Stroke

ORIGINAL CONTRIBUTION

Functional Outcomes of Human Urinary Kallindinogenases in Treatment of Acute Ischemic Stroke

Diandian Huang, MD; Yuxuan Lu, MD; Weiping Sun, MD; Wei Sun, MD; Yongan Sun, MD; Yining Huang, MD; Yijun Song, MD; Liwen Tai, MD; Guozhong Li, MD; Huisheng Chen, MD; Guiru Zhang, MD; Lei Zhang, MD; Xuwen Sun, MD; Jinhua Qiu, MD; Yan Wei, MD; Haiqiang Jin, MD

BACKGROUND: The neurorestorative potential of HUK (human urinary kallidinogenase) has drawn considerable clinical attention. Our study aimed to explore the therapeutic efficacy of HUK in patients with acute ischemic stroke.

METHODS: Our data were retrospectively extracted from CASTOR (Chinese Acute Ischemic Stroke Treatment Outcome Registry), a prospective, multicenter study from 2015 to 2019 in China. The data was separated into 2 categories, the mild group (0–5 points) and the moderate group (6–25 points), according to the National Institutes of Health Stroke Scale score measured at admission and analyzed by propensity score matching with HUK or non-HUK ratio of 1:1. The percentage of patients with modified Rankin Scale score ≤1 at 3 months after onset was the primary outcome.

RESULTS: Ten thousand two patients were recruited, after the criteria were filtered, 9005 patients were investigated. Following propensity score matching, a total of 6530 patients were ultimately enrolled in the analysis, consisting of 4284 patients in the mild group and 2246 patients in the moderate group. In the mild group, the mean age was 63.5±11.7 years, and females accounted for 31.91%. In the moderate group, the mean age was 64.7±10.9 years, and females occupied a proportion of 36.78%. At the 3-month follow-up, a significantly higher proportion of HUK-treated patients achieved the primary outcome compared with controls in both mild (76.89% [1647/2142] versus 74.13% [1588/2142]; *P*=0.0013) and moderate (43.10% [484/1123] versus 38.02% [427/1123]; *P*=0.03) groups.

CONCLUSIONS: HUK therapy has potential efficacy in improving the prognosis of patients with both mild and moderate severity of acute ischemic stroke. Nevertheless, additional rigorously designed randomized controlled trials are essential to substantiate these findings.

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GRAPHIC ABSTRACT: A graphic abstract is available for this article.

Key Words: antioxidants ■ dementia ■ prognosis ■ quality of life ■ thrombectomy

As the second most common cause of mortality and disability worldwide, stroke is responsible for ≈6.55 million deaths and 143 million disability-adjusted life years annually.[1] A cross-sectional study conducted in China revealed that 17.8 million individuals were affected by stroke, including 3.4 million new cases and 2.3 million deaths.[2] Acute ischemic stroke (AIS), the most common subtype, accounts for 60% to 80% of all stroke cases and is the primary contributor to stroke-related mortality.[3]

Despite advancements in therapeutic approaches, the most effective treatment strategies for AIS are intravenous thrombolysis and mechanical thrombectomy.

Correspondence to: Haiqiang Jin, MD, Department of Neurology, Peking University First Hospital, Xicheng District, XishiKu St, No. 8, Beijing 100034, China. Email jhq911@bjmu.edu.cn

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Nonstandard Abbreviations and Acronyms

AE	adverse event
AIS	acute ischemic stroke
CASTOR	Chinese Acute Ischemic Stroke Treatment Outcome Registry
HUK	human urinary kallidinogenase
MMSE	mini-mental state examination
mRS	modified Rankin Scale
NIHSS	National Institutes of Health Stroke Scale
PSCI	poststroke cognitive impairment
PSM	propensity score matching
QALY	quality-adjusted life year
QoL	quality of life

However, these interventions are limited by strict time windows and procedural complexities.[4–6] Efforts to develop other acute-phase treatments, such as neuroprotective agents and therapies aimed at enhancing collateral circulation, have been largely insufficiently validated.[7] Consequently, identifying alternative treatments for AIS remains a critical area of research.

HUK (human urinary kallidinogenase), a relatively novel tissue-type kininogenase,[8] has attracted attention for its multitargeted neuroprotective and reparative effects, including antioxidant, anti-inflammatory, and nerve regeneration-promoting properties.[9] The clinical efficacy of HUK in treating AIS remains a topic of debate. Previous studies with small sample sizes, inconsistent disease severity classifications, nonmulticenter designs, and single-time point assessments have yielded inconsistent conclusions.[10,11] Studies with over 1000 participants are scarce, with the notable exceptions being the RESK study[12] and investigations derived from the DEVT and RESCUE BT trials focusing on patients with AIS with large vessel occlusion.[13] However, the RESK study primarily concentrated on the incidence of adverse events (AEs), and its inclusion criteria were restricted to patients with National Institutes of Health Stroke Scale (NIHSS) scores ranging from 6 to 25. Similarly, studies on patients with AIS with large vessel occlusion enrolled participants with NIHSS scores between 12 and 20. Although the prescribing guidelines for HUK recommend its use for mild to moderate AIS, real-world evidence on its effectiveness, particularly in patients with mild stroke (NIHSS scores, 0–5), remains insufficient.

This discrepancy highlights the necessary for further study to evaluate HUK's efficacy across a broader spectrum of stroke severities. A prospective, multicenter, real-world study involving a large cohort with well-defined stroke severity classifications is essential to validate its therapeutic potential and provide potent evidence for optimizing AIS management strategies. To address this, our study extended its scope to include patients with mild stroke, aiming to comprehensively assess the efficacy and safety of HUK in a more diverse patient population.

METHODS

Data Availability Statement

The data that support the findings of this study are available from the corresponding author on reasonable request.

Study Design

This study retrospectively extracted data from the database of the CASTOR (Chinese Acute Ischemic Stroke Treatment Outcome Registry), which is a multicenter registry study involving 80 hospitals (including 40 tertiary hospitals) in China lasting from September 2015 to September 2019. The detailed information of this study has been published previously.[14] The study protocol was approved by the Ethics Committee of Peking University First Hospital (institutional review board approval number: 2015[922]). All patients or their suitable relatives provided written informed consent. Every procedure was executed in compliance with the Declaration of Helsinki and the ICH GCP. The study was reported according to the STROBE statement. All data were collected via electronic case report forms and an online electronic data capture system, following standard clinical routines. Before the implementation of this study, local clinicians at each participating center reported follow-up data, which were then recorded by CASTOR investigators using the electronic data capture system. To maintain methodological rigor, all evaluators received comprehensive standardized training before data collection, ensuring high interobserver agreement in the application of study rating criteria.

Patient Eligibility Criteria

The requirements for patient enrollment in the CASTOR study were as follows: (1) patients >18 years were diagnosed as AIS according to the Chinese Guidelines for the Diagnosis and Treatment of Acute Ischemic Stroke (2014),[15] (2) admission to the hospital within 1 week after the onset of AIS, and (3) consent to engage in this study. The exclusion criteria were as follows: (1) patients with cerebral hemorrhage verified by cranial computerized tomography or magnetic resonance imaging, and (2) patients with a predicted survival of less than 3 months and complicated by severe systemic diseases. Due to contraindications to HUK, patients taking angiotensin-converting enzyme inhibitors were filtered in our analysis.[12,16] Patients who underwent intravenous thrombolysis or mechanical thrombectomy were also excluded. In our study, since NIHSS scores were critical for classifying patients into mild, moderate, or severe groups, we excluded cases with missing NIHSS data at admission or discharge. According to the severity measured by the NIHSS score at admission (mild, 0–5; moderate, 6–25; and severe, ≥26),[17] the mild group (n=5765) and the moderate group (n=3180) were screened. The inclusion and exclusion criteria and patient filtering flow chart are shown in Figure 1.

