Supplementary material

Impact of premorbid hypertension and antihypertensive medications on the severity of aneurysmal subarachnoid hemorrhage: a multicenter study

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Section S1: STROBE checklist

The presentation was following The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement, and the checklist was provided below.

	Item No.	Recommendation	Page No.
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	1-2
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	3-5
Objectives	3	State specific objectives, including any prespecified hypotheses	4
Methods			
Study design	4	Present key elements of study design early in the paper	5
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	5
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	5-6
		(*b*) For matched studies, give matching criteria and number of exposed and unexposed	NA
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	6
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	6-7
Bias	9	Describe any efforts to address potential sources of bias	6-10
Study size	10	Explain how the study size was arrived at	S4.1
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	8
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	8-11; S4

		(*b*) Describe any methods used to examine subgroups and interactions	10
		(*c*) Explain how missing data were addressed	8; S4.2
		(*d*) If applicable, explain how loss to follow-up was addressed	NA
		(*e*) Describe any sensitivity analyses	10
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	Figure 1
		(b) Give reasons for non-participation at each stage	Figure 1
		(c) Consider use of a flow diagram	Figure 1
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	10
		(b) Indicate number of participants with missing data for each variable of interest	Table 1
		(c) Summarise follow-up time (eg, average and total amount)	NA
Outcome data	15*	Report numbers of outcome events or summary measures over time	11
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	11; Table 2
		(*b*) Report category boundaries when continuous variables were categorized	NA
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	NA
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	9-11; Table 2, Figure 2
Discussion			
Key results	18	Summarise key results with reference to study objectives	12
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	17
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of	12-16

		analyses, results from similar studies, and other relevant evidence	
Generalisability	21	Discuss the generalisability (external validity) of the study results	16
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	Title page

Section S2: inclusion and exclusion criteria **of study population**

During the process of analyzing the impact of blood pressure control on the severity of aSAH (step 1 analysis)**,** the study population was adult patients with aSAH registered in the database. The inclusion criteria were as follows: 1) Adult patients (≥ 18 years old) with SAH registered in this database between 2016 and 2021; 2) The cause of SAH was an intracranial aneurysm rupture and the diagnosis was confirmed using digital subtraction angiography (DSA); 3) The admission attributable to aSAH was within 48h after the disease onset; The exclusion criteria were as follows: 1) The ruptured aneurysm belonged to fusiform aneurysms, traumatic aneurysms, or feeding artery aneurysms to arteriovenous malformations (AVM); 2) The diagnosis of aSAH was indefinite or established only based on CT. During the process of analyzing the effect of preadmission RAAS inhibitors use on the disease severity (step 2 analysis), the **study population** was hypertensive patients with aSAH who had been regularly treated with antihypertensive medications before admission. The inclusion criteria were as follows: 1) aSAH patients who had the presence of premorbid hypertension; 2) Premorbid hypertension had been treated with any antihypertensive medications for at least 3 months before admission. The exclusion criteria were as follows: 1) The diagnosis of hypertension was indefinite or established after admission; 2) Those who did not start antihypertensive medications and /or only received lifestyle interventions.

Section S3 Two clinical grading scales for the stroke severity of aneurysmal subarachnoid hemorrhage (aSAH)

1.1 Hunt-Hess scale

Grade	Hunt-Hess scale
Grade 1	Asymptomatic or mild headache and slight nuchal rigidity
Grade 2	Moderate to severe headache, nuchal rigidity, no focal neurological deficit other than cranial nerve palsy
Grade 3	Confusion, lethargy, or mild focal neurological deficit other than cranial nerve palsy
Grade 4	Stupor or moderate to severe hemiparesis
Grade 5	Coma, extensor posturing, moribund appearance

1.2 World Federation of Neurological Surgeons (WFNS) scale

Grade	WFNS scale
Grade 1	GCS 15
Grade 2	GCS 14–13 without major focal deficit (aphasia or hemiparesis/hemiplegia)
Grade 3	GCS 14–13 with major focal deficit
Grade 4	GCS 12–7 with or without major focal deficit
Grade 5	GCS 6–3 with or without major focal deficit

Section S4: Statistical analysis

S4.1 Sample size considerations

With variable selection procedures (seeing below), the number of confounders in this study was estimated to be no more than 20 finally. According to the principle of event per variable (EPV), one can assume that ten events (binary outcome) per independent variable are sufficient to estimate the adjusted effect of exposure. For a binary outcome for severe aSAH, like evaluating by the 2 poor clinical grading scales, with an anticipated prevalence of between 15% and 20%, it would result in a sample size of 1000 to 1333 to be sufficient for analysis.

