npj | aging

Article

Published in partnership with the Japanese Society of Anti-Aging Medicine

https://doi.org/10.1038/s41514-025-00202-7

Early vascular aging ambulatory score in acute ischemic stroke

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Understanding the impact of early vascular aging (EVA) on acute ischemic stroke (AIS) outcomes may provide new insights for improving prognostic assessments and developing targeted therapeutic strategies. This study aimed to validate the EVA ambulatory score (EVAAs) in AIS patients, assessing its association with stroke type, severity, and prognosis. Among the 2,730 AIS patients with a mean age of 72.0 ± 14.4 years, 83.4% exhibited EVA. EVA was identified as an independent predictor of poor outcome at both discharges (aOR:1.72, 95%CI:1.25–2.36, $p < 0.001$) and at 90 days (aOR:2.22, 95% CI:1.49–3.31, $p < 0.001$). In subgroup analyses, EVAAs showed improved predictive value in AIS patients with a lower cardiovascular disease burden and a non-atherogenic lipid profile. The EVAAs, as an indicator of EVA that could be easily integrated into daily clinical practice, are a significant predictor of adverse outcomes in AIS patients.

Despite advancements in acute and secondary management for acute ischemic stroke (AIS), substantial residual risk for poor functional outcomes, stroke recurrence, other cardiovascular diseases (CVD), and mortality remains[1–5]. Lately, the concept of vascular aging, specifically arterial stiffening, has emerged as a crucial factor in the development of CVD and a potential target to improve outcomes beyond traditional therapeutic measures[6–10].

Early vascular aging (EVA) syndrome was introduced in 2008 and represents the premature changes (arteriosclerosis) in artery structure and function, particularly arterial stiffness, reflecting the aging process[11]. A recent meta-analysis has provided evidence that EVA is present in patients with AIS, as indicated by PWV measurements taken shortly after stroke onset[12]. Furthermore, patients with AIS and advanced vascular aging, assessed through PWV measurements during hospitalization, face an increased likelihood of adverse outcomes, including functional impairment, mortality, major adverse cardiovascular events, and stroke recurrence over various time periods[13–16].

Pulse wave velocity (PWV), the gold standard for measuring arterial stiffness, is a proven superior predictor of cardiovascular events compared to traditional risk factors[7,8,17]. However, measuring PWV during the acute phase of stroke requires specialized devices and expertise, making it impractical for routine clinical use and limiting its application to experimental settings[18]. Under this perspective, the early vascular aging ambulatory score (EVAA), calculated using 24-h ambulatory blood pressure

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monitoring (ABPM) values and classic cardiovascular risk factors, demonstrating great accuracy, sensitivity, and specificity in predicting EVA in hypertensive patients[19], could be used efficiently in daily clinical practice, as a proxy of PWV.

The aim of this study is to externally validate the EVAAs in patients with AIS for its prognostic role of and its association with stroke type and severity, using individual patient data (IPD) pooled from previously conducted relevant studies. Enhancing the understanding of vascular aging's impact on AIS outcomes could offer a new avenue for improving prognostic assessments and targeted therapeutic strategies in stroke management.

Results

General characteristics

In the present pooled analysis, 13 AIS Clinical Research Centres from seven different countries (United Kingdom, Switzerland, Greece, Finland, Italy, Korea, and Japan) participated (Table 1). From a total of 2939 AIS patients, 209 were excluded due to missing EVAA values (including one patient under 18 years of age). Compared to the included AIS patients, the excluded group had higher percentages of European origin, dyslipidemia, prior history of stroke or TIA, and cancer, while showing lower incidences of diabetes, CAD, and previous disability. They also had higher BMI and NIHSS scores (Supplemental Table 2).

Finally, the analyses included 2730 patients with a mean age of 72.0 ± 14.4 years, 31.9% of whom were over the age of 80, and 56.8% were male. Among these patients, 69.3% had hypertension, 28.2% had diabetes, 43.1% had dyslipidemia, 24.4% had atrial fibrillation, 23.2% had CAD, 18% had a prior history of stroke or TIA, and 25.7% were smokers. Additionally, 17.5% had prior disability. According to the TOAST classification, 18.7% had LAA, 23.7% had CE, 16.5% had SVD, 9.8% had stroke due to other determined etiology, and 31.2% had IUC (Table 2, Fig. 1). Regarding stroke severity, 50.9% experienced minor stroke (NIHSS 0–4), 32.2% moderate stroke (NIHSS 5–15), 7.8% moderate to severe stroke (NIHSS 16–20), and 9.1% severe stroke (NIHSS 21–42) (Table S2, Fig. 2).

24-h BP monitoring was performed in the hyper-acute phase (0–24 h) in 35.0% of the patients, in the acute phase (1–7 days) in 27.8%, and in the sub-acute phase (>7 days) in 37.2% (Supplemental Table S3). mRS outcome at discharge was reported for 2,138 AIS patients, with 45.7% showing poor outcomes. Mortality at discharge was reported for 2544 AIS patients, with a 3.9% mortality rate. The 90-day mRS outcome was reported for 1488 AIS patients, with 44.6% showing poor outcomes and 9.3% mortality. Mortality beyond one year was reported for 498 AIS patients, with a 37.6% mortality rate. Stroke recurrence was reported in 638 AIS patients, with a 7.7% recurrence rate (Table 2).

Comparison of AIS patients with EVA versus NoVA

Among the 2730 patients with AIS, 83.4% exhibited EVA, with a mean EVAAs of 69.8 ± 9.8%. Patients with EVA differed in the variables used for calculating EVAAs and had a higher incidence of hypertension (71.7% vs. 57.5%, $p < 0.001$), diabetes (30.0% vs. 19.6%, $p < 0.001$), and pre-stroke disability (18.8% vs. 10.2%, $p < 0.001$). They also presented with more severe strokes, as indicated by higher NIHSS score (p = 0.014), but received thrombolytic treatment less frequently (17.5% vs. 22.9%, $p = 0.013$). Interestingly, AIS patients with EVA had a lower prevalence of smoking (24.3% vs. 33.1%, $p < 0.001$) (Table 2). This finding may reflect the "smoking paradox," where younger patients, typically with NoVA, experience strokes at a younger age[20]. It could suggest that age, hypertension, and diabetes play a more significant role in vascular aging than smoking.

In the various AIS subtypes classified by TOAST, the mean EVAAs was approximately 65%. Patients with large artery atherosclerotic and cardioembolic strokes had a mean EVAAs of 65.5%, while those with infarct of undetermined cause had the lowest mean EVAAs value of 64.6% (Fig. 1). Neither the mean EVAAs values ($p = 0.66$) nor the incidence of EVA ($p = 0.34$) showed statistically significant differences among the different TOAST categories (Supplemental Table S4).

Across the different categories of AIS based on stroke severity at admission, as measured by the NIHSS, mean EVAAs values increased progressively from minor to severe strokes ($p = 0.010$). However, the incidence of EVA did not show statistically significant differences among these stroke severity categories ($p = 0.30$) (Supplemental Table S5). Similarly, the multivariate shift analysis assessing the odds ratio of EVA within NIHSS categories found no statistically significant association ($p = 0.42$) (Fig. 2). However, when the EVAA score was considered as a continuous variable, it was independently and significantly associated with increased stroke severity (adjusted OR: 1.01, 95%CI: 1.00–1.01, $p = 0.039$). This analysis was adjusted for total and LDL cholesterol levels, as well as hypertension, dyslipidemia, atrial fibrillation, CAD, previous stroke or TIA and smoking (Supplemental Table S6).