Descriptions of the Variables

Patients with AIS were investigated at admission, at discharge, and 3 months after stroke onset. The modified

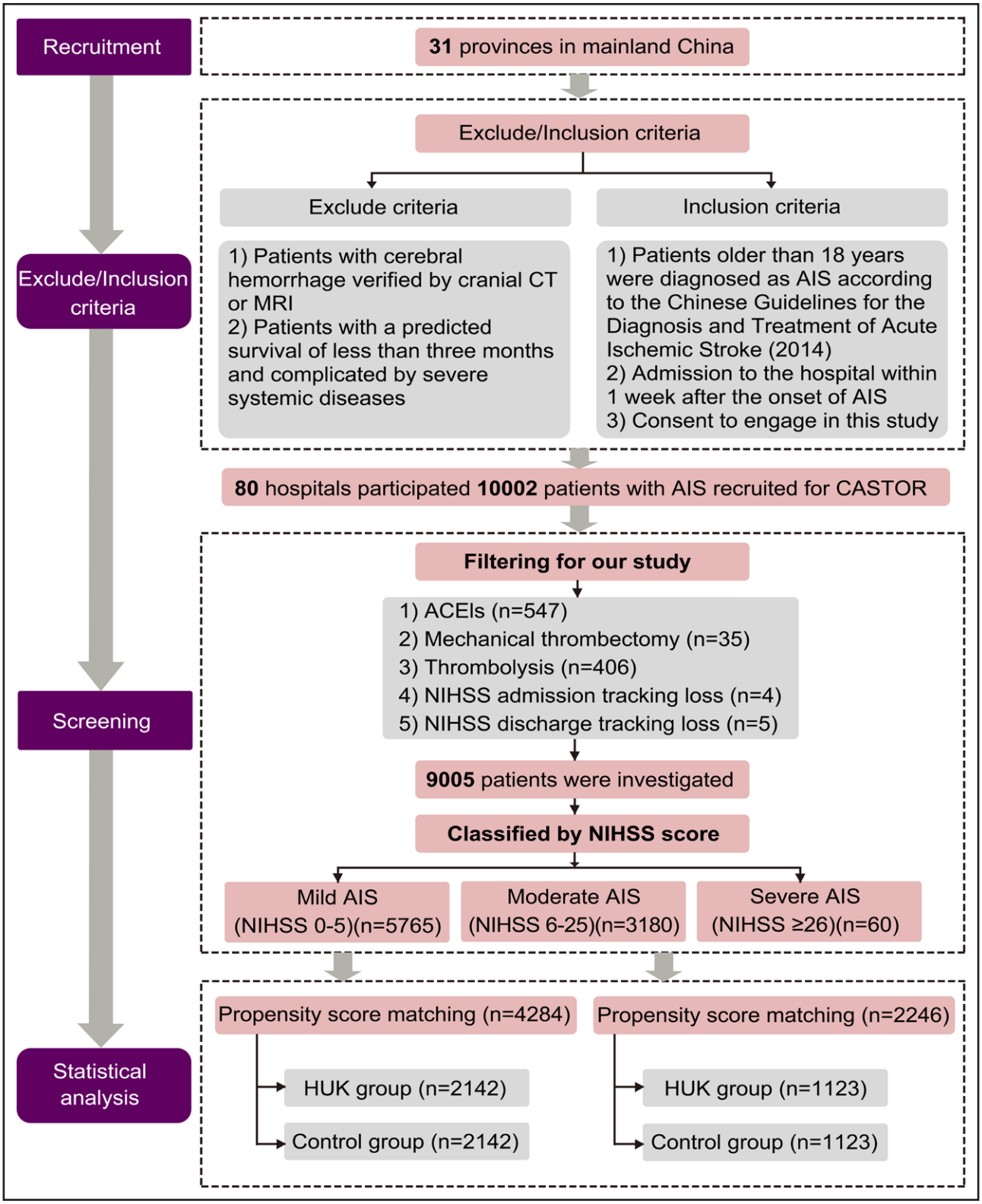

Figure 1. The flow chart of the study.
The inclusion and exclusion criteria of CASTOR (Chinese Acute Ischemic Stroke Treatment Outcome Registry) and the category criterion for the study. ACEI indicates angiotensin-converting enzyme inhibitor; AIS, acute ischemic stroke; CT, computed tomography; HUK, human urinary kallidinogenase; MRI, magnetic resonance imaging; and NIHSS, National Institutes of Health Stroke Scale.

Rankin Scale (mRS) score and EuroQol 5-dimensional score were evaluated at admission and at the 3-month follow-up. The NIHSS scores were only recorded at admission and discharge. The mini-mental state examination (MMSE) score was recorded at 3 months after stroke onset (Figure S1). The MMSE, which has been translated into Chinese and validated as a reliable screening instrument for cognitive impairment within the Chinese population, has a maximum score of 30. Patients with MMSE scores <27 points at the 3-month follow-up after AIS were defined as poststroke cognitive impairment (PSCI),[18,19] whereas those with MMSE scores ranging from 0 to 22 were defined as having poststroke dementia (Table S1).

Quality of life, as measured by the EuroQol 5-dimensional score, is a descriptive measure of mobility, self-care, usual activities, pain or discomfort, and anxiety or depression, with 3 levels for each dimension: no problems, some problems, and extreme problems.[20] The detailed EuroQol 5-dimensional measurements are shown in Tables S2 and S3. The calculation of quality-adjusted life years (QALYs) was based on values of the EuroQol 5-dimensional score at 2 time points—admission and 3 months after stroke onset. The QALY values were derived by applying the time required for a quality of life improvement as the weighting factor.[21]

The percentage of patients with an mRS score ≤1 at 3 months after onset was the primary outcome. The secondary outcomes were as follows: the proportion of patients with mRS score ≤2 at 3 months after disease onset; the proportion of patients with NIHSS score decreased at least 4 points between baseline and discharge; the proportion of patients with NIHSS score increased by ≥4 points, 3 points, 2 points, or 1 point between baseline and discharge; the QALYs at admission and the 3 month reinvestigation and the MMSE score at the 3-month follow-up.

Treatment

All enrolled patients received standard treatment in accordance with current stroke guidelines.[15] Participants were stratified into 2 groups based on their exposure to HUK: the HUK-treated group and the non-HUK-treated group (control group). The decision to administer HUK was made at the discretion of the treating physician, guided by clinical indications and patient-specific considerations. HUK (TECHPOOL BIO-PHARMA Co, Ltd) was intravenously infused within 48 hours of symptom onset. There was no stratified design for dosage differences. Based on the recommended dosage provided in the product instructions, the fixed dose consisted of 0.15 PNA units dissolved in 250 mL of sodium chloride, was administered intravenously over 60 minutes per day consecutively for at least 14 days.

