Application of hyperglycemia/diabetes-derived polygenic risk scores on the risk of poor outcomes after an ischemic stroke

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ABSTRACT

Background: Unfavorable prognoses are often accompanied for hyperglycemic stroke patients. This study aimed to construct a hyperglycemia/diabetes-derived polygenic risk score (PRS) to improve the predictive performance for poor outcome risks after a stroke and to evaluate its potential clinical application.

Methods: A hospital-based cohort study was conducted including 1320 first-ever acute ischemic stroke (AIS) patients and 1210 patients who completed the follow-up at 3 months. PRSs were calculated for hyperglycemia/diabetes mellitus using results from genome-wide association studies in Asians. An unfavorable functional outcome was defined as a modified Rankin Scale score of ≥3 at 3, 6, and 12 months of follow-up. The prediction of a poor prognosis was evaluated using measures of model discrimination, calibration, and net reclassification improvement (NRI).

Results: The second to fourth PRS quartiles (≥Q2) were significantly associated with higher risks of unfavorable outcomes at 3 months compared with the first quartile as the reference group after adjusting for age, baseline stroke severity, hypertension, diabetes, dyslipidemia, smoking, heart disease, and ischemic stroke subtype (p for trend <0.0001). The addition of the PRS to traditional risk predictors of poor outcomes after an AIS significantly improved the model fit (likelihood ratio test $p < 0.0001$) and enhanced measures of reclassification (NRI, 0.245; 95% confidence interval [CI], 0.195-0.596). The corrected C-index for the PRS combining traditional risk factors at 3 months after a stroke was 0.899 (95% CI, 0.878-0.980). Among hyperglycemic AIS patients, those who did not take an antidiabetic drug and whose PRS was ≥Q2 had higher risks of an unfavorable outcome at 3 months compared with patients who took the medicine.

Conclusion: The hyperglycemia/diabetes-derived PRS was associated with poor outcomes after an AIS, but further studies are needed to validate its use for clinical applications.

Keywords: Diabetes mellitus; Functional outcome; Hyperglycemia; Ischemic stroke; Polygenic risk score

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1. INTRODUCTION

Stroke is the second leading cause of death in the world and fourth leading cause in Taiwan. With the rapid rise of the elderly population in Taiwan, the burdens of disabilities after a stroke are difficult to imagine, although the incidence of stroke has declined in recent years.[1–3] According to statistics, reports indicated that cerebrovascular disease has the third highest disability-adjusted life years in Taiwan.[4]

Hyperglycemia on admission which is frequently observed in acute ischemic stroke (AIS) patients is associated with a worse clinical prognosis, including a large infarct, poor functional outcomes, cognitive impairment, and increased mortality.[5–8] However, results of controlling hyperglycemia in AIS using

intravenous insulin are disappointing.[9] A recent randomized controlled trial further indicated there was no therapeutic benefit with intensive blood glucose management.[10] Since emerging studies found that susceptible loci of diabetes may be associated with therapeutic effects of antidiabetic drugs,[11–13] the magnitude of the beneficial effects of glucose control might be due to genetic susceptibilities.

Establishment of diagnostic and prognostic prediction models is an indispensable factor for precision medicine; however, assessments of complex diseases like stroke are challenging due to many environmental and genetic variants simultaneously affecting disease risks. Currently, polygenic risk scores (PRSs) are being widely applied in research studies including estimating lifetime genetic risks of disease, assisting diagnoses, and informing treatment choices,[14] and also in clinical studies by improving biomedical outcomes.[15,16] Recently, a growing number of studies used PRSs integrated with conventional clinical predictors or with established biomarkers to predict the risk of postoperative atrial fibrillation in patients receiving coronary artery bypass grafting or valve surgery[17–19]; however, there is limited research on PRSs in forecasting stroke outcomes. In addition, most PRS studies were derived from genome-wide association studies (GWASs) of Caucasian populations. Since the utility of PRSs in clinical areas might encounter unequal applicability across different ethnic groups,[20] applying the well-powered and equitable potential of PRSs is paramount to ensuring that health disparities do not increase given the heightened attention to clinical uses of PRSs.

In the present study, we aimed to construct a hyperglycemia/diabetes-derived PRS obtained from Asian population-based GWASs and evaluate the performance of the PRS for predicting unfavorable poststroke outcomes at 3, 6, and 12 months by integration with traditional risk factors. Furthermore, the risk of poor outcomes for hyperglycemic patients who did not receive antidiabetic treatment at discharge was evaluated based on their PRSs.

