Atherosclerosis 334 (2021) 30–38

Contents lists available at ScienceDirect

Atherosclerosis

journal homepage: www.elsevier.com/locate/atherosclerosis

Intracranial aneurysm is predicted by abdominal aortic calcification index: A retrospective case-control study

Ville Rantasalo [a,*], Jarmo Gunn [a], Tuomas Kiviniemi [d], Jussi Hirvonen [e], Ilkka Saarenpää [b,c], Juri Kivelev [b,c], Melissa Rahi [b,c], Elli Lassila [b], Jaakko Rinne [b,c], Dan Laukka [b,c]

[a] Department of Surgery, Turku University Hospital and University of Turku, Turku, Finland
[b] Clinical Neurosciences, University of Turku, Turku, Finland
[c] Department of Neurosurgery, Neurocenter, Turku University Hospital, Turku, Finland
[d] Heart Center, Turku University Hospital, University of Turku, Turku, Finland
[e] Department of Radiology, Turku University Hospital and University of Turku, Turku, Finland

ARTICLE INFO

Keywords:
Intracranial aneurysm
Calcification
Atherosclerosis
Subarachnoid hemorrhage

ABSTRACT

Background and aims: Patients with intracranial aneurysms (IA) have excess mortality for cardiovascular diseases, but little is known on whether atherosclerotic manifestations and IA coexist. We investigated abdominal aortic calcification index (ACI) association with unruptured and ruptured IAs.

Methods: This retrospective case-control study reviews all tertiary centers patients (n = 24,660) who had undergone head computed tomography angiography (CTA), magnetic resonance angiography (MRA) or digital subtraction angiography (DSA) for any reason between January 2003 and May 2018. Patients (n = 2020) with unruptured or ruptured IAs were identified, and patients with available abdominal CT were included. IA patients were matched by sex and age to controls (available abdomen CT, no IAs) in ratio of 1:3. ACI was measured from abdomen CT scans and patient records were reviewed.

Results: 1720 patients (216 ruptured IA (rIA), 246 unruptured IA (UIA) and 1258 control) were included. Mean age was 62.9 ± 11.9 years and 58.2% were female. ACI (OR 1.02 per increment, 95%CI 1.01–1.03) and ACI>3 (OR 5.77, 95%CI 3.29–10.11) increased risk for rIA compared to matched controls. UIA patients' ACI was significantly higher but ACI did not increase odds for UIA compared to matched controls. History of coronary artery disease was less frequent in rIA patients. There was no calcification in aorta in 8.8% rIA and 13.6% UIA patients (matched controls 25.7% and 22.6% respectively, $p < 0.01$).

Conclusions: Aortic calcification is greater in rIA and UIA patients than matched controls. ACI increases risk for rIAs.

1. Introduction

The prevalence of unruptured intracranial aneurysms (UIA) is around 3% in the general population [1] and only a small portion of UIAs rupture during lifetime, as the incidence of ruptured IAs (rIA), is around 10/100,000 per year. Smoking and hypertension are well-known modifiable risk factors for many cardiovascular diseases and also for UIAs and rIAs [2,3]. Vessel wall inflammation is related to IA formation and rupture. Inflammation plays a critical role in peripheral and coronary artery atherosclerosis as well [4–8]. Intracranial aneurysm wall and atherosclerotic plaque have many common inflammation-mediating cytokines and leucocytes [6,9]. Hence, it is suggested a shared underlying pathophysiology between atherosclerosis and intracranial aneurysms [8,10].

Abdominal aortic calcification index (ACI) reflects general atherosclerotic burden and correlates with coronary artery calcium, which in turn predicts atherosclerotic cardiovascular diseases [11,12]. Atherosclerosis is considered to be a chronic systemic inflammatory disease with increased levels of circulating inflammatory cytokines. As a marker of atherosclerotic disease, ACI has been linked to coronary artery disease – and IAs could be linked to cerebrovascular atherosclerotic burden [13–17].

