Supplemental material

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Supplemental materials for *"A model based on single-nucleotide polymorphism to discriminate patients with aspirin resistance"*

Supplemental tables

Supplemental table 1. Genetic type of ASR patients and non-ASR patients

Genetic type	ASR n=87	Non-ASR n=125	*P* value
PTGS1~rs10306114			1.000
A/A	87	125	
LTC4S~rs730012			0.952
A/A	55 (63.2%)	79 (63.2%)	
A/C	31 (35.6%)	46 (36.8%)	
C/C	1 (1.1%)	0 (0.0%)	
GP1BA~rs6065			0.008[†]
A/A	68 (78.2%)	114 (91.2%)	
A/C	19 (21.8%)	10 (8.0%)	
C/C	0 (0.0%)	1 (0.8%)	
TBXA2R~rs1131882			0.008[†]
A/A	22 (25.3%)	50 (40.0%)	
G/A	42 (48.3%)	57 (45.6%)	
G/G	23 (26.4%)	18 (14.4%)	
TBXA2R~rs4523			0.013[†]
A/A	39 (44.8%)	76 (60.8%)	
A/G	37 (42.5%)	42 (33.6%)	
G/G	11 (12.6%)	7 (5.6%)	
PTGS2~rs12042763			0.001[†]
G/G	38 (43.7%)	84 (67.2%)	
G/T	43 (49.4%)	35 (28.0%)	
T/T	6 (6.9%)	6 (4.8%)	
PTGS2~rs20417			0.008[†]
C/C	76 (87.4%)	121 (96.8%)	
C/G	11 (12.6%)	4 (3.2%)	

PEAR1~rs12041331			0.357
G/G	18 (20.7%)	26 (20.8%)	
G/A	37 (42.5%)	42 (33.6%)	
A/A	32 (36.8%)	57 (45.6%)	
P2RY1~rs1065776			0.950
C/C	79 (90.8%)	113 (90.4%)	
C/T	6 (6.9%)	11 (8.8%)	
T/T	2 (2.3%)	1 (0.8%)	
NTRK1~rs2768759			0.587
A/A	77 (88.5%)	107 (85.6%)	
A/C	8 (9.2%)	18 (14.4%)	
C/C	2 (2.3%)	0 (0.0%)	
NOS3~rs1799983			0.005[†]
G/G	55 (63.2%)	101 (80.8%)	
G/T	26 (29.9%)	19 (15.2%)	
T/T	6 (6.9%)	5 (4.0%)	
NAT2~rs4271002			0.351
G/G	55 (63.2%)	88 (70.4%)	
G/C	28 (32.2%)	29 (23.2%)	
C/C	4 (4.6%)	8 (6.4%)	
ITGB3~rs5918			0.231
T/T	86 (98.9%)	125 (100.0%)	
T/C	1 (1.1%)	0 (0.0%)	
ITGA2~rs1062535			0.658
A/A	8 (9.2%)	11 (8.8%)	
G/A	43 (49.4%)	67 (53.6%)	
G/G	36 (41.4%)	47 (37.6%)	
ITGA2~rs1126643			0.658
C/C	36 (41.4%)	47 (37.6%)	
C/T	43 (49.4%)	67 (53.6%)	

T/T	8 (9.2%)	11 (8.8%)	
GP6~rs1613662			0.698
A/A	85 (97.7%)	121 (96.8%)	
G/A	2 (2.3%)	4 (3.2%)	
F13A1~rs5985			0.796
C/C	86 (98.9%)	124 (99.2%)	
C/A	1 (1.1%)	1 (0.8%)	
CYP4F2~rs2108622			0.493
C/C	39 (44.8%)	61 (48.8%)	
C/T	38 (43.7%)	53 (42.4%)	
T/T	10 (11.5%)	11 (8.8%)	
CYP2D6~rs28360521			0.617
C/C	25 (28.7%)	41 (32.8%)	
C/T	41 (47.1%)	55 (44.0%)	
T/T	21 (24.1%)	29 (23.2%)	
ACE~rs4291			0.935
A/A	29 (33.3%)	46 (36.8%)	
T/A	48 (55.2%)	60 (48.0%)	
T/T	10 (11.5%)	19 (15.2%)	
ACE~rs4292			0.857
T/T	29 (33.3%)	46 (36.8%)	
C/T	47 (54.0%)	60 (48.0%)	
C/C	11 (12.6%)	19 (15.2%)	
COL26A1~rs10279545			0.882
T/T	72 (82.8%)	102 (81.6%)	
T/C	12 (13.8%)	21 (16.8%)	
C/C	3 (3.4%)	2 (1.6%)	

†, the difference was significant.