Imaging Classification and Interpretation

Based on the imaging findings of the infarct location, patients were categorized into 3 types: anterior circulation infarction, posterior circulation infarction, and undefined location. Anterior circulation infarction was identified by lesions in regions supplied by the anterior cerebral artery, middle cerebral artery, or internal carotid artery. Posterior circulation infarction was defined as lesions supplied by the posterior cerebral artery, cerebellar arteries, basilar artery, or vertebral artery. Besides, cases that did not meet these criteria and those with involvement of both anterior circulation infarction and posterior circulation infarction territories were classified as undefined locations (Tables 1 and 2).[22]

Insurance Status and Regional Distribution

Patients' insurance status was categorized into 6 categories: self-payment, urban employee basic medical insurance, public medical care, new rural cooperative medical schema, commercial insurance, and urban resident basic medical insurance. Geographically, patients were divided into 4 groups: the eastern China, the northeastern China, the central China, and the western China (Tables 1 and 2; Table S4).[23]

PSM Process

A propensity score matching (PSM) process was introduced in our study to simulate randomized controlled trials. A multivariable logistic regression model was applied to determine the propensity scores for each item based on the following covariates factors: age, sex, clinical history of previous stroke, hypertension, diabetes, dyslipidemia, atrial fibrillation, coronary heart disease, concomitant treatment (antiplatelet, anticoagulant, antihypertensive, antidiabetic, statin-lipid-lowering), socioeconomic status (represented as the insurance status), regional distribution, imaging classification and ratio of patients with mRS scores ≤2 at admission for the mild and moderate groups separately. A 1-to-1 matching procedure was conducted using the nearest neighbor method without replacement. The caliper width was chosen at 0.02 of the logit SD of the propensity score. The postmatching diagnostic results indicate that the common support plot, kernel density plot, and standardized mean difference plot all exhibit favorable outcomes, suggesting that the matching process was highly effective in the supplement (Figures S2 through S4).

Statistical Analysis

SAS statistical software (version 9.4, SAS Institute) and Stata/MP 18.0 (StataCorp LLC, College Station, TX) were used for statistical analyses. Categorical variables are presented as frequencies and proportions, whereas continuous variables are presented as the means±SD. Appropriate summary statistics were computed for each variable in accordance with the data type. The Kolmogorov–Smirnov test was used to determine normalcy. The Wilcoxon rank test was used for ordinal or nonparametric data related to the baseline characteristics, whereas the Student *t* test and Pearson χ^2 test were used for statistical analyses of normally distributed continuous data. The Newcombe–Wilson scoring technique was used to estimate the variations in the proportions of the bivariate results between the groups and the corresponding 95% CIs.[24]

Logistic regression analysis and odds ratios were used to evaluate the primary and secondary outcomes. A generalized linear model with a logarithmic connection was used to calculate the relative risk. Additionally, numerous predetermined subgroups (including age, sex, clinical history, concomitant treatment, socioeconomic status, regional distributions, and imaging classification) were examined for treatment effects (primary outcome). $P<0.05$ was considered statistically significant, and

Table 1. Baseline Characteristics of Patients With AIS Before and After PSM for Mild Classification in the HUK and Control Group

Characteristics, n, (%)	Unmatched (n=5765)			Matched (n=4284)		
	Control group(n=2673)	HUK group (n=3092)	*P* value	Control group (n=2142)	HUK group (n=2142)	*P* value
Sex, female/male (%)	886/1787 (33.14)	984/2108 (31.82)	0.28	693/1449 (32.35)	674/1468 (31.47)	0.53
Age, mean±SD	61.7±11.7	66.0±11.9	0.01*	63.1±11.5	64.2±10.1	0.22
<65 y	1598 (59.78)	1667 (53.91)		1202 (56.12)	1228 (57.33)	
≥65 y	1075 (40.22)	1425 (46.09)		940 (43.88)	914 (42.67)	
History, n (%)						
Previous stroke	604 (22.60)	645 (20.86)	0.11	449 (20.96)	490 (22.88)	0.05
Hypertension	1672 (62.55)	1921 (62.13)	0.74	1334 (62.28)	1329 (62.04)	0.87
Diabetes	704 (26.34)	738 (23.87)	0.03*	543 (25.35)	587 (27.40)	0.12
Dyslipidemia	66 (2.47)	134 (4.33)	0.01*	64 (2.99)	77 (3.59)	0.26
CHD	350 (13.09)	357 (11.55)	0.07	263 (12.28)	282 (13.17)	0.38
AF	68 (2.54)	94 (3.04)	0.25	58 (2.71)	64 (2.99)	0.58
Region distribution			<0.001*			0.81
Eastern China	1156 (43.25)	1620 (52.39)		1142 (53.31)	1132 (52.85)	
Northeast China	1045 (39.09)	519 (16.78)		533 (24.89)	519 (24.23)	
Central China	441 (16.50)	652 (21.09)		436 (20.35)	461 (21.52)	
Western China	31 (1.16)	301 (9.74)		31 (1.45)	30 (1.40)	
Concomitant agents						
Antiplatelet	2652 (99.21)	3077 (99.51)	0.14	2129 (99.39)	2128 (99.35)	0.84
Anticoagulant	334 (12.50)	316 (10.22)	<0.001*	234 (10.92)	249 (11.62)	0.46
Antihypertensive	1672 (62.55)	1921 (62.13)	0.74	980 (45.75)	970 (45.28)	0.75
Antidiabetic	796 (29.78)	829 (26.81)	0.01*	652 (30.44)	680 (31.75)	0.35
Statin-lipid-lowering	1841 (68.87)	2041 (66.01)	0.02*	1491 (69.61)	1483 (69.23)	0.79
Insurance			<0.001*			0.61
self-payment	445 (16.65)	512 (16.56)		345 (16.11)	349 (16.29)	
UEBMI	1179 (44.11)	1214 (39.26)		874 (40.80)	841 (39.27)	
PMC	8 (0.30)	56 (1.81)		8 (0.37)	37 (1.73)	
NRCMS	441 (16.50)	661 (21.38)		385 (17.97)	467 (21.80)	
CI	86 (3.22)	8 (0.26)		84 (3.93)	5 (0.23)	
URBMI	514 (19.22)	641 (20.73)		446 (20.82)	443 (20.68)	
Imaging classification			<0.001*			0.12
ACI	1613 (60.34)	1981 (64.07)		1405 (65.59)	1346 (62.84)	
PCI	429 (16.05)	557 (18.01)		337 (15.73)	348 (16.25)	
Undefined	631 (23.61)	554 (17.92)		400 (18.68)	448 (20.91)	
mRS score ≤2 at admission	2109 (78.90)	2514 (81.31)	0.02*	1758 (82.07)	1722 (80.39)	0.05

The data are presented as the mean±SD, n (%). Covariates matched by PSM included age, sex, clinical history of previous stroke, hypertension, diabetes, dyslipidemia, atrial fibrillation, coronary heart disease, imaging classification and ratio of patients with mRS score ≤2 at admission and the concomitant treatment (antiplatelet, anticoagulant, antihypertensive, antidiabetic, statin-lipid-lowering), the socioeconomic status (represented as the insurance status), and regional difference. ACI indicates anterior circulation infarction; AF, atrial fibrillation; AIS, acute ischemic stroke; CHD, coronary heart disease; CI, commercial insurance; HUK, human urinary kallidinogenase; mRS, modified Rankin Scale; NRCMS, new rural cooperative medical schema; PCI, posterior circulation infarction; PMC, public medical care; PSM, propensity score matching; UEBMI, urban employee basic medical insurance; and URBMI, urban resident basic medical insurance.

*$P<0.05$.

all statistical experiments were conducted via 2-sided tests. The hospital variable was incorporated as a random effect in the final multivariate model to address the clustering effect at the multicenter level.

