428 153	<0.0001

Variable	Level	Overall (N=425808)		Shock Index <0.5 (N=203807)		Shock Index 0.50-0.70 (N=163980)		Shock Index > 0.7 (N=58021)		P-value+
(mg/dL)*	(IQR)		(136, 197)		(140, 201)		(135, 196)		(125, 185)	
	Missing (%)		17.82		16.55		17.42		23.43	
HDL (mg/dL)*	Median	346385	43.0	168392	43.0	134006	42.0	43987	40.0	<0.0001
	(IQR)		(34.0, 53.0)		(35.0, 54.0)		(34.0, 53.0)		(32.0, 51.0)	
	Missing (%)		18.65		17.38		18.28		24.19	
LDL (mg/d)*	Median	356058	94.0	173700	97.0	137543	94.0	44815	86.0	<0.0001
	(IQR)		(71.0,122.0)		(73.0,125.0)		(70.0,121.0)		(65.0,113.0)	
	Missing (%)		16.38		14.77		16.12		22.76	
Triglycerides (mg/dL)*	Median	348247	110.0	169262	112.0	134735	110.0	44250	105.0	<0.0001
	(IQR)		(78.0,160.0)		(79.0,162.0)		(78.0,160.0)		(76.0,150.0)	
	Missing (%)		18.22		16.95		17.83		23.73	
Creatinine (mg/dL)*	Median	411819	1.00	197298	1.00	158564	1.00	55957	1.00	<0.0001
	(IQR)		(0.80,1.30)		(0.80,1.30)		(0.80,1.30)		(0.80,1.40)	
	Missing (%)		3.29		3.19		3.30		3.56	
Systolic blood pressure (mmHg)*	Mean (SD)		159 (31)		177 (27)		149 (23)		126 (23)	<0.0001
Heart rate (bpm)*	Mean (SD)		82 (18)		71 (12)		86 (14)		105 (20)	<0.0001
BMI (kg/m^2)*	Mean (SD)		28.0 (6.8)		28.2 (6.6)		28.1 (6.9)		27.5 (7.2)	<0.0001
	Missing (%)		11.11		10.90		11.21		11.61	
NIHSS score*	Median (IQR)	344100	4 (1, 10)	167163	3 (1, 9)	132722	4 (1, 10)	44215	6 (2, 14)	<0.0001
	Missing (%)		19.19		17.98		19.06		23.79	
		N	**(%)**	**N**	**(%)**	**N**	**(%)**	**N**	**(%)**	
Hospital characteristics										
Region	West	77212	(18.15)	36559	(17.95)	29849	(18.22)	10804	(18.64)	<0.0001
	South	150665	(35.41)	73109	(35.90)	57350	(35.00)	20206	(34.86)	
	Midwest	77841	(18.30)	37440	(18.39)	29773	(18.17)	10628	(18.33)	
	Northeast	119722	(28.14)	56514	(27.75)	46879	(28.61)	16329	(28.17)	
	Missing	368	(0.09)	185	(0.09)	129	(0.08)	54	(0.09)	
Teaching Hospital	Yes	239688	(58.47)	112943	(57.67)	93151	(58.92)	33594	(60.01)	<0.0001

Variable	Level	Overall (N=425808)	Shock Index <0.5 (N=203807)	Shock Index 0.50-0.70 (N=163980)	Shock Index > 0.7 (N=58021)	P-value+
	No	170245 (41.53)	82913 (42.33)	64941 (41.08)	22391 (39.99)	
	Missing	15875 (3.73)	7951 (3.90)	5888 (3.59)	2036 (3.51)	
Primary Stroke Center	Yes	186487 (43.80)	89369 (43.85)	71698 (43.72)	25420 (43.81)	0.74
	No	239321 (56.20)	114438 (56.15)	92282 (56.28)	32601 (56.19)	
Outcomes						
In-hospital mortality	Yes	27903 (6.55)	11895 (5.84)	9601 (5.85)	6407 (11.04)	<0.0001
	No	397905 (93.45)	191912 (94.16)	154379 (94.15)	51614 (88.96)	
LOS greater than 4 days	Yes	164760 (39.90)	75788 (37.96)	62682 (39.42)	26290 (48.43)	<0.0001
	No	248164 (60.10)	123851 (62.04)	96323 (60.58)	27990 (51.57)	
	Missing	12884 (3.03)	4168 (2.05)	4975 (3.03)	3741 (6.45)	
Independent ambulatory status	Yes	195133 (50.90)	96017 (51.93)	77071 (51.84)	22045 (44.30)	<0.0001
	No	188221 (49.10)	88897 (48.07)	71606 (48.16)	27718 (55.70)	
	Missing	42454 (9.97)	18893 (9.27)	15303 (9.33)	8258 (14.23)	
mRS > 2 (in documented patient cohort)	Yes	146562 (61.34)	68182 (60.03)	55344 (60.05)	23036 (69.42)	<0.0001
	No	92367 (38.66)	45399 (39.97)	36820 (39.95)	10148 (30.58)	

+ Note: P-values were calculated by comparing non-missing row values only; these percents sum to 100%. The percent of missing row values is informative and therefore also presented here for convenience.
+ P-values are based on Pearson chi-square tests for all categorical row variables.
* P-values are based on chi-square rank based group means score statistics for all continuous/ordinal row variables (designated by *).
* This is equivalent to Kruskal-Wallis tests.
EMS: emergency medical service; INR: international normalized ratio; LOS: length of stay; NIHSS: National Institute of Health Stroke Scale; mRS: modified Rankin Scale; TIA: Transient Ischemic Attack; CAD: coronary artery disease; MI: myocardial infarction; PVD: peripheral vascular disease; HDL: high density lipoprotein; LDL: low density lipoprotein; BMI: body mass index; IV rt-PA: intravenous recombinant tissue plasminogen activator.

Table S2. Characteristics and outcomes by shock index (Acute Ischemic Stroke cohort).

Variable	Level	Overall (N=381872)	Shock Index <0.5 (N=180229)	Shock Index 0.50-0.70 (N=149002)	Shock Index > 0.7 (N=52641)	P-value+
Demographics						
Age*	Mean (SD)	71.2 (14.4)	72.6 (13.4)	70.1 (15.0)	69.5 (15.8)	<0.0001
		N (%)	**N (%)**	**N (%)**	**N (%)**	
Sex	Female	196653 (51.50)	90732 (50.34)	77035 (51.70)	28886 (54.87)	<0.0001
	Male	185219 (48.50)	89497 (49.66)	71967 (48.30)	23755 (45.13)	
Race	Other (includes UTD)	11898 (3.12)	5501 (3.05)	4735 (3.18)	1662 (3.16)	<0.0001
	Asian	10831 (2.84)	5411 (3.00)	4090 (2.75)	1330 (2.53)	
	Hispanic (any race)	26753 (7.01)	12324 (6.84)	10810 (7.26)	3619 (6.88)	
	Black	70913 (18.58)	33872 (18.80)	27478 (18.45)	9563 (18.18)	
	White	261293 (68.46)	123048 (68.30)	101809 (68.36)	36436 (69.26)	
	Missing	184 (0.05)	73 (0.04)	80 (0.05)	31 (0.06)	
Insurance	Not Documented	1681 (0.46)	773 (0.45)	682 (0.48)	226 (0.45)	<0.0001
	Self Pay/No Insurance	22023 (6.05)	10146 (5.90)	8917 (6.28)	2960 (5.89)	
	Medicare	138468 (38.03)	67881 (39.48)	52068 (36.69)	18519 (36.87)	
	Medicaid	41567 (11.42)	17255 (10.04)	17072 (12.03)	7240 (14.41)	
	Private/VA/Champus/Other Insurance	160338 (44.04)	75883 (44.13)	63171 (44.51)	21284 (42.37)	
	Missing	17795 (4.66)	8291 (4.60)	7092 (4.76)	2412 (4.58)	
Arrival and Admission Information						
Ambulatory status on Admission	ND	67479 (18.72)	31534 (18.55)	26202 (18.64)	9743 (19.57)	<0.0001
	Unable to ambulate	91637 (25.43)	38574 (22.69)	35951 (25.57)	17112 (34.36)	
	With assistance (from person)	81249 (22.54)	40039 (23.55)	31351 (22.30)	9859 (19.80)	

Variable	Level	Overall (N=381872)	Shock Index <0.5 (N=180229)	Shock Index 0.50-0.70 (N=149002)	Shock Index > 0.7 (N=52641)	P-value+
	Able to ambulate independently (no help from another person) w/ or w/o device	120033 (33.31)	59874 (35.22)	47078 (33.49)	13081 (26.27)	
	Missing	21474 (5.62)	10208 (5.66)	8420 (5.65)	2846 (5.41)	
Arrival Mode	ND or Unknown	3789 (1.03)	1790 (1.02)	1530 (1.06)	469 (0.96)	<0.0001
	Private transport/taxi/other from home/scene	149094 (40.49)	75124 (42.79)	57700 (40.16)	16270 (33.24)	
	EMS from home/scene	215322 (58.48)	98666 (56.19)	84449 (58.78)	32207 (65.80)	
	Missing	13667 (3.58)	4649 (2.58)	5323 (3.57)	3695 (7.02)	
Advanced notification by EMS?	N/A	6137 (2.94)	2829 (2.96)	2294 (2.80)	1014 (3.24)	0.0007
	No/ND	69936 (33.48)	31943 (33.40)	27416 (33.43)	10577 (33.81)	
	Yes	132841 (63.59)	60854 (63.64)	52298 (63.77)	19689 (62.94)	
	Missing	172958 (45.29)	84603 (46.94)	66994 (44.96)	21361 (40.58)	
Arrival during Off Hours (Regular hours: 7 AM - 6 PM, M-F)	Yes	167200 (43.78)	78373 (43.49)	65336 (43.85)	23491 (44.62)	<0.0001
	No	214672 (56.22)	101856 (56.51)	83666 (56.15)	29150 (55.38)	
Medications Prior to Admission						
Antiplatelet or Anticoagulation medications	Yes	207973 (54.52)	99754 (55.40)	79948 (53.72)	28271 (53.76)	<0.0001
	No	173490 (45.48)	80298 (44.60)	68879 (46.28)	24313 (46.24)	
	Missing	409 (0.11)	177 (0.10)	175 (0.12)	57 (0.11)	
Antiplatelet	Yes	181509 (50.90)	89168 (52.42)	69188 (49.88)	23153 (48.46)	<0.0001
	No	175100 (49.10)	80945 (47.58)	69526 (50.12)	24629 (51.54)	
	Missing	25263 (6.62)	10116 (5.61)	10288 (6.90)	4859 (9.23)	