Increasing amount of UIAs are found as incidental findings or as screening results. However, invasive treatment of intracranial

* Corresponding author. Department of Surgery, University of Turku, Kiinanmyllynkatu 4-8 PL 52, 20521, Turku, Finland.
E-mail address: vheran@utu.fi (V. Rantasalo).

https://doi.org/10.1016/j.atherosclerosis.2021.08.027
Received 27 April 2021; Received in revised form 6 August 2021; Accepted 12 August 2021
Available online 15 August 2021
0021-9150/© 2021 The Authors. Published by Elsevier B.V. This is an open access article under the CC BY license (http://creativecommons.org/licenses/by/4.0/).

aneurysms is not without risk, and IAs known risk factors are not yet sufficient for guiding preventive risk reduction. Therefore, there is a growing need to distinguish rupture-prone IAs more reliably from UIAs to select patients most likely to benefit from treatment.

In this study, we investigated if higher ACI index is related to UIAs and rIAs compared to controls without IAs. We hypothesized that higher ACI index could reflect more severe atherosclerotic burden and cardiovascular risk and could also be a risk factor for IAs.

2. Materials and methods

This is a retrospective study based on Turku University hospitals TuFIAS register data of patients with cerebrovascular imaging. Aneurysm and control patients are both selected from this register as shown in Fig. 1A. Turku University Hospital is a tertiary center responsible for IAs in its geographical catchment areas population of 870,000 people. This study was approved by the Southwest Finland hospital district's ethical committee and institutional review board. Research number ID is T110/2018 and number for approval decision is T04/005/18. Patient consent was waived based on the retrospective registry design. TuFIAS register data consists of consecutive patients examined or treated in the department of neurosurgery between January 2003 and May 2018. Patients with IA were categorized as patients with incidental finding of UIA or as patients who had suffered a subarachnoidal hemorrhage due to an rIA. Control patients had no IA. Diagnostic imaging for IA was computed tomography (CT), computed