2. METHODS

2.1. Study population

This study was conducted within the Formosa Stroke Genetic Consortium (FSGC), an ongoing hospital-based registry cohort study in Taiwan with the aim of investigating causes and prognoses of stroke. The study was initiated in 2005, and detailed procedures were published elsewhere.[21] All study participants were confirmed to have an AIS by brain computed tomography or magnetic resonance imaging, were invited from hospitals cooperating with the FSGC and were followed-up at 1, 3, 6, and 12 months.

There were 4431 stroke patients recruited from 2005 to 2019. After excluding those with recurrent stroke (n = 108), transient ischemic attack (n = 143), hemorrhagic stroke (n = 333), other stroke subtypes (n = 19), missing information of basic characteristics (n = 286), no blood samples (n = 454) or available genotyping data (n = 1565), and who were lost to follow-up at 1 month (n = 203), 1320 first-ever unrelated ischemic stroke patients were enrolled in this study. Fig. 1 depicts an overview of the selection of study subjects presented in a flowchart. All study subjects or their relatives provided written informed consent. This study was performed according to the *Declaration of Helsinki* and was approved by the Institutional Review Board or Ethics Committee of Taipei Medical University (201207007) and our collaborating hospitals (200807061R, 201911029RINB, and 201908008RINA from National Taiwan University Hospital, and IRB08605-004 from Chi-Mei Medical Center).

2.2. Clinical data collection

Preadmission data, inpatient clinical data, and discharge data were gathered using a standard registry form by well-trained assistants or study nurses. The National Institute of Health Stroke Scale (NIHSS) was also conducted to evaluate the severity of stroke at the baseline. Biochemical data were determined within 24 h after the onset of an AIS in each participating hospital. In addition, anthropometric factors and blood pressure were measured at admission.

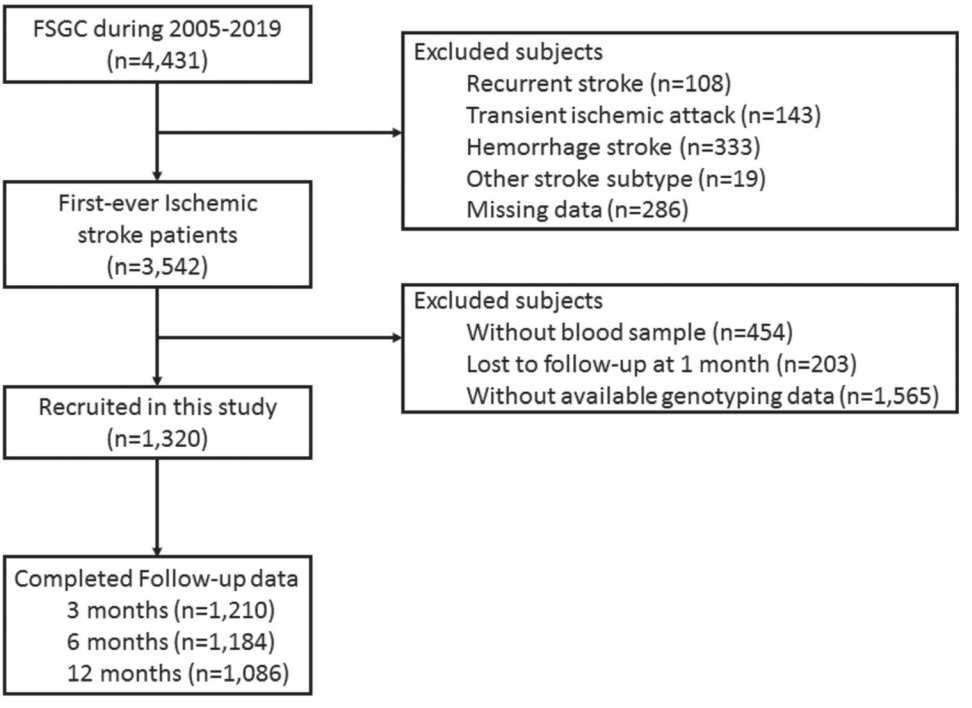

Fig. 1 Flow chart of study participant selection.