Variable	Level	Overall (N=381872)	Shock Index <0.5 (N=180229)	Shock Index 0.50-0.70 (N=149002)	Shock Index > 0.7 (N=52641)	P-value+
Anticoagulation	Yes	40470 (18.06)	16340 (16.08)	16418 (18.41)	7712 (23.14)	<0.0001
	No	183650 (81.94)	85280 (83.92)	72749 (81.59)	25621 (76.86)	
	Missing	157752 (41.31)	78609 (43.62)	59835 (40.16)	19308 (36.68)	
Medical History						
Prosthetic heart valve	Yes	4876 (1.28)	2057 (1.14)	2013 (1.35)	806 (1.53)	<0.0001
	No	376909 (98.72)	178137 (98.86)	146955 (98.65)	51817 (98.47)	
Previous stroke / TIA	Yes	122605 (32.11)	57691 (32.02)	48090 (32.28)	16824 (31.97)	0.2
	No	259180 (67.89)	122503 (67.98)	100878 (67.72)	35799 (68.03)	
CAD/ prior MI	Yes	96240 (25.21)	47269 (26.23)	35965 (24.14)	13006 (24.72)	<0.0001
	No	285545 (74.79)	132925 (73.77)	113003 (75.86)	39617 (75.28)	
Diabetes (combined)	Yes	132595 (34.73)	62749 (34.82)	52028 (34.93)	17818 (33.86)	<0.0001
	No	249190 (65.27)	117445 (65.18)	96940 (65.07)	34805 (66.14)	
PVD	Yes	18630 (4.88)	8666 (4.81)	7146 (4.80)	2818 (5.36)	<0.0001
	No	363155 (95.12)	171528 (95.19)	141822 (95.20)	49805 (94.64)	
Hypertension	Yes	297119 (77.82)	148336 (82.32)	111465 (74.82)	37318 (70.92)	<0.0001
	No	84666 (22.18)	31858 (17.68)	37503 (25.18)	15305 (29.08)	
Smoker	Yes	67996 (17.81)	29441 (16.34)	28180 (18.92)	10375 (19.72)	<0.0001
	No	313789 (82.19)	150753 (83.66)	120788 (81.08)	42248 (80.28)	
Heart failure	Yes	36131 (9.46)	14710 (8.16)	14479 (9.72)	6942 (13.19)	<0.0001
	No	345654 (90.54)	165484 (91.84)	134489 (90.28)	45681 (86.81)	
Medical History Panel missing	Yes	87 (0.02)	35 (0.02)	34 (0.02)	18 (0.03)	0.142
	No	381785 (99.98)	180194 (99.98)	148968 (99.98)	52623 (99.97)	
Labs/Vitals at Admission						
Glucose (mg/dL)*	Median (IQR)	359869 120 (101, 158)	169952 117 (100, 153)	140472 120 (102, 160)	49445 125 (104, 167)	<0.0001

Variable	Level	Overall (N=381872)		Shock Index <0.5 (N=180229)		Shock Index 0.50-0.70 (N=149002)		Shock Index > 0.7 (N=52641)		P-value+
	Missing (%)		5.76		5.70		5.72		6.07	
INR*	Median	322082	1.0	151612	1.0	125670	1.0	44800	1.1	<0.0001
	(IQR)		(1.0, 1.1)		(1.0, 1.1)		(1.0, 1.1)		(1.0, 1.2)	
	Missing (%)		15.66		15.88		15.66		14.90	
Total Cholesterol (mg/dL)*	Median	329507	165	158541	168	128509	164	42457	152	<0.0001
	(IQR)		(136, 197)		(140, 201)		(135, 196)		(125, 185)	
	Missing (%)		13.71		12.03		13.75		19.35	
HDL (mg/dL)*	Median	326356	42.0	157073	43.0	127235	42.0	42048	40.0	<0.0001
	(IQR)		(34.0, 53.0)		(35.0, 53.0)		(34.0, 52.0)		(32.0, 51.0)	
	Missing (%)		14.54		12.85		14.61		20.12	
LDL (mg/dL)*	Median	335305	95.0	161935	97.0	130545	94.0	42825	86.0	<0.0001
	(IQR)		(71.0,123.0)		(73.0,126.0)		(70.0,121.0)		(65.0,113.0)	
	Missing (%)		12.19		10.15		12.39		18.65	
Triglycerides (mg/dL)*	Median	327831	111.0	157716	113.0	127838	111.0	42277	105.0	<0.0001
	(IQR)		(79.0,161.0)		(80.0,164.0)		(79.0,161.0)		(77.0,151.0)	
	Missing (%)		14.15		12.49		14.20		19.69	
Creatinine (mg/dL)*	Median	369488	1.0	174569	1.0	144125	1.0	50794	1.0	<0.0001
	(IQR)		(0.8, 1.3)		(0.8, 1.3)		(0.8, 1.3)		(0.8, 1.4)	
	Missing (%)		3.24		3.14		3.27		3.51	
Systolic blood pressure (mmHg)*	Mean (SD)		158 (31)		175 (27)		148 (23)		125 (22)	<0.0001
Heart rate (bpm)*	Mean (SD)		82 (18)		71 (12)		86 (13)		105 (20)	<0.0001
BMI (kg/m^2)*	Mean (SD)		28.1 (6.8)		28.2 (6.5)		28.2 (6.9)		27.6 (7.2)	<0.0001
	Missing (%)		10.92		10.69		11.06		11.34	
NIHSS score*	Median (IQR)	315612	4 (1, 9)	151092	3(1, 8)	123151	4 (1, 9)	41369	5 (2, 13)	<0.0001
	Missing (%)		17.35		16.17		17.35		21.41	
		N (%)		**N (%)**		**N (%)**		**N (%)**		

Variable	Level	Overall (N=381872)	Shock Index <0.5 (N=180229)	Shock Index 0.50-0.70 (N=149002)	Shock Index > 0.7 (N=52641)	P-value+
Hospital characteristics						
Region	West	68216 (17.88)	31747 (17.63)	26769 (17.98)	9700 (18.44)	<0.0001
	South	135832 (35.60)	65024 (36.11)	52387 (35.18)	18421 (35.02)	
	Midwest	70033 (18.35)	33216 (18.45)	27137 (18.23)	9680 (18.40)	
	Northeast	107481 (28.17)	50081 (27.81)	42602 (28.61)	14798 (28.13)	
	Missing	310 (0.08)	161 (0.09)	107 (0.07)	42 (0.08)	
Teaching Hospital	Yes	211514 (57.61)	97990 (56.67)	83497 (58.19)	30027 (59.14)	<0.0001
	No	155660 (42.39)	74917 (43.33)	60000 (41.81)	20743 (40.86)	
	Missing	14698 (3.85)	7322 (4.06)	5505 (3.69)	1871 (3.55)	
Primary Stroke Center	Yes	165606 (43.37)	78075 (43.32)	64579 (43.34)	22952 (43.60)	0.50
	No	216266 (56.63)	102154 (56.68)	84423 (56.66)	29689 (56.40)	
Outcomes						
In-hospital mortality	Yes	16859 (4.41)	5980 (3.32)	6243 (4.19)	4636 (8.81)	<0.0001
	No	365013 (95.59)	174249 (96.68)	142759 (95.81)	48005 (91.19)	
LOS greater than 4 days	Yes	142028 (38.40)	63252 (35.87)	55035 (38.12)	23741 (48.29)	<0.0001
	No	227862 (61.60)	113106 (64.13)	89329 (61.88)	25427 (51.71)	
	Missing	11982 (3.14)	3871 (2.15)	4638 (3.11)	3473 (6.60)	
Independent ambulatory status	Yes	184672 (52.49)	90512 (53.88)	73185 (53.21)	20975 (45.30)	<0.0001
	No	167155 (47.51)	77473 (46.12)	64354 (46.79)	25328 (54.70)	
	Missing	30045 (7.87)	12244 (6.79)	11463 (7.69)	6338 (12.04)	
mRS > 2 (in documented patient cohort)	Yes	124114 (58.59)	56032 (56.58)	47965 (57.79)	20117 (67.46)	<0.0001
	No	87727 (41.41)	42997 (43.42)	35028 (42.21)	9702 (32.54)	

+ Note: P-values were calculated by comparing non-missing row values only; these percents sum to 100%. The percent of missing row values is informative and therefore also presented here for convenience.

+ P-values are based on Pearson chi-square tests for all categorical row variables.

* P-values are based on chi-square rank based group means score statistics for all continuous/ordinal row variables (designated by *).

* This is equivalent to Kruskal-Wallis tests.

EMS: emergency medical service; INR: international normalized ratio; LOS: length of stay; NIHSS: National Institute of Health Stroke Scale; mRS: modified Rankin Scale; TIA: Transient Ischemic Attack; CAD: coronary artery disease; MI: myocardial infarction; PVD: peripheral vascular disease; HDL: high density lipoprotein; LDL: low density lipoprotein; BMI: body mass index; IV rt-PA: intravenous recombinant tissue plasminogen activator.

Table S3. Characteristics and outcomes by shock index (Intracerebral Hemorrhage cohort).

Variable	Level	Overall (N=43936)	Shock Index <0.5 (N=23578)	Shock Index 0.50-0.70 (N=14978)	Shock Index > 0.7 (N=5380)	P-value+
Demographics						
Age*	Mean (SD)	69.7 (15.3)	70.6 (14.7)	69.4 (15.4)	66.6 (16.8)	<0.0001
		N (%)	**N (%)**	**N (%)**	**N (%)**	
Sex	Female	21392 (48.69)	11212 (47.55)	7406 (49.45)	2774 (51.56)	<0.0001
	Male	22544 (51.31)	12366 (52.45)	7572 (50.55)	2606 (48.44)	
Race	Other (includes UTD)	1731 (3.94)	923 (3.92)	586 (3.91)	222 (4.13)	<0.0001
	Asian	2303 (5.24)	1294 (5.49)	758 (5.06)	251 (4.67)	
	Hispanic (any race)	4049 (9.22)	2178 (9.24)	1377 (9.20)	494 (9.19)	
	Black	8372 (19.06)	4729 (20.07)	2661 (17.78)	982 (18.26)	
	White	27460 (62.53)	14443 (61.28)	9588 (64.05)	3429 (63.76)	
	Missing	21 (0.05)	11 (0.05)	8 (0.05)	2 (0.04)	
Insurance	Not Documented	317 (0.76)	163 (0.73)	107 (0.75)	47 (0.91)	<0.0001
	Self Pay/No Insurance	3458 (8.25)	1994 (8.87)	1068 (7.48)	396 (7.69)	
	Medicare	14982 (35.76)	8173 (36.36)	5086 (35.64)	1723 (33.46)	
	Medicaid	5387 (12.86)	2728 (12.14)	1876 (13.15)	783 (15.20)	
	Private/VA/Champus/Other Insurance	17757 (42.38)	9422 (41.91)	6134 (42.98)	2201 (42.74)	
	Missing	2035 (4.63)	1098 (4.66)	707 (4.72)	230 (4.28)	
Arrival and Admission Information						
Ambulatory status on Admissio	ND	8063 (19.31)	4353 (19.47)	2746 (19.26)	964 (18.72)	<0.0001
	Unable to ambulate	21228 (50.83)	11337 (50.72)	6990 (49.02)	2901 (56.34)	
	With assistance (from person)	5413 (12.96)	2930 (13.11)	1900 (13.32)	583 (11.32)	