ASR, aspirin resistance.

Supplemental table 2. Univariate logistic analysis of factors related to ASR based on the derivation cohort

Parameters	OR (95%CI)	*P* value
Ever-or-now smokers	2.00 (1.07-3.74)	0.030
GP1BA (C/C *vs.* C/T & T/T)	3.72 (1.71-8.13)	0.001
TBXA2R		
A/A & A/A	Reference	
A/A & A/G, A/A & G/G	1.49 (0.67-3.30)	0.328
A/G & A/G, A/G & G/G, G/G & G/G	2.55 (1.33-4.91)	0.005
PTGS2		
G/G & C/C	Reference	
G/G & C/G, G/T & C/C, T/T & C/C	2.94 (1.65-5.24)	<0.001
G/T & C/G, T/T & C/G	12.66 (1.42-112.60)	0.023
NOS3 (G/G vs. G/T & T/T)	2.45 (1.31-4.57)	0.005

ASR, aspirin resistance.

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Supplemental table 3. Multivariate logistic analysis of SNP related to ASR based on the derivation cohort

Parameters	β coefficient	β coefficient weight§	OR (95%CI)	*P* value
GP1BA (C/C *vs.* C/T & T/T)	0.881	1.65	2.41 (1.01-5.75)	0.047
TBXA2R				
A/A & A/A			Reference	
A/A & A/G, A/A & G/G	0.534	1.00	1.71 (0.77-3.78)	0.188
A/G & A/G, A/G & G/G, G/G & G/G	0.911	1.71	2.49 (1.21-5.13)	0.014
PTGS2				
G/G & C/C			Reference	
G/G & C/G, G/T & C/C, T/T & C/C	1.374	2.57	3.95 (2.20-7.09)	<0.001
G/T & C/G, T/T & C/G	2.572	4.82	13.09 (1.33-128.68)	0.027
NOS3 (G/G vs. G/T & T/T)	0.847	1.59	2.33 (1.16-4.69)	0.018

§, the weight was evaluated based on the parameter with lowest β coefficient.

ASR, aspirin resistance; SNP, single-nucleotide polymorphism.

Supplemental table 4. The demographic and clinical features of patients in validation cohort, grouped by ASR and non-ASR

Characteristics	ASR n=130	Non-ASR n=242	*P* value
Age, years, m (IQR)	55 (49-61)	55 (49-63)	0.494
Male gender, n (%)	65 (50.0%)	112 (46.3%)	0.354
Comorbidities, n (%)			
Hypertension	45 (34.6%)	97 (40.1%)	0.301
Dyslipidemia	14 (10.8%)	21 (8.7%)	0.511
Diabetes mellitus	39 (30.0%)	66 (27.3%)	0.578
CA diseases	10 (7.7%)	21 (8.7%)	0.743
Ischemic stroke	70 (53.8%)	125 (51.7%)	0.687
Ever-or-now smokers, n (%)	39 (30.0%)	94 (38.8%)	0.090
Regular drinkers, n (%)	8 (6.2%)	26 (10.7%)	0.144
Laboratory findings			
Platelet count, $\times 10^9$, m (IQR)	216 (205-238)	216 (206-229)	0.971
APTT, m (IQR)	24.8 (24.1-30.4)	24.8 (24.5-30.4)	0.753
PT, m (IQR)	1 (1-1)	1 (1-1)	0.070
Fbg, m (IQR)	2.80 (2.34-3.15)	2.80 (2.37-3.51)	0.425
Aneurysm locations, n (%)			0.816
AcomA/ACA	10 (7.7%)	22 (9.1%)	
ICA	84 (64.6%)	147 (60.7%)	
MCA	32 (24.6%)	65 (26.9%)	
PC	4 (3.1%)	8 (3.3%)	
Aneurysm size, ml, m (IQR)	6.3 (6.1-8.7)	6.3 (6.0-8.7)	0.558
SNPs related to ASR, n (%)			
GP1BA~rs6065 (A>C)			<0.001[†]
A/A	100 (76.9%)	234 (96.7%)	
A/C	30 (23.1%)	6 (2.5%)	
C/C	0 (0.0%)	2 (0.8%)	