Outcome

Table 3 presents the results of the multivariate analyses, which assessed the independent predictive role of the presence of EVA as a dichotomous variable and EVAAs as a continuous variable for several outcomes. The presence of EVA was found to be an independent predictor of mRS score (shift analysis) and poor outcome (mRS>2) at both discharge (mRS adjusted odds ratio [aOR]: 1.52, 95% confidence interval [CI]: 1.21–1.91, $p < 0.001$; mRS > 2 aOR: 1.72, 95%CI: 1.25–2.36, $p < 0.001$) and at 90 days (mRS aOR: 1.87, 95%CI: 1.41–2.47, $p < 0.001$; mRS>2 aOR: 2.22, 95%CI: 1.49–3.31, $p < 0.001$) after adjusting for total cholesterol levels, triglycerides (only at discharge), LDL cholesterol (only at discharge), NIHSS score on admission, and the presence of hypertension, atrial fibrillation, CAD, previous stroke or TIA, and smoking history (Table 3, Fig. 3).

Subgroup analysis of AIS patients based on clinical and laboratory characteristics revealed that the presence of EVA was a better independent predictor for poor outcome (mRS > 2) at discharge in males, hypertensive patients, those without diabetes, atrial fibrillation, CAD, prior stroke or TIA, non-smokers, and those without prior disability. (Fig. 4, Supplemental Table S16, Fig. S1). For the predictive value of EVA for poor outcomes (mRS > 2) at 3 months (90 days), EVA was a better predictor in patients aged 70–80 years, in both sexes, irrespective of hypertension, diabetes, dyslipidemia, and smoking habit, but only in those without atrial fibrillation, CAD, prior stroke, and prior disability, and those with normal weight (≤25 kg/m²). Additionally, EVA was a better predictor in AIS patients who underwent 24-h ABPM either in the hyper-acute (0–24 h) or acute (1–7 days) phase of stroke, with normal heart rate (60–100 bpm). EVA was also a predictor in AIS patients of minor (NIHSS 0–4) and moderate severity (NIHSS 5–15) suffering from LAA or CE stroke or undetermined cause (IUC) in those who do not undergo thrombolysis or thrombectomy (Fig. 4, Supplemental Table S28, Fig. S1).

Subgroup analysis for EVAAs as a continuous variable, revealed that it was a better independent predictor for poor outcome (mRS >2) at discharge in almost the same subgroups as the analysis with the presence of EVA as a dichotomous variable. However, the difference from the analysis with EVA was that the predictive value of the EVAA score was also significant in patients aged 70–80 years, those with diabetes, CAD, prior stroke or TIA, and those with renal function (eGFR) > 60 mL/min/1.73 m². Additionally, EVAAs were a better independent predictor in AIS patients who underwent 24-h ABPM at all three phases: hyper-acute (0–24 h), acute (1–7 days), and sub-acute (>7 days). Its predictive value was also significant in AIS patients of minor, moderate, and moderate to severe (NIHSS < 21) stroke severity, in those with LAA stroke and IUC, and in those who did not undergo thrombolysis (Supplemental Table S17, Supplemental Figs. S2, S3). Similarly, subgroup analysis for EVAAs as a continuous variable showed that it was a better independent predictor for poor outcome (mRS > 2) at 90 days in almost the same subgroups as the analysis with the presence of EVA as a dichotomous variable (Supplemental Table S29, Supplemental Figs. S2, S3).

Regarding mortality outcomes, only EVAAs as a continuous variable was an independent predictor of death at 90 days (aOR: 1.03, 95%CI: 1.01–1.05, $p = 0.003$) and according to the Cox proportional hazards survival regression analysis for general mortality over time (adjusted hazard

https://doi.org/10.1038/s41514-025-00202-7

Table 1 | Acute ischemic stroke studies and registries participating in the IPD pooled analysis

Study/Registry	Institute/Town/Country	Design	AIS	Study period	Stroke onset to ABPM	ABPM device	Intervals of 24 h-ABPM	Outcome
ASTRAL Registry[38]	Lausanne University Hospital (CHUV), Lausanne, Switzerland	Prospective Cohort	629	2023	51.2 h	NR	NR	mRS (discharge)
Local Registry	"Laiko" General Hospital, Athens, Greece	Prospective Cohort	65	10/ 2020–2/2021	47.4 h	Mobil-O-Graph 24 h PWA v.20 (I.E.M. GmbH, Germany)	15 min (day) & 30 min (night)	mRS (discharge, 90 days), stroke recurrence
Published Study[39]	Siena University Hospital, Siena, Italy	Prospective Cohort	148	NR	24 h	Bedside Monitor Life Scope I BSM-2303K (International Div., Nihon Kohden Corp., Tokyo, Japan)	30 min (06:00-00:00) & 60 min (00:00–06:00)	mRS (discharge, 90 days)
SECRETO study[22]	University Hospitals of Helsinki (HUS), Kuopio, Tampere and Turku, Finland	Prospective Multicentre Case-control	132	10/ 2015–2/2020	20.4 days	Spacelabs Healthcare (Snoqualmie, WA, USA) or Novacor (Rueil-Malmaison, France) or Schiller AG (Baar, Switzerland)	20 min (06:00-22:00) & 30 min (22:00–06:00)	mRS (90 days)
Published Study[40]	University Hospital Zurich, Zurich, Switzerland	Cross-sectional	105	NR	70 days	Mobil-O-Graph 24 h PWA v.20 (I.E.M. GmbH, Germany)	15 min (08:00–22:00) & 30 min (22:00–08:00)	NIHSS
Published Study[41]	Hiroshima University Hospital, Chikamori Hospital, Hiroshima and Kochi, Japan	Retrospective Double-centre Cohort	856	4/2010–3/2018	7.8 days	FB-270 (Fukuda Denshi Company Ltd, Tokyo, Japan)	30 min	mRS (discharge, 90 days)
PREVISE Study[42]	University Hospitals of Thessaloniki "AHEPA", Larissa and Ioannina, Greece	Prospective Multicentre Cohort	228	11/ 2013–9/2017	18.9 h	TM-2430 (A&D Company Ltd, Tokyo, Japan)	20 min	mRS (discharge, 90 days, 1 year)
Published Study[43]	Hanyang University Hospital, Seoul, Republic of Korea	Retrospective Cohort	369	3/2011–2/2014	7–14 days	TM-2430 (A&D Medical, Milpitas, CA, USA)	15 min (day) & 30 min (night)	mRS (discharge), stroke recurrence
Athens Stroke Registry[44]	"Alexandra" General Hospital, Athens, Greece	Prospective Cohort	239	2006–2010	10.8 h	SpaceLabs 90207 (Spacelabs Inc, Redmond, WA, USA)	15 min	mRS (discharge, 90 days, 5 years), stroke recurrence
PhD Thesis[45]	"Papageorgiou" General Hospital, Thessaloniki, Greece	Prospective Cohort	84	9/2007–7/2009	24.6 h	SpaceLabs 90207 (Spacelabs Inc, Redmond, WA, USA)	NR	Death (1 year)
GTN-2 Trial[46]	Nottingham City Hospital, Nottingham, United Kingdom	Randomized Controlled Trial	84	12/ 1998–6/2001	55.1 h	SpaceLabs 90207 (Spacelabs Inc, Redmond, WA, USA)	20 min (07:00–23:00) & 60 min (23:00–07:00)	mRS (90 days)

The "Stroke onset to ABPM" column displays the mean time in hours or days.