Variable	Level	Overall (N=43936)	Shock Index <0.5 (N=23578)	Shock Index 0.50-0.70 (N=14978)	Shock Index > 0.7 (N=5380)	P-value+
	Able to ambulate independently (no help from another person) w/ or w/o device	7056 (16.90)	3732 (16.70)	2623 (18.40)	701 (13.61)	
	Missing	2176 (4.95)	1226 (5.20)	719 (4.80)	231 (4.29)	
Arrival Mode	ND or Unknown	375 (0.88)	168 (0.72)	146 (1.00)	61 (1.20)	<0.0001
	Private transport/taxi/other from home/scene	10216 (23.86)	5372 (23.17)	3731 (25.65)	1113 (21.86)	
	EMS from home/scene	32224 (75.26)	17641 (76.10)	10666 (73.34)	3917 (76.94)	
	Missing	1121 (2.55)	397 (1.68)	435 (2.90)	289 (5.37)	
Advanced notification by EMS?	N/A	879 (2.81)	448 (2.62)	303 (2.93)	128 (3.36)	<0.0001
	No/ND	10066 (32.19)	5393 (31.53)	3350 (32.35)	1323 (34.70)	
	Yes	20327 (65.00)	11262 (65.85)	6703 (64.73)	2362 (61.95)	
	Missing	12664 (28.82)	6475 (27.46)	4622 (30.86)	1567 (29.13)	
Arrival during Off Hours (Regular hours: 7 AM - 6 PM, M-F)	Yes	21536 (49.02)	11597 (49.19)	7302 (48.75)	2637 (49.01)	0.71
	No	22400 (50.98)	11981 (50.81)	7676 (51.25)	2743 (50.99)	
Medications Prior to Admission						
Antiplatelet or Anticoagulation medications	Yes	20130 (45.89)	11004 (46.74)	6763 (45.23)	2363 (43.98)	0.0002
	No	23739 (54.11)	12538 (53.26)	8191 (54.77)	3010 (56.02)	
	Missing	67 (0.15)	36 (0.15)	24 (0.16)	7 (0.13)	
Antiplatelet	Yes	15411 (39.03)	8685 (40.60)	5088 (37.97)	1638 (34.89)	<0.0001
	No	24075 (60.97)	12705 (59.40)	8313 (62.03)	3057 (65.11)	
	Missing	4450 (10.13)	2188 (9.28)	1577 (10.53)	685 (12.73)	

Variable	Level	Overall (N=43936)	Shock Index <0.5 (N=23578)	Shock Index 0.50-0.70 (N=14978)	Shock Index > 0.7 (N=5380)	P-value+
Anticoagulation	Yes	7325 (22.93)	3615 (21.71)	2599 (23.44)	1111 (26.46)	<0.0001
	No	24614 (77.07)	13036 (78.29)	8491 (76.56)	3087 (73.54)	
	Missing	11997 (27.31)	6927 (29.38)	3888 (25.96)	1182 (21.97)	
Medical History						
Prosthetic heart valve	Yes	622 (1.42)	313 (1.33)	215 (1.44)	94 (1.75)	0.06
	No	43301 (98.58)	23259 (98.67)	14758 (98.56)	5284 (98.25)	
Previous stroke / TIA	Yes	11729 (26.70)	6093 (25.85)	4119 (27.51)	1517 (28.21)	<0.0001
	No	32194 (73.30)	17479 (74.15)	10854 (72.49)	3861 (71.79)	
CAD/ prior MI	Yes	8269 (18.83)	4645 (19.71)	2694 (17.99)	930 (17.29)	<0.0001
	No	35654 (81.17)	18927 (80.29)	12279 (82.01)	4448 (82.71)	
Diabetes (combined)	Yes	11653 (26.53)	6322 (26.82)	3955 (26.41)	1376 (25.59)	0.17
	No	32270 (73.47)	17250 (73.18)	11018 (73.59)	4002 (74.41)	
PVD	Yes	1540 (3.51)	813 (3.45)	516 (3.45)	211 (3.92)	0.21
	No	42383 (96.49)	22759 (96.55)	14457 (96.55)	5167 (96.08)	
Hypertension	Yes	33055 (75.26)	18899 (80.18)	10663 (71.21)	3493 (64.95)	<0.0001
	No	10868 (24.74)	4673 (19.82)	4310 (28.79)	1885 (35.05)	
Smoker	Yes	5449 (12.41)	2818 (11.95)	1904 (12.72)	727 (13.52)	0.0027
	No	38474 (87.59)	20754 (88.05)	13069 (87.28)	4651 (86.48)	
Heart failure	Yes	3036 (6.91)	1507 (6.39)	1047 (6.99)	482 (8.96)	<0.0001
	No	40887 (93.09)	22065 (93.61)	13926 (93.01)	4896 (91.04)	
Medical History Panel missing	Yes	13 (0.03)	6 (0.03)	5 (0.03)	2 (0.04)	0.85
	No	43923 (99.97)	23572 (99.97)	14973 (99.97)	5378 (99.96)	
Labs/Vitals at Admission						
Glucose (mg/dL)*	Median (IQR)	40732 131 (108, 169)	21875 130 (107, 167)	13902 130 (107, 168)	4955 139 (111, 184)	<0.0001

Variable	Level	Overall (N=43936)		Shock Index <0.5 (N=23578)		Shock Index 0.50-0.70 (N=14978)		Shock Index > 0.7 (N=5380)		P-value+
	Missing (%)		7.29		7.22		7.18		7.90	
INR*	Median (IQR) Missing (%)	39825	1.0 (1.0, 1.2) 9.36	21513	1.0 (1.0, 1.1) 8.76	13524	1.0 (1.0, 1.2) 9.71	4788	1.1 (1.0, 1.4) 11.00	<0.0001
Total Cholesterol (mg/dL)*	Median (IQR) Max Missing (%)	20414	165 (138, 195) 671.00 53.54	11544	168 (141, 198) 671.00 51.04	6899	163 (136, 193) 401.00 53.94	1971	156 (125, 186) 382.00 63.36	<0.0001
HDL (mg/dL)*	Median (IQR) Missing (%)	20029	47.0 (37.0, 58.0) 54.41	11319	47.0 (38.0, 59.0) 51.99	6771	47.0 (37.0, 58.0) 54.79	1939	44.0 (34.0, 56.0) 63.96	<0.0001
LDL (mg/dL)*	Median (IQR) Missing (%)	20753	93.0 (71.0,119.0) 52.77	11765	95.0 (73.0,121.0) 50.10	6998	91.0 (70.0,117.0) 53.28	1990	88.0 (65.0,113.0) 63.01	<0.0001
Triglycerides (mg/dL)*	Median (IQR) Missing (%)	20416	95.0 (69.0,136.0) 53.53	11546	96.0 (69.0,137.0) 51.03	6897	94.0 (69.0,135.0) 53.95	1973	97.0 (70.0,137.0) 63.33	0.22
Creatinine (mg/dL)*	Median (IQR) Missing (%)	42331	1.0 (0.8, 1.2) 3.65	22729	1.0 (0.8, 1.2) 3.60	14439	0.9 (0.7, 1.2) 3.60	5163	1.0 (0.8, 1.3) 4.03	<0.0001
Systolic blood pressure (mmHg)*	Mean (SD)		169 (35)		187 (30)		155 (27)		128 927)	<0.0001
	Mean (SD)		83 (19)		73 (13)		90 (16)		109 (21)	<0.0001
BMI (kg/m^2)*	Mean Missing (%)		27.5 (6.9) 12.75		27.7 (6.8) 12.46		27.5 (7.0) 12.67		26.9 (7.0) 14.31	<0.0001
NIHSS score*	Median (IQR) Missing (%)	28488	9 (3, 20) 35.16	16071	10 (3, 20) 31.84	9571	8 (2, 19) 36.10	2846	11 (3, 23) 47.10	<0.0001

Variable	Level	Overall (N=43936)	Shock Index <0.5 (N=23578)	Shock Index 0.50-0.70 (N=14978)	Shock Index > 0.7 (N=5380)	P-value+
		N (%)	N (%)	N (%)	N (%)	
Hospital characteristics						
Region	West	8996 (20.50)	4812 (20.43)	3080 (20.59)	1104 (20.57)	0.09
	South	14833 (33.81)	8085 (34.33)	4963 (33.18)	1785 (33.25)	
	Midwest	7808 (17.79)	4224 (17.93)	2636 (17.63)	948 (17.66)	
	Northeast	12241 (27.90)	6433 (27.31)	4277 (28.60)	1531 (28.52)	
	Missing	58 (0.13)	24 (0.10)	22 (0.15)	12 (0.22)	
Teaching Hospital	Yes	28174 (65.89)	14953 (65.16)	9654 (66.15)	3567 (68.40)	<0.0001
	No	14585 (34.11)	7996 (34.84)	4941 (33.85)	1648 (31.60)	
	Missing	1177 (2.68)	629 (2.67)	383 (2.56)	165 (3.07)	
Primary Stroke Center	Yes	20881 (47.53)	11294 (47.90)	7119 (47.53)	2468 (45.87)	0.03
	No	23055 (52.47)	12284 (52.10)	7859 (52.47)	2912 (54.13)	
Outcomes						
In-hospital mortality	Yes	11044 (25.14)	5915 (25.09)	3358 (22.42)	1771 (32.92)	<0.0001
	No	32892 (74.86)	17663 (74.91)	11620 (77.58)	3609 (67.08)	
LOS greater than 4 days	Yes	22732 (52.82)	12536 (53.85)	7647 (52.23)	2549 (49.86)	<0.0001
	No	20302 (47.18)	10745 (46.15)	6994 (47.77)	2563 (50.14)	
	Missing	902 (2.05)	297 (1.26)	337 (2.25)	268 (4.98)	
Independent ambulatory status	Yes	10461 (33.18)	5505 (32.52)	3886 (34.89)	1070 (30.92)	<0.0001
	No	21066 (66.82)	11424 (67.48)	7252 (65.11)	2390 (69.08)	
	Missing	12409 (28.24)	6649 (28.20)	3840 (25.64)	1920 (35.69)	
mRS > 2 (in documented patient cohort)	Yes	22448 (82.87)	12150 (83.49)	7379 (80.46)	2919 (86.75)	<0.0001
	No	4640 (17.13)	2402 (16.51)	1792 (19.54)	446 (13.25)	

+ Note: P-values were calculated by comparing non-missing row values only; these percents sum to 100%. The percent of missing row values is informative and therefore also presented here for convenience.

+ P-values are based on Pearson chi-square tests for all categorical row variables.

* P-values are based on chi-square rank based group means score statistics for all continuous/ordinal row variables (designated by *).

* This is equivalent to Kruskal-Wallis tests.
EMS: emergency medical service; INR: international normalized ratio; LOS: length of stay; NIHSS: National Institute of Health Stroke Scale; mRS: modified Rankin Scale; TIA: Transient Ischemic Attack; CAD: coronary artery disease; MI: myocardial infarction; PVD: peripheral vascular disease; HDL: high density lipoprotein; LDL: low density lipoprotein; BMI: body mass index; IV rt-PA: intravenous recombinant tissue plasminogen activator.

Figure S1a. Study Cohort Development and Exclusions -Acute Ischemic Stroke (AIS).