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TBXA2R~rs1131882 (A>G)			0.003[†]
A/A	36 (27.7%)	94 (38.8%)	
G/A	60 (46.2%)	115 (47.5%)	
G/G	34 (26.2%)	33 (13.6%)	
TBXA2R~rs4523 (A>G)			0.016[†]
A/A	62 (47.7%)	143 (59.1%)	
A/G	52 (40.0%)	85 (35.1%)	
G/G	16 (12.3%)	14 (5.8%)	
PTGS2~rs12042763 (G>T)			<0.001[†]
G/G	47 (36.2%)	171 (70.7%)	
G/T	75 (57.7%)	59 (24.4%)	
T/T	8 (6.2%)	12 (5.0%)	
PTGS2~rs20417 (C>G)			<0.001[†]
C/C	110 (84.6%)	234 (96.7%)	
C/G	20 (15.4%)	8 (3.3%)	
NOS3~rs1799983 (G>T)			0.300
G/G	99 (76.2%)	194 (80.2%)	
G/T	25 (19.2%)	45 (18.6%)	
T/T	6 (4.6%)	3 (1.2%)	
ASR-CN score, m (IQR)	4 (3-6)	2 (1-4)	<0.001[†]
CYP2C19 metabolizer, n (%)			0.995
EM	47 (36.2%)	91 (37.6%)	
IM	70 (53.8%)	122 (50.4%)	
PM	13 (10.0%)	29 (12.0%)	

†, the difference was significant.

ASR, aspirin resistance; CA, coronary artery; APTT, activated partial thromboplastin time; PT, Prothrombin time; Fbg, fibrinogen; ACA, anterior cerebral artery; AcomA, anterior communicating artery; ICA, internal carotid artery; MCA, middle cerebral artery; PC, posterior circulation; SNP, single-nucleotide polymorphism; EM, extensive metabolizer; IM, intermediate metabolizer; PM, poor metabolizer.

Supplemental table 5. Multivariate logistic analysis of factors related to ASR

Parameters	Crude		Adjusted[§]	
	OR (95%CI)	*P* value	OR (95%CI)	*P* value
ASR-CN score	1.69 (1.48-1.93)	<0.001	1.73 (1.51-1.99)	<0.001

§, the result was adjusted by age, gender, dyslipidemia, diabetes mellitus and platelet count.

ASR, aspirin resistance.

Supplemental table 6. The ischemic events in ASR patients and non-ASR patients

| Events, n (%)	ASR n=130	Non-ASR n=242	*P* value
Ischemic stroke	20 (15.4%)	17 (7.0%)	0.016
Stent thrombosis	1 (0.8%)	1 (0.4%)	0.655
Transient ischemic attack	1 (0.8%)	4 (1.7%)	0.481
Death from cerebrovascular causes	0 (0.0%)	1 (0.4%)	0.464

ASR, aspirin resistance.

Supplemental table 7. Univariate logistic analysis of factors related to 30-day ischemic events

Parameters	OR (95%CI)	*P* value
Age	0.99 (0.96-1.02)	0.558
Male gender	1.28 (0.68-2.40)	0.443
Hypertension	1.09 (0.58-2.06)	0.788
Dyslipidemia	1.58 (0.62-4.05)	0.340
Diabetes mellitus	1.17 (0.60-2.30)	0.647
CA diseases	1.86 (0.72-4.81)	0.202
Ischemic stroke	1.96 (1.02-3.79)	0.044[†]
Ever-or-now smokers	1.23 (0.65-2.33)	0.527
Regular drinkers	0.43 (0.10-1.85)	0.257
Platelet count	1.00 (1.00-1.01)	0.482
APTT	1.00 (0.97-1.02)	0.873
PT	0.42 (0.13-1.37)	0.148
Fbg	1.19 (0.84-1.70)	0.326
Aneurysm locations		
AcomA/ACA	Reference	
ICA	0.81 (0.29-2.25)	0.681
MCA	0.62 (0.20-1.97)	0.419
PC	…	…
Aneurysm size	1.06 (0.95-1.18)	0.315
ASR (TEG-AA <50%)	1.94 (1.04-3.64)	0.039[†]
ASR-CN score	1.21 (1.05-1.40)	0.010
CYP2C19 metabolizer		
EM	Reference	
IM	6.20 (2.13-18.05)	0.001[†]
PM	11.89 (3.55-39.83)	<0.001[†]

[†], the difference was significant.

