

ORIGINAL RESEARCH

Stress Hyperglycemia Ratio and Hemoglobin to RDW Ratio in Predicting the Outcomes of Thrombolysis-Treated Stroke: A Retrospective Cohort Study

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Abstract: **Introduction:** High stress hyperglycemia ratio (SHR) and low hemoglobin-to-red blood cell distribution width ratio (HB/RDW) are each known predictors of mortality in acute ischemic stroke (AIS). This study aimed to assess the predictive performance of high SHR (≥ 1.18) and low HB/RDW (≤ 0.76) together in stroke patients treated with thrombolysis. **Methods:** We retrospectively collected data from 345 AIS patients treated with thrombolysis. HB/RDW values were obtained from pre-recombinant tissue plasminogen activator complete blood counts; while fasting plasma glucose (FPG) and glycated hemoglobin (HbA1c) levels were measured in the morning after an 8–14-hour overnight fast. Patients were categorized into four groups based on SHR and HB/RDW levels. We used multivariable Poisson regression with robust variance to estimate risk ratios (RRs) and 95% confidence intervals (CIs). Models assessed associations with in-hospital mortality (IHM), early neurological deterioration (END), and functional outcomes at discharge and 3 months, adjusting for age, sex, prior stroke, pre-existing disability, myocardial infarction, atrial fibrillation, heart failure, chronic kidney disease, and malignancy. Propensity score weighting analysis was further conducted as a sensitivity analysis. **Results:** Among 345 patients, only 37 were in the high SHR (SHR+) and low HB/RDW (HB/RDW+) group. A total of 65 patients (18.8%) died during hospitalization. The SHR+ HB/RDW+ group had significantly higher risks of IHM (adjusted RR: 9.97, 95% CI: 4.95–20.08), END (adjusted RR: 2.95, 95% CI: 1.51–5.77), 3-month mortality (adjusted RR: 6.23, 95% CI: 3.49–11.12), and poor 3-month functional outcomes (adjusted RR: 2.86, 95% CI: 2.01–4.06) compared to the SHR-HB/RDW- group. These associations remained robust across sensitivity analyses. The combination of SHR ≥ 1.18 and HB/RDW ≤ 0.76 predicted IHM with an AuROC of 0.78 (95% CI: 0.73–0.83). Although the combined biomarker improved sensitivity and net benefit, its AUROC was not statistically superior to that of individual markers. **Conclusion:** Combined high SHR and low HB/RDW levels at admission significantly predict poor outcomes in thrombolysis-treated AIS, performing better than either biomarker alone. Further validation in larger, diverse cohorts is warranted.

Keywords: Mortality; Stress hyperglycemia ratio; Thrombolytic therapy; Ischemic stroke; Prognosis

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1. Introduction

Acute ischemic stroke (AIS) is a leading cause of mortality and disability worldwide (1). Although its incidence has declined in high-income countries, it remains stable or increasing in low- and middle-income regions (2). Timely administration of recombinant tissue plasminogen activator (rt-PA) within 4.5 hours of symptom onset significantly improves

outcomes (3). However, reliable, and accessible biomarkers are still needed to improve prognostic accuracy and guide clinical decisions (4).

The stress hyperglycemia ratio (SHR), defined as fasting plasma glucose (FPG) divided by glycated hemoglobin (HbA1c), has emerged as a prognostic marker in AIS patients treated with rt-PA or mechanical thrombectomy (MT) (5–7). High SHR has been associated with increased mortality, poor functional outcomes, symptomatic intracerebral hemorrhage, cerebral edema (8–10), and recurrent strokes (11). The hemoglobin-to-red blood cell distribution width ratio (HB/RDW), is another promising biomarker (12). HB/RDW is associated with inflammation, oxidative stress, and mor-

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tality in AIS patients treated with rt-PA (13) or MT (14). It is also linked to stroke severity and mortality (13, 15), especially in those with atrial fibrillation (12).

Given their distinct but complementary pathophysiological roles, the combined use of these biomarkers may enhance risk stratification in thrombolysis-treated AIS patients. However, a significant evidence gap remains regarding the prognostic value of this approach, and its clinical utility has yet to be established. We primarily investigated whether the combination of high SHR and low HB/RDW is independently associated with in-hospital mortality (IHM) in thrombolysis-treated AIS patients. Secondary objectives included assessing their association with early neurological deterioration (END) and functional outcomes post thrombolysis. We also compared prognostic performance, discrimination, and clinical utility of the combined biomarker versus individual markers.

2. Methods

2.1. Study design and setting

This retrospective cohort study included consecutive AIS patients who received intravenous rt-PA at Saraburi Hospital, a tertiary stroke center in central Thailand, from January 2015 to July 2022. The screening performance of SHR and HB/RDW combination in predicting the outcomes of thrombolytic treated stroke patients was evaluated.

This report follows the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guideline for cohort studies. Data were extracted from electronic medical records. Treatment informed consent was obtained prior to treatment.

All patient data were anonymized prior to analysis; identifiers were removed, replaced with study codes, and stored in the Saraburi Hospital database on a password-protected institutional server accessible only to authorized personnel. Three-month follow-up data were collected via structured telephone interviews conducted by trained staff, with patients or their proxies informed of the process during hospitalization. No participants declined participation or opted out, and no identifiable information was used during data collection or analysis. The study protocol, including data protection and follow-up procedures, was approved by the Saraburi Hospital Ethics Committee (EC 039/2567).

2.2. Participants

Patients with AIS diagnosis per World Health Organization criteria (16), with rt-PA given within 4.5 hours of onset under the hospital's fast-track protocol; and age 18–85 years were included. Patients with recent infection or surgery (≤ 2 weeks), autoimmune or hematologic disorders, liver disease (Child-Pugh $> B$), abnormal coagulation, immunosuppressive therapy, referral with un-trackable mortality status, loss to follow-up, or incomplete records were excluded. Patients who underwent MT were excluded to minimize population

heterogeneity. In addition, to minimize reverse causality, we excluded patients who died within 2 and 7 days of admission, based on the likelihood of early stroke-related deaths (17, 18).

2.3. Data gathering

All patients underwent emergency non-contrast computed tomography (NCCT) to exclude hemorrhage and tumors before rt-PA (0.9 mg/kg, max 90 mg) was administered.

RDW and Hb values were obtained from complete blood counts (CBC) before rt-PA administration. FPG and HbA1c values were collected after 8–14 hours of fasting, irrespective of the timing of rt-PA administration, as part of routine laboratory measurements for all stroke patients. Specimen collection protocols, including laboratory instruments and calibration procedures, are detailed in our prior publications (9, 13). Laboratory protocols are publicly available at: <https://doi.org/10.17605/OSF.IO/4BT92>.

SK was responsible for data gathering. The two main exposures were calculated as follows:

$SHR = [FPG \text{ (mmol/L)}] / [HbA1c \text{ (\%)}]$.

$HB/RDW \text{ ratio} = [Hb \text{ (g/dL)}] / [RDW \text{ (\%)}]$.