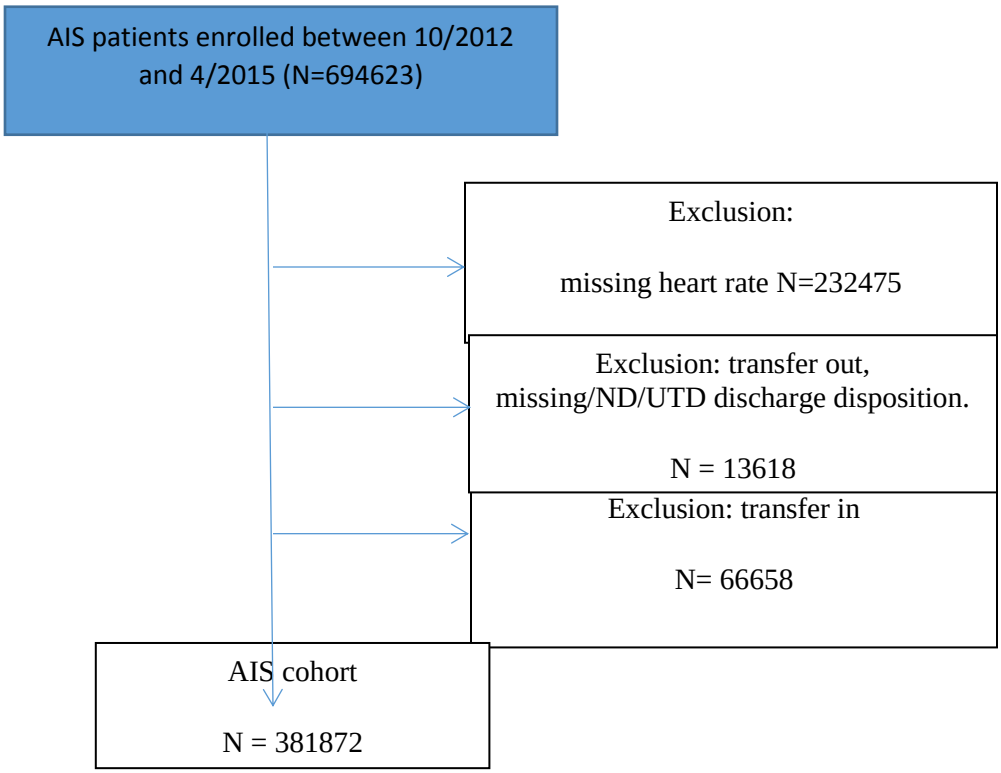


Figure S1b. Study Cohort Development and Exclusions - Intracerebral Hemorrhage (ICH).

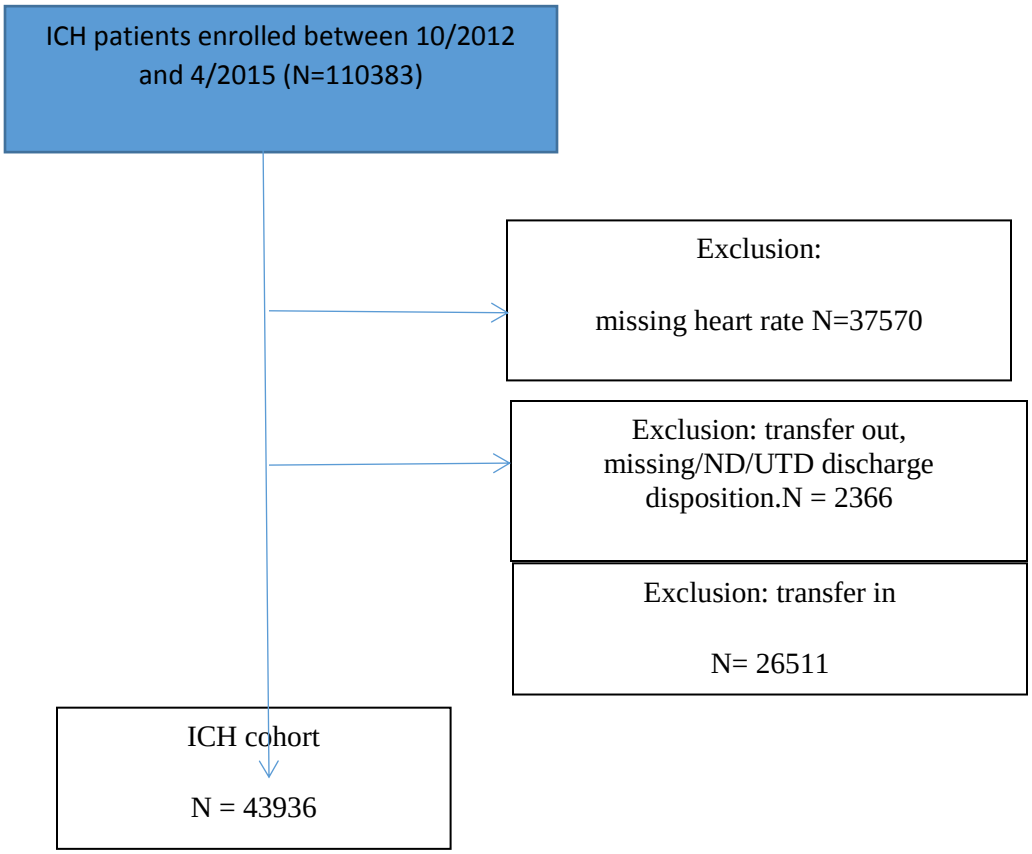


Figure S2a. Shock Index distribution of the whole sample.

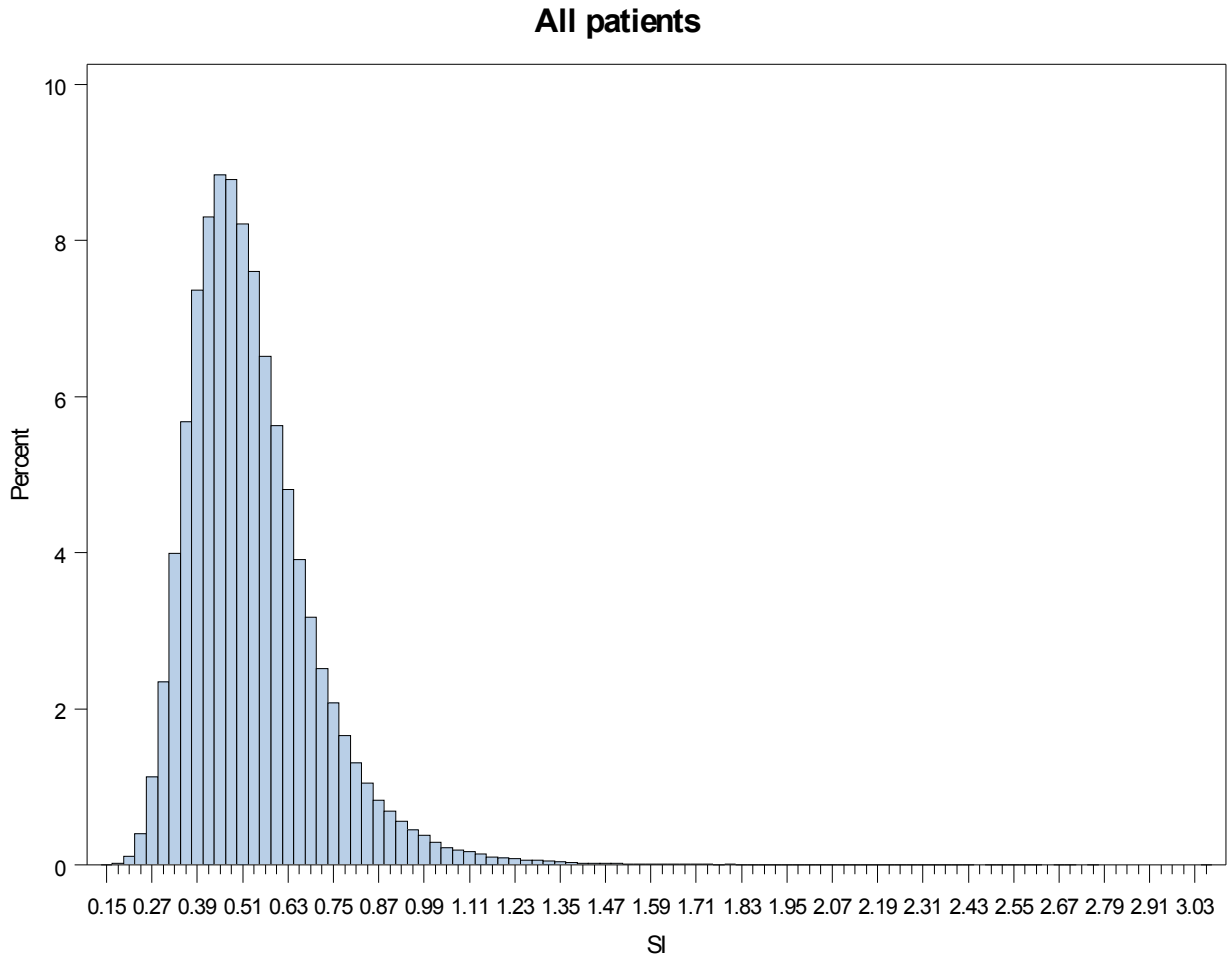


Figure S2b. Shock Index distribution of Acute Ischemic Stroke (AIS) Patients.

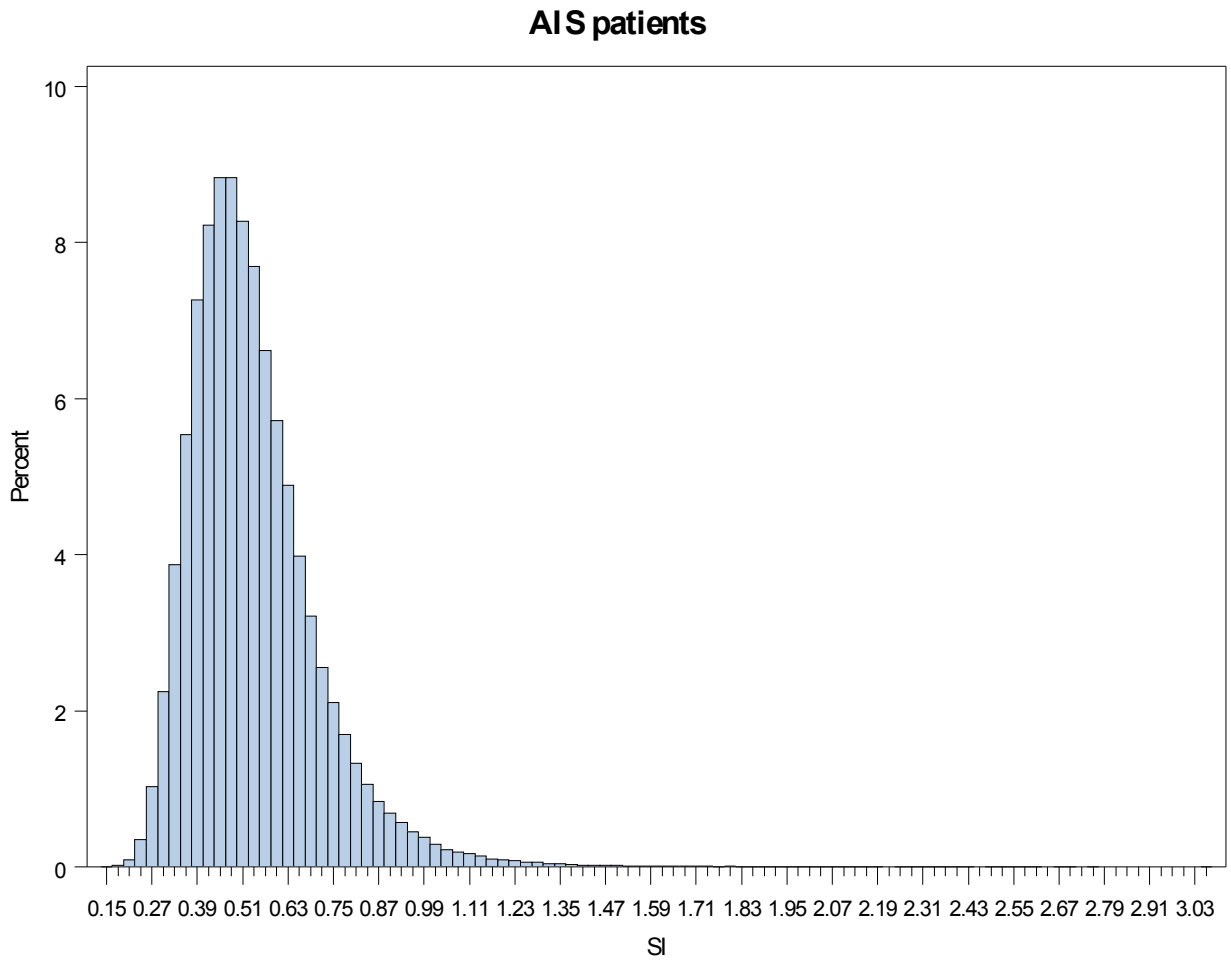


Figure S2c. Shock Index distribution of Intracerebral Hemorrhage (ICH) Patients.