Missing Data

Patients with missing values were retained to minimize bias and the loss of statistical power that could have been introduced

Table 2. Baseline Characteristics of Patients With AIS Before and After PSM for Moderate Classification in the HUK and Control Group

Characteristics, n (%)	Unmatched (n=3180)			Matched (n=2246)		
	Control group (n=1269)	HUK group (n=1911)	*P* value	Control group (n=1123)	HUK group (n=1123)	*P* value
Sex, female/male (%)	486/783 (38.30)	695/1216 (36.37)	0.27	430/693 (38.29)	396/727 (35.26)	0.13
Age, mean±SD	67.4±12.0	63.4±10.1	0.02*	64.0±11.1	64.8±10.9	0.61
<65 y	630 (49.64)	998 (52.22)		592 (52.71)	580 (51.65)	
≥65 y	639 (50.36)	913 (47.78)		531 (47.29)	543 (48.35)	
History, n (%)						
Previous stroke	345 (27.19)	473 (24.75)	0.12	312 (27.78)	273 (24.31)	0.06
Hypertension	804 (63.36)	1227 (64.21)	0.62	729 (64.92)	710 (63.22)	0.40
Diabetes	329 (25.93)	502 (26.27)	0.82	295 (26.27)	278 (24.76)	0.41
Dyslipidemia	49 (3.86)	36 (1.88)	0.00*	37 (3.29)	29 (2.58)	0.31
CHD	181 (14.26)	291 (15.23)	0.45	168 (14.96)	162 (14.43)	0.72
AF	75 (5.91)	101 (5.29)	0.45	66 (5.88)	57 (5.08)	0.40
Region distribution			<0.001*			0.67
Eastern China	606 (47.75)	1012 (52.96)		601 (53.52)	582 (51.83)	
Northeast China	186 (14.66)	516 (27.00)		186 (16.56)	169 (15.05)	
Central China	312 (24.59)	347 (18.16)		304 (27.07)	336 (29.92)	
Western China	165 (13.00)	36 (1.88)		32 (2.85)	36 (3.21)	
Concomitant agents						
Antiplatelet	1250 (98.50)	1880 (98.38)	0.78	1104 (98.31)	1109 (98.75)	0.38
Anticoagulant	217 (17.10)	339 (17.74)	0.64	204 (18.17)	192 (17.10)	0.50
Antihypertensive	569 (44.84)	823 (43.07)	0.32	491 (43.72)	499 (44.43)	0.73
Antidiabetic	393 (30.97)	621 (32.50)	0.36	360 (32.06)	333 (29.65)	0.21
Statin-lipid-lowering	856 (67.45)	1357 (71.01)	0.03*	778 (69.28)	783 (69.72)	0.81
Insurance			<0.001*			0.73
Self-payment	242 (19.08)	392 (20.51)		198 (17.63)	233 (20.75)	
UEBMI	472 (37.19)	633 (33.13)		421 (37.49)	390 (34.73)	
PMC	17 (1.34)	5 (0.26)		17 (1.51)	3 (0.27)	
NRCMS	323 (25.45)	444 (23.23)		289 (25.74)	275 (24.49)	
CI	10 (0.79)	38 (1.99)		10 (0.89)	29 (2.58)	
URBMI	205 (16.15)	399 (20.88)		188 (16.74)	193 (17.18)	
Imaging classification			<0.001*			0.78
ACI	1027 (80.93)	1473 (77.08)		937 (83.44)	941 (83.79)	
PCI	132 (10.40)	293 (15.33)		100 (8.90)	104 (9.26)	
Undefined	110 (8.67)	145 (7.59)		86 (7.66)	78 (6.95)	
mRS score ≤2 at admission	307 (24.19)	264 (13.81)	<0.001*	233 (20.75)	270 (24.04)	0.06

The data are presented as the mean±SD, n (%). Covariates matched by PSM included age, sex, clinical history of previous stroke, hypertension, diabetes, dyslipidemia, atrial fibrillation, coronary heart disease, imaging classification and ratio of patients with mRS score ≤2 at admission and the concomitant treatment (antiplatelet, anticoagulant, antihypertensive, antidiabetic, statin-lipid-lowering), the socioeconomic status (represented as the insurance status) and regional difference. ACI indicates anterior circulation infarction; AF, atrial fibrillation; AIS, acute ischemic stroke; CHD, coronary heart disease; CI, commercial insurance; HUK, human urinary kallidinogenase; mRS, modified Rankin Scale; NRCMS, new rural cooperative medical schema; PCI, posterior circulation infarction; PMC, public medical care; PSM, propensity score matching; UEBMI, urban employee basic medical insurance; and URBMI, urban resident basic medical insurance.

*$P<0.05$.

by patient exclusion (including mRS and QALYs at day 90). To handle missing data, we employed multiple imputation using chained equations. Fifty imputed data sets were produced using this method; each data set was generated via 5 iterations of the imputation procedure. Our methodology for imputation was tailored to each variable: we employed predictive mean matching for continuous variables, logistic regression for binary variables, and polynomial regression for categorical variables. Missing data on the primary and secondary outcomes were addressed using the last observation carried forward method

and the multiple imputation technique in the sensitivity analysis (Tables S5 and S6).

RESULTS

Baseline Characteristics

A total of 10 002 patients with AIS were recruited. A total of 547 patients treated with angiotensin-converting enzyme inhibitors, 406 patients treated with thrombolysis, and 35 patients treated with mechanical thrombectomy were excluded. In addition, 9 patients with NIHSS tracking loss were excluded. After PSM, the final cohort comprised 4284 patients in the mild group (HUK: n=2142; control: n=2142) and 2246 patients in the moderate group (HUK: n=1123; control: n=1123). After PSM, no statistically significant difference was observed between the matched HUK group and the control group in terms of age, sex, clinical history, regional distribution, insurance status, concomitant treatment, imaging classification, or ratio of patients with mRS scores ≤2 at hospital admission among patients in both mild and moderate groups (P>0.05).

In the mild group, females accounted for 32.35% (693/2142) and 31.47% (674/2142; control and HUK), whereas in the moderate group, 38.29% (430/1123) and 35.26% (396/1123) in the control and HUK groups, respectively. Among concomitant medications, the proportion of patients taking antiplatelet agents was the highest (mild group: 99.39% [2129/2142] in the control group and 99.35% [2128/2142] in the HUK group; moderate group: 98.31% [1104/1123] in the control group and 98.75% [1109/1123] in the HUK group). Geographically, patients predominantly resided in eastern China (mild group: 53.31% [1142/2142] in the control group and 52.85% [1132/2142] in the HUK group; moderate group: 53.52% [601/1123] in the control group and 51.83% [582/1123] in the HUK group). In terms of image classification in the mild group, anterior circulation infarction accounted for 65.59% (1405/2142) and 62.84% (1346/2142) in the control and HUK group, respectively. Besides, a similar proportion was observed in the moderate group (control for 83.44% [937/1123] and HUK for 83.79% [941/1123]). Regarding insurance coverage, urban employee basic medical insurance, new rural cooperative medical schema, commercial insurance, and urban resident basic medical insurance collectively accounted for ≈80% of the participants in each group. All the baseline presentation was indicated in Tables 1 and 2. The mRS scores at admission and at 3 months of follow-up between the groups are shown in Figure 2.