Patient-level risk factors were extracted from medical records and included prior stroke, AF, myocardial infarction (MI), congestive heart failure (CHF), diabetes mellitus (DM), hypertension, chronic kidney disease (CKD), and hyperlipidemia. Stroke etiology was classified per the Trial of ORG 10172 in Acute Stroke Treatment (TOAST) criteria (19). Early ischemic changes were quantified using the Alberta Stroke Program Early CT Score (ASPECTS) on NCCT. Stroke severity at admission was assessed by board-certified neurologists using the NIHSS.

2.4. Outcome assessments

The primary outcome was IHM, defined as all-cause death during hospitalization, determined from discharge summaries. Secondary outcomes included poor functional outcome at discharge (modified Rankin Scale [mRS] ≥ 3), END, and 3-month mortality. Three-month mRS scores were further classified as excellent (0–1), functionally independent (0–2), or poor (3–6). END was defined as an increase of ≥ 2 points in the National Institutes of Health Stroke Scale (NIHSS) score within 72 hours of baseline assessment (20). The mRS score was obtained through telephone follow-up interviews conducted by stroke-trained nurses.

2.5. Statistical analysis

Previous studies reported IHM rates of 36.7% in patients with low HB/RDW (≤ 0.76) versus 12.6% in others (13). Assuming a 46.7% IHM rate among those with both low HB/RDW and high SHR (≥ 1.18) (9, 21), a sample of 108 (27 per group) was needed for 80% power ($\alpha = 0.05$). Including 345 patients allowed subgroup analyses and accounted for missing data. Patients were categorized into four groups based on SHR and HB/RDW levels (The cutoffs for high SHR (≥ 1.18) and low HB/RDW (≤ 0.76) were determined based on our previous

studies (9, 13)):

Not high SHR and not low HB/RDW (SHR- and HB/RDW-)

Not high SHR and low HB/RDW (SHR- and HB/RDW+)

High SHR and not low HB/RDW (SHR+ and HB/RDW-)

High SHR and low HB/RDW (SHR+ and HB/RDW+)

Baseline characteristics were compared using the Kolmogorov–Smirnov and Levene's tests for normality and variance. Categorical variables were summarized as frequencies and percentages; continuous data were reported as mean $\pm$ SD or median (interquartile range(IQR)). Statistical comparisons used chi-square/Fisher's exact tests for categorical data and t-tests or Mann–Whitney U tests for continuous variables. To guide covariate selection and avoid over-adjustment, we constructed a directed acyclic graph (DAG) using DAGitty (www.dagitty.net) to model the hypothesized causal relationships between exposures (SHR and HB/RDW), covariates, and outcomes. Multivariable Poisson regression with robust variance was used to estimate risk ratios (RRs) and 95% confidence intervals (CIs) for associations with IHM (primary outcome), END, and functional outcomes at discharge and at 3 months (measured by the mRS), adjusting for age, sex, prior stroke, preexisting disability, MI, AF, CHF, CKD, and malignancy (22). Confounders were identified using a DAG (23), informed by a comprehensive literature review and expert opinion (Figure S1A). Although NIHSS and ASPECTS are strong prognosticators, we excluded them from our models as they are likely mediators rather than confounders in the relationship between metabolic stress and outcome. Adjusting for them would obscure the total effect of the exposures. To minimize reverse causality, we excluded patients who died within 2 and 7 days of admission, based on the likelihood of early stroke-related deaths (17, 18). Bonferroni correction was further applied to adjust p-values and CIs for multiple comparisons.

We conducted a propensity score weighting analysis to reduce confounding while preserving sample size, which is crucial for small studies. Propensity scores were estimated using multinomial logistic regression with covariates including age, sex, smoking, prior stroke, pre-existing disability, AF, MI, CHF, CKD, malignancy, and onset of stroke symptoms. Age was modelled using 4-knot restricted cubic splines. Related interaction terms were also included. Stabilized weights were trimmed at the 1st and 99th percentiles. Weighted standardized mean differences assessed covariate balance, and score distributions were plotted to confirm the positivity assumption. This propensity score weighting analysis was performed as a sensitivity check and not a replacement for the primary model.

We assessed predictive accuracy using the area under the Receiver Operating Characteristic (ROC) curve (AuROC), sensitivity, specificity, predictive values, and likelihood ratios, with the Youden index defining optimal cutoffs. Kaplan–Meier survival curves with log-rank tests evaluated IHM across groups. Three models were compared: 1) the combined SHR and HB/RDW model, 2) the SHR-only model, and 3) the

HB/RDW-only model. Pairwise AuROC comparisons were done using DeLong's test with Bonferroni adjustment. Decision curve analysis (DCA) assessed net clinical benefit across threshold probabilities by comparing models to “treat-all” and “treat-none” strategies.

Poisson regression tested interactions between exposures and key variables (e.g., DM, AF) using cross-product terms. Two-sided p-values < 0.05 were considered statistically significant. To control for type I error due to multiple comparisons, the primary outcome (IHM) was adjusted using the Bonferroni approach. The results of other outcomes should, therefore, be interpreted as exploratory, warranting further investigation rather than serving as definitive conclusions. All analyses were complete-case and conducted using Stata 16MP (StataCorp LLC, College Station, Texas). A forest plot for subgroup results was generated in R (v4.3.1). Missing brain NCCT data in 22 individuals reflects limitations due to retrospective data collection and is likely unrelated to study variables and to have occurred at random. We consider it to be missing completely at random (MCAR), justifying the use of complete-case analysis for greater efficiency.

3. Results

3.1. Baseline characteristics of studied patients

Of 387 AIS patients who received intravenous rt-PA between January 1, 2015, and July 31, 2022, 42 were excluded due to autoimmune conditions or immunosuppressive use ($n = 5$), incomplete follow-up ($n = 9$), un-trackable outcomes due to referral ($n = 6$) or missing records ($n = 22$), resulting in 345 patients for analysis (Figure 1).

The mean age of patients was 68.6 ± 12.9 (range: 22–98) years, and the median NIHSS score was 11 (IQR: 8–17). Table 1 compares the baseline characteristics of studied patients between the 4 groups. Patients in the SHR+ HB/RDW+ group tended to be older ($p = 0.011$), had more severe strokes ($p < 0.001$), and had a higher prevalence of AF ($p = 0.034$), MI ($p = 0.017$), CHF ($p = 0.002$), DM ($p = 0.025$), CKD ($p = 0.006$), and malignancy ($p = 0.031$). They also had higher glucose and creatinine levels ($p < 0.001$), lower ASPECTS scores ($p < 0.001$), and longer lengths of hospital stay ($p = 0.021$). Stroke etiologies in this group more frequently included large artery atherosclerosis and cardio-embolism. The weighted standardized mean differences (SMDs) indicated that most baseline characteristics were balanced between groups (SMDs < 0.1) following the propensity score weighting analysis.