ABPM ambulatory blood pressure monitoring, *AIS* acute ischemic stroke (number of patients), *ASTRAL* Acute STroke Registry and Analysis of Lausanne, *GTN* glyceryl trinitrate, *hrs* hours, *IPD* individual patient data, *mRS* modified Rankin Scale, *NIHSS* National Institutes of Health Stroke Scale, *NR* not reported, *PREVISE* blood pressure variability in acute ischemic stroke, *SECRETO* searching for explanations for cryptogenic stroke in the young: revealing the etiology, triggers, and outcome.

Table 2 | Clinical and laboratory characteristics of AIS patients with comparison based on the presence of EVA

Variable	Valid values	All AIS patients	EVA (n = 2276)	NoVA (n = 454)	p
EVAAs (%)	2730	65.0 ± 14.4	69.8 ± 9.8	40.9 ± 8.0	**<0.001***
Demographic/somatometric data					
Age (years)	2730	72.0 ± 14.4	72.7 ± 15.0	68.7 ± 10.7	**<0.001***
Sex (male)	2730	1551 (56.8%)	1256 (55.2%)	295 (65.0%)	**<0.001***
BMI (kg/m^2)	2730	25.4 ± 16.3	25.2 ± 17.8	26.3 ± 4.4	**<0.001***
Clinical risk factors					
Hypertension	2730	1892 (69.3%)	1631 (71.7%)	261 (57.5%)	**<0.001***
Diabetes	2730	771 (28.2%)	682 (30.0%)	89 (19.6%)	**<0.001***
Dyslipidemia	2730	1176 (43.1%)	967 (42.5%)	209 (46.0%)	0.16
Atrial fibrillation	2649	646 (24.4%)	554 (25.0%)	92 (21.2%)	0.091
Coronary artery disease	2583	598 (23.2%)	504 (23.4%)	94 (22.1%)	0.56
Prior stroke or TIA	2594	468 (18.0%)	399 (18.5%)	69 (15.8%)	0.19
Valvular disease	1590	66 (4.4%)	55 (4.3%)	11 (4.7%)	0.82
Cancer	1506	66 (4.4%)	55 (4.3%)	11 (4.6%)	0.83
Smoking	2618	672 (25.7%)	534 (24.3%)	138 (33.1%)	**<0.001***
ABPM data					
Stroke onset-ABPM (hours)	2135	206.6 ± 1943.4	197.6 ± 1995.0	252.5 ± 1658.0	0.14
24-h SBP (mmHg)	2730	135.9 ± 20.2	138.6 ± 20.2	122.2 ± 13.3	**<0.001***
24-h DBP (mmHg)	2730	78.7 ± 11.6	79.6 ± 11.7	73.8 ± 9.8	**<0.001***
24-h HR (bpm)	2730	74.7 ± 13.8	75.6 ± 13.8	70.0 ± 12.8	**<0.001***
Laboratory data					
Admission Glu (mmol/l)	786	7.4 ± 2.7	7.5 ± 2.8	6.7 ± 1.7	**0.003***
Total cholesterol (mmol/l)	2523	4.8 ± 1.3	4.8 ± 1.3	4.9 ± 1.2	0.061
Triglycerides (mmol/l)	2246	1.4 ± 1.0	1.4 ± 1.0	1.5 ± 1.0	0.85
LDL cholesterol (mmol/l)	2470	2.9 ± 1.1	2.9 ± 1.1	3.0 ± 1.0	0.19
HDL cholesterol (mmol/l)	2234	1.3 ± 0.4	1.3 ± 0.4	1.3 ± 0.4	0.94
eGFR (ml/min/1.73 m^2)	2730	73.1 ± 30.2	70.3 ± 25.3	86.9 ± 45.1	**<0.001***
Stroke data					
Pre-stroke disability	2025	355 (17.5%)	325 (18.8%)	30 (10.2%)	**<0.001***
Admission NIHSS	2540	4 (2–11)	4 (2–12)	4 (2–11)	**0.014***
TOAST	2607				
LAA		488 (18.7%)	407 (18.7%)	81 (18.9%)	0.34
CE		619 (23.7%)	528 (24.2%)	91 (21.2%)	
SVD		431 (16.5%)	365 (16.8%)	66 (15.4%)	
Other		255 (9.8%)	215 (9.9%)	40 (9.3%)	
IUC		814 (31.2%)	663 (30.4%)	151 (35.2%)	
Acute interventions					
Thrombolysis	2401	439 (18.3%)	355 (17.5%)	84 (22.9%)	**0.013***
Thrombectomy	695	50 (7.2%)	40 (6.7%)	10 (10.3%)	0.20
Anti-HT agents during ABPM	275	153 (55.6%)	137 (54.4%)	16 (69.6%)	0.16
Outcomes					
Discharge poor outcome	2138	977 (45.7%)	868 (48.0%)	109 (33.0%)	**<0.001***
Discharge mortality	2544	100 (3.9%)	88 (4.1%)	12 (2.9%)	0.22
90 days poor outcome	1488	664 (44.6%)	596 (47.1%)	68 (30.5%)	**<0.001***
90 days mortality	1488	139 (9.3%)	127 (10.0%)	12 (5.4%)	**0.028***
>1 year mortality	498	187 (37.6%)	157 (38.0%)	30 (35.3%)	0.64
Stroke recurrence	638	49 (7.7%)	43 (8.1%)	6 (5.5%)	0.34

Data are numbers (%) for categorical variables, mean ± SD for continuous variables, except NIHSS which is median (IQR), p-values derived from the chi-squared tests and the Mann–Whitney tests and statistically significant values ($p < 0.05$) have been indicated bold with an asterisk (*).

ABPM ambulatory blood pressure monitoring, *AIS* acute ischemic stroke, *BMI* body mass index, *CE* cardioembolic, *DBP* diastolic blood pressure, *eGFR* estimated glomerular filtration rate, *EVA* early vascular aging, *EVAAs* early vascular aging ambulatory score, *Glu* glucose, *HDL* high-density lipoprotein, *HR* heart rate, *HT* hypertension, *IUC* infarct of undetermined cause, *LAA* large artery atherosclerosis, *LDL* low-density lipoprotein, *NIHSS* National Institutes of Health stroke scale, *NoVA* normal vascular aging, *Other* stroke of other determined causes, *SBP* systolic blood pressure, *SVD* small vessel disease or lacunar stroke, *TIA* transient ischemic attack, *TOAST* Trial of Org 10172 in acute stroke treatment.