Efficacy Outcomes

At 3-month follow-up, the proportion of patients achieving the primary outcome (mRS score ≤1) was significantly higher in the HUK group compared with control group for both mild subgroup (76.89% [1647/2142] versus 74.13% [1588/2142]; P=0.0013) and moderate subgroup (43.10% [484/1123] versus 38.02% [427/1123]; P=0.03), demonstrating statistically superior efficacy of HUK therapy across severity strata (Tables 3 and 4). Furthermore, when assessing favorable functional outcome (defined as mRS score ≤2), HUK group showed significantly higher rates than that of the control group in both mild (87.25% [1869/2142] versus 85.90% [1840/2142]; P=0.0012) and moderate (68.12% [765/1123] versus 57.52% [646/1123]; P<0.001) severity subgroups (Tables 3 and 4).

The comparison of QALYs values at 3 month reinvestigation revealed that patients in HUK group exhibited significantly greater improvements in quality of life than those in control group, both in patients with mild (HUK, 0.89±0.17; control, 0.86±0.19; P=0.0033; Table 3) and moderate severity (HUK, 0.71±0.20; control, 0.66±0.25; P<0.001; Table 4), at 3-month follow-up. The sensitivity analysis yielded similar results (P<0.001 and P<0.001, respectively; Tables S5 and S6).

In terms of cognitive function, no statistically significant difference was observed between control and HUK groups among patients with mild and moderate stroke severities (P=0.46 and P=0.86, respectively; Tables 3 and 4). Interestingly, a statistically significant difference was observed in the incidence of PSCI for patients with mild stroke severity in the HUK group (P=0.02). However, no statistically significant difference was observed in PSCI or poststroke dementia for patients with moderate stroke severity or in poststroke dementia for patients with mild stroke severity (P=0.05, P=0.35, and P=0.84, respectively; Table S1).

Subgroup analysis of patients indicated no significant difference in the comparable efficacy (P>0.05; Figures 3 and 4).

Safety Analysis

The overall incidence of treatment-emergent AEs was 44.64% (2915/6530). AE severity was categorized into 3 levels: mild, 66.96% (1952/2915); moderate, 25.04% (730/2915); and severe, 7.99% (233/2915). The commonly reported AEs (defined as ≥2% incidence) included hyperlipidemia (4.07%, 266/6530), hyperhomocysteinemia (2.94%, 192/6530), constipation (2.41%, 158/6530), hypokalemia (2.25%, 147/6530), fever (2.22%, 145/6530) and pulmonary infection (2.21%, 144/6530) in all patients (Table S7). For the terms of serious AEs, there was no statistically significant difference detected between control and HUK groups in both mild and moderate groups (P=0.79 and P=0.69, respectively; Tables 3 and 4). Only 2 cases, specifically facial flushing (1 patient) and intracranial hemorrhage transformation (1 patient), were determined to be related to

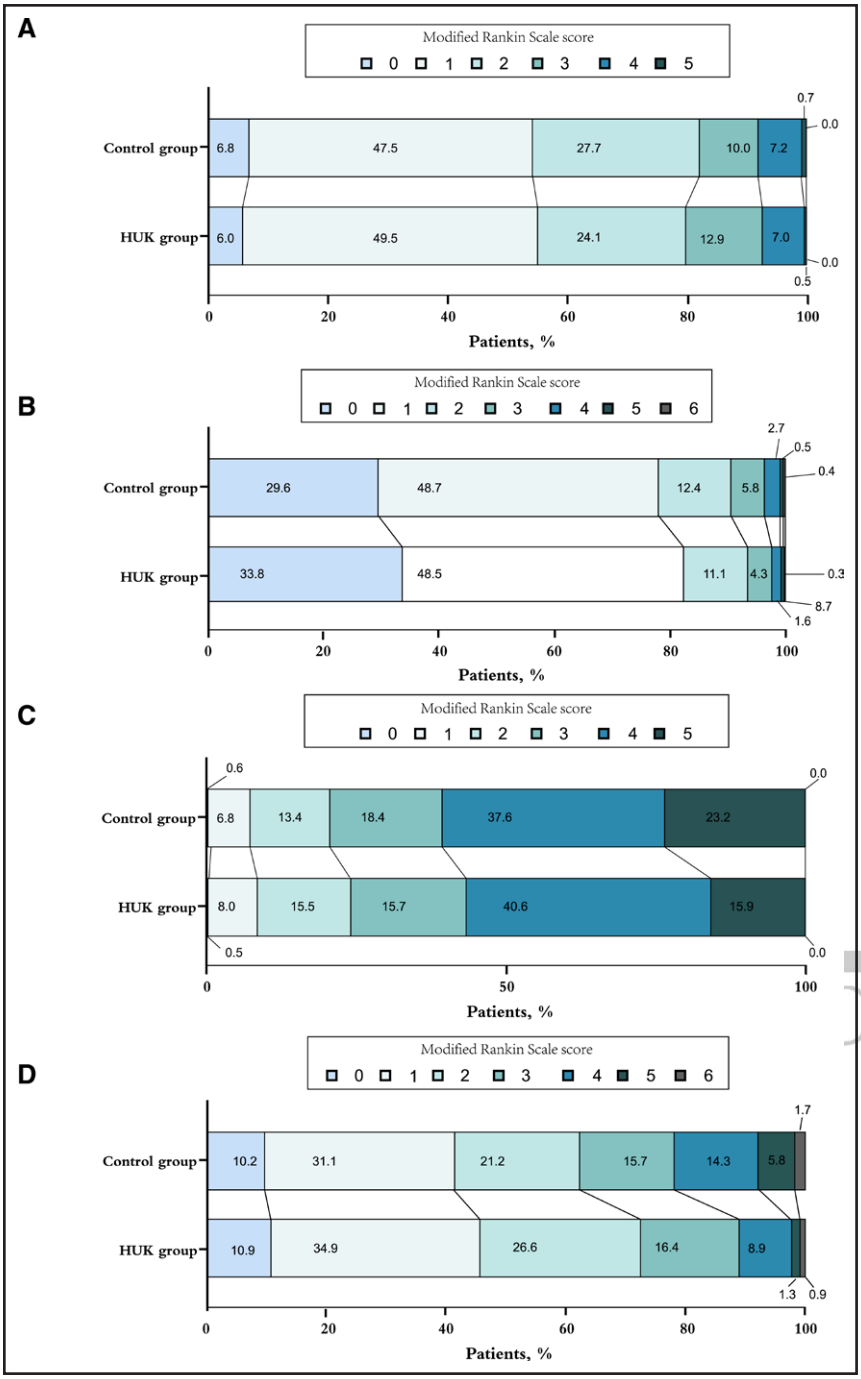

Figure 2. Distribution of magnetic Rankin Scale (mRS) scores in control and HUK (human urinary kallidinogenase) group at admission and 3 months of follow-up.
A, The mRS score distribution at admission between the HUK and control groups in mild classification. **B**, The mRS score distribution at 3 months between the HUK and control groups in mild classification. **C**, The mRS score distribution at admission between the HUK and control groups in moderate classification. **D**, The mRS score distribution at 3 months between the HUK and control groups in moderate classification. The mRS score ranges from 0 (no symptoms or complete recovery) to 6 (death). Each cell corresponds to a score on the mRS; the width of the cell indicates the proportion of patients with equivalent scores. The percentage of patients in each category is shown within the cell.

the study medication, both of which completely resolved after symptomatic treatment.

DISCUSSION

Our study revealed that HUK may improve the functional outcomes of patients with AIS with both mild and moderate severity, as evidenced by the proportion of patients attaining encouraging neurofunctional results compared with those in the control group.