S4.2: Multiple imputation for missing data

To deal with the missing data, a multiple imputation approach as well a sensitivity analysis comparing complete case and multiply imputed analyses was performed according to the guidance for multiple imputation [1].

1) There were eight variables that had missing data (diabetes, hyperlipidemia, PKD, ischemic stroke, previous SAH, location and size of intracranial aneurysms, and irregular aneurysm). The proportion of missing data were 0.5%, 1.3%, 7.4%, 0.7%, 0.9%, 13.1%, 22.1%, and 22.3%, respectively;

2) Since the proportions of missing data were less than 30% and the reason for missing data was the absence of the entering, the assumption that the missing data were missing at random was made;

3) Based on the assumption, a multiple imputation approach was used to account for

missing data;

4) A fully conditional specification method was used to impute missing values for variables. We used a predictive mean matching method for scale variables. The imputations were done using SPSS (version 25.0);

5) The variables that were included in the imputation procedure were age, sex, ethnicity, BMI, smoking, drinking, control of hypertension, prescribed antihypertensive medications, number of antihypertensive medications, diabetes, hyperlipidemia, atrial fibrillation, coronary heart diseases, polycystic kidney diseases, genetic diseases, peripheral vascular diseases, ischemic stroke, previous SAH, and number, location, size, and irregularity of intracranial aneurysms. Additionally, the outcome variables, including Hunt-Hess scale and WFNS scale, were also included in the model.

6) Since at least 20 imputed datasets is preferable to reduce sampling variability from the imputation process, 25 imputed datasets were constructed in this study finally.

7) A sensitivity analysis comparing complete data and imputed data was performed (Table 2).

Section S5 Tables

Table S1 Comparisons of baseline characteristics between hypertensive patients and non-hypertensive patients

Characteristics	Miss-ing	Hypertensive patients (*n*=1959)	Non-hypertensive patients (*n*=2586)		P
Age (years)	0	59.55±10.47	55.17±11.31	13.356	<0.001
≤60 [*n*(%)]		996(50.8)	1706(66.0)	105.820	<0.001
>60 [*n*(%)]		963(49.2)	880(34.0)		
Sex [*n*(%)]	0				
Male		667(34.0)	1006(38.9)	11.290	0.001
Female		1292(66.0)	1580(61.1)		
Ethnicity [*n*(%)]	0				
Han		1871(95.5)	2500(96.7)	4.119	0.042
Others		88(4.5)	86(3.3)		
BMI (kg/m^2)	0				
<24.0 [*n*(%)]		1030(52.6)	1698(65.7)	79.513	<0.001
≥24.0 [*n*(%)]		929(47.4)	888(34.4)		
Smoking status [*n*(%)]	0				
Never		1597(81.5)	2141(82.8)	2.998	0.392
Ever		27(1.4)	36(1.4)		
Current		296(15.1)	373(14.4)		
Passive		39(2.0)	36(1.4)		
Drinking status [*n*(%)]	0				
Never		1749(89.3)	2331(90.1)	2.666	0.446
Moderate drinking		136(6.9)	179(6.9)		
Heavy drinking		66(3.4)	66(2.6)		
Drinking but quit		8(0.4)	10(0.4)		
Diabetes [*n*(%)]	13				
No diabetes		1802(92.5)	2556(99.0)	127.790	<0.001
Diabetes with antihyperglycemic agents		103(5.3)	22 (0.9)		
Diabetes without antihyperglycemic agents		44(2.3)	5(0.2)		
Polycystic kidney diseases [*n*(%)]	490	3(0.2)	3(0.1)	0.081	0.775
Atrial fibrillation [*n*(%)]	0	5(0.3)	1(0.0)	3.965	0.091
Coronary heart diseases [*n*(%)]	0	99(5.1)	24(0.9)	72.050	<0.001
Other heart diseases [*n*(%)]	0	69(3.5)	10(0.4)	64.160	<0.001
Hyperlipidemia [*n*(%)]	44				
No hyperlipidemia		1901(98.7)	2570(99.8)	20.686	<0.001
Hyperlipidemia with antihyperlipidemic agents		10(0.5)	1(0.0)		
Hyperlipidemia without antihyperlipidemic agents		15(0.8)	4(0.2)		
Ischemic stroke [*n*(%)]	208	87(4.5)	27(1.1)	48.431	<0.001