3.2. Outcomes

Table 2 shows the association of SHR and HB/RDW levels with the 5 studied outcomes (In-hospital mortality, In-hospital function, END, 3-month mortality, and 3-month function), which was as follow:

- In-hospital mortality and functional outcomes

A total of 65 patients (18.8%) died during hospitalization. Median survival was 28 (95% CI: 22–42) days. Kaplan–Meier

analysis showed that the SHR+ HB/RDW+ group had the highest IHM (log-rank $p < 0.001$; Figure 2A). SHR+ HB/RDW+ was associated with the highest risks for IHM and poor discharge outcomes in both univariable and multivariable analyses. In the fully adjusted model, the adjusted RRs for IHM were 9.42 (95% CI: 4.70, 18.90) for SHR+ HB/RDW+, 5.27 (2.55, 10.89) for SHR+ HB/RDW−, and 2.93 (1.29, 6.63) for SHR− HB/RDW+, compared to SHR− HB/RDW− (Table 2).

- END

SHR+ HB/RDW+ was also linked to an elevated risk of END (adjusted RR: 2.68; 95% CI: 1.40, 5.14), followed by SHR+ HB/RDW− (adjusted RR: 2.21; 1.25, 3.92). No significant association was found for SHR− HB/RDW+ (adjusted RR: 0.91; 0.36, 2.27) (Table 2).

- Three-month mortality and functional outcomes

By 3 months, 83 patients (24.1%) had died. At 3 months, SHR+ HB/RDW+ showed the strongest associations with mortality (adjusted RR: 6.42; 95% CI: 3.54, 11.67) and poor functional outcome (adjusted RR: 2.91; 2.05, 4.15), and the lowest likelihood of excellent recovery (mRS 0–1, RR: 0.26; 0.12, 0.58) or independence (mRS 0–2, RR: 0.34; 0.18, 0.62) compared to SHR− HB/RDW− (Table 2). SHR+ HB/RDW+ had the highest 3-month mortality (64.9%), followed by SHR+ HB/RDW− (48.1%), SHR− HB/RDW+ (24.3%), and SHR− HB/RDW− (6.7%) (Figure S1B).

3.3. Subgroup and sensitivity analyses

Subgroup analyses indicated that the association between biomarkers and IHM was consistent across comorbidities such as DM and AF (p for interaction = 0.69 and 0.81, respectively; Figure 2B). Bonferroni correction confirmed the robustness of the findings. Excluding patients who died within 2 or 7 days yielded similar results. Additionally, the propensity score weighting analysis yielded consistent results with the main findings. The propensity score distribution across exposure groups supported the adequacy of the positivity (common support) assumption (Figure S1C).

3.4. Predictive performance and net clinical benefit

Table 3 shows the performance of SHR+ HB/RDW+ in predicting the studied outcomes. ROC analysis showed comparable performance between SHR+ HB/RDW+ (AuROC: 0.78; 95% CI: 0.73, 0.83), SHR+ alone (0.78; 0.72, 0.84), and HB/RDW+ alone (0.74; 0.68, 0.80). The resulting AuROC p -values were: 0.38 for IHM, 0.68 for in-hospital poor functional outcome, 0.80 for END, 0.03 for 3-month mortality, 0.49 for 3-month poor functional outcome, 0.16 for 3-month excellent functional outcome, and 0.04 for 3-month functional independence.

SHR+ HB/RDW+ demonstrated the highest sensitivity for predicting IHM (84.6%; 95% CI: 73.5%, 92.4%), outperforming SHR+ (70.8%) and HB/RDW+ (76.9%) alone. The combined biomarkers also showed the highest sensitivity for poor functional outcomes at discharge, END, and 3-month

outcomes (Figure S1D). Moreover, the combined SHR and HB/RDW model provided the highest net benefit across most clinically relevant thresholds (Figure S1E). It outperformed individual models from 0.10 to 0.20 and above 0.25. Between 0.20 and 0.25, SHR-only had slightly greater net benefit. Across all thresholds, the HB/RDW-only model performed worst.

4. Discussion

In this retrospective cohort of 345 rt-PA-treated AIS patients, the combination of high SHR (≥ 1.18) and low HB/RDW (≤ 0.76) was independently associated with an increased risk of mortality and poorer outcomes both during hospitalization and at three months post-discharge. These associations remained significant after adjustment for confounders and propensity score weighting analysis. These effects were consistent across subgroups, including patients with or without DM or AF. Moreover, the combined biomarkers showed numerically higher—though not statistically significant—discrimination for IHM. The combination also improved sensitivity and negative predictive value compared to either biomarker alone, potentially reducing false negatives and aiding early risk stratification in thrombolysis-treated AIS patients.

Our findings align with prior studies linking high SHR to worse outcomes in AIS (8, 11, 24). A meta-analysis of over 183,000 patients reported that SHR was significantly associated with mortality, hemorrhagic transformation, poor functional outcomes, and infections, regardless of DM status or treatment modality (25). Additional studies have confirmed SHR's value in predicting END and poor outcomes after MT (26). Similarly, HB/RDW has been associated with cardiovascular mortality (27, 28). A retrospective study using the MIMIC-IV database found that low HB/RDW predicted higher mortality in AIS patients with AF (12), while other reports showed a nearly threefold increase in post-thrombolysis mortality risk for those with low HB/RDW (13). Together, these data support SHR and HB/RDW as meaningful prognostic indicators in AIS. The underlying mechanisms of these associations differ. SHR reflects acute metabolic stress from hyperglycemia, which worsens neuronal injury through several pathways: increased oxidative stress and inflammation from glucose fluctuations (29), enhanced thrombosis due to platelet aggregation and endothelial dysfunction (30), and lactic acidosis-induced calcium signaling disruption and DNA fragmentation (31, 32). In contrast, HB/RDW is shaped by systemic inflammation and oxidative stress (33). Low Hb levels weaken immune defenses and increase susceptibility to infection and inflammation (34). The U-shaped relationship between Hb and stroke severity further underscores its prognostic relevance (35, 36). High RDW, which reflects anisocytosis and ineffective erythropoiesis, exacerbates tissue hypoxia and necrosis (37). It also correlates with coagulation abnormalities and thromboembolism, contributing to stroke recurrence and poor outcomes (38).

The combined use of SHR and HB/RDW notably improved sensitivity (84.6%) for predicting IHM compared to using SHR (70.8%) or HB/RDW (76.9%) alone. This enhanced sensitivity likely results from their complementary pathophysiological roles—SHR capturing acute metabolic dysregulation, and HB/RDW reflecting systemic stress and impaired oxygen delivery. Although this combination did not improve overall model discrimination (as measured by AuROC) and slightly reduced specificity, the trade-off may be acceptable in high-stakes clinical scenarios like AIS, where failing to identify high-risk patients can have critical consequences.

This study has several strengths. To our knowledge, it is the first to evaluate the joint prognostic performance of SHR and HB/RDW in thrombolysis-treated AIS. These biomarkers are derived from routine, low-cost laboratory tests, making them especially suitable for use in resource-limited settings. The robustness of our findings is supported by multiple sensitivity analyses, propensity score weighting, and consistent subgroup effects.