In China, HUK has been approved exclusively for patients with AIS of mild to moderate severity. Previous studies have focused predominantly on a single NIHSS classification or, in some cases, omitted detailed descriptions of stroke severity.[12,13] In a phase III trial of 480 patients with ischemic stroke without an exact NIHSS score classification, HUK was also proven to be effective at the 21-day evaluation.[25] Furthermore, a previous study reported its therapeutic efficacy in combination with butylphthalide for patients with chronic cerebral circulation insufficiency without a clear classification of the NIHSS score.[26] However, accumulating data support the possibility that HUK could be effective across a more extensive continuum of stroke severity. Xie

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Table 3. Efficacy Outcomes of Mild Classification After PSM Between the HUK Group and the Control Group

	HUK group (n=2142)	Control group (n=2142)	RD (95% CI)	OR (95% CI)	RR (95% CI)	*P* value
Primary outcome						
mRS score ≤1 at day 90, N (%)	1647 (76.89)	1588 (74.13)	4.08 (1.62–6.54)	1.29 (1.11–1.51)	1.05 (1.02–1.08)	0.0013*
Secondary outcomes						
mRS score ≤2 at day 90, N (%)	1869 (87.25)	1840 (85.90)	2.76 (1.08–4.45)	1.46 (1.16–1.84)	1.03 (1.01–1.05)	0.0012*
QALY at admission, mean±SD	0.68±0.18	0.69±0.19	…	…	…	0.61
QALY at day 90, mean±SD	0.89±0.17	0.86±0.19	…	…	…	0.0033*
MMSE	24.99±8.68	24.80±8.71	…	…	…	0.46
NIHSS score change of ≤−4 from baseline to discharge, N (%)	48 (2.24)	73 (3.40)	−1.90 (−3.72 to −0.1)	0.67 (0.46–0.98)	0.69 (0.48–0.98)	0.03*
NIHSS score change of ≥4 from baseline to discharge, N (%)	110 (5.13)	112 (5.22)	0.23 (−2.16 to 2.62)	1.03 (0.78–1.35)	1.02 (0.80–1.32)	0.84
NIHSS score change of ≥3 from baseline to discharge, N (%)	173 (8.07)	186 (8.68)	−0.46 (−3.38 to 2.48)	0.97 (0.77–1.21)	0.97 (0.80–1.17)	0.75
NIHSS score change of ≥2 from baseline to discharge, N (%)	364 (16.99)	360 (16.80)	1.31 (−2.46 to 5.07)	1.06 (0.89–1.27)	1.04 (0.92–1.18)	0.49
NIHSS score change of ≥1 from baseline to discharge, N (%)	461 (21.52)	471 (21.98)	0.82 (−3.16 to 4.8)	1.04 (0.88–1.22)	1.02 (0.92–1.13)	0.68
SAE, N (%)	68 (3.17)	71 (3.31)	−0.14 (−1.21 to 0.93)	0.96 (0.68–1.33)	0.96 (0.69–1.33)	0.79

HUK indicates human urinary kallidinogenase; MMSE, mini-mental state examination; mRS, modified Rankin Scale; NIHSS, National Institutes of Health Stroke Scale; OR, odds ratio; PSM, propensity score matching; QALY, quality-adjusted life years; RD, risk difference; RR, relative risk; and SAE, serious adverse events.
*$P<0.05$.

et al[10] reported that HUK could improve the prognosis of patients with NIHSS scores ranging from 0 to 25 at 3 months after onset. These findings gain particular significance in terms of the mild disease severity of AIS. Cohort studies revealed that ≈30% of patients with mild AIS experienced functional deficits at 3 months after stroke onset, despite presenting with nonsevere disability at admission.[27] Notably, the probability of a significant improvement was 17% at 3 months after stroke onset among patients with mild stroke, supporting the hypothesis that patients with mild stroke may have greater potential for functional recovery than patients

Table 4. Efficacy Outcomes of Moderate Classification After PSM Between the HUK Group and the Control Group

Outcomes	HUK group (n=1123)	Control group (n=1123)	RD (95% CI)	OR (95% CI)	RR (95% CI)	*P* value
Primary outcome						
mRS score ≤1 at day 90, N (%)	484 (43.10)	427 (38.02)	4.54 (0.31–8.74)	1.20 (1.01–1.43)	1.11 (1.01–1.22)	0.03*
Secondary outcomes						
mRS score ≤2 at day 90, N (%)	765 (68.12)	646 (57.52)	9.97 (5.98–13.91)	1.58 (1.31–1.90)	1.16 (1.09–1.23)	<0.001*
QALY at admission, mean±SD	0.67±0.20	0.68±0.20	…	…	…	0.92
QALY at day 90, mean±SD	0.71±0.20	0.66±0.25	…	…	…	<0.001*
MMSE	24.78±8.99	24.84±8.81	…	…	…	0.86
NIHSS score change of ≤−4 from baseline to discharge, N (%)	3 (0.26)	21 (1.86)	−2.00 (−3.17 to 1.06)	0.13 (0.04–0.43)	0.13 (0.04–0.43)	<0.001*
NIHSS score change of ≥4 from baseline to discharge, N (%)	621 (55.29)	504 (44.87)	6.59 (2.28 to 10.87)	1.31 (1.09–1.58)	1.12 (1.04–1.21)	0.0035*
NIHSS score change of ≥3 from baseline to discharge, N (%)	144 (12.82)	144 (12.82)	−1.45 (−4.59 to 1.68)	0.89 (0.70–1.15)	0.91 (0.73–1.12)	0.37
NIHSS score change of ≥2 from baseline to discharge, N (%)	146 (13.00)	148 (13.17)	−1.69 (−4.86 to 1.47)	0.88 (0.69–1.13)	0.90 (0.73–1.11)	0.30
NIHSS score change of ≥1 from baseline to discharge, N (%)	90 (8.01)	95 (8.45)	−1.45 (−4.07 to 1.14)	0.85 (0.63–1.15)	0.86 (0.65–1.13)	0.28
SAE, N (%)	55 (4.90)	51 (4.54)	0.36 (−1.42 to 2.14)	1.08 (0.73–1.60)	1.08 (0.74–1.56)	0.69

HUK indicates human urinary kallidinogenase; MMSE, mini-mental state examination; mRS, modified Rankin Scale; NIHSS, National Institutes of Health Stroke Scale; OR, odds ratio; PSM, propensity score matching; QALY, quality-adjusted life years; RD, risk difference; RR, relative risk; and SAE, serious adverse events.
*$P<0.05$.