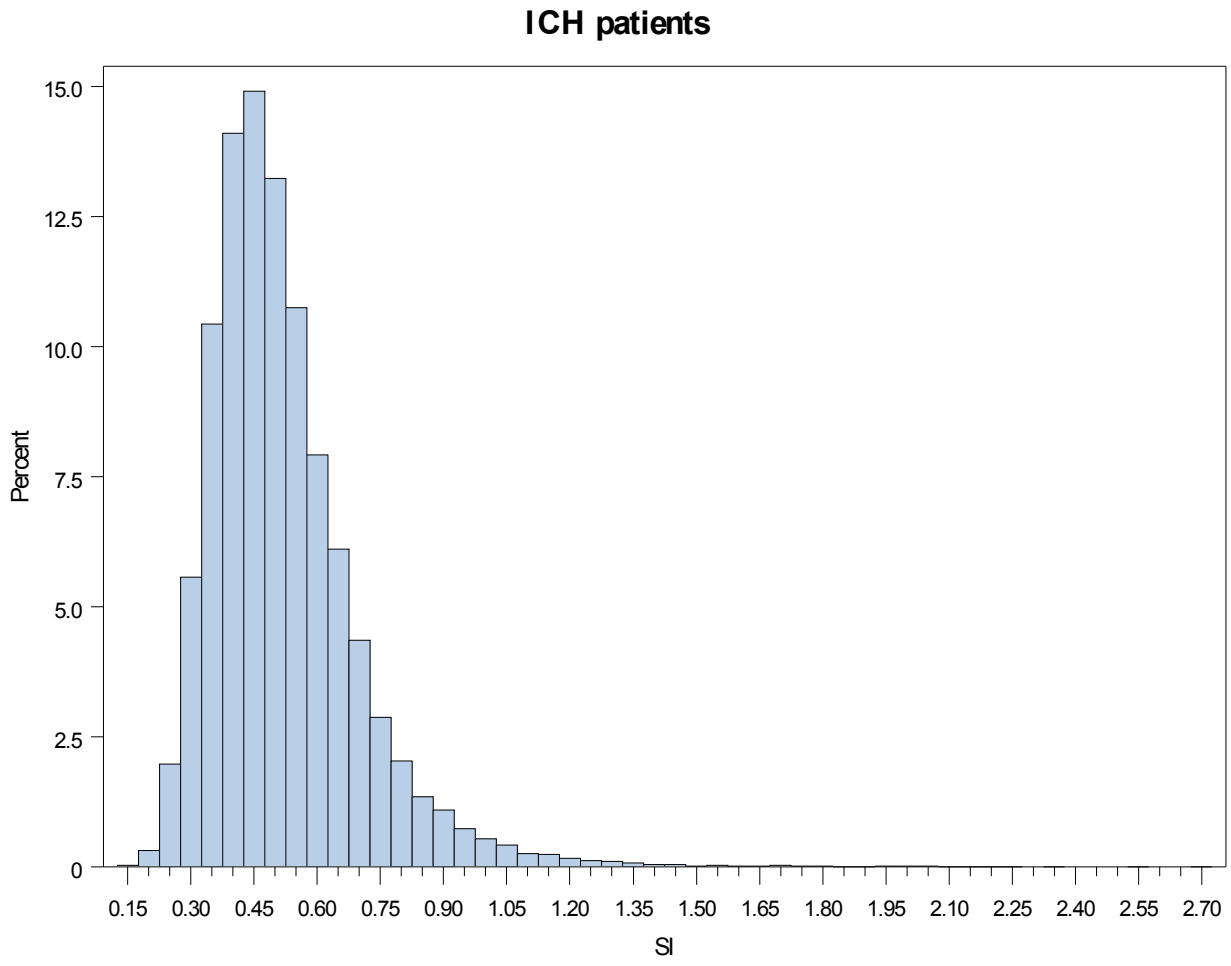
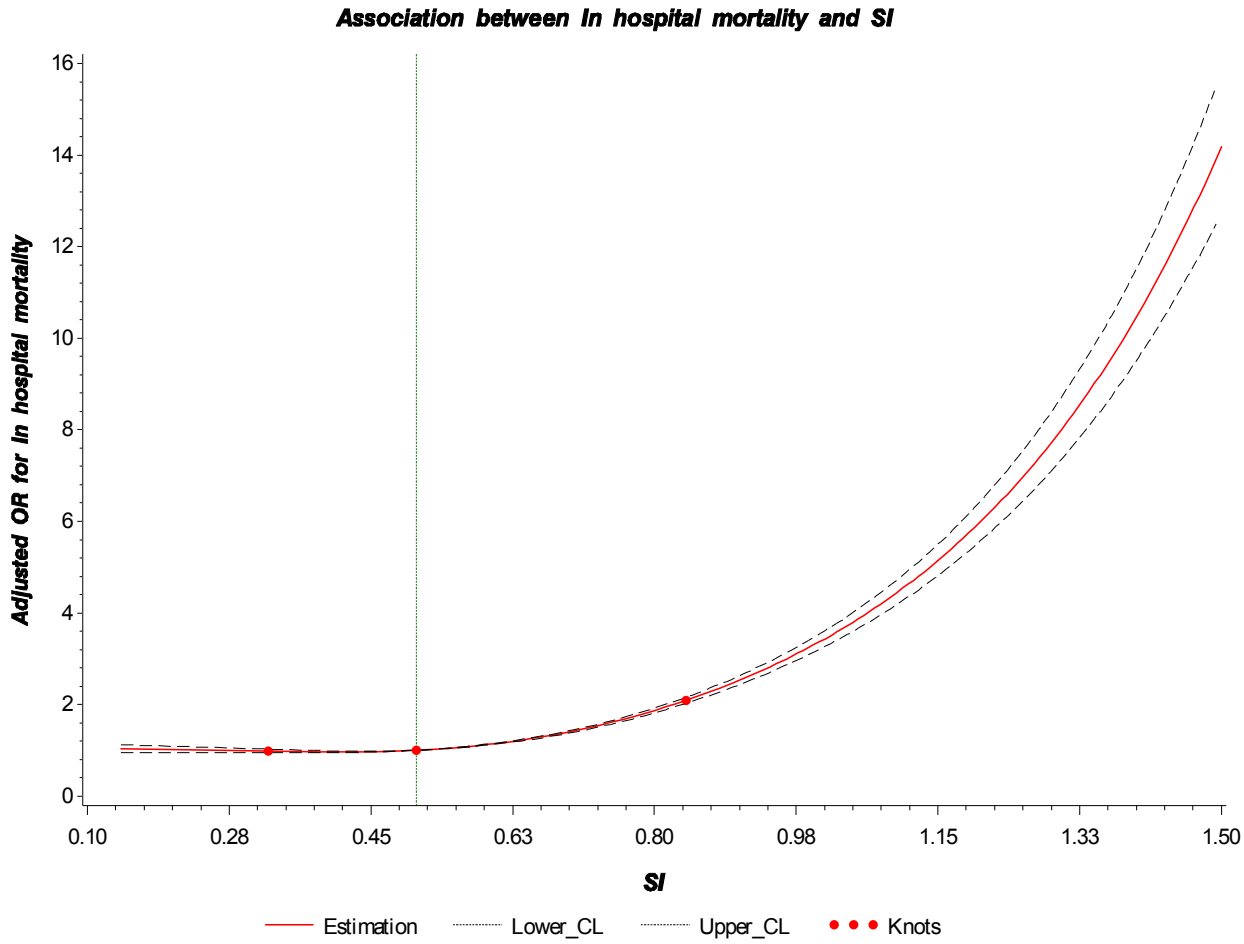
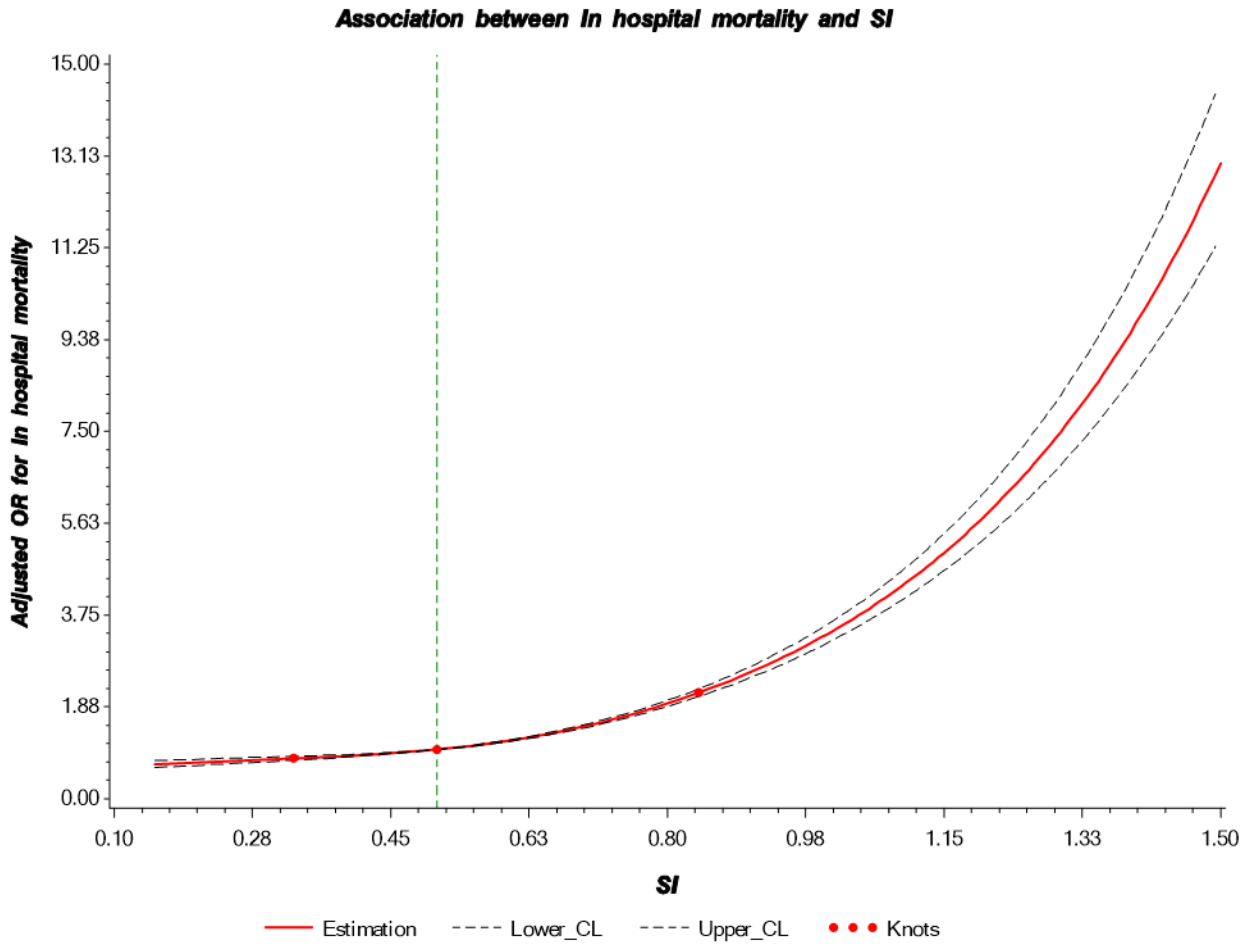


Figure S3. Outcomes vs. Shock Index (Shock Index was model as cubic splines) truncated at SI value of 1.5 to remove extreme outliers.