This study has both clinical and research implications. Clinically, combining SHR and HB/RDW provides a simple, cost-effective tool for early risk stratification and guiding interventions in AIS. Their complementary roles make them useful across diverse healthcare settings, particularly where advanced diagnostic tools are limited. From a research perspective, future work should explore dynamic changes in these biomarkers after thrombolysis and assess their utility in patients treated with MT. Integrating SHR and HB/RDW into existing risk scores, such as the THRIVE score, could further enhance prognostic precision (39). Multicenter and multinational studies are warranted to validate and expand upon these findings.

5. Limitations

First, the retrospective observational design precludes causal inference. Still, confounder selection via DAGs and consistent results across analyses mitigate concerns about residual confounding or bias (23). Second, FPG used to calculate SHR was obtained 8–14 hours after admission, often following thrombolysis and initial treatment. This delay may lead to misclassification of acute stress hyperglycemia, particularly in patients whose glucose levels were affected by early interventions, potentially attenuating the true association. However, this concern may be minimal, as most interventions administered during the acute phase of stroke—and in routine clinical practice—do not substantially influence blood glucose levels. Third, the HB/RDW ratio may be influenced by unmeasured confounders such as iron deficiency, anemia of chronic disease, or systemic inflammation—common in AIS patients and not fully captured in our dataset. However, we attempted to exclude patients with hematologic disorders, abnormal coagulation, or systemic inflammatory conditions (e.g., recent infection, surgery within 2 weeks, or autoimmune diseases), adjusted for key comorbidities, and conducted multiple sensitivity analyses to enhance internal

validity. Fourth, the exclusion of 6.4% of patients due to missing data may have introduced selection bias. However, complete-case analysis remains valid given the small proportion of missingness and the assumption of an MCAR mechanism (40, 41). Fifth, as a single-center, single-ethnicity cohort composed entirely of Thai patients, the generalizability of our findings may be limited. Finally, we excluded patients undergoing MT to maintain population homogeneity; however, the growing accessibility of MT since the study period presents future opportunities to evaluate these biomarkers in that population.

6. Conclusions

The combination of high SHR and low HB/RDW at admission is significantly associated with an increased risk of mortality and poorer prognosis in AIS patients treated with rt-PA. Combining these markers enhances predictive sensitivity and net clinical benefit, offering a reliable, practical, and cost-saving tool for guiding AIS management. Further research is warranted to explore their dynamic changes post-thrombolysis and validate their prognostic value in broader and more diverse populations.

7. Declarations

7.1. Acknowledgments

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7.2. Author contributions

All authors made significant contributions and approved the protocol and final manuscript. SK was responsible for the concept, design, and data acquisition. SK and NN performed the statistical analysis and interpreted the data. NN was responsible for conceptualizing the study and supervising it. The initial draft of the manuscript was written by SK and NN conducted the subsequent review and editing.

7.3. Ethical considerations

All patient data were anonymized prior to analysis; identifiers were removed, replaced with study codes, and stored in the Saraburi Hospital database on a password-protected institutional server accessible only to authorized personnel. Three-month follow-up data were collected via structured telephone interviews conducted by trained staff, with patients or their proxies informed of the process during hospitalization. No participants declined participation or opted out, and no identifiable information was used during data collection or analysis. The study protocol, including data protection and follow-up procedures, was approved by the

Saraburi Hospital Ethics Committee (EC 039/2567).

7.4. Consent to participate

The ethics committee waived the requirement for research informed consent due to the retrospective design of the study. All the data used in this study were fully anonymized.

7.5. Consent for publication

Not applicable.

7.6. Conflict of interest

The authors have no potential conflicts of interest to disclose.

7.7. Funding and support

This study was funded by the Medical Education Center at Saraburi Hospital (No. MC009-2567) and the University of Phayao and Thailand Science Research and Innovation Fund (Fundamental Fund 2024). The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

7.8. Data availability

All data and code are available in the Open Science Framework at <https://doi.org/10.17605/OSF.IO/4BT92>.

7.9. Using artificial intelligence chatbots

During the preparation of this work the author(s) used ChatGPT (OpenAI) for English language proofreading. After using this tool/service, the author(s) reviewed and edited the content as needed and take(s) full responsibility for the content of the publication. No unedited AI-generated text remains in the final submitted manuscript.

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Table 1: Comparing the baseline characteristics of studied patients between 4 groups according to the stress hyperglycemia ratio (SHR) and hemoglobin-to-red blood cell distribution width ratio (HB/RDW) levels (n=345)

Characteristic	High SHR (≥ 1.18) – low HB/RDW (≤ 0.76)				P
	No-No (n= 180)	NNo-Yes (n=53)	Yes-No (n=75)	Yes-Yes (n=37)	
Age, years					
Mean $\pm$ SD	59.49 $\pm$ 14.91	64.55 $\pm$ 16.59	62.51 $\pm$ 13.56	67.46 $\pm$ 16.23	0.011
Sex					
Male	100 (55.56)	27 (50.94)	42 (56.00)	14 (37.84)	0.241
Female	80 (44.44)	26 (49.06)	33 (44.00)	23 (62.16)	
Comorbidities					
Smoking	69 (38.33)	14 (26.42)	29 (38.67)	11 (29.73)	0.346
Current alcohol drinking	74 (41.11)	18 (33.96)	37 (49.33)	13 (35.14)	0.297
Prior stroke	20 (11.11)	6 (11.32)	6 (8.00)	9 (24.32)	0.109
Atrial fibrillation	41 (22.78)	19 (35.85)	28 (37.33)	14 (37.84)	0.034
Myocardial infarction	10 (5.56)	6 (11.32)	5 (6.67)	8 (21.62)	0.017
Chronic heart failure	12 (6.67)	13 (24.53)	6 (8.00)	6 (16.22)	0.002
Diabetes mellitus	39 (21.67)	12 (22.64)	28 (37.33)	14 (37.84)	0.025
Hypertension	116 (64.44)	39 (73.58)	59 (78.67)	29 (78.38)	0.081
Chronic kidney disease	17 (9.44)	14 (26.42)	6 (8.00)	7 (18.92)	0.006
History of malignancy	3 (1.67)	2 (3.77)	0 (0.00)	3 (8.11)	0.031
Dyslipidemia	77 (42.78)	10 (18.87)	37 (49.33)	17 (45.95)	0.003
Preexisting dependency					
Yes (mRS 3-5)	2 (1.11)	5 (9.43)	3 (4.00)	3 (8.11)	0.007
Onset to treatment time (minutes)					
Mean $\pm$ SD	145.36 $\pm$ 58.21	136.89 $\pm$ 46.52	133.28 $\pm$ 60.59	150.65 $\pm$ 58.04	0.304
< 3 hours	127 (70.56)	45 (84.91)	62 (82.67)	22 (59.46)	0.010
3-4.5 hours	53 (29.44)	8 (15.09)	13 (17.33)	15 (40.54)	
Onset to door (minutes)					
Mean $\pm$ SD	94.48 $\pm$ 51.36	82.30 $\pm$ 37.85	89.97 $\pm$ 53.91	107.27 $\pm$ 57.76	0.178
Blood pressure at admission (mmHg)					
Systolic	156.46 $\pm$ 26.12	154.98 $\pm$ 28.38	164.53 $\pm$ 32.14	167.81 $\pm$ 33.03	0.034
Diastolic	91.67 $\pm$ 17.70	90.51 $\pm$ 18.46	96.53 $\pm$ 22.22	92.19 $\pm$ 19.81	0.191
Admitted NIHSS					
Mean $\pm$ SD	11.17 $\pm$ 4.88	12.26 $\pm$ 5.76	14.60 $\pm$ 6.29	15.13 $\pm$ 5.77	<0.001
5-15	143 (79.44)	34 (64.15)	40 (53.33)	15 (40.54)	<0.001
16-20	30 (16.67)	15 (28.30)	16 (21.33)	15 (40.54)	
>20	7 (3.89)	4 (7.55)	19 (25.33)	7 (18.92)	
TOAST classification					
Large artery atherosclerosis	33 (18.33)	7 (13.21)	23 (30.67)	13 (35.14)	0.001
Cardioembolic stroke	49 (27.22)	22 (41.51)	31 (41.33)	17 (45.95)	
Small-vessel occlusion	89 (49.44)	20 (37.74)	18 (24.00)	7 (18.92)	
Stroke of other determined etiology	4 (2.22)	3 (5.66)	2 (2.67)	0 (0.00)	
Stroke of undetermined etiology	5 (2.78)	1 (1.89)	1 (1.33)	0 (0.00)	
Baseline ASPECTS					
Median (IQR)	10 (9 - 10)	9 (8 - 10)	9 (7 - 10)	8 (7 - 10)	<0.001
Hospital stays (days)					
Median (IQR)	5 (3 - 8)	5 (4 - 11)	5 (3 - 9)	8 (4 - 17)	0.021
Laboratory data					
WBC (103cells/mm3)	8.68 $\pm$ 2.23	8.89 $\pm$ 2.74	9.39 $\pm$ 3.05	9.53 $\pm$ 6.27	0.301
Platelet (103cells/mm3)	249.68 $\pm$ 60.61	249.94 $\pm$ 71.91	249.84 $\pm$ 83.81	252.24 $\pm$ 125.93	0.230
Creatinine (mg/dL)	0.99 $\pm$ 0.47	1.52 $\pm$ 1.59	0.98 $\pm$ 0.30	1.09 $\pm$ 0.50	<0.001
Admission plasma glucose (mg/dL)	123.63 $\pm$ 53.50	119.59 $\pm$ 56.56	165.41 $\pm$ 69.57	168.35 $\pm$ 77.27	<0.001