2.3. Outcome measurement

The study adopted the modified Rankin Scale (mRS) to evaluate the prognostic status of patients at 3, 6, and 12 months after the stroke, which is a common functional outcome evaluation tool for clinical assessment of handicaps in stroke patients. The mRS score ranges 0–6, with 0 indicating no symptoms at all and 5 representing severe disability; grade 6 is denoted as death. Patients were categorized as having a favorable outcome if their mRS score ranged 0–2 points, while subjects were considered to be in the unfavorable outcome group when their mRS score was ≥3 points.

2.4. Genotyping and construction of a hyperglycemia/diabetes-derived PRS

To construct a hyperglycemia/diabetes-derived PRS, there were 864 study subjects including 321 ischemic stroke patients with hyperglycemia (as indicated by a nonfasting blood glucose level of ≥200 mg/dL on admission) and 543 normoglycemic patients genotyped using an Axiom Genome-Wide TWB 2.0 Array Plate (National Center for Genome Medicine, Taiwan) due to a limited budget. Samples with a call rate below 97% were removed. Imputation of genotypes was performed at the Michigan Imputation Server (https://imputationserver.sph.umich.edu) using the 1000G phase 1 versus 3 reference panel.[22] Quality control and filtering criteria were applied using PLINK software. Imputed single-nucleotide polymorphisms (SNPs) were removed if they had (i) a minor allelic frequency of <0.05; (ii) an info score of <0.80; (iii) an average maximum posterior call of <0.90; (iv) a genotyping rate of <0.05; or (v) an identity-by-descent (IBD) of <0.1875. The remaining variants were mapped using GRCh37/hg19 coordinates, and the Eagle v2.4 algorithm was used for phasing. Results of relatedness quality control parameters and genotyping are respectively shown in Supplementary Figs. 1 and 2, http://links.lww.com/JCMA/A116. The promising risk locus at chromosome 9q21 (rs6475687, $p = 10^{-6}$) associated with a risk of hyperglycemia was selected as a candidate SNP for the PRS after adjustments of covariates (Supplementary Fig. 3, http://links.lww.com/JCMA/A116). Additional candidate SNPs were selected from three previous GWASs on the risk of diabetes in Asians.[23–25] These SNPs are summarized in Supplementary Table 1, http://links.lww.com/JCMA/A116, and a meta-analysis was performed using METAL software weighted by the sample size.[26] After directly analyzing consolidated data from multiple studies based on Z statistics in each study, 14 promising resulting SNPs were chosen and are listed in Supplementary Table 2, http://links.lww.com/JCMA/A116. In addition, our previous study identified the *FAS* gene, which is associated with hyperglycemia after a stroke to play an important role in poor prognoses in ischemic stroke.[27] Thus, the frequently observed SNP in the *FAS* promoter (rs2234767) was also selected.[28,29] All 16 candidate SNPs were then genotyped in remaining study subjects (n = 456) including 158 hyperglycemic and 298 normoglycemic AIS patients using the Sequenom iPLEX MassARRAY system (Sequenom, San Diego, CA) and TaqMan allele discrimination assays (Applied Biosystems, Foster City, CA). A PRS was developed using candidate SNPs related to hyperglycemia/diabetes to estimate polygenic contributions of unfavorable outcomes based on any one of the per-allele, dominant, or recessive logistic regression models. The sum of the product of the number of risk allele copies of the selected SNPs and their corresponding log odds estimates were then calculated as a weighted PRS. According to the quartile grouping of PRS, percentages of patients with hyperglycemia were 31.6%, 33.2%, 37.1%, and 38.8%, respectively (p for trend = 0.0591), indicating that the PRS showed a slight hyperglycemia dependence.