A. Overall population



B. Acute Ischemic Stroke cohort.



C. Intracerebral Hemorrhage cohort.

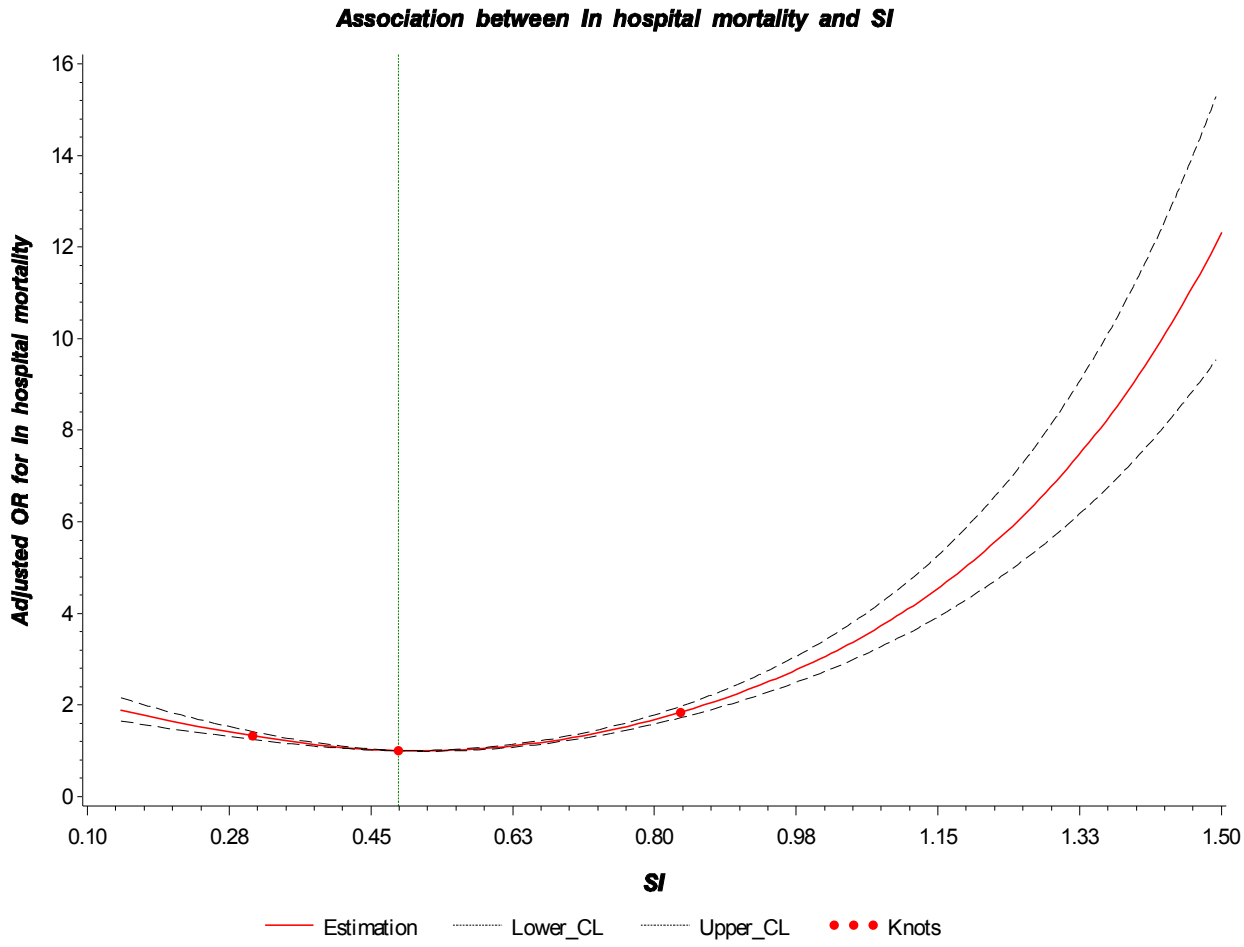
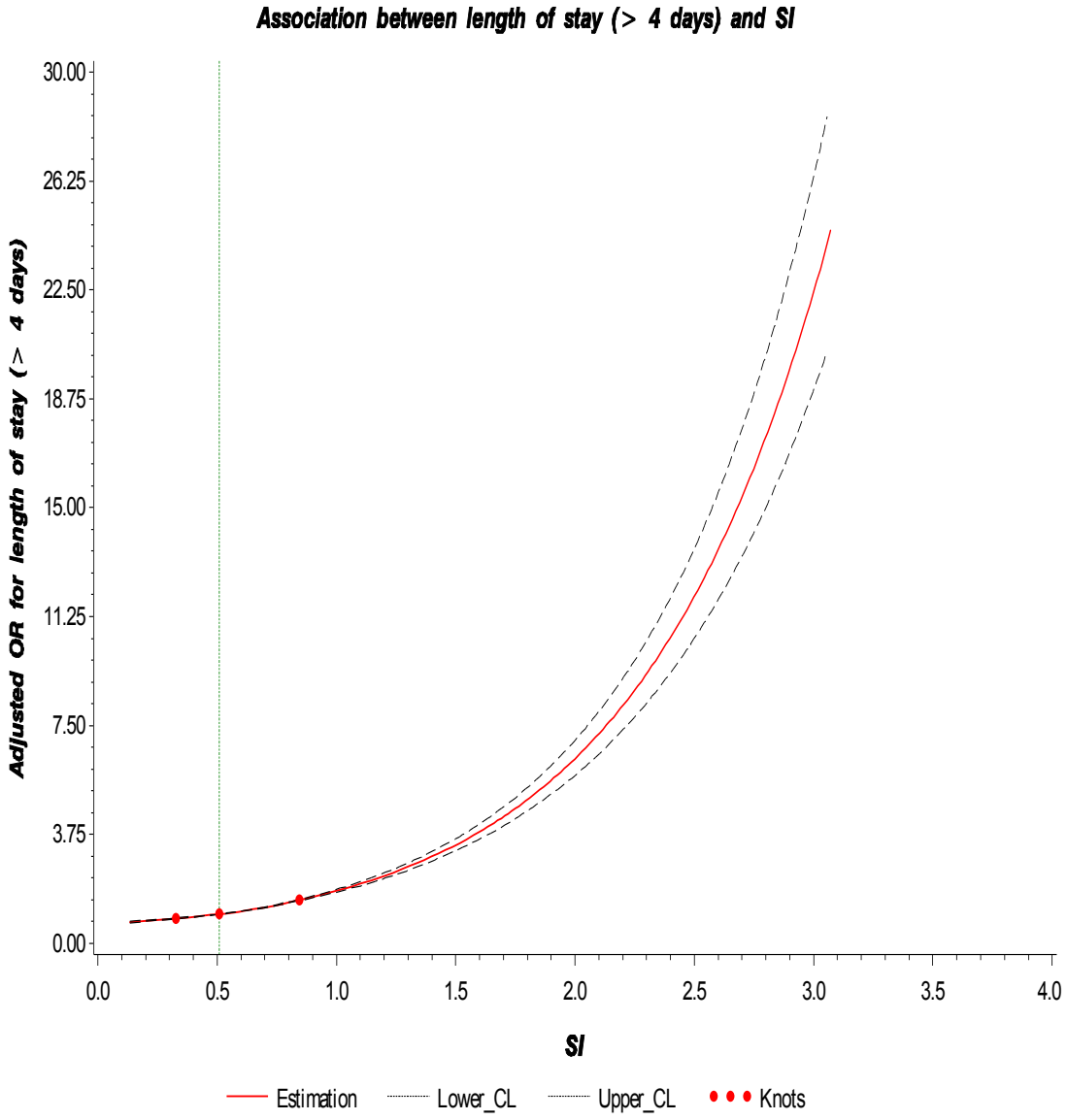
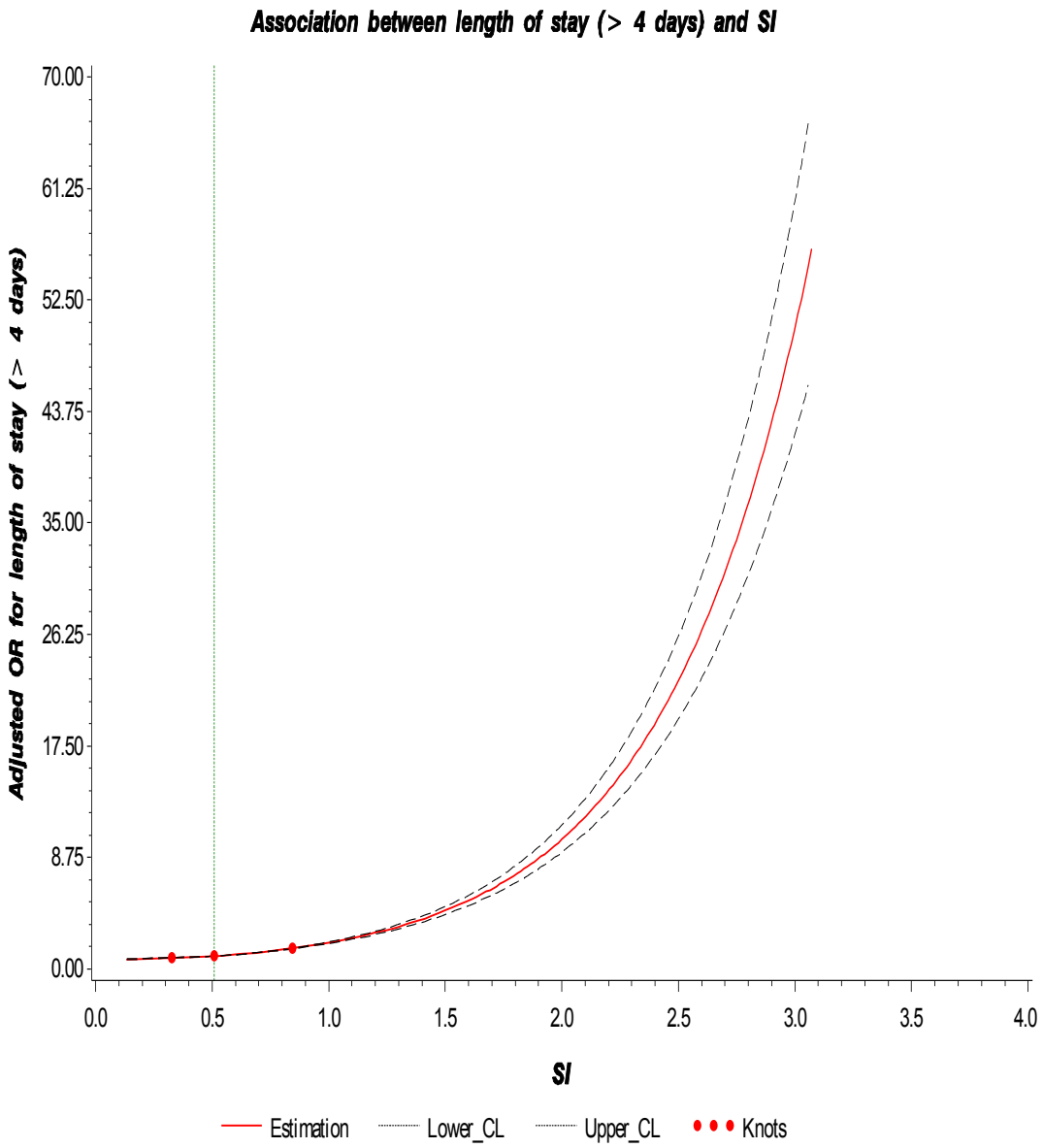


Figure S4. Outcomes vs. Shock Index (Shock Index was model as cubic splines).