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ASR, aspirin resistance; CA, coronary artery; APTT, activated partial thromboplastin
time; PT, Prothrombin time; Fbg, fibrinogen; ACA, anterior cerebral artery; AcomA,
anterior communicating artery; ICA, internal carotid artery; MCA, middle cerebral
artery; PC, posterior circulation; EM, extensive metabolizer; IM, intermediate
metabolizer; PM, poor metabolizer.

Supplemental figures
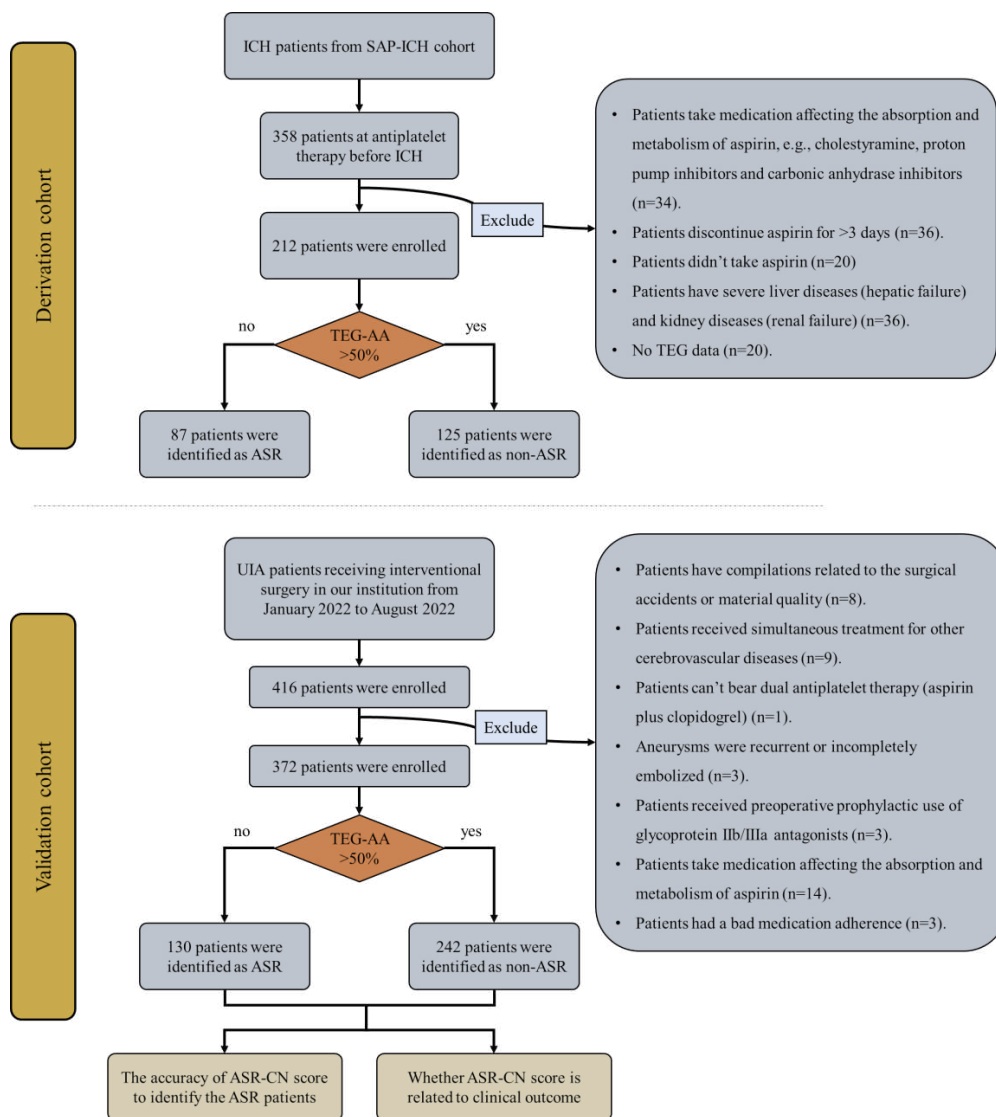
Supplemental figure 1. Flow char of patient enrollment.
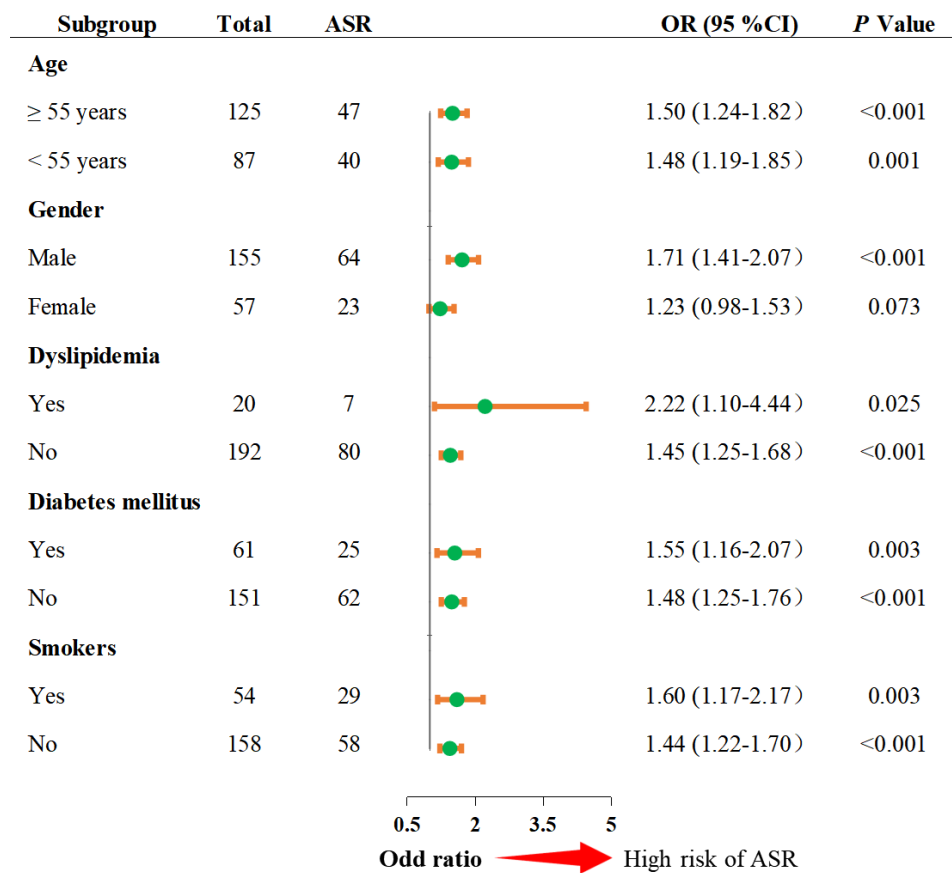
We included 212 ICH patients from SAP-ICH cohort as the derivation cohort. Among them, 87 patients were identified as the ASR (with TEG-AA <50%, at discontinuing aspirin for no more than 