ORIGINAL CONTRIBUTION

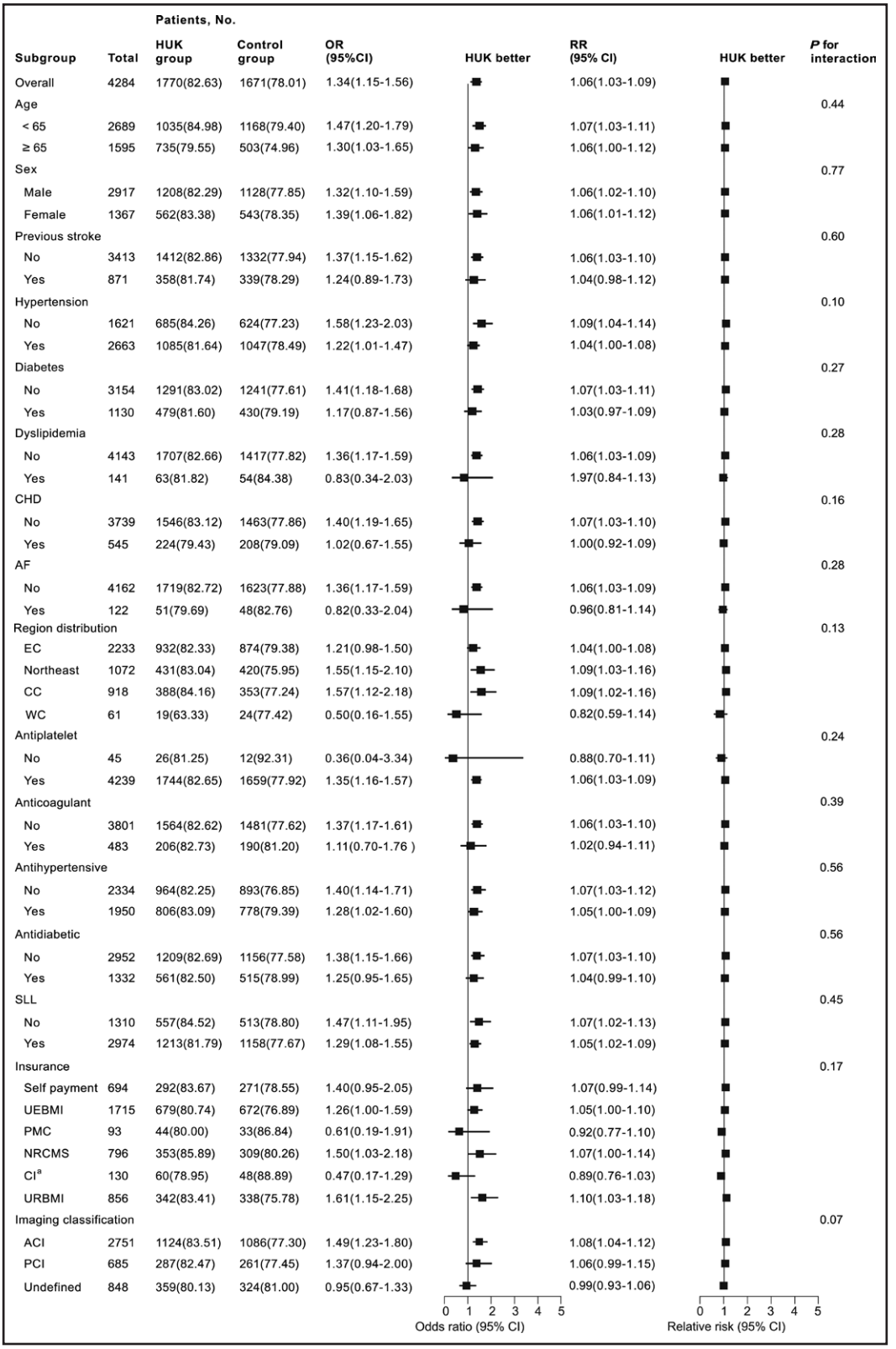

Figure 3. Odds ratio (OR) for the primary outcome in mild subgroups.
The *P* value for the interaction value was calculated based on the ORs with logistic regression. ACI indicates anterior circulation infarction; AF, atrial fibrillation; CC, central China; CHD, coronary heart disease; CI[a], commercial insurance; EC, eastern China; HUK, human urinary kallidinogenase; NRCMS, new rural cooperative medical schema; PCI, posterior circulation infarction; PMC, public medical care; RR, relative risk; SLL, statin-lipid-lowering; UEBMI, urban employee basic medical insurance; URBMI, urban resident basic medical insurance; and WC, western China.

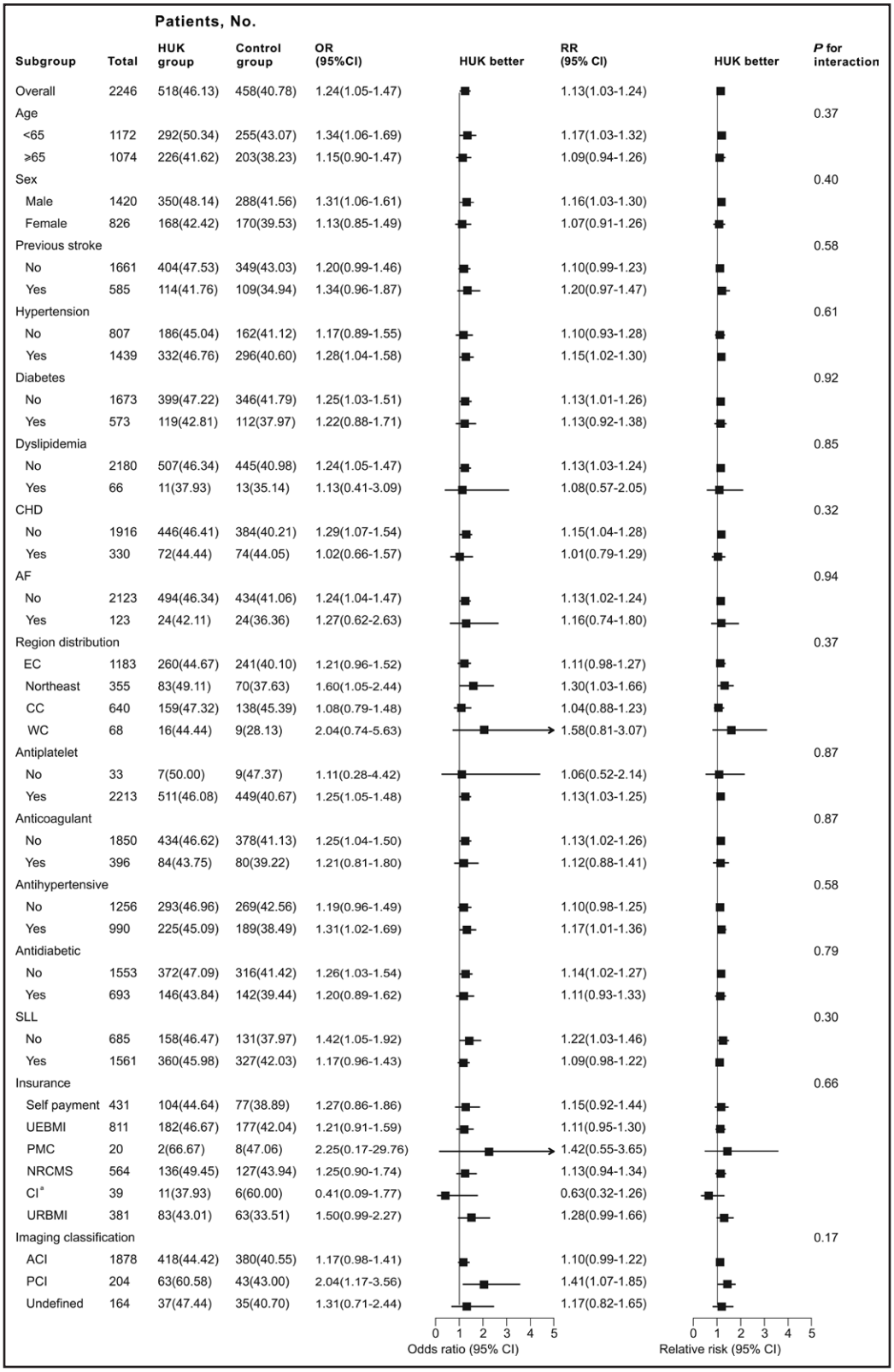

Figure 4. Odds ratio (OR) for the primary outcome in moderate subgroups.
The *P* value for the interaction value was calculated based on the odds ratios (ORs) with logistic regression. ACI indicates anterior circulation infarction; AF, atrial fibrillation; CC, central China; CHD, coronary heart disease; CI[a], commercial insurance; EC, eastern China; HUK, human urinary kallidinogenase; NRCMS, new rural cooperative medical schema; PCI, posterior circulation infarction; PMC, public medical care; RR, relative risk; SLL, statin-lipid-lowering; UEBMI, urban employee basic medical insurance; URBMI, urban resident basic medical insurance; and WC, western China.

with severe stroke.[28] In terms of therapeutic strategies, the management of mild AIS differs significantly from that of severe AIS, particularly in terms of thrombolysis or thrombectomy interventions.[29] Although many pharmaceutical-supported studies for mild ischemic stroke are still ongoing, our study indicated that HUK may also be an effective choice.