A. Overall population (LOS > 4 days vs <= 4 days)



B. Acute Ischemic Stroke cohort.



C. Intracerebral Hemorrhage cohort.

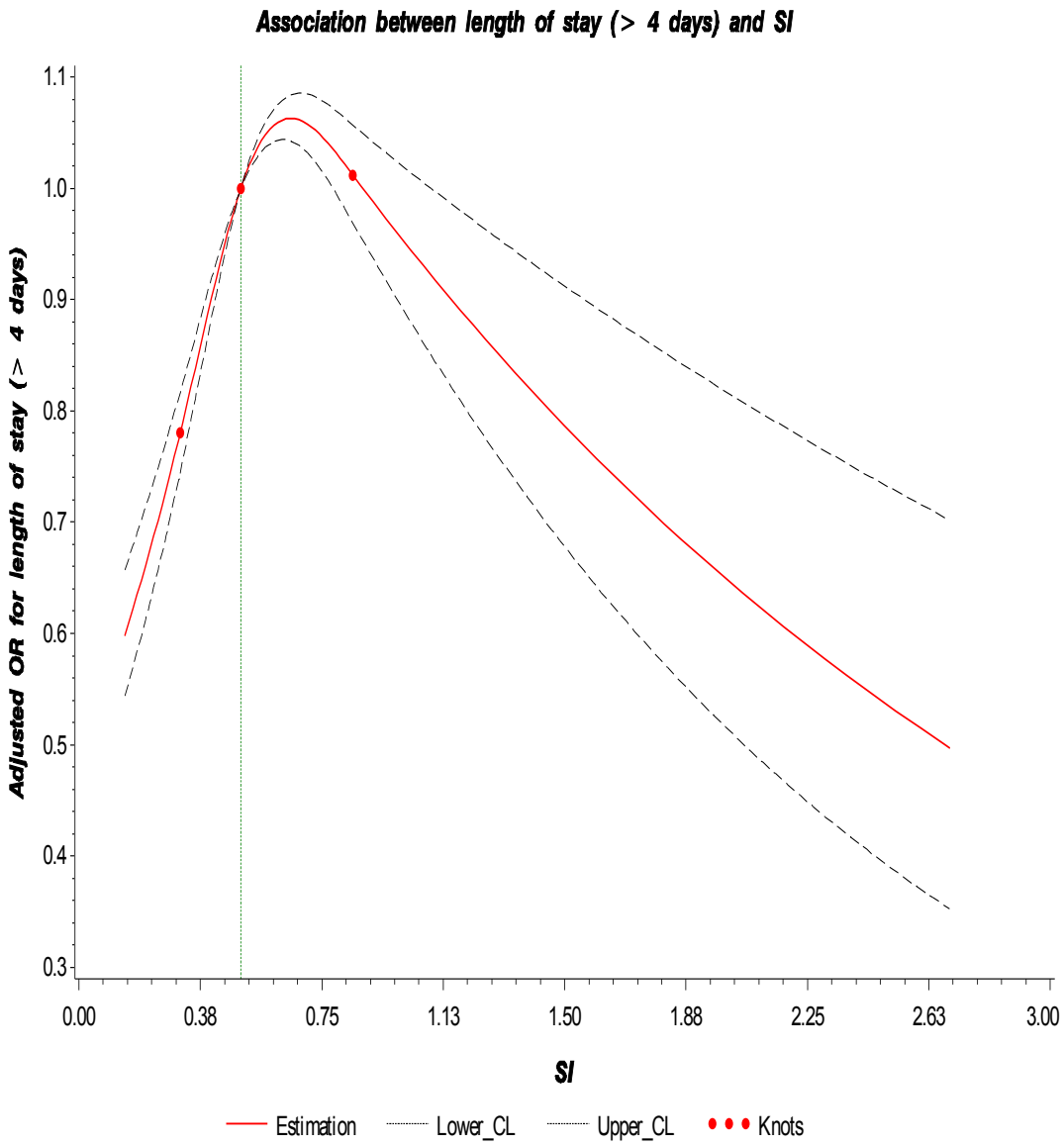
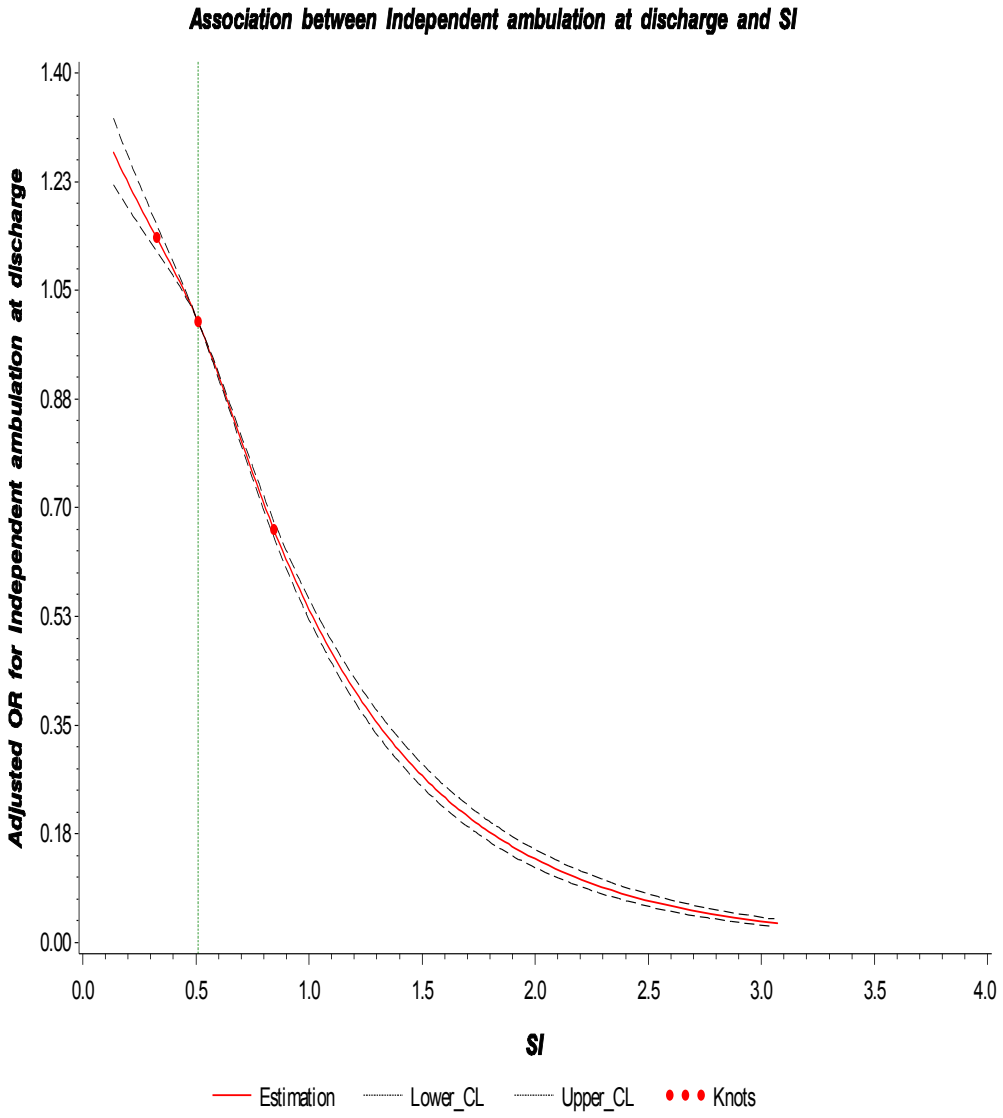
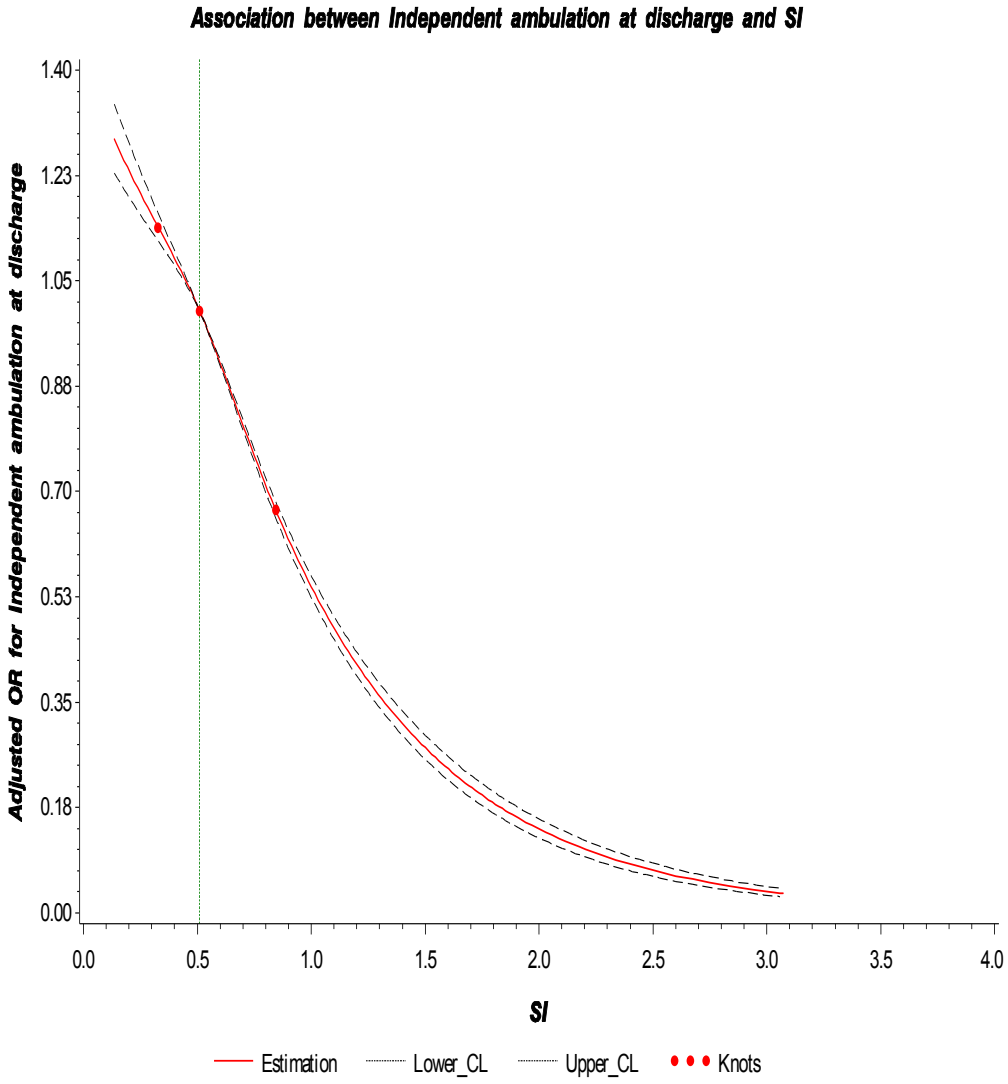


Figure S5. Outcomes vs. Shock Index (Shock Index was model as cubic splines).