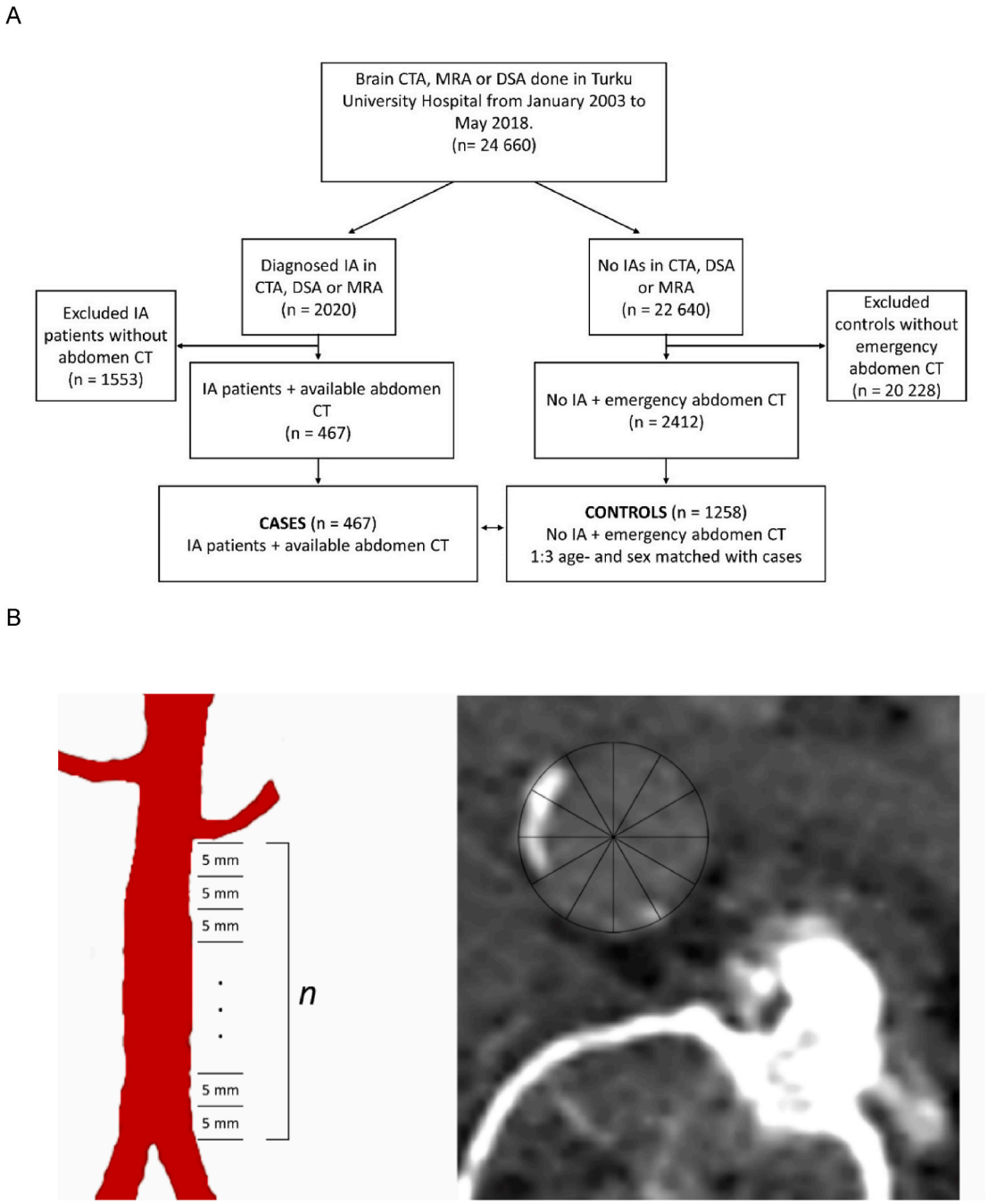

Fig. 1. (A) Flow-chart presenting TuFIAS registers aneurysm- and control patients selection and exclusion together with ACI measurements. (B) Aortic calcification index measurement method. Left panel = number of slices 5 mm apart (=n), right panel = individual CT slice, 12-part pie-chart represents template which is used to estimate degree of calcification.

tomography angiography (CTA), magnetic resonance angiography (MRA) or DSA (digital subtraction angiography).

2.1. Aneurysm patients

Patient records and PACS (Picture archiving and communication system) were reviewed manually for radiological studies, comorbidities and cardiovascular risk factors. Patients with missing patient records or no adequate abdominal aorta imaging data were not included in this study. Patients with diagnosed connective tissue disorder (Marfan syndrome, Ehlers-Danlos syndrome type IV and Loeys-Dietz syndrome) were excluded. Included patient's records were reviewed for full medical history including relevant diagnoses and cardiovascular risk factors.

2.2. Control patients

For control patients, similar demographic data (diagnosed diseases and common risk factors) was searched manually from patient records. They had undergone cranial and abdominal computed tomography imaging in emergency department showing abdominal aorta and had no evidence of an IA (Supplemental data 1). Each rIA and UIA patient was matched 1:3 to control patients based on age and gender. Age was noted as the patients' age at the time of abdominal aortic imaging. Study population demographics are described in Table 1.

2.3. ACI-index

The abdominal aortic calcification index was measured from included cases and controls. Measurement of the ACI included the whole length of the abdominal aorta, from the level of the renal arteries to bifurcation. Computed tomography studies were viewed as multiplanar reformation (MPR) with slices 5 mm apart. Thus, every individual measurement included the number of slices 5 mm apart and the degree of calcification in each slice on a scale from 0 to 12. Index (ACI) was calculated using the following formula:

$$ACI = \frac{total\ sum\ of\ calcification\ in\ all\ slices}{12^{*}n} * 100$$

where n is the number of 5 mm slices in abdominal aorta. (Fig. 1B.)

2.4. Statistical analysis

Statistical analysis was carried out with IBM SPSS statistics 27 software for Windows (IMB, Armonk, NY). Between-group differences were evaluated with Chi-square test for proportions. Continuous variables are reported as mean and standard error, and between-group differences in variance were evaluated with independent samples *t*-test and one-way ANOVA test. Equality of variance was tested with Levene's test. Binary logistic regression analysis was performed with all demographic variables reported in Table 1 with backward selection (Wald). *p*-values <0.05 were considered statistically significant. Classification and regression tree (CART) analysis was performed for the total population to identify cutoff values for variables independently associated with IAs. Validation was assessed by cross-validation through 10 folds. The minimum number of patients for a parent node was set at 100 and at 50 for child nodes and maximum tree depth was set at 5. Gini's method was used to measure impurity and minimum change in improvement was set at 0.0001. Receiver-operating characteristic (ROC) analyses were also performed. ROC curves area under curve (AUC) was used to measure the quality of test. ROC analysis curves are reported in Supplementary Materials. Multiple imputation was used for missing data. Interclass correlation (ICC) was used to assess the inter-rater reliability of imaging measurements. The subset of randomly selected subject's ACI measurements was repeated by a neuroradiologist. The following scale for ICC was used to determine the inter-rater reliability: poor (<0.5), moderate (0.5–0.75), good (0.75–0.9) and excellent (≥ 0.9) [18].