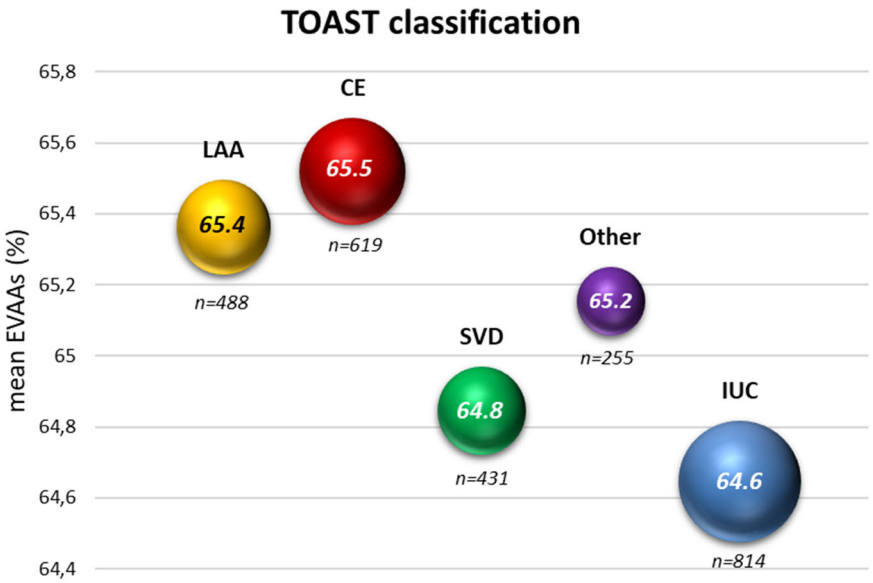

Fig. 1 | Mean EVAAs in different AIS subtypes classified by TOAST. AIS acute ischemic stroke, CE cardioembolic, EVAAs early vascular aging ambulatory score, IUC infarct of undetermined cause, LAA large artery atherosclerotic, Other stroke of other determined causes, SVD small vessel disease or lacunar stroke, TOAST Trial of Org 10172 in Acute Stroke Treatment.

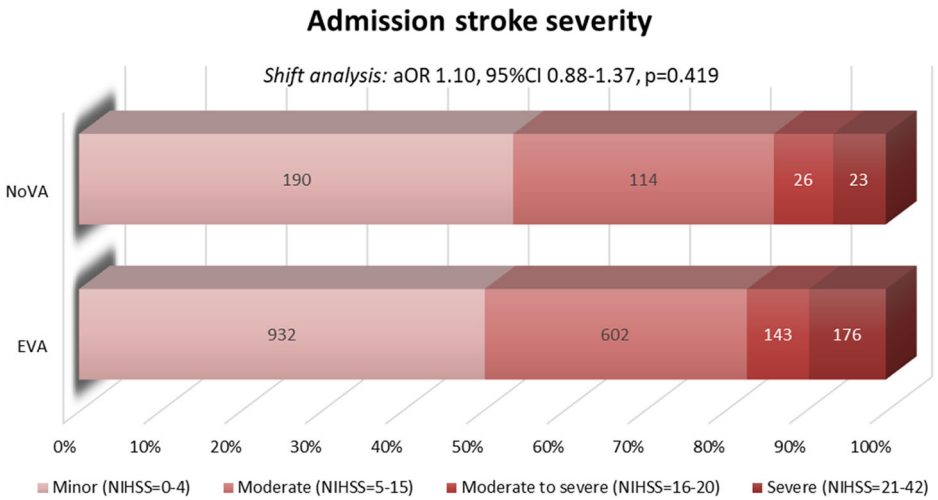

Fig. 2 | Multivariate shift analysis assessing the odds ratio of EVA within NIHSS categories. aOR adjusted odds ratio, CI confidence interval, EVA early vascular aging, NIHSS National Institutes of Health stroke scale, NoVA normal vascular aging.

ratio [aHR]: 1.02, 95%CI: 1.01–1.04, $p < 0.001$), indicating a 2% increase in the risk of death for every 1% increase in the EVAA score, considering total cholesterol levels, NIHSS score, and the presence of hypertension, atrial fibrillation, CAD, and smoking habit (Table 3). Kaplan–Meier survival curves showed a clear separation between the EVA and NoVA groups, with the NoVA group having a higher survival probability over time (Log-Rank [Mantel–Cox] $p = 0.006$), indicating a statistically significant difference in survival between the two groups (Fig. 5).

In our multivariate analysis, several clinical and laboratory variables were identified as independent predictors of stroke outcomes. For the mRS at discharge, significant predictors included the NIHSS score, hypertension, CAD, and smoking (Supplemental Tables S10, S11, S13, S14). Predictors of mortality at discharge were the NIHSS score, atrial fibrillation, and a history of previous stroke or TIA (Supplemental Tables S18, S19). For the mRS at 90 days, the NIHSS score, atrial fibrillation, CAD, and smoking were significant predictors (Supplemental Tables S22, S23, S25, S26). Mortality at 90 days was predicted by the NIHSS score, atrial fibrillation, and previous stroke or TIA (Supplemental Tables S30, S31). Mortality beyond one year was associated with the NIHSS score and a history of previous stroke or TIA (Supplemental Tables S33, S34). Finally, stroke recurrence was predicted by the NIHSS score and levels of LDL cholesterol (Supplemental Tables S36, S37).

From the sensitivity analyses conducted for all outcomes using models that included the eight variables used to calculate the EVAAs and the statistically significant predictors identified in univariate regression, the possibility of multicollinearity was assessed to ensure an accurate interpretation of the EVA/EVAAs effects. The analyses revealed that the predictive value of the EVA and EVAA score was primarily driven by the variables of age and the values of the 24-hour ABPM (SBP, DBP, HR). Additionally, in most of these analyses, the other clinical or laboratory predictors that were statistically significant in the initial analyses remained statistically significant in most cases (Supplemental Tables S12, S15, S20, S24, S27, S32, S35, S38, S41).

Discussion

This study is the first to evaluate the new EVAA score in a large multinational pooled analysis of IPD from several cohorts. The analysis suggested that EVA, calculated by the EVAAs using 24-h ABPM conducted shortly after stroke onset, may serve as an independent predictor of poor outcomes, as measured by the mRS, both at discharge and 90 days post-stroke.

In terms of the widely used and clinically significant outcome measure of the mRS at 3 months, the EVAAs indicate independent predictive value.