Values are presented as mean $\pm$ standard deviation (SD), frequency (percentage), or median (interquartile range (IQR)).

ASPECTS: Alberta Stroke Program Early CT Score; mRS: modified Rankin Scale; NIHSS: National Institutes of Health Stroke Scale; OTT: onset to treatment time; TOAST: Trial of ORG 10172 in Acute Stroke Treatment; WBC: white blood cell.

Table 2: Association between stress hyperglycemia ratio (SHR) and hemoglobin-to-red blood cell distribution width ratio (HB/RDW) and stroke outcomes (n=345)

Outcomes	High SHR (≥ 1.18) – low HB/RDW (≤ 0.76)			
	No-No	No-Yes	Yes-No	Yes-Yes
In-hospital mortality				
N (%)	9 (5.00)	11 (20.75)	23 (30.67)	22 (59.46)
AAR	0.06(0.02, 0.09)	0.17(0.08, 0.25)	0.30(0.20, 0.40)	0.53(0.39, 0.68)
ARR	1.00(Reference)	2.93(1.29, 6.63)	5.27(2.55, 10.89)	9.42(4.70, 18.90)
P	NA	0.010	<0.001	<0.001
In-hospital poor functional outcome (mRS ≥ 3)				
N (%)	94 (52.22)	31 (58.49)	58 (77.33)	30 (81.08)
AAR	0.54(0.47, 0.62)	0.53(0.41, 0.65)	0.77(0.67, 0.86)	0.78(0.65, 0.92)
ARR	1.00(Reference)	0.97(0.74, 1.27)	1.41(1.17, 1.69)	1.44(1.15, 1.79)
P	NA	0.842	<0.001	<0.001
In-hospital Early neurological deterioration†				
N (%)	20 (11.11)	6 (11.32)	20 (26.67)	12 (34.43)
AAR	0.12(0.07, 0.16)	0.11(0.02, 0.19)	0.26(0.16, 0.36)	0.31(0.16, 0.46)
ARR	1.00(Reference)	0.91(0.36, 2.27)	2.21(1.25, 3.92)	2.68(1.40, 5.14)
P	NA	0.834	0.006	0.003
3-month all-cause mortality‡				
N (%)	15 (8.33)	13 (24.53)	32 (42.67)	24 (64.86)
AAR	0.09(0.05, 0.14)	0.20(0.11, 0.28)	0.43(0.31, 0.54)	0.55(0.39, 0.70)
ARR	1.00(Reference)	2.09(1.08, 4.06)	4.57(2.62, 7.98)	5.84(3.27, 10.42)
P	NA	0.029	<0.001	<0.001
3-month poor functional outcome (mRS ≥ 3)				
N (%)	39 (21.67)	22 (41.51)	54 (72.00)	29 (78.38)
AAR	0.23(0.17, 0.30)	0.36(0.24, 0.47)	0.72(0.62, 0.83)	0.68(0.54, 0.82)
ARR	1.00(Reference)	1.52(0.99, 2.33)	3.09(2.26, 4.21)	2.91(2.05, 4.15)
P	NA	0.054	<0.001	<0.001
3-month excellent functional outcome (mRS 0-1)				
N (%)	112 (62.22)	29 (54.72)	19 (25.33)	5 (13.51)
AAR	0.59(0.52, 0.65)	0.61(0.47, 0.76)	0.26(0.16, 0.36)	0.15(0.03, 0.27)
ARR	1.00(Reference)	1.04(0.80, 1.36)	0.44(0.30, 0.66)	0.26(0.12, 0.58)
P	NA	0.745	<0.001	0.001
3-month functional independence (mRS 0-2)				
N (%)	141 (78.33)	31 (58.49)	21 (28.00)	8 (21.62)
AAR	0.74(0.68, 0.80)	0.66(0.53, 0.80)	0.28(0.18, 0.38)	0.25(0.10, 0.40)
ARR	1.00(Reference)	0.90(0.72, 1.12)	0.38(0.26, 0.54)	0.34(0.18, 0.62)
P	NA	0.348	<0.001	<0.001

Data are presented with 95% confidence interval. †Early neurological deterioration was characterized by an increase of ≥ 2 points in the NIHSS score between baseline and the 72-hour evaluation. ‡All-cause mortality at the 3-month follow-up was derived from a combination of in-hospital mortality and post-discharge mortality. Adjusting factors: age, sex, prior stroke, preexisting dependency, atrial fibrillation, myocardial infarction, congestive heart failure, chronic kidney disease, and history of malignancy. AAR; adjusted absolute risk; ARR: adjusted relative risk; mRS: modified Rankin Scale; NA: not available; NIHSS: National Institutes of Health Stroke Scale.