The main variable of interest in this study was the abdominal aortic calcification index and its difference in distribution between rIA and UIA patients. Abdominal aortas calcification measurements produced ACI values on continuous scale and also on a categorical scale as study subjects were also categorized as patients with completely calcification-free aorta and patients with at least some calcification in the aorta (ACI $= 0$ meaning completely calcification free aorta, ACI >0 meaning at least one plaque of calcification in abdominal aorta). Another derivative categorical variable used in the analysis was ACI over 3, meaning patients were categorized as patients with ACI >3 and ACI <3.

3. Results

From 2020 IA patients, 462 patients with abdominal CT were included. There were 216/462 (46.8%) rIA patients and 246/462 (53.2%) UIA patients. For the control group, a total of 1258 patients with abdominal imaging and sufficient patient records were selected from 22,640 patients without IAs. Baseline differences between groups are shown in Tables 1 and 2.

Table 1
Study population demographics.

	All controls	rIA	UIA	*p*-value
Age	63.0 (±12.0)	62.9 (±12.3)	62.5 (±11.0)	0.683
Abdominal aortic calcification index	17.9 (±22.7 95%CI 16.6–19.1)	25.9 (±22.7 95%CI 22.9–29.0	23.4 (±24.2 95%CI 20.3–26.4)	<0.001*
Smoking	746 (67.0%)	120 (67, 0%)	161 (70.3%)	0.626
Prior percutaneous coronary intervention	125 (9.9%)	8 (3.8%)	22 (9.0%)	0.019
Female	722 (57.4%)	128 (60.7%)	145 (59.7%)	0.578
Male	536 (42.6%)	83 (39.3%)	98 (40.3%)	0.578
Coronary artery disease	279 (22.2%)	28 (13.4%)	53 (21.7%)	0.015*
Prior myocardial infarction	139 (11.0%)	14 (6.7%)	38 (15.6%)	0.011*
Treatment for hypertension	791 (62.9%)	153 (73.2%)	185 (75.8%)	$p < 0.001$*
Treatment for dyslipidemia	460 (36.6%)	58 (27.8%)	102 (41.8%)	0.007*
Type 2 diabetes	317 (25.2%)	45 (10.9%)	49 (11.9%)	0.158
Type 1 diabetes	60 (4.8%)	2 (3.1%)	3 (1.2%)	0.003*
Dialysis	34 (2.7%)	5 (2.3%)	17 (6.9%)	0.003*
Chronic-obstructive pulmonary disease	170 (13.5%)	30 (17.6%)	43 (20.3%)	0.02*
Calcified aorta	954 (74.0%)	196 (91.2%)	210 (86.4%)	$p < 0.001$*
Calcification free aorta	302 (24.0%)	19 (8.8%)	33 (13.6%)	$p < 0.001$*
Prior coronary bypass	60 (4.8%)	4 (1.9%)	12 (4.9%)	0.169
Asthma	317 (25.2%)	33 (19.5%)	37 (17.5%)	0.02*
Peripheral artery disease	92 (7.3%)	15 (7.2%)	16 (6.6,%)	0.918
Alcohol abuse	399 (31.7%)	32 (15.5%)	55 (22.5%)	$p < 0.001$*

Table 2
(A) rIA patients and matched controls. (B) UIA patients and matched controls. (C) UIA and rIA patients.

(A)			
	Matched controls	rIA	*p*-value
Alcohol abuse	179 (32.0%)	32 (15.5%)	$p < 0.001$*
Calcification free aorta	144 (25.7%)	19 (8.8%)	$p < 0.001$*
Prior percutaneous coronary intervention	68 (12.1%)	8 (3.8%)	$p < 0.001$*
Type 1 diabetes	30 (5.4%)	2 (1.0%)	0.007*
Coronary artery disease	122 (21.8%)	28 (13.4%)	0.01*
Dyslipidemia	211 (37.7%)	58 (27.8%)	0.011*
Prior coronary bypass	30 (5.4%)	4 (1.9%)	0.04*
Prior myocardial infarction	68 (12.1%)	14 (6.7%)	0.035*
Abdominal calcification index	18.0 (22.7 95% CI 16.2–19.9)	25.9 (22.7 95%CI 18.6–21.8)	0.001*
Calcified aorta	416 (74.3%)	196 (91.2%)	0.001*
Hypertension	351 (62.7%)	153 (73.2%)	0.006*
Age	63.6 (11.7, 62.6–64.5	63.9 (12.3, 61.2–64.6)	0.448
Asthma	139 (24.8%)	33 (19.5%)	0.155
Type 2 diabetes	150 (26.8%)	45 (21.6%)	0.158
Male	236 (42.1%)	83 (39.3%)	0.578
Female	324 (57.9%)	128 (60.7%)	0.578
Dilaysis	18 (3.2%)	5 (2.3%)	0.64
Peripheral artery disease	47 (8.4%)	15 (7.2%)	0.657
Chronic obstructive pulmonary disease	80 (14.3%)	30 (17.6%)	0.283
Smoking	321 (66.0%)	120 (67.0%)	0.853

(B)			
	Matched controls	UIA	*p*-value
Hypertension	435 (63.1%)	185 (75.8%)	$p < 0.001$*
Abdominal calcification index	17.8 (22.7, 95%CI 16.1–19.5)	23.4 (24.2 95%CI 20.3–26.4)	$p < 0.001$*
Dialysis	16 (2.3%)	17 (6.9%)	$p < 0.001$*
Calcified aorta	533 (77.4%)	210 (86.4%)	0.003*
Calcification free aorta	156 (22.6%)	33 (13.6%)	0.003*
Alcohol abuse	218 (31.6%)	55 (22.5%)	0.009*
Chronic obstructive pulmonary disease	89 (12.9%)	43 (20.3%)	0.01*
Type 1 diabetes	30 (4.4%)	3 (1.2%)	0.013*
Asthma	176 (25.5%)	37 (17.5%)	0.016*
Prior myocardial infarction	71 (10.3%)	38 (15.6%)	0.036*
Dyslipidemia	248 (36.0%)	102 (41.8%)	0.124
Type 2 diabetes	166 (24.1%)	49 (20.1%)	0.216
Prior coronary bypass	30 (4.4,%)	12 (4.9%)	0.412
Female	392 (56.9%)	145 (59.7%9	0.497
Male	297 (43.1%)	98 (24.8%)	0.497
Smoking	421 (67.9%)	161 (70.3%)	0.507
Prior percutaneus coronary intervention	57 (8.3%)	22 (9.0%)	0.789
Coronary artery disease	157 (22.8%)	53 (21.7%)	0.789
Age	62.6 (12.1)	62.5 (11.0)	0.841
peripheral artery disease	43 (6.2%)	16 (6.6%)	0.879

(C)			
	rIA	IUA	*p*-value
Dyslipidemia	58 (27.8%)	102 (41.8%)	0.002*
Prior myocardial infarct	14 (6.7%)	38 (15.6%)	0.003*
Dialysis	5 (2.3%)	17 (6.9%)	0.021*
Coronary artery disease	28 (13.4%)	53 (21.7%)	0.021*
Prior percutaneous coronary intervention	8 (3.8%)	22 (9.0%)	0.028*
Alcohol abuse	32 (15.5%)	55 (22.5%)	0.058
Prior coronary bypass	4 (1.9%)	12 (4.9%)	0.084
Calcification free aorta	19 (8.8%)	33 (13.6%)	0.11
Calcified aorta	196 (91.2%)	210 (86.4%)	0.11
Abdominal calcification index	25.9 (22.9–29.0)	23.4 (24.2, 20.3–26.4)	0.242
Smoking	120 (67.0%)	161 (70.3%)	0.479
chronic obstructive pulmonary disease	30 (17.6%)	43 (20.3%)	0.515
Hypertension	153 (73.2%)	185 (75.8%)	0.524
Asthma	33 (19.5%)	37 (17.5%)	0.604
Age	62.9 (12.3, 61.3–64.6)	62.5 (11.0, 61.1–63.9)	0.658
Type 2 diabetes	45 (216%)	49 (20.1%)	0.685
peripheral artery disease	15 (7.2%)	16 (6.6%)	0.784
Type 1 diabetes	2 (1.0%)	3 (1.2%)	0.786
Male	85 (39.4%)	99 (40.2%)	0.845
Female	131 (60.6%)	147 (59.8%)	0.845

3.1. rIA vs. matched controls