Previous SAH	226	54(2.8)	50(2.1)	2.422	0.120
Genetic diseases [*n*(%)]	0	16(0.8)	10(0.4)	3.624	0.057
Peripheral vascular diseases [*n*(%)]	0	9(0.5)	7(0.3)	1.132	0.287
Preadmission anti-PLT medications [*n*(%)]	0	123(6.3)	41(1.60)	70.587	<0.001
Preadmission anti-coagulation medications [*n*(%)]	0	4(0.2)	8(0.3)	0.468	0.494
Location of the ruptured aneurysms [*n*(%)]	659				
ICA		449(26.4)	571(26.1)	4.327	0.115
MCA		282(16.6)	314(14.4)		
ACA/PCoA/posterior		967(56.9)	1303(59.6)		
Size of the ruptured aneurysm(mm)		5.00[3.80-6.50]	4.90[3.50-6.40]	1.171	0.242
<5mm [*n*(%)]		746(49.6)	955(50.4)	0.241	0.623
≥5mm [*n*(%)]		758(50.4)	938(49.6)		
Number of aneurysms [*n*(%)]	0				
1		1658(84.6)	2320(89.7)	34.623	<0.001
2		224(11.4)	224(8.7)		
≥3		77(3.9)	42(1.6)		
Irregular aneurysm [*n*(%)]	1317	314(21.4)	282(16.0)	15.049	<0.001
Hunt-Hess scale	0				
1-3		1668(85.1)	2323(89.8)	22.851	<0.001
4-5		291(14.9)	263(10.2)		
WFNS scale	0				
1-3		1373(70.1)	1988(76.9)	26.666	<0.001
4-5		586(29.9)	598(23.1)		

Table S2 Comparisons of baseline characteristics between RAAS inhibitors users and non-RAAS inhibitors users

Characteristics	Miss-ing	Non-RAAS inhibitors users (*n*=948)	RAAS inhibitors users (*n*=290)		P
Age (years)	0	60.5±9.8	61.3±10.3	1.263	0.207
≤60 [*n*(%)]		448 (47.3)	130 (44.8)	0.527	0.468
>60 [*n*(%)]		500 (52.7)	160 (55.2)		
Sex [*n*(%)]	0				
Male		300 (31.6)	89 (30.7)	0.094	0.759
Female		648 (68.4)	201 (69.3)		
Ethnicity [*n*(%)]	0				
Han		913 (96.3)	287 (99.0%)	5.271	0.022
Others		35 (3.7)	3 (1.0)		
BMI (kg/m^2)	0	24.0±3.1	24.4±2.9	1.911	0.056
<24.0 [*n*(%)]		492 (51.9)	143 (49.3)	0.596	0.440
≥24.0 [*n*(%)]		456 (48.1)	147 (50.7)		
Smoking status [*n*(%)]	0				
Never		779 (82.2)	239 (82.4)	1.011	0.794
Ever		16 (1.7)	4 (1.4)		
Current		132 (13.9)	38 (13.1)		
Passive		21 (2.2)	9 (3.1)		
Drinking status [*n*(%)]	0				
Never		848 (89.5)	270 (93.1)	4.059	0.235
Moderate drinking		70 (7.4)	12 (4.1)		
Heavy drinking		26 (2.7)	7 (2.4)		
Drinking but quit		4 (0.4)	1 (0.3)		
Control of hypertension [*n*(%)]	0				
Controlled		364 (38.4)	126 (43.4)	20.320	<0.001
Uncontrolled		317 (33.4)	120 (41.4)		
Unmonitored		267 (28.2)	44 (15.2)		
Number of antihypertensive drugs [*n*(%)]	0				
1		846 (89.2)	145 (50.0)	214.104	<0.001
≥2		102 (10.8)	145 (50.0)		
Diabetes [*n*(%)]	6				
No diabetes		870 (92.3)	262 (90.7)	4.106	0.127
Diabetes with antihyperglycemic agents		60 (6.4)	26 (9)		
Diabetes without antihyperglycemic agents		13 (1.4)	1 (0.3)		
Polycystic kidney diseases [*n*(%)]	91	1 (0.1)	2 (0.7)	2.949	0.148
Atrial fibrillation [*n*(%)]	0	4 (0.4)	0 (0.0)	1.228	0.579
Coronary heart diseases [*n*(%)]	0	56 (5.9)	18 (6.2)	0.035	0.851
Other heart diseases [*n*(%)]	0	45 (4.7)	13 (4.5)	0.035	0.852