A. Overall population



B. Acute Ischemic Stroke cohort



C. Intracerebral Hemorrhage cohort

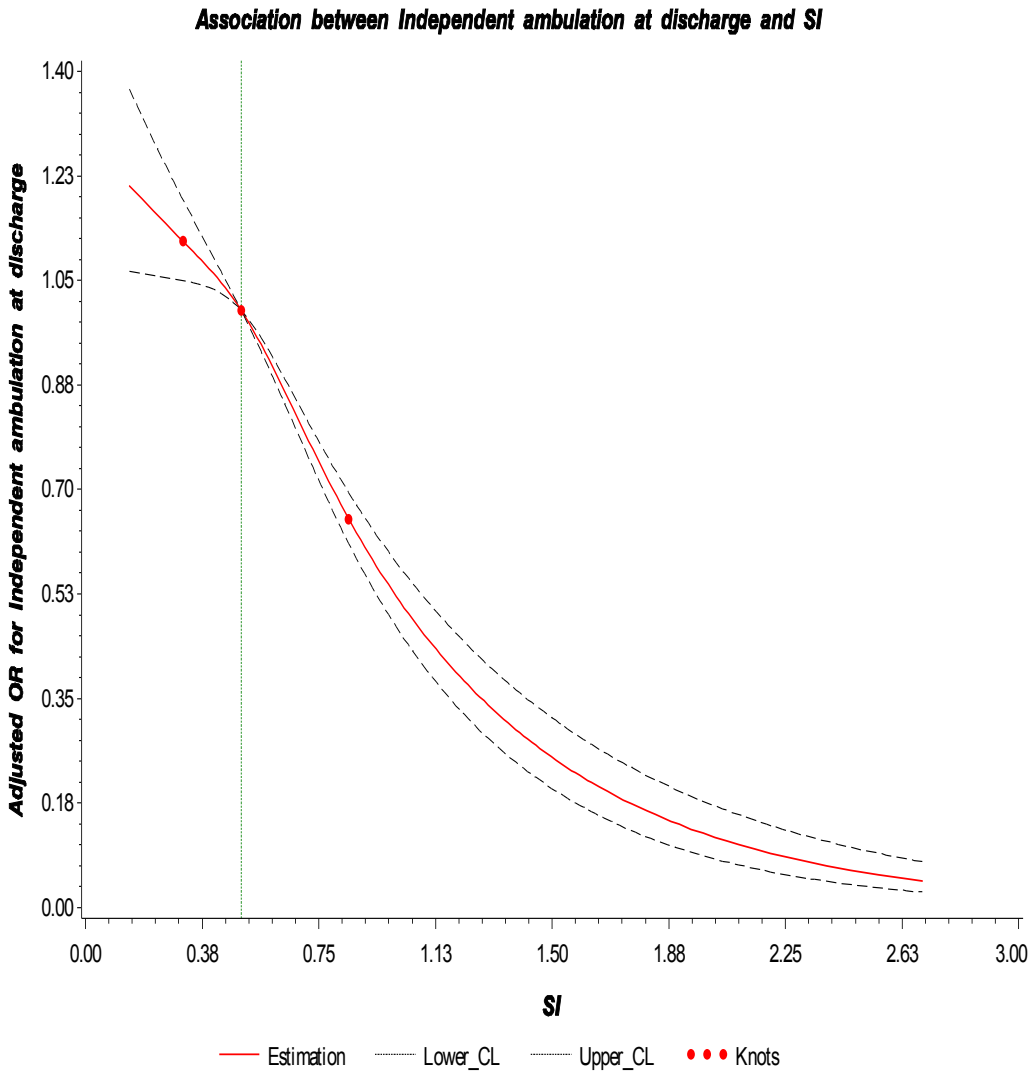
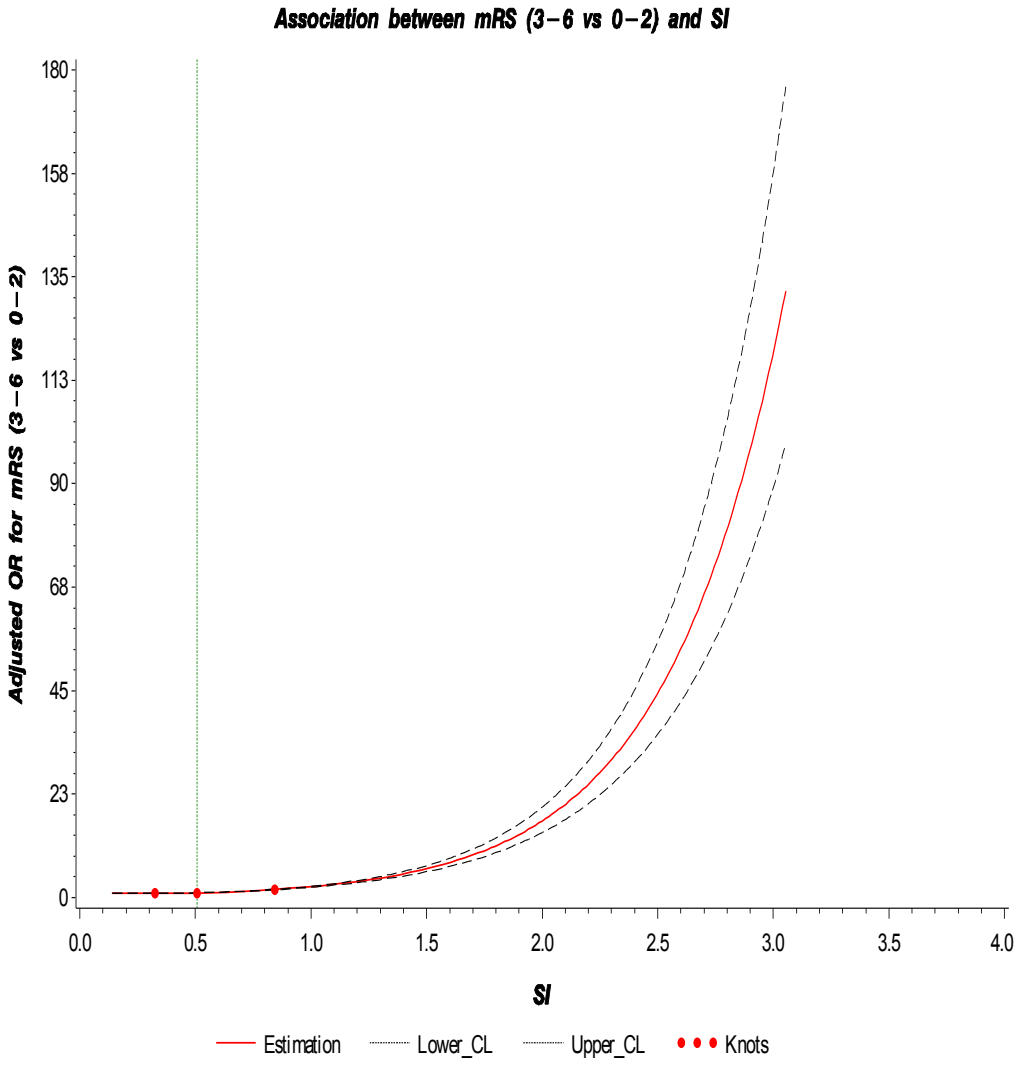
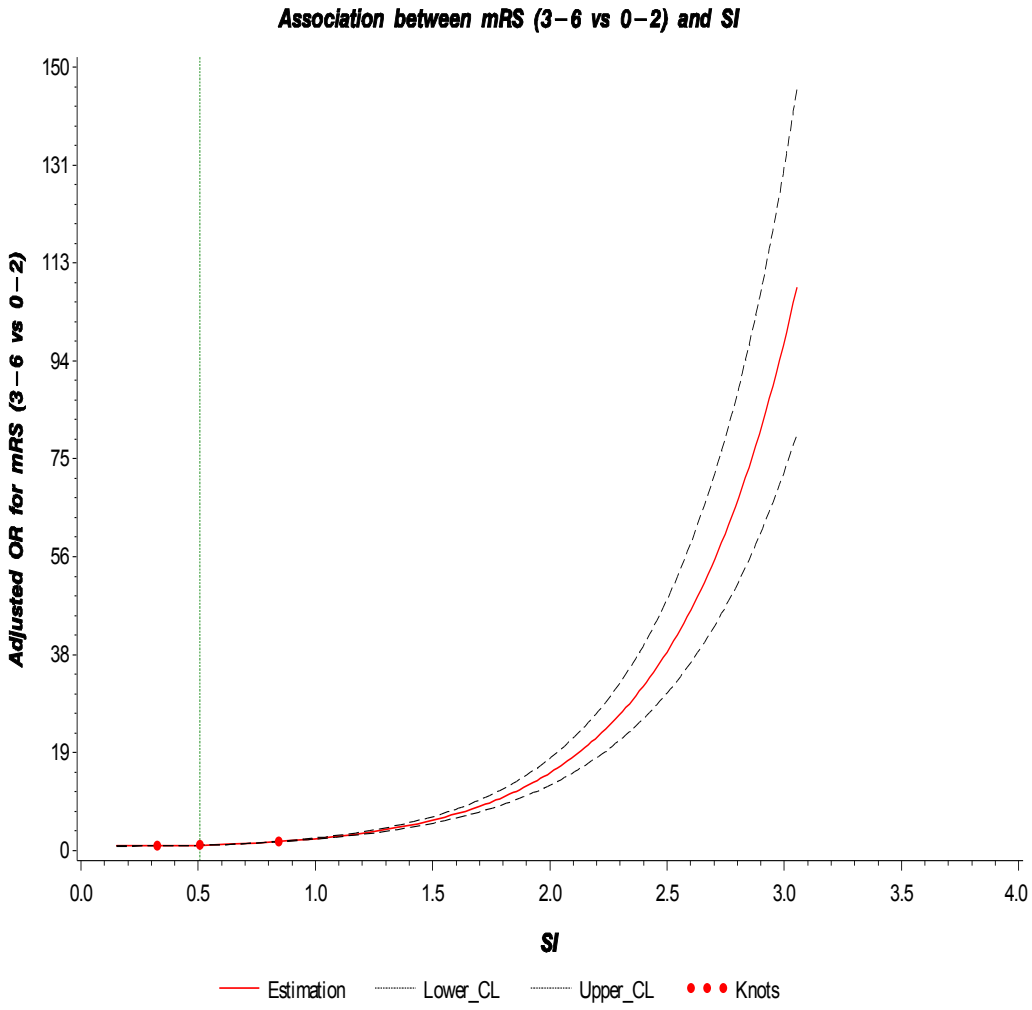


Figure S6. Outcomes vs. Shock Index (Shock Index was model as cubic splines).

A. Overall population



B. Acute Ischemic Stroke cohort



C. Intracerebral Hemorrhage cohort