Table 3 | Multivariate analyses of the independent predictive role of EVA and EVAAs for several outcomes

Multivariate regression analysis	AIS (*n*)	EVA (vs. NoVA)		EVAAs	
		aOR (95% CI)	*p*	aOR (95% CI)	*p*
mRS at discharge§[1]	1898	1.52 (1.21–1.91)	**<0.001***	1.01 (1.01–1.02)	**<0.001***
mRS > 2 at discharge†[1]	1898	1.72 (1.25–2.36)	**<0.001***	1.02 (1.01–1.02)	**<0.001***
Death at discharge†[2]	2167	0.87 (0.42–1.80)	0.70	1.02 (0.99–1.04)	0.10
mRS at 90 days§[3]	1225	1.87 (1.41–2.47)	**<0.001***	1.02 (1.02–1.03)	**<0.001***
mRS > 2 at 90 days†[3]	1225	2.22 (1.49–3.31)	**<0.001***	1.03 (1.02–1.04)	**<0.001***
Death at 90 days†[4]	1244	1.76 (0.84–3.67)	0.14	1.03 (1.01–1.05)	**0.003***
Death at > 1 year†[5]	438	1.27 (0.68–2.35)	0.45	1.01 (0.99–1.03)	0.18
Stroke recurrence†[6]	575	1.68 (0.63–4.47)	0.30	1.01 (0.98–1.03)	0.62
Death over time‡[7]	1350	1.47 (0.92–2.37)	0.11	1.02 (1.01–1.04)	**<0.001***

Multivariate analyses (§: Ordinal/shift logistic regression analysis, †: Logistic regression analysis, ‡: Cox proportional hazards survival regression analysis) included all statistically significant ($p < 0.1$) clinical/laboratory variables from initial univariate analysis. [1]Total cholesterol, triglycerides, LDL cholesterol, NIHSS, hypertension, atrial fibrillation, coronary artery disease, previous stroke or TIA, Smoking. [2]Total cholesterol, LDL cholesterol, NIHSS, hypertension, atrial fibrillation, coronary artery disease, previous stroke or TIA, smoking. [3]Total cholesterol, NIHSS, hypertension, atrial fibrillation, coronary artery disease, previous stroke or TIA, smoking. [4]Total cholesterol, LDL cholesterol, NIHSS, atrial fibrillation, previous stroke or TIA. [5]NIHSS, dyslipidemia, previous stroke or TIA, smoking. [6]Total cholesterol, LDL cholesterol, NIHSS. [7]Total cholesterol, NIHSS, hypertension, atrial fibrillation, coronary artery disease, smoking. Statistically significant values ($p < 0.05$) have been indicated in bold with an asterisk (*).
AIS acute ischemic stroke, *aOR* adjusted odds ratio, *EVA* early vascular aging, *EVAAs* early vascular aging ambulatory score, *mRS* modified Rankin Scale, *NoVA* normal vascular aging, *CI* confidence interval.

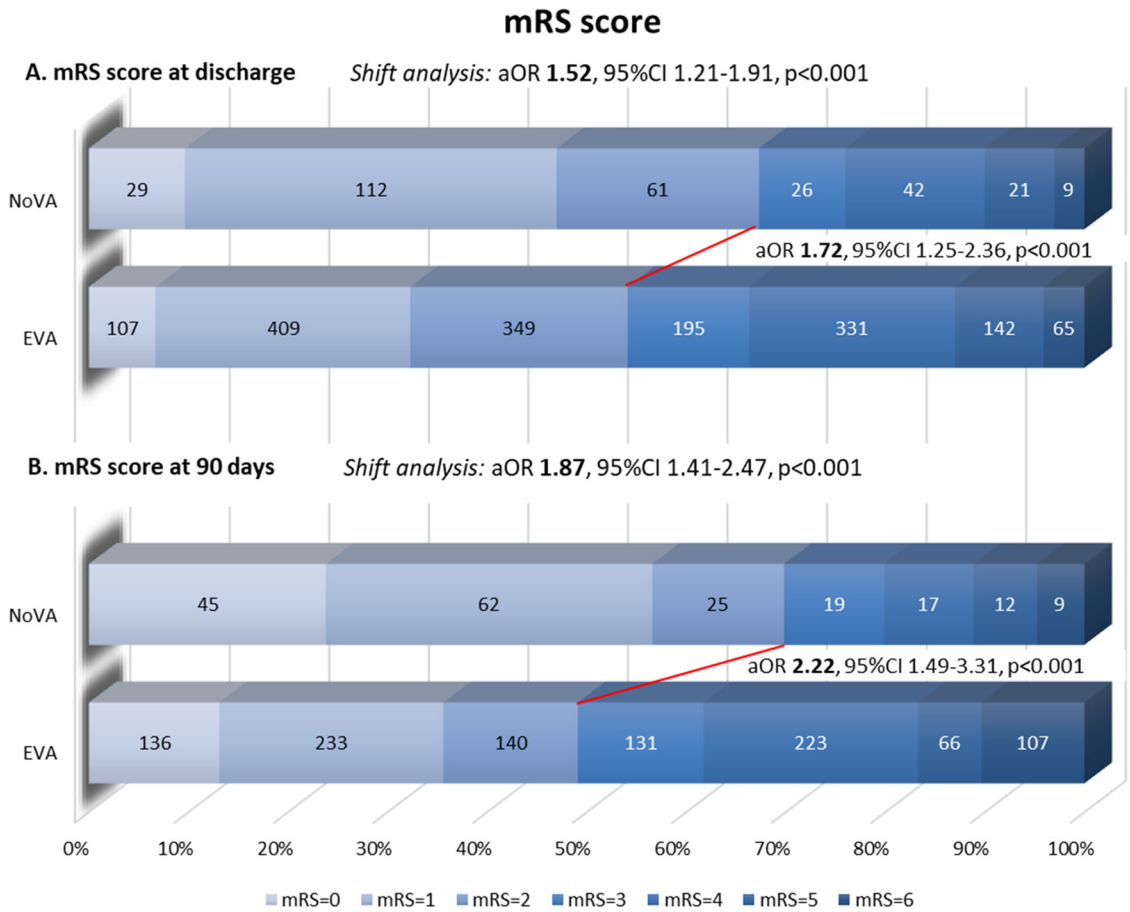

Fig. 3 | Multivariate analysis assessing the odds ratio of EVA for mRS score (shift analysis) and poor outcome (mRS > 2) at both discharge (A) and at 90 days (B). aOR adjusted odds ratio, CI confidence interval, EVA early vascular aging, mRS modified Rankin Scale, NoVA normal vascular aging. The aOR for poor outcomes is displayed between the bars.

This value is particularly evident in specific subgroups of AIS patients, such as those aged 70–80 years, who have no prior disability, possess normal body weight, have an eGFR above 60 ml/min/1.73 m^2, and have no history of other established cardiovascular diseases (such as atrial fibrillation, CAD, stroke or TIA). The predictive value of EVAAs is especially important in AIS patients with minor to moderate strokes classified as LAA, CE, or IUC according to the TOAST classification, independent of thrombolysis treatment. Furthermore, EVAAs appear to be applicable to AIS patients who underwent 24-h ABPM during all phases of stroke (hyper-acute, acute, and sub-acute). Regarding lipid profile, the EVAAs hold statistically