2.5. Statistical analysis

Continuous variables with a normal distribution are presented as the mean with the SD and were tested using Student's *t*-test to compare unfavorable and favorable outcome patients, while variables with a nonnormal distribution are shown as the median with the interquartile range (IQR) and were examined by the Mann-Whitney *U* test. Categorical variables were summarized using frequency and percentages and evaluated using a Chi-squared test for comparisons between study patients with good and worse outcomes. A logistic regression model was performed to calculate the odds ratio (OR) and 95% confidence interval (CI) to evaluate associations between SNPs and risks of unfavorable outcomes after a stroke after adjusting for traditional risk factors, including age, sex, stroke severity at the beginning, hypertension, diabetes mellitus (DM), dyslipidemia, cigarette smoking, heart disease, and ischemic stroke subtype. Discrimination and calibration were adopted to evaluate the predictive performance of the model. The area under the receiver operating characteristic (ROC) curve was conducted to estimate the performance of the PRS and traditional risk factors to discriminate the risk of unfavorable outcomes in AIS patients. The optimism-corrected C-statistic was provided after 1000 repetitions. Calibration was performed by loss-based calibration plots[30] and examined using the Hosmer-Lemeshow goodness-of-fit test. The net reclassification index (NRI) was used to evaluate how the addition of the PRS variable to the traditional risk factor model changed the risk classification.[31] All statistical analyses were performed using SAS vers. 9.4. (SAS Institute, Cary, NC) on two-sided probabilities.

3. RESULTS

3.1. Patient characteristics

Out of all study participants, there were 1210 ischemic stroke patients who completed the 3-month follow-up, and their detailed demographic and clinical characteristics are presented in Table 1. Mean ages were 68.67 (SD, 12.59) and 59.19 (SD, 11.31) years for the unfavorable and favorable outcome patients, respectively. Females were prone to have poorer outcomes. Compared with patients with good outcomes, poor outcome cases had significantly higher percentages of hypertension, DM, and heart disease histories as well as lower smoking frequencies. The average body mass index, blood pressure, low-density lipoprotein level, triglyceride level, and cholesterol level were lower in unfavorable outcome patients than in favorable outcome subjects. Patients with worse outcomes had significantly higher fasting glucose levels at admission than patients with good outcomes. After adjusting for covariates including age, sex, initial stroke severity, hypertension, DM, dyslipidemia, cigarette smoking, heart disease, and ischemic stroke subtype, patients with hyperglycemia/diabetes were independently associated with unfavorable outcomes (OR, 1.42; 95% CI, 1.01-1.98; $p = 0.0445$, data not shown), which is consistent with our assumption.

3.2. Construction of the PRS and its association with poor outcomes after a stroke

The PRS was generated using candidate SNPs related to hyperglycemia and DM according to the predictive ability of the logistic regression analysis under any one of the additive, dominant, or recessive models (Supplementary Table 3, http://links.lww.com/JCMA/A116). In the present study, associations between the PRS and unfavorable outcomes after a stroke at 3, 6, and 12 months were examined after adjusting for covariates, including age, sex, stroke severity at the beginning, hypertension, DM, dyslipidemia, cigarette smoking, heart disease, and ischemic stroke subtype. Fig. 2 indicates that the risk of a poor

Table 1

Basic characteristics between ischemic stroke patients with favorable and unfavorable outcomes at 3 months

	Total (N = 1,210)		mRS ≥ 3 (N = 288)		mRS ≤ 2 (N = 922)		*p*
Age, mean (SD), year	61.45	(12.30)	68.67	(12.59)	59.19	(11.31)	<0.0001
BMI, mean ± SD, kg/m^2	25.63	(3.93)	24.62	(3.68)	25.94	(3.96)	<0.0001
Males, n (%)	835	(69.01)	169	(58.68)	666	(72.23)	<0.0001
Cigarette smoking, n (%)	606	(50.17)	124	(43.06)	482	(52.39)	0.006
Alcohol drinking, n (%)	217	(17.96)	44	(15.28)	173	(18.80)	0.174
Biological measurements							
SBP, mean (SD), mmHg	165.77	(32.70)	162.37	(33.34)	166.83	(32.45)	0.044
DBP, mean (SD), mmHg	95.49	(20.93)	90.54	(20.12)	97.05	(20.95)	<0.0001
LDL, mean (SD), mmol/L	3.16	(0.97)	3.01	(0.98)	3.21	(0.97)	0.003
HDL, mean (SD), mmol/L	1.08	(0.31)	1.10	(0.35)	1.08	(0.29)	0.465
Triglyceride, mean (SD), mmol/L	1.81	(1.49)	1.60	(1.21)	1.88	(1.57)	0.002
Cholesterol, mean (SD), mmol/L	5.02	(1.23)	4.82	(1.20)	5.08	(1.24)	0.002
Fasting glucose, mean (SD), mmol/L	7.17	(2.85)	7.61	(2.98)	7.05	(2.80)	0.006
HbA1c, mean (SD), %	7.03	(2.07)	7.06	(2.11)	6.93	(1.94)	0.381
NIHSS at beginning, median (Q3-Q1), score	3	(5-1)	6	(11-4)	2	(4-1)	<0.0001
Disease history							
Hypertension, n (%)	957	(79.09)	248	(86.11)	709	(76.90)	0.001
Diabetes mellitus, n (%)	500	(41.32)	134	(46.53)	366	(39.70)	0.040
Dyslipidemia, n (%)	717	(59.26)	161	(55.90)	556	(60.30)	0.185
Heart disease, n (%)	272	(22.48)	99	(34.38)	173	(18.76)	<0.0001
Drug history							
Antihypertensive drug, n (%)	690	(57.02)	168	(58.33)	522	(56.62)	0.607
Antidiabetic drug, n (%)	423	(34.96)	108	(37.50)	315	(34.16)	0.300
Lipid lowering drug, n (%)	452	(37.36)	107	(37.15)	345	(37.42)	0.935
Stroke subtype, n (%)							
Large artery atherosclerosis	344	(31.24)	116	(42.96)	228	(27.44)	<0.0001
Small vessel occlusion	520	(47.23)	86	(31.85)	434	(52.23)	
Cardioembolism	113	(10.26)	48	(17.78)	65	(7.82)	
Specific etiology	26	(2.36)	3	(1.11)	23	(2.77)	
Undetermined etiology	98	(8.90)	17	(6.30)	81	(9.75)	