3 days). Moreover, we also enrolled 372 UIA patients receiving interventional surgery as the validation cohort. Among them, 130 patients were identified as the ASR (with TEG-AA <50%).
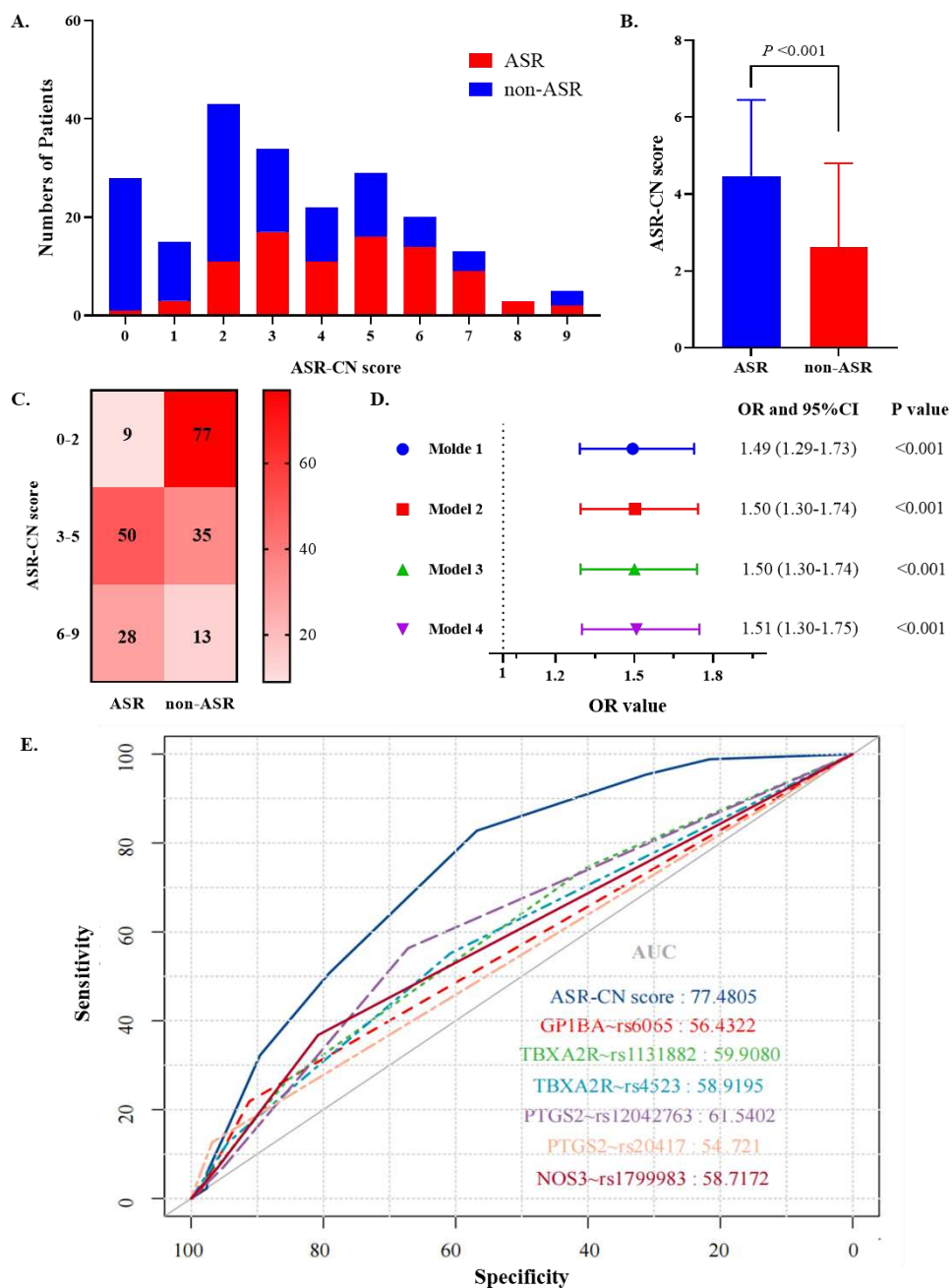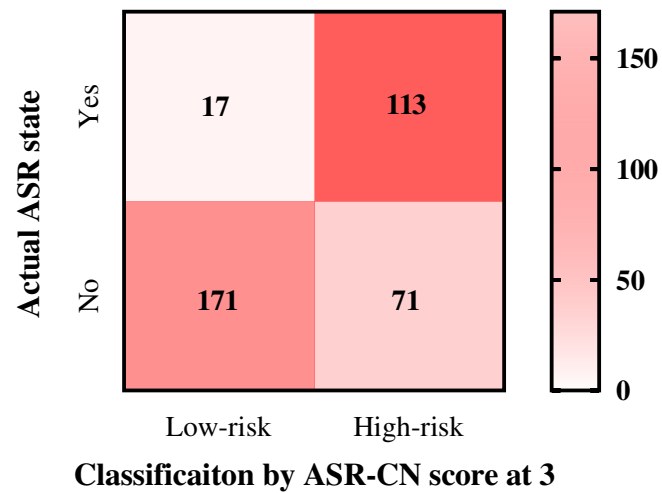
Supplemental figure 2. The accuracy of ASR-CN score to discriminate the ASR patients within the derivation cohort.