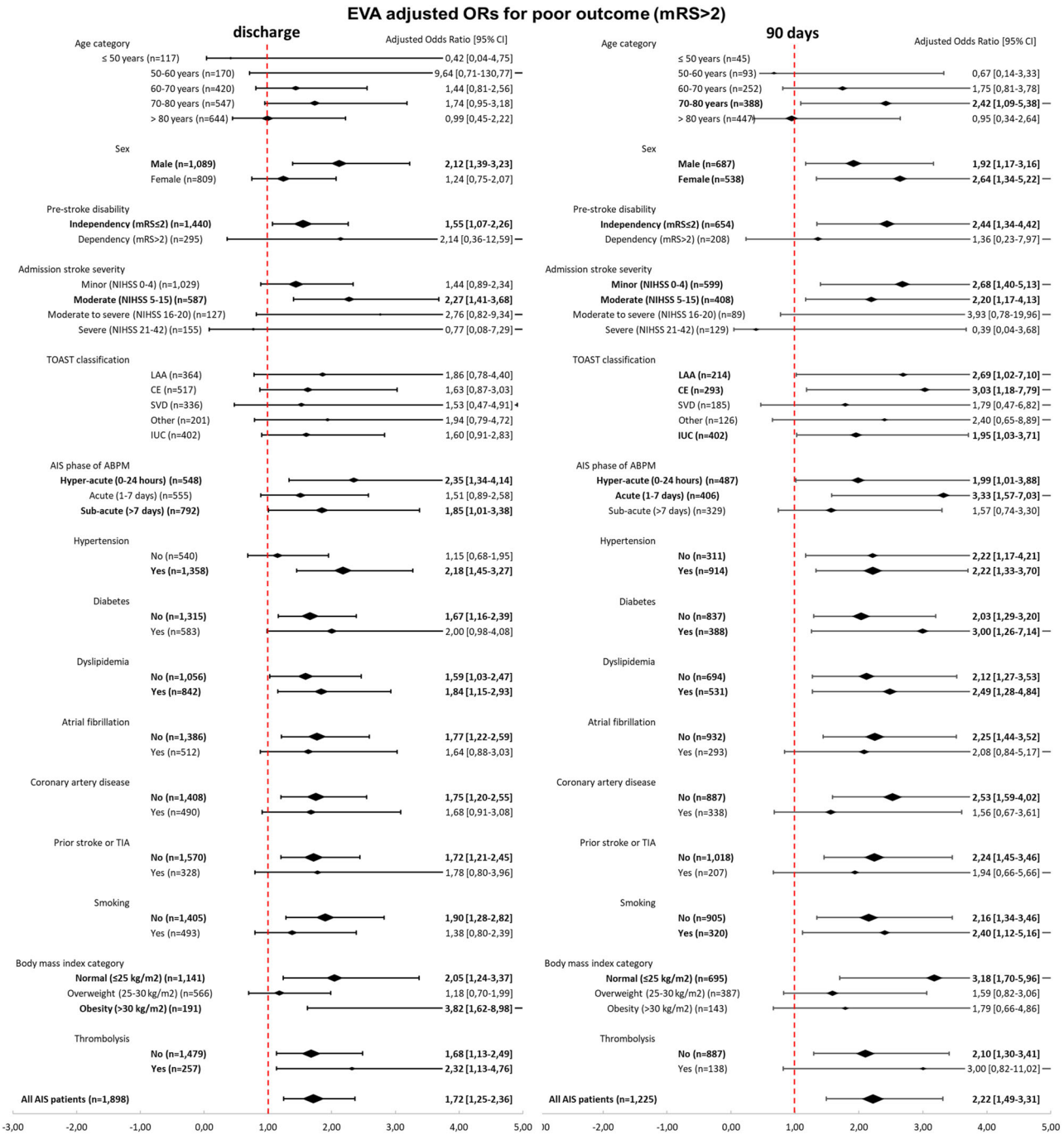

Fig. 4 | Multivariate analysis assessing the odds ratio of EVA for poor outcome (mRS > 2) at both discharge and at 90 days in different AIS subgroups (demographic, clinical, and stroke characteristics). ABPM ambulatory blood pressure monitoring, AIS acute ischemic stroke, CE cardioembolic, CI confidence interval, EVA early vascular aging, IUC infarct of undetermined cause, LAA large artery atherosclerotic, mRS modified Rankin Scale, NIHSS National Institutes of Health stroke scale, Other stroke of other determined causes, SVD small vessel disease or lacunar stroke, TIA transient ischemic attack, TOAST Trial of Org 10172 in Acute Stroke Treatment.

significant independent predictive value in AIS patients with a non-atherogenic lipid profile, characterized by low total and LDL cholesterol, low triglycerides, and high HDL cholesterol.

The results of this study are crucial as EVAAs could be effectively used for the reclassification of AIS patients, particularly those with a lower general cardiovascular risk burden, by assessing their "arteriosclerotic" or "pre-atherosclerotic" burden (vascular aging), which is associated with worse outcomes. This reclassification is especially important for patients with strokes of undetermined cause (IUC), where therapeutic decisions for secondary prevention are challenging, such as in patients with ESUS or younger stroke patients who may have a very low cardiovascular risk and a normal lipid profile[21,22].

Assessing vascular aging in AIS patients could offer several potential clinical benefits, such as enhancing the perception of cardiovascular risk, improving communication between patients and healthcare providers, and fostering better adherence to therapy[23]. Prioritizing the assessment and intervention of vascular aging in stroke research is crucial for enhancing outcomes in this patient cohort, although further evidence is needed to optimize secondary prevention approaches[24,25].