Table 3: Predictive performance of SHR and HB/RDW in predicting in-hospital mortality (n=345) (continue)

Performance	HB/RDW+	SHR+	SHR+ & HB/RDW+
In-hospital mortality			
AuROC	0.74 (0.68 – 0.80)	0.78 (0.72 – 0.84)	0.78 (0.73 – 0.83)
Sensitivity	76.9 (64.8 – 86.5)	70.8 (58.2 – 81.4)	84.6 (73.5 – 92.4)
Specificity	71.1 (65.4 – 76.3)	85.4 (80.7 – 89.3)	71.8 (66.1 – 77.0)
Positive predictive value	38.2 (29.8 – 47.1)	52.9 (41.9 – 63.7)	41.0 (32.6 – 49.9)
Negative predictive value	93.0 (88.7 – 96.0)	92.6 (88.7 – 95.5)	95.3 (91.5 – 97.8)
Positive likelihood ratio	2.66 (2.12 – 3.34)	4.83 (3.50 – 6.68)	3.00 (2.42 – 3.71)
Negative likelihood ratio	0.32 (0.21 – 0.51)	0.34 (0.23 – 0.50)	0.21 (0.12 – 0.38)
Accuracy	72.2 (67.1 – 76.8)	82.6 (78.2 – 86.5)	74.2 (69.2 – 78.7)
Poor functional outcome at hospital discharge (mRS≥3)			
AuROC	0.66 (0.61 – 0.71)	0.68 (0.63 – 0.73)	0.68 (0.63 – 0.73)
Sensitivity	62.4 (55.6 – 69.0)	63.4 (56.5 – 69.9)	63.8 (57.0 – 70.3)
Specificity	68.9 (60.3 – 76.7)	72.7 (64.3 – 80.1)	72.0 (63.5 – 79.4)
Positive predictive value	76.4 (69.4 – 82.5)	78.9 (72.1 – 84.8)	78.6 (71.7 – 84.5)
Negative predictive value	53.2 (45.4 – 60.9)	55.2 (47.5 – 62.7)	55.2 (47.5 – 62.8)
Positive likelihood ratio	2.01 (1.53 – 2.65)	2.32 (1.73 – 3.13)	2.38 (1.70 – 3.05)
Negative likelihood ratio	0.54 (0.44 – 0.67)	0.50 (0.41 – 0.62)	0.50 (0.41 – 0.62)
Accuracy	64.9 (59.6 – 70.0)	70.0 (61.7 – 71.9)	70.0 (61.7 – 71.9)
Early neurological deterioration			
AuROC	0.63 (0.56 – 0.70)	0.66 (0.59 – 0.73)	0.66 (0.59 – 0.73)
Sensitivity	60.3 (46.6 – 73.0)	58.6 (44.9 – 71.4)	58.6 (44.9 – 71.4)
Specificity	66.2 (60.4 – 71.7)	73.5 (68.0 – 78.5)	73.5 (68.0 – 78.5)
Positive predictive value	26.5 (19.2 – 34.9)	30.9 (22.4 – 40.4)	30.9 (22.4 – 40.4)
Negative predictive value	89.2 (84.2 – 93.0)	89.8 (85.2 – 93.3)	89.8 (85.2 – 93.3)
Positive likelihood ratio	1.79 (1.37 – 2.33)	2.21 (1.66 – 2.96)	2.21 (1.66 – 2.96)
Negative likelihood ratio	0.60 (0.43 – 0.83)	0.56 (0.41 – 0.77)	0.56 (0.41 – 0.77)
Accuracy	65.2 (59.9 – 70.2)	71.0 (65.9 – 75.7)	71.0 (65.9 – 75.7)
3-month mortality			
AuROC	0.62 (0.56 – 0.68)	0.78 (0.73 – 0.83)	0.79 (0.74 – 0.84)
Sensitivity	43.9 (33.0 – 55.3)	74.4 (63.6 – 83.4)	78.0 (67.5 – 86.4)
Specificity	79.8 (74.5 – 84.5)	81.7 (76.5 – 86.2)	79.8 (74.5 – 84.5)
Positive predictive value	40.4 (30.2 – 51.4)	56.0 (41.6 – 65.5)	54.7 (45.2 – 63.9)
Negative predictive value	82.0 (76.8 – 86.5)	91.1 (86.7 – 94.4)	92.1 (87.8 – 95.3)
Positive likelihood ratio	2.18 (1.55 – 3.07)	4.08 (3.06 – 5.42)	3.87 (2.97 – 5.06)
Negative likelihood ratio	0.70 (0.58 – 0.86)	0.31 (0.22 – 0.46)	0.27 (0.18 – 0.42)
Accuracy	71.3 (66.2 – 76.0)	80.0 (75.4 – 84.1)	79.4 (74.8 – 83.6)
3-month poor functional outcome (mRS ≥3)			
AuROC	0.70 (0.65 – 0.75)	0.74 (0.69 – 0.78)	0.74 (0.69 – 0.78)
Sensitivity	75.2 (67.2 – 82.1)	70.2 (61.9 – 77.6)	67.4 (59.0 – 75.0)
Specificity	64.7 (57.7 – 71.3)	77.0 (70.6 – 82.6)	79.9 (73.7 – 85.2)
Positive predictive value	59.6 (52.0 – 66.8)	67.8 (59.6 – 75.3)	69.9 (61.4 – 77.4)
Negative predictive value	79.0 (72.1 – 84.9)	78.9 (72.6 – 84.3)	78.0 (71.8 – 83.4)
Positive likelihood ratio	2.13 (1.73 – 2.62)	3.05 (2.32 – 4.00)	3.35 (2.49 – 4.51)
Negative likelihood ratio	0.38 (0.28 – 0.52)	0.39 (0.30 – 0.50)	0.41 (0.32 – 0.52)
Accuracy	69.0 (63.8 – 73.8)	74.2 (69.2 – 78.7)	74.7 (69.9 – 79.3)
3-month excellent functional (mRS 0-1)			
AuROC	0.66 (0.61 – 0.71)	0.71 (0.66 – 0.75)	0.71 (0.66 – 0.75)
Sensitivity	67.9 (60.2 – 74.9)	67.9 (60.2 – 74.9)	67.3 (59.5 – 74.4)
Specificity	64.4 (57.0 – 74.1)	73.3 (66.2 – 79.6)	74.4 (67.4 – 80.6)
Positive predictive value	63.6 (56.1 – 70.7)	70.0 (62.3 – 77.0)	70.7 (62.9 – 77.7)
Negative predictive value	68.6 (61.1 – 75.5)	71.4 (64.3 – 77.7)	71.3 (64.2 – 77.6)
Positive likelihood ratio	1.91 (1.53 – 2.39)	2.55 (1.95 – 3.31)	2.63 (2.01 – 3.45)
Negative likelihood ratio	0.50 (0.39 – 0.64)	0.44 (0.35 – 0.56)	0.44 (0.35 – 0.56)
Accuracy	66.1 (60.8 – 71.1)	70.7 (65.6 – 75.5)	71.0 (65.9 – 75.7)
3-month functional independent (mRS 0-2)			
AuROC	0.58 (0.54 – 0.63)	0.76 (0.71 – 0.80)	0.76 (0.71 – 0.81)
Sensitivity	81.1 (75.0 – 86.3)	84.6 (78.8 – 89.3)	80.6 (84.4 – 85.8)
Specificity	35.4 (27.6 – 43.8)	66.7 (58.3 – 74.3)	71.5 (63.4 – 78.7)
Positive predictive value	63.7 (57.5 – 69.6)	78.0 (71.9 – 83.3)	79.8 (73.6 – 85.1)
Negative predictive value	57.3 (46.4 – 67.7)	75.6 (67.2 – 82.8)	72.5 (64.4 – 79.7)