BMI = body mass index; DBP = diastolic blood pressure; HbA1c = hemoglobin A1C; HDL = high density lipoprotein; LDL = low density lipoprotein; NIHSS = National Institutes of Health Stroke Scale; SBP = systolic blood pressure; TOAST = Trial of ORG 10172 in Acute Stroke Treatment.

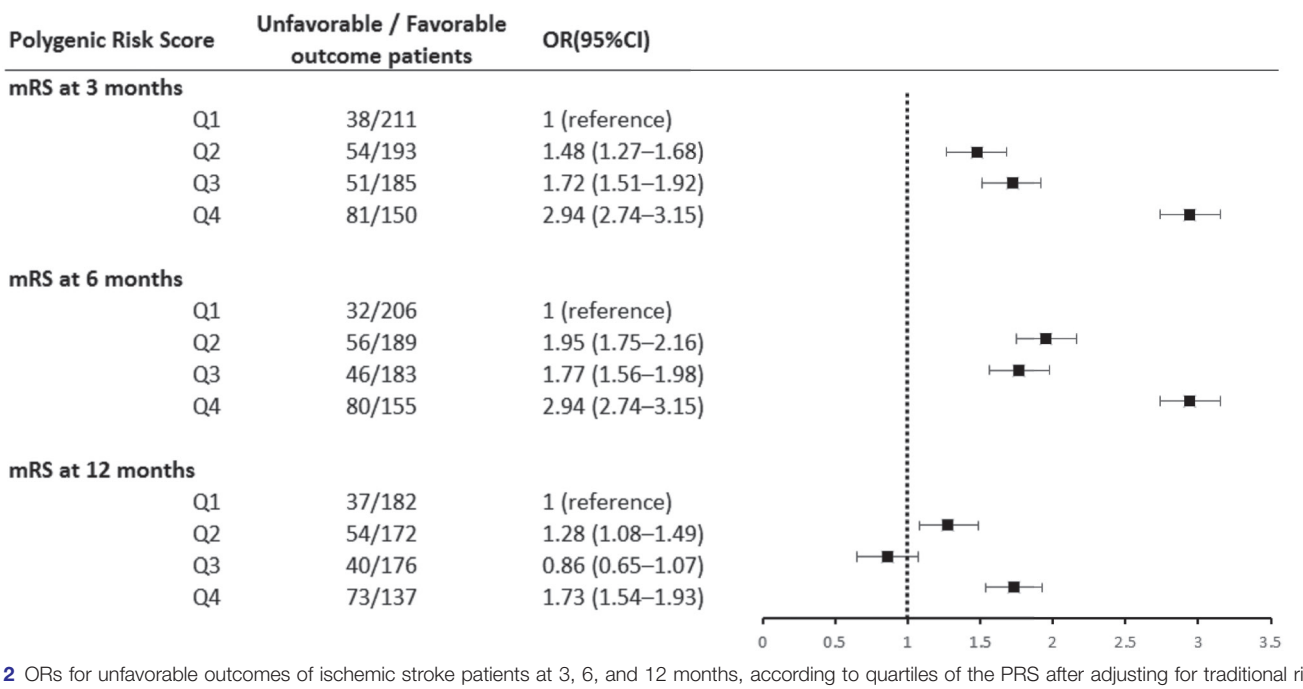

Fig. 2 ORs for unfavorable outcomes of ischemic stroke patients at 3, 6, and 12 months, according to quartiles of the PRS after adjusting for traditional risk factors, including age, sex, initial stroke severity, hypertension, diabetes mellitus, dyslipidemia, cigarette smoking, heart disease, and ischemic stroke subtype. ORs, odds ratios; PRS, polygenic risk score.

outcome after a stroke at 3 months substantially increased for those in the second (Q2) (OR, 1.48; 95% CI, 1.27-1.68), third (Q3) (OR, 1.72; 95% CI, 1.51-1.92), and fourth quartiles (Q4) (OR, 2.94; 95% CI, 2.74-3.15) of the PRS compared with those in the first quartile of the PRS as the reference group (p for trend <0.0001). At 6 months after a stroke, patients whose PRS scores were in the Q2, Q3, and Q4, respectively, had 1.95-, 1.77-, and 2.94-fold risks of unfavorable outcomes, compared with the lowest PRS quartile. Similar poor prognostic risks were observed for ischemic stroke patients after being followed-up for 1 year except for patients in the third quartile PRS group.

3.3. Discrimination and reclassification

An ROC analysis was performed to evaluate the discriminative ability of the PRS in addition to traditional risk factors. Table 2 shows that the C statistic of the model based only on traditional risk factors related to unfavorable outcomes after a stroke at 3 months, including age, sex, initial stroke severity, hypertension, DM, dyslipidemia, cigarette smoking, heart disease, and ischemic stroke subtypes, was 0.902 (95% CI, 0.879-0.925), while after integration with the PRS, the C statistic increased to 0.907 (95% CI, 0.885-0.930). The addition of the PRS to traditional risk predictors of unfavorable outcomes improved the model fit (likelihood ratio