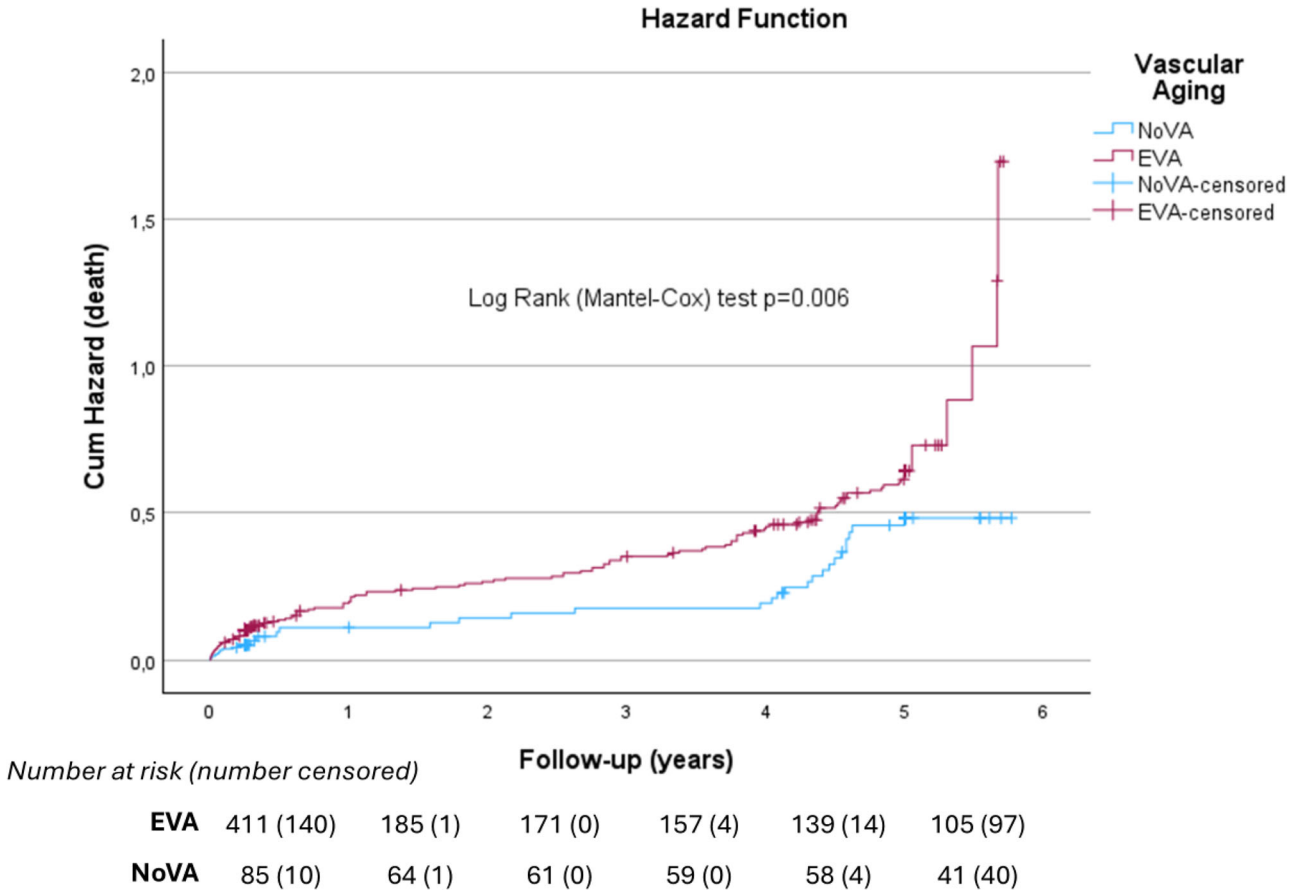

Fig. 5 | Kaplan–Meier survival curves between the EVA and NoVA groups. EVA early vascular aging, NoVA normal vascular aging.

Targeted therapies for vascular aging have the potential to mitigate adverse outcomes, underscoring the importance of investigating treatments that address the fundamental processes of arteriosclerosis and arterial stiffness. This approach could enhance outcomes for AIS patients with EVA. While many current treatments primarily address the symptoms rather than the underlying causes of vascular aging, emerging pharmacological interventions show promise[17]. These include PCSK9 inhibitors for dyslipidemia, SGLT-2 inhibitors, and GLP-1 receptor agonists for diabetes and obesity management[26–28], along with anti-inflammatory agents and certain antihypertensive drugs[6]. Such treatments may improve arterial function and alter the progression of vascular aging, potentially leading to better functional outcomes, decreased stroke recurrence, reduced mortality rates, and overall enhanced cardiovascular health[28–31].

The main limitation of the present study is its observational design, with two of the cohorts being retrospective, which introduces potential biases inherent to such studies. Furthermore, we could not strictly control the delays from stroke onset to ABPM nor ABPM methodology and had to use outcome measures applied in the original studies. Despite these facts, the inclusion of a diverse range of AIS patients from multiple clinical centers across various countries enhances the generalizability of the findings. Additionally, the exclusion of AIS patients with missing data may introduce selection bias. To address this, several comparisons were conducted between included and excluded patients to better understand and interpret this potential bias. A key strength of the study was also the multiple sensitivity analyses, which confirmed that the EVA and EVAA score's predictive value was primarily influenced by age and 24-hour ABPM values, with most initial significant clinical or laboratory predictors remaining consistent. Another limitation of the study is the absence of methods to adjust for multiple testing, which is crucial for controlling type 1 errors. Due to the study's specific and complex design, no adequate and powerful multiple-test procedures exist. Consequently, the interpretation of the results of this analysis should be approached with caution, as they are primarily exploratory.

It should be acknowledged as a limitation that the EVAAs were originally developed to identify EVA in hypertensive patients based on ABPM values and traditional cardiovascular risk factors, primarily during the preclinical phase before overt CVD manifests. The application of EVAAs in AIS patients represents an exploratory evaluation within a population already experiencing advanced atherosclerosis and significant vascular events. Although EVAAs offer a convenient and feasible clinical tool compared to PWV measurements, their capacity to predict residual risk in this context remains hypothetical. Direct comparative studies between EVAAs and established vascular aging indices like PWV are warranted to validate their predictive performance and clarify their relevance in populations with AIS.

In conclusion, EVAAs, as indicator of early vascular aging that can be readily integrated into daily clinical practice, is suggested as a key predictor of adverse outcomes in acute ischemic stroke patients. This highlights the critical need to incorporate vascular aging assessment into clinical practice. This can enhance risk perception, improve secondary prevention strategies, and explore novel therapeutic options targeting arterial stiffening, thus optimizing stroke prognosis.

Methods

Study design, study population, selection criteria

For this IPD pooled analysis, data were gathered from a combination of previously conducted interventional and observational studies, as well as prospective registries. These studies involved patients >18 years old with AIS who underwent 24-h ABPM during the hyper-acute, acute, or subacute phase following stroke onset. To identify relevant studies, a comprehensive

search of the international literature was conducted across multiple databases, including PubMed, Cochrane Library, Web of Science, and Scopus. The inclusion criteria focused on studies that evaluated the predictive value of 24-h ABPM in AIS patients. The study protocol was presented and discussed at the 2023 Vascular Aging Network and European Stroke Science Workshops. An open call for collaboration was issued to research teams that had previously examined the role of 24-h ABPM in AIS. Invitation emails were sent to the corresponding or supervising authors of these studies to solicit their participation.

Eligible studies needed to report the eight specific variables required for calculating EVAAs: 24-h systolic blood pressure (SBP), 24-h diastolic blood pressure (DBP), 24-h heart rate (HR), age, sex, body mass index (BMI), presence or not of diabetes mellitus, and estimated glomerular filtration rate (eGFR). Additionally, studies were required to report at least one outcome measure, such as the National Institutes of Health Stroke Scale (NIHSS) score on admission, stroke recurrence, mortality, or functional outcome assessed by the modified Rankin Scale (mRS) at any/various time points. A detailed summary of the participating studies, including their origin, design, sample size, study period, phase of stroke during which 24-h ABPM was conducted, the type of ABPM device used, frequency of blood pressure measurements, and reported stroke outcomes, is provided in Table 1. Additional information regarding the characteristics of these studies, as well as any modifications or assumptions made for this analysis, is available in the Supplemental material and Supplemental Table S1.

Clinical and laboratory data collection

Demographic and somatometric data were collected, including age, sex, ethnicity, and BMI. Patients were categorized by age into decades: ≤50, 50–60, 60–70, 70–80, and >80 years. Geographic origin was classified as European or Asian, and BMI was categorized as follows: normal weight (<25 kg/m^2), overweight (25–29.9 kg/m^2), and obesity (≥30 kg/m^2). Data on clinical cardiovascular risk factors were collected, which included hypertension, diabetes mellitus, dyslipidemia, atrial fibrillation, coronary artery disease (CAD), history of prior stroke or transient ischemic attack (TIA), valvular disease, renal failure (eGFR <60 ml/min/1.73 m^2), cancer, and smoking habit. These factors were documented based on existing diagnoses under medical treatment as well as newly diagnosed conditions according to study-specific definitions.

For 24-h ABPM, the mean 24-h SBP, DBP, and HR were collected. To qualify as an acceptable 24-h ABPM recording, at least 20 valid measurements were needed during the daytime and 7 valid measurements during the nighttime[32]. Additionally, the duration (in hours) from stroke onset to ABPM initiation was recorded. For analysis purposes, the stroke phase during ABPM was categorized as hyper-acute (0–24 h), acute (1–7 days), and sub-acute (>7 days).