Table 3: Predictive performance of SHR and HB/RDW in predicting in-hospital mortality (n=345)

Performance	HB/RDW+	SHR+	SHR+ & HB/RDW+
Positive likelihood ratio	1.26 (1.09 – 1.44)	2.54 (2.00 – 3.22)	2.83 (2.17 – 3.70)
Negative likelihood ratio	0.53 (0.37 – 0.77)	0.23 (0.16 – 0.33)	0.27 (0.20 – 0.37)
Accuracy	62.0 (56.7 – 67.2)	77.1 (72.3 – 81.4)	76.8 (71.9 – 81.2)

Data are presented with 95% confidence intervals. SHR ≥ 1.18 defined as SHR+; HB/RDW ≤ 0.76 defined as HB/RDW+.

AuROC: area under the receiver operating characteristic curve; HB/RDW: hemoglobin-to-red blood cell distribution width ratio; mRS: modified Rankin Scale; SHR: stress hyperglycemia ratio.

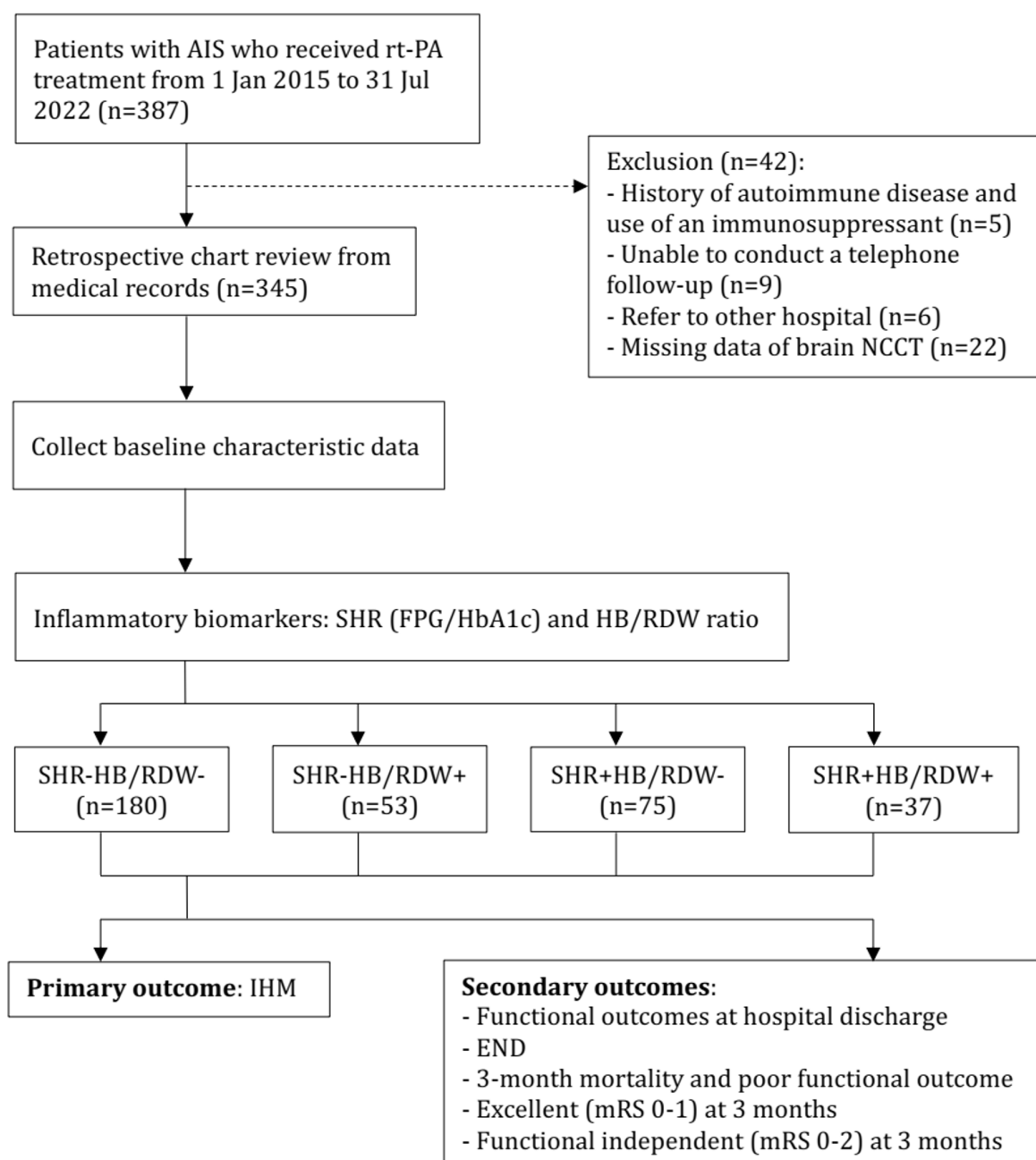


Figure 1: Flow diagram of patients' inclusion. AIS, Acute ischemic stroke; END, early neurological deterioration; FPG, fasting plasma glucose; HB/RDW, hemoglobin to red blood cell distribution width ratio; IHM, In-hospital mortality; mRS, modified Rankin Scale; NCCT, Non-contrast computed tomography; rt-PA, recombinant tissue-Plasminogen activator; SHR, Stress hyperglycemia ratio.