Stroke survivors frequently encounter substantial emotional and psychological difficulties that collectively impair their quality of life.[30] This issue is particularly pertinent for individuals classified as having an mRS score ≤1. Despite minimal physical disability, these patients often face underrecognized challenges in mental health, cognitive performance, and social engagement.[31] A thorough assessment of self-reported concerns in these domains is crucial to accurately capture the multifaceted burden of stroke, which extends beyond physical limitations. Consequently, a holistic evaluation of these interconnected aspects is indispensable for designing targeted rehabilitation interventions and optimizing long-term functional and psychosocial outcomes.[31]

Zhao et al[32] reported that HUK decreased the serum levels of both Aβ1-40 and Aβ1-42, thus preventing the development and progression of an impaired cognitive status. Yan et al.[33] suggested that HUK significantly reduces the risk of PSCI, as evidenced by notably decreased serum levels of cystatin C. Similarly, our analysis indicated that the patients with mild stroke in the HUK group presented a significant reduction in PSCI. However, the absence of evaluations of specific biomarkers precludes us from providing detailed mechanistic explanations for this phenomenon. Moreover, no statistically significant difference was detected in poststroke dementia outcomes or PSCI incidence in the moderate stroke group. The lack of baseline MMSE data at admission further restricts our capacity to conduct a thorough assessment. Consequently, these results should be interpreted with caution. Future investigations should prioritize the implementation of rigorously designed, large-scale, multicenter randomized clinical trials to corroborate these findings and explore the underlying mechanisms.

Even after PSM, residual confounding factors, including drug interactions, regional distribution disparities, and differences in socioeconomic status (as reflected by the insurance type and influenced by multiple determinants), along with unmeasured variables (eg, rehabilitation-related factors), may persist between groups, potentially biasing the estimation of causal effects through the effects of their complex interactions on the final outcomes. First, subgroup analyses and logistic regression analysis were performed to assess the influence of concomitant medications on the efficacy of HUK (Tables 1 and 2; Figures 3 and 4). Although most concomitant medications were not associated with functional independence, these findings emphasize the importance of considering such factors in clinical decision-making.[12] Second, differences between regions are inevitable due to China's immense geographic size.[2] Third, socioeconomic status, as represented by the insurance type, significantly influences health outcomes due to variations in health care access restrictions. The diversity of health insurance systems results in differential benefit packages and unequal access to necessary care and financial protection.[34] Despite urban employees' basic medical insurance and urban residents' basic medical insurance accounting for >80% of the patient population and serving as protective factors for primary outcomes, complex patterns were still observed between HUK and control groups, suggesting potential confounding effects. Finally, the literature presents inconsistent evidence regarding the association between the timing of rehabilitation initiation (early versus late) and the extent of stroke recovery.[28,35] Although numerous therapeutic approaches have been developed, no approved and effective treatment currently exists to promote recovery during the subacute phase following a stroke.[36] Furthermore, although poststroke rehabilitation offers diverse pathways that influence 3-month mRS outcomes, large-scale, double-blind, multicenter randomized controlled trials on tenecteplase for stroke at 4.5 to 24 hours with perfusion imaging selection continue to employ the 3-month mRS score as the primary end point without clear rehabilitation information records,[37] which is consistent with our study.[38,39]

The analysis of visit evaluations revealed no notable difference in safety profiles in both the control and HUK group. The limited AEs were unrelated to the investigational agent, and the occurrence of serious AEs was minimal. The overall incidence of AEs in our study (44.64%) was <55.99% reported in the RESK trial. Furthermore, the total incidence of mild AEs in the RESK study was reported to be 79.23%, >66.96% in our study. This difference is likely influenced by variations in study design and patient enrollment between those 2 studies.

Limitations

Our study has limitations described below. First, in terms of the stroke etiological classification, the data from the TOAST (Trial of Org 10 172 in Acute Stroke Treatment) were incomplete in our study. However, the approved indication of HUK in China is mild to moderate acute cerebral infarction, regardless of the AIS cause. Second, our study included only the classification of the infarct location without specific calculations of the infarct volume, which may attenuate the impact of the infarct volume on the stroke prognosis. However, the clinical translatability of infarct volume is constrained by inconsistent associations with functional outcomes and inadequate predictive power for individual prognosis.[40,41] Nonlinear relationships emerge between final infarct volume and neurological outcomes, with documented cases of both disproportionately severe disability in patients with

restricted infarcts and unexpectedly favorable recovery in those with extensive parenchymal involvement.[40] Besides, distinct lesion topographies may influence post-stroke recovery by differentially altering structural and functional connectivity, likely reflecting heterogeneous patterns of cerebral reorganization.[42] Third, the primary limitation, as with all observational studies, stems from potential biases introduced by the inclusion and exclusion criteria. Extensive efforts have been undertaken to employ advanced statistical methods to mitigate bias and ensure equitable group balancing. However, the influence of bias cannot be entirely eliminated, even if the findings across all conducted studies demonstrate consistency.[43] In addition, the selection of HUK treatment was determined by clinical judgment, potentially introducing residual confounding factors that may not have been adequately balanced across groups, despite the implementation of PSM to minimize their influences on prospective outcomes. Additionally, due to the complexity of traditional Chinese medicine, no other relevant traditional Chinese medicine information was recorded in our database, which may influence the long-term outcomes of patients with AIS.

Conclusions

Our findings indicate that HUK treatment may improve the prognosis of patients with mild-to-moderate AIS with a favorable safety profile. Nevertheless, additional large-scale randomized controlled trials and mechanistic investigations are warranted to further validate these results.

ARTICLE INFORMATION

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Affiliations

Department of Neurology, Peking University First Hospital, Beijing, China (D.H., Y.L., Weiping Sun, Wei Sun, Y. Sun, Y.H., H.J.). Department of Internal Neurology, Yantai Penglai Traditional Chinese Medicine Hospital, China (Y. Song). Department of Neurology, Second Hospital of Hebei Medical University, Shijiazhuang, China (L.T.). Department of Neurology, First Affiliated Hospital of Harbin Medical University, Neurology, China (G.L.). Department of Neurology, The General Hospital of Shenyang Military Command, China (H.C.). Department of Neurology, Penglai People's Hospital, China (G.Z.). Department of Neurology, Fifth Affiliated Hospital of Sun Yat-sen University, Zhuhai, China (L.Z.). Department of Neurology, Qindao University Medical College Affiliated Yantai Yuhuangding Hospital, China (X.S.). Department of Neurology, Huizhou First Hospital, China (J.Q.). Department of Neurology, Harrison International Peace Hospital, Hengshui, China (Y.W.).

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Disclosures

None.

Supplemental Material

Tables S1–S7
Figures S1–S4
List of Participating Study Groups in the CASTOR

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