If available, laboratory findings on admission were recorded, including serum glucose and serum creatinine for calculating the estimated glomerular filtration rate (eGFR) using the CKD-EPI 2021 equation. Lipid profiles, including total cholesterol, HDL and LDL cholesterol, and triglycerides, were also documented.

Stroke severity on admission was assessed using the NIHSS score[33]. For analysis purposes, NIHSS scores were categorized into four groups: 0–4 (minor stroke), 5–15 (moderate stroke), 16–20 (moderate to severe stroke), and 21–42 (severe stroke)[34]. If available, data on the patients' pre-stroke functional status, assessed using the mRS score, were classified as dependent or pre-stroke disability (mRS > 2) versus independent. Stroke subtypes were classified according to the Trial of Org 10172 in Acute Stroke Treatment (TOAST) criteria[35]. The strokes were grouped into five subtypes: large artery atherosclerotic (LAA), cardioembolic (CE), small vessel disease or lacunar (SVD), stroke of other determined causes (Other), and infarcts of undetermined causes (IUC), which includes cases with multiple potential causes, negative, or incomplete evaluations. When available, data on the embolic stroke of undetermined source (ESUS), defined by the Cryptogenic Stroke/ESUS International Working Group criteria, were collected and categorized AIS as ESUS or non-ESUS[36]. Information on acute management and post-stroke therapy was recorded, including thrombolysis, thrombectomy, and the administration of antihypertensive agents during 24-h blood pressure monitoring.

The analysis received approval from the Institutional Review Board of Aristotle University of Thessaloniki (approval number 1270/29-10-2020). Each study included in the analysis complied with local ethics and scientific committee procedures, as detailed in their respective publications.

Early Vascular Aging Ambulatory score (EVAAs)

Early Vascular Aging Ambulatory score (EVAAs), developed in 2018, is designed to accurately identify hypertensive patients with EVA using ABPM values, including 24-h SBP, DBP, and HR, along with traditional cardiovascular risk factors such as age, sex, BMI, diabetes mellitus, and eGFR[19]. EVAAs have demonstrated high accuracy, sensitivity, and specificity, with recent external validation in an independent cohort of 879 patients, 60.7% of whom were hypertensive. It demonstrated 98% sensitivity, 75% specificity, 95% positive predictive value, and 92% negative predictive value. These findings suggest that EVAAs are as reliable as carotid-femoral PWV for identifying patients with EVA[18].

The EVAAs were calculated using a free application developed by the score's creators, available at https://medapps.shinyapps.io/evaas/[19]. The probability of EVA presence in each patient was reported as a percentage (%). EVAAs were analyzed as a continuous variable or dichotomized (EVA vs. NoVA), with EVA defined as EVAAs >50% and normal vascular aging (NoVA) as EVAAs ≤50%, according to the original creators of the score.

Outcomes

Neurological function was assessed using the modified Rankin Scale (mRS) at discharge, 90 days, and more than one year after stroke onset[37]. The endpoints included the following: mRS score (ordinal/shift analysis), poor outcome defined as mRS > 2, death (mRS = 6) at discharge and 90 days, death (mRS = 6) at more than one year, and stroke recurrence.

Statistical analysis

Continuous variables were presented as mean ± standard deviation, except for NIHSS and mRS, which were presented as median (IQR). Categorical variables were shown as absolute numbers and percentages. The Kolmogorov–Smirnov test was used to assess normality, and since none of the variables were normally distributed, the non-parametric Mann–Whitney *U*-test was applied to compare the means of two continuous variables. For comparisons involving more than two groups, the Kruskal–Wallis test was used. Categorical variables were analyzed using Pearson's Chi-Square test or Fisher's Exact test, as appropriate.

Comparisons of clinical and laboratory characteristics, outcomes, and blood pressure among AIS patients were made between subgroups categorized by the presence of early vascular aging (EVA) or normal vascular aging (NoVA). Additionally, mean EVAA values, as a continuous variable, were compared between subgroups based on the TOAST stroke subtype and stroke severity (NIHSS category). Both EVA, as a categorical variable, and EVAAs, as a continuous variable, were examined for their predictive value. Ordinal regression (shift) analysis was employed for the ordinal mRS score outcomes at discharge and 90 days, and for calculating the odds ratio with NIHSS categories (stroke severity). Logistic regression analysis was used for dichotomous outcomes such as poor outcomes, death, and stroke recurrence. Cox proportional hazards survival regression analysis and Kaplan–Meier plots were used to assess overall survival.

Univariate regression analysis identified statistically significant predictors, which were then used in a multivariate regression analysis to determine the independent predictive value of EVA and EVAAs. Only variables with $p < 0.10$ in the univariate analysis and with <10% missing values were included to maintain data integrity. The eight variables used to calculate the EVAAs were excluded from the multivariate model to avoid multicollinearity and ensure accurate interpretation of the EVA and EVAAs effect. Sensitivity analyses were conducted using separate models with individual EVAA components to compare predictive values.

Some AIS cases were excluded due to insufficient data for EVAA calculation. Patients with missing values for outcomes or confounding factors were also excluded from specific regression analyses. Comparisons of clinical and laboratory characteristics, as well as outcomes, were made between included and excluded patients to assess potential selection bias.

All statistical tests were two-sided, with a p-value < 0.05 considered statistically significant. Statistical analyses and Kaplan-Meier plots were performed using IBM SPSS Statistics for Windows (Version 29.0, Armonk, NY, USA: IBM Corp. Released 2022). Microsoft Excel 365 MSO (Version 2301, Released 2022) was used to create forest plots of adjusted odds ratios and graphics for ordinal (shift) analysis.

Data availability

Data from additional unpublished analyses (including univariate and other comparisons) related to this article can be shared upon reasonable request to the corresponding author. However, individual participant data (IPD) from separate studies and registries cannot be shared, as the license was granted exclusively for this study. Requests for such data should be directed to the specific clinical research centres involved.

Received: 6 December 2024; Accepted: 25 January 2025;
Published online: 21 February 2025

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Acknowledgements

This study was conducted under the auspices of the Hellenic Stroke Organization Research Network and has not received any funding. We extend our gratitude to all our dedicated colleagues who contributed to each registry or study, helping to collect valuable data and advance the improvement of stroke care management.

Author contributions

N.K.: Conceived and designed the study, conducted the data analysis, and wrote the manuscript. V.K.: Contributed to the conception and design of the study, assisted in writing the original draft, and verified the accuracy of specific data and statistical methods. C.S.: Contributed to the conception and design of the study, served as the supervising author, and oversaw the project to ensure the integrity of the research. All authors (N.H., T.N., P.M., T.G., D.S., Y.S.K., W.S., K.V., E.K., M.A., J.P., L.T., M.H., P.R., P.M.B., L.J.W., A.D.P., E.A., H.M., G.N.) reviewed and revised the draft and contributed to verifying the accuracy of their respective datasets.

Competing interests

The authors declare no competing interests directly related to this study. Any potential financial support for specific studies is detailed in the Brief Descriptions of participating stroke studies/registries in the Supplemental Material.

Additional information

Supplementary information The online version contains supplementary material available at https://doi.org/10.1038/s41514-025-00202-7.

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