A. The distribution of ASR patients in each ASR-CN score.

B. The histogram presents that the ASR patients had a higher ASR-CN score comparing with non-ASR patients.

C. The confusion matrix presents the number and percentage of ASR in each ASR-CN

score interval. The patients with higher ASR-CN score are more likely to have ASR.

D. The forest plot presents the result of logistic analysis of ASR-CN score for ASR. Model 1 was the crude result. Model 2 was the result adjusted by age and gender. Models 3 was the result adjusted by dyslipidemia and diabetes mellitus. Model 4 was the result adjusted by platelet count, APTT, PT, and fibrinogen.

E. The accuracy of ASR-CN score and genetic types of *GP1BA, TBXA2R, PTGS2* and *NOS3* to discriminate ASR patients from non-ASR patients.

ASR, aspirin resistance; APTT, activated partial thromboplastin time; PT, prothrombin time.

Subgroup	Total	ASR		OR (95 %CI)	*P* Value
Age					
≥ 55 years	125	47		1.50 (1.24-1.82)	<0.001
< 55 years	87	40		1.48 (1.19-1.85)	0.001
Gender					
Male	155	64		1.71 (1.41-2.07)	<0.001
Female	57	23		1.23 (0.98-1.53)	0.073
Dyslipidemia					
Yes	20	7		2.22 (1.10-4.44)	0.025
No	192	80		1.45 (1.25-1.68)	<0.001
Diabetes mellitus					
Yes	61	25		1.55 (1.16-2.07)	0.003
No	151	62		1.48 (1.25-1.76)	<0.001
Smokers					
Yes	54	29		1.60 (1.17-2.17)	0.003
No	158	58		1.44 (1.22-1.70)	<0.001

0.5 2 3.5 5

Odd ratio High risk of ASR

Supplemental figure 3. Subgroup analysis of ASR-CN score for ASR within the derivation cohort.

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Supplemental figure 4. The performance of ASR-CN score in classifying ASR and non-ASR patients within the validation cohort.

ASR, aspirin resistance.
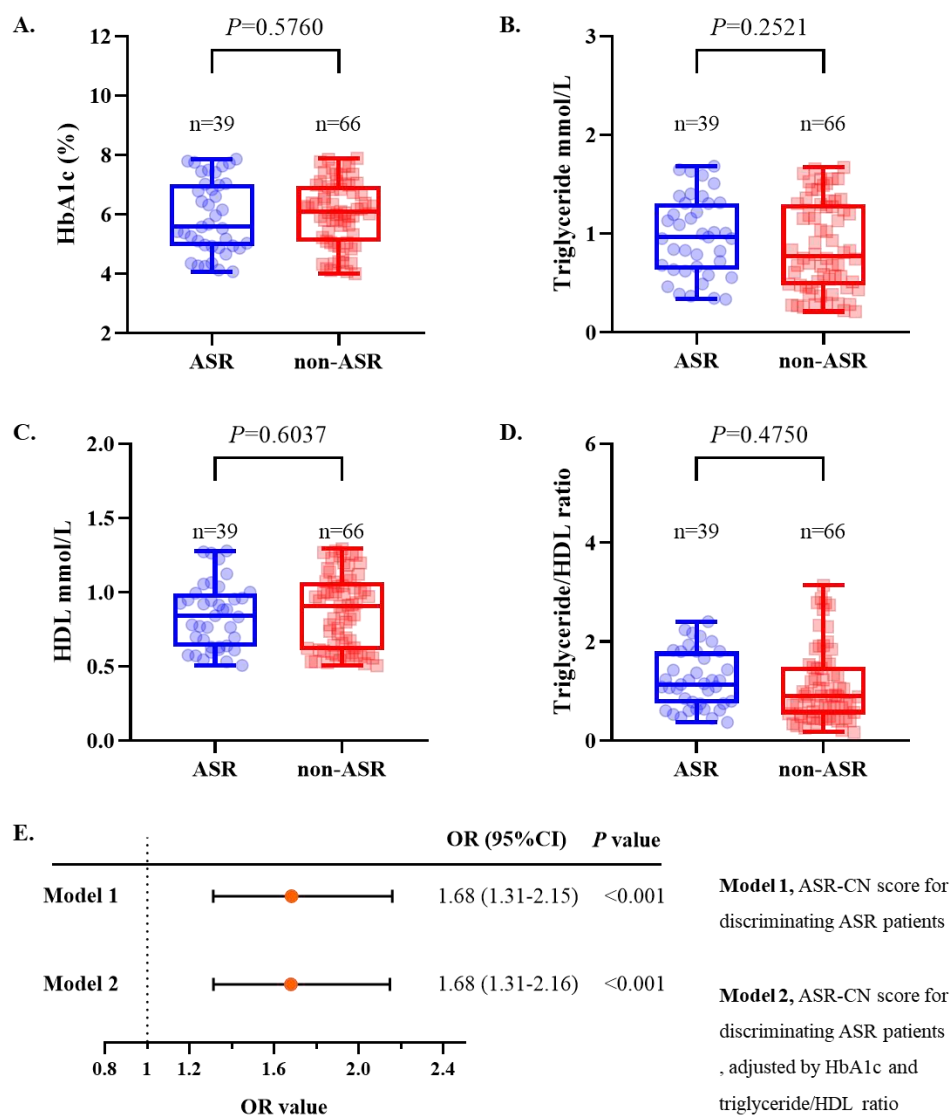
Supplemental figure 5. Subgroup analysis of ASR-CN score for discriminating the ASR based on the patients with diabetes mellitus within the validation cohort.