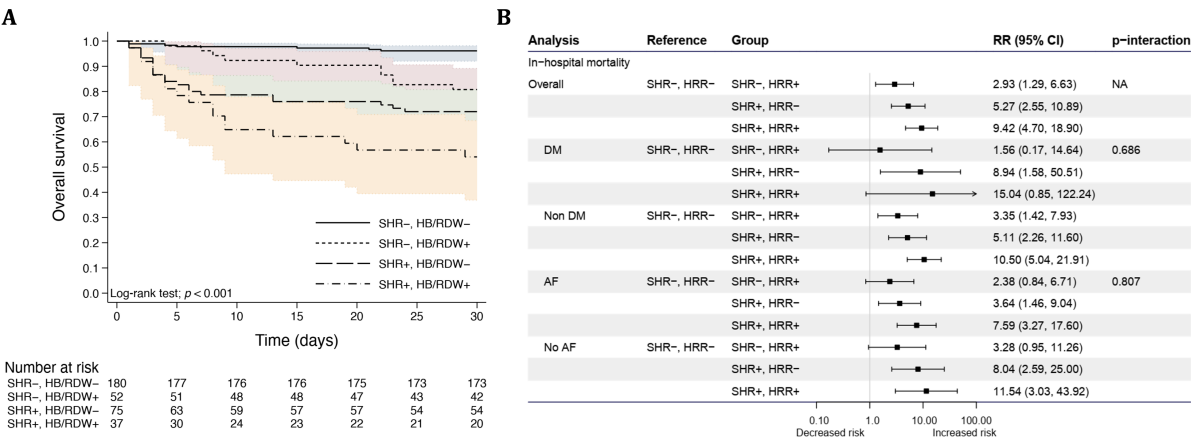


Figure 2: A: Kaplan–Meier of cumulative survival probability (in-hospital mortality outcome) across groups according to SHR and HB/RDW categories (n=344). Note: One patient in SHR-, HB/RDW+ group was excluded from the analysis due to death on the first day of admission, leading to automatic exclusion from the survival analysis. Shaded area represents the 95% confidence interval. B: Subgroup analyses of SHR and HB/RDW and the risk of IHM according to co-existing diabetes mellitus and atrial fibrillation (n=345). SHR-, FPG/HbA1c <1.18; SHR+, FPG/HbA1c ≥1.18; HB/RDW-, HB/RDW ratio >0.76; HB/RDW+, HB/RDW ratio ≤0.76. AF: atrial fibrillation; DM: diabetes mellitus; HB/RDW: hemoglobin to red blood cell distribution width ratio; RR: relative risk; SHR: stress hyperglycemia ratio.

Not elevated SHR and not low HB/RDW (SHR- and HB/RDW-)
Not elevated SHR and low HB/RDW (SHR- and HB/RDW+)
Elevated SHR and not low HB/RDW (SHR+ and HB/RDW-)
Elevated SHR and low HB/RDW (SHR+ and HB/RDW+)

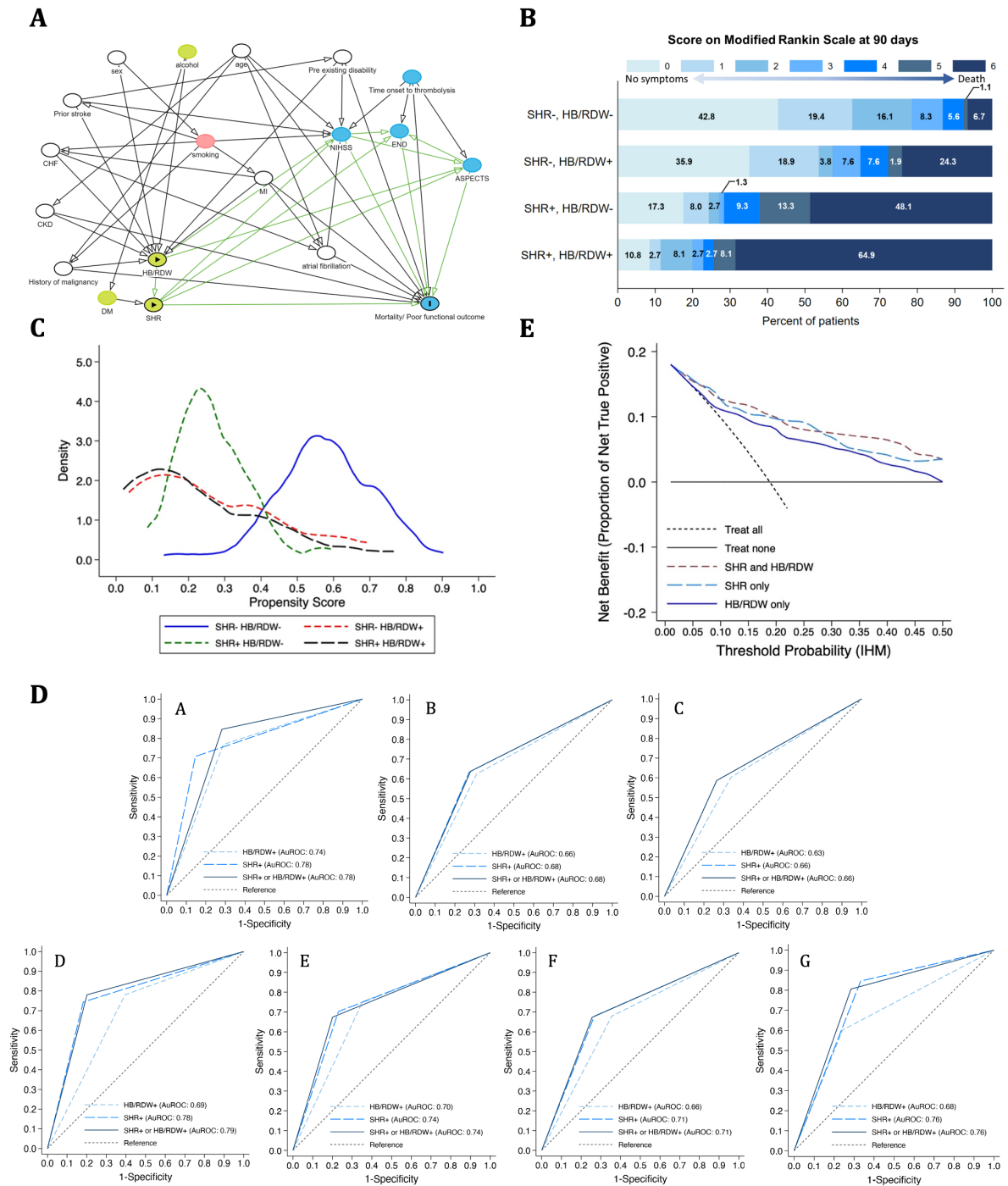


Figure S1: A: Directed acyclic graph for the causal inference between SHR and HB/RDW levels, mortality, and poor functional outcomes among AIS patients receiving rt-PA; B: mRS at 3-month across groups categorized by SHR and HB/RDW levels; C: Propensity score distribution by exposure group; D: ROC curve of the combined SHR ≥ 1.18 and HB/RDW ≤ 0.76 for various stroke outcomes (A: IHM, B: poor functional outcome at hospital discharge [mRS ≥ 3], C: END, D: 3-month mortality, E: 3-month poor functional outcome, F: Excellent functional outcome [mRS 0-1] at 3 months, and G: Functional independence [mRS 0-2] at 3 months); E: Decision curve analysis comparing predictive models for in-hospital mortality. AIS: acute ischemic stroke; END: early neurological deterioration; HB/RDW: hemoglobin-to-red blood cell distribution width ratio; IHM: in-hospital mortality; mRS: modified Rankin Scale; ROC: receiver operating characteristic; rt-PA: recombinant tissue plasminogen activator; SHR: stress hyperglycemia ratio.