test $p < 0.0001$), and the measure of reclassification was significantly improved with the NRI (0.245; 95% CI, 0.195-0.596; $p < 0.0001$). The addition of the PRS still increased the C statistics after following up to 6 and 12 months (6 months, 0.898; 95% CI, 0.874-0.922; 12 months, 0.886; 95% CI, 0.858-0.915). Across the 1000 bootstrap resamplings, values of the optimism-corrected C-index for the PRS integrated with traditional risk factors at 3, 6, and 12 months of follow-up after a stroke were 0.899 (95% CI, 0.878-0.980), 0.888 (95% CI, 0.859-0.961), and 0.876 (95% CI, 0.847-0.949), respectively, which were more-accurate and -robust performance estimates (Fig. 3). All calibration plots for the 3-, 6-, and 12-month follow-up time points also presented good accordance between the predicted risk and the actual absolute risk (by the Hosmer-Lemeshow test, $p > 0.05$).

3.4. Evaluation of potential clinical applications

Among hyperglycemic AIS patients, the risk of a poor prognosis at 3 months after a stroke of those who did not take antidiabetic drugs at the time of discharge and whose PRS was ≥Q2 was significantly 2.01-fold higher compared with patients who took the drugs (Fig. 4). Similar results were found for patients with a PRS of <Q2 and who received no antidiabetic treatment, but this did not reach a significant level.

Table 2

Area under receiver operating curve and discrimination by PRS for unfavorable outcomes at 3, 6, and 12 months

mRS (months)	C statistic (95%CI)		NRI (95%CI)	p
	Traditional Model	Traditional Model + PRS		
3	0.902 (0.879-0.925)	0.907 (0.885-0.930)	0.245 (0.195-0.596)	<.0001
6	0.893 (0.868-0.918)	0.898 (0.874-0.922)	0.111 (-0.048-0.270)	0.172
12	0.884 (0.856-0.913)	0.886 (0.858-0.915)	0.085 (-0.077-0.246)	0.309

Traditional model includes age, sex, stroke severity at beginning, hypertension, diabetes mellitus, dyslipidemia, cigarette smoking, heart disease, and ischemic stroke subtypes.
CI = confidence interval; mRS = modified Rankin Scale; NRI = net reclassification improvement; PRS = polygenic risk score.

4. DISCUSSION

The PRS which was constructed from common variants related to hyperglycemia or DM in Asian populations in the present study provides new ways to improve risk assessments of poor clinical outcomes after a stroke and contributes to a better understanding of the risk of an unfavorable prognosis after a stroke. In this study, we established a hyperglycemia/diabetes-derived PRS, which was constituted of common SNPs in Asian populations and found that the score remarkably improved the risk discrimination and reclassification compared with a conventional risk factor model.

To our knowledge, this is the first study to utilize a PRS combined with traditional well-known risk factors to predict unfavorable clinical outcomes after an ischemic stroke. Specifically speaking, our study developed a hyperglycemia/diabetes-derived PRS which was based on our results and previous findings that pointed to hyperglycemia as an independent and important risk factor for poor clinical outcomes after an AIS.[5–8] In addition, to decrease health disparities, it was based on GWAS results associated with hyperglycemia or DM in Asian populations. Our results revealed that patients in the higher quartiles of the PRS had higher risks of unfavorable functional outcomes after an AIS at 3 months of follow-up, and the risk persisted for up to 6 and 12 months. Overall, the data presented here provide further evidence that the PRS exhibited a strong association with unfavorable outcomes of AIS patients.

Previously, various prognostic risk scores were established to estimate stroke-related consequences,[32–38] since predicting functional outcomes following a stroke is increasingly vital to facilitate subsequent needs for intervention planning, resource use, and lifestyle adjustments.[39] Most of those scales were incorporated into conventional clinical practice; however, some were too complex to use or required information that was not routinely available such as neuroimaging.[35,40] Moreover, the discriminatory power of those scales ranged 0.61-0.85.[35] Our study demonstrated a high predictive ability of unfavorable outcomes after a stroke at 3 months when considering adding the PRS to traditional risk factors (AUC = 0.907), and the optimal-corrected C-index for the PRS achieved a nearly excellent discrimination level (C-index = 0.899 at 3 months poststroke) after a stroke for up to 12 months. Additionally, risk reclassification and the discriminatory power attributable to the addition of the PRS further improved, implying that the PRS combined with traditional risk factors has the potential to be a precise prognostic tool for AIS in Asians.

Currently, the application of PRS can identify high-risk populations for screening or early intervention,[41–43] and also identify subjects who will most benefit from medical drug prescriptions[16,44,45] and estimate lifetime risk trajectories.[46] In this study, our findings indicated that hyperglycemic AIS patients who did not take antidiabetic drugs at discharge and whose PRS was ≥Q2 had a significantly increased risk of an unfavorable outcome at 3 months. Considering that not taking an antidiabetic drug when discharged might be related to relatively normal blood sugar levels or other underlying condition remaining unknown, our results implied that even though hyperglycemic AIS patients recovered during hospitalization, the patients with higher PRS scores still needed to continually monitor their blood sugar levels after discharge. Therefore, the PRS could be a screening tool for potential clinical utility.

There are some limitations to the current study that need to be acknowledged. First, we cannot preclude additional baseline confounding variables that could affect patient outcomes in spite of controlling for established ischemic stroke outcome predictors. Second, there was a relatively small sample size in our study; as a rule of thumb, a target sample of around 2000

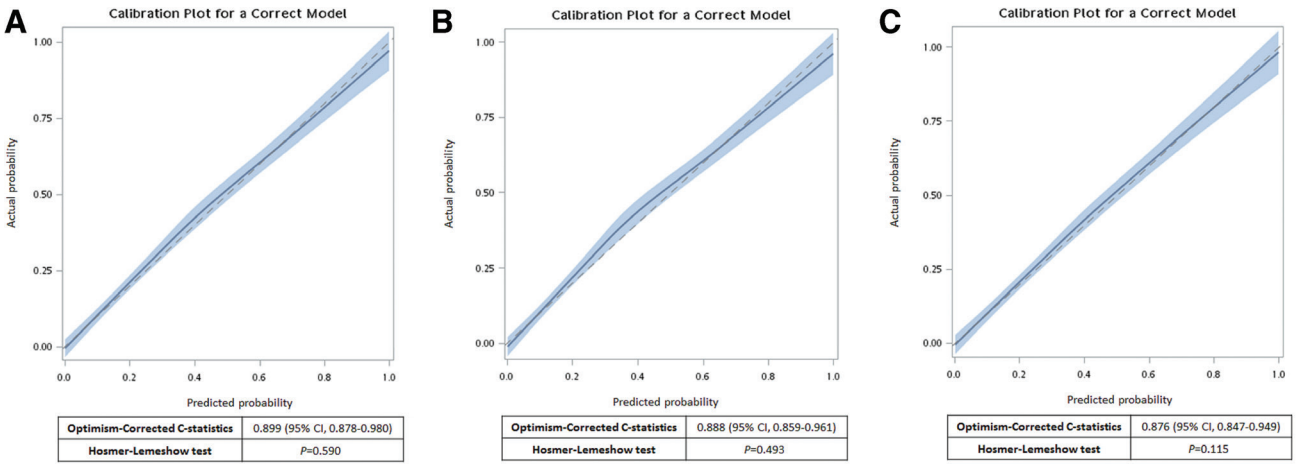

Fig. 3 Bias-corrected calibration plots for predicting unfavorable outcomes of ischemic stroke patients at 3 (A), 6 (B), and 12 months (C), using a bootstrap procedure with 1000 repetitions.

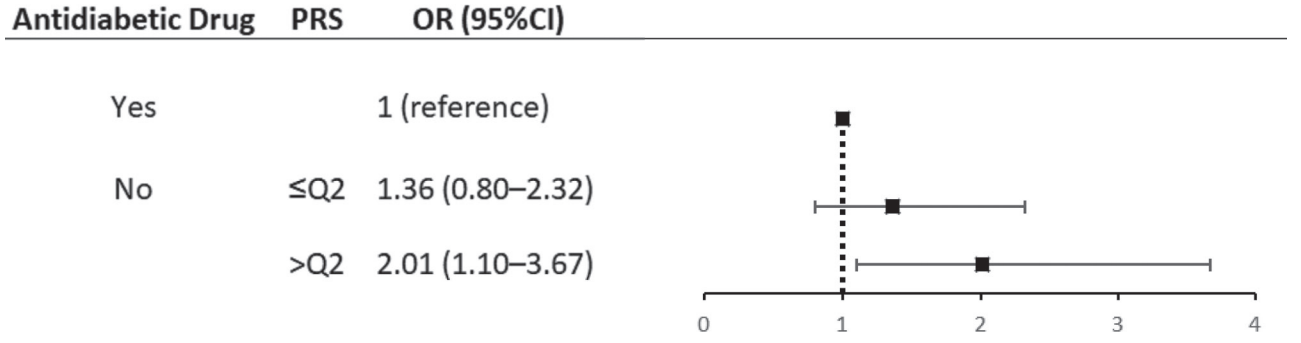

Fig. 4 ORs for unfavorable outcomes of hyperglycemic ischemic stroke patients at 3 months, stratified by antidiabetic drug use at the time of discharge and the PRS after adjusting for traditional risk factors, including age, sex, initial stroke severity, hypertension, dyslipidemia, cigarette smoking, heart disease, and ischemic stroke subtype. ORs, odds ratios; PRS, polygenic risk score.

subjects is suggested to provide sufficient power to detect a remarkable difference.[47] Third, predictive modeling always requires cross-validation with another independent sample. Although our bootstrap analyses suggested that the effect of the PRS was robust, a replication study is warranted. In addition, through use of larger and more-diverse cohorts and advanced methods of deriving and applying the PRS, the prediction accuracy of the PRS can be further improved, all of which may enhance the potential clinical utility of the PRS and accelerate precision medicine for strokes. Finally, the established PRS in the present study was comprised of SNPs from Asian GWASs and might not can be generalized to other ethnicities.

In conclusion, common genetic variants related to hyperglycemia and diabetes may underlie glucose regulation deficits among AIS patients in terms of their subsequent neurological functional performance. Our findings suggest that patients in the higher quartiles of the hyperglycemia/diabetes-derived PRS were associated with higher risks of unfavorable outcomes after an AIS. Furthermore, combining the PRS with conventional risk factors not only enhanced the prognostic ability of ischemic stroke but also provided information for treatment decisions.

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APPENDIX A. SUPPLEMENTARY DATA

Supplementary data related to this article can be found at http://links.lww.com/JCMA/A116.

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