A. The histogram presents the difference of HbA1c level between ASR patients and non-ASR patients.

B. The histogram presents the difference of triglyceride level between ASR patients and non-ASR patients.

C. The histogram presents the difference of HDL level between ASR patients and non-ASR patients.

D. The histogram presents the difference of triglyceride/HDL ratio between ASR

patients and non-ASR patients.

E. The forest plot presents the result of logistic analysis of ASR-CN score for the risk of 30-day ischemic events. Model 1 was ASR-CN score only for discriminating ASR patients. Model 2 was ASR-CN score for discriminating ASR patients, adjusted by HbA1c and triglyceride/HDL ratio.

ASR, aspirin resistance; HbA1c, glycosylated hemoglobin; HDL, high density lipoprotein.
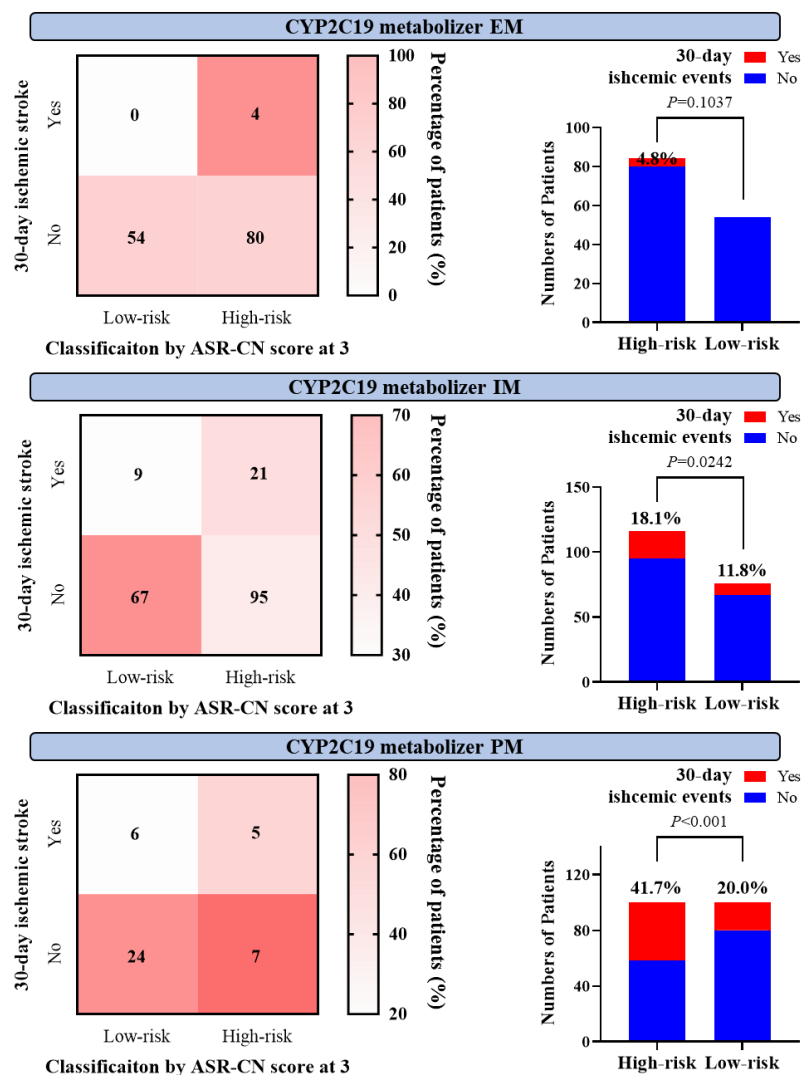
Supplemental figure 6. Subgroup analysis of ASR-CN score for evaluating the risk of 30-day ischemic events based on the CYP2C19 metabolizer within the validation cohort.

Subgroup analysis based on difference CYP2C19 metabolizer within the validation cohort. For EM metabolizers, no difference was found in the percentage of ischemic events between high-risk patients (ASR-CN score ≥3) and low-risk patients (ASR-CN score <3). For IM and PM metabolizers, the high-risk patients had a higher percentage of ischemic events compared with low-risk patients.

EM, extensive metabolizer; IM, intermediate metabolizer; PM, poor metabolizer.