Hyperlipidemia [*n*(%)]	16				
No hyperlipidemia		919 (98.1)	283 (99.3)	1.374	0.490
Hyperlipidemia with antihyperlipidemic agents		9 (1.0)	1 (0.4)		
Hyperlipidemia without antihyperlipidemic agents		9 (1.0)	1 (0.4)		
Ischemic stroke [*n*(%)]	9	44 (4.7)	22 (7.8)	3.738	0.053
Previous SAH	11	30 (3.2)	10 (3.5)	0.054	0.817
Genetic diseases [*n*(%)]	0	5 (0.5)	3 (1.0)	0.889	0.400
Peripheral vascular diseases [*n*(%)]	0	4 (0.4)	2 (0.7)	0.330	0.629
Preadmission anti-PLT medications [*n*(%)]	0	75 (7.9)	38 (13.1)	7.217	0.007
Preadmission anti-coagulation medications [*n*(%)]	0	0 (0.0)	2 (0.7)	5.816	0.055
Location of the ruptured aneurysms [*n*(%)]	162				
ICA		212 (25.8)	72 (28.2)	0.593	0.743
MCA		131 (16.0)	40 (15.7)		
ACA/PCoA/posterior		478 (58.2)	143 (56.1)		
Size of the ruptured aneurysm(mm)	273	5.0[3.9-6.4]	4.6[3.6-6.0]	1.040	0.298
<5mm [*n*(%)]		360 (48.6)	117 (52.0)	0.775	0.379
≥5mm [*n*(%)]		380 (51.4)	108 (48.0)		
Number of aneurysms [*n*(%)]	0				
1		778 (82.1)	253 (87.2)	4.274	0.118
2		123 (13.0)	27 (9.3)		
≥3		47 (5)	10 (3.4)		
Irregular aneurysm [*n*(%)]	276	158 (21.3)	68 (31.1)	9.011	0.003

Table S3 treatment effect of RAAS inhibitors on the stroke severity of aSAH based on varied classifications of the two clinical grading scales

Outcomes	Exposures	Imputed data		Completed data	
		OR	P	OR	P
Hunt-Hess scale	Non-RAAS inhibitors use	Reference		Reference	
1 vs. 2-5	RAAS inhibitors use	0.714[0.521-0.977]	0.035	0.698[0.510-0.957]	0.025
1-2 vs. 3-5	RAAS inhibitors use	0.604[0.409-0.891]	0.011	0.552[0.334-0.911]	0.020
1-3 vs. 4-5	RAAS inhibitors use	0.653[0.430-0.992]	0.046	0.558[0.340-0.918]	0.022
1-4 vs. 5	RAAS inhibitors use	0.460[0.188-1.123]	0.088	0.610[0.237-1.569]	0.305
WFNS scale	Non-RAAS inhibitors use	Reference		Reference	
1 vs. 2-5	RAAS inhibitors use	0.786[0.563-1.096]	0.156	0.663[0.437-1.005]	0.053
1-2 vs. 3-5	RAAS inhibitors use	0.697[0.506-0.959]	0.027	0.656[0.447-0.965]	0.032
1-3 vs. 4-5	RAAS inhibitors use	0.656[0.469-0.918]	0.014	0.587[0.391-0.882]	0.010
1-4 vs. 5	RAAS inhibitors use	0.761[0.450-1.288]	0.309	0.713[0.394-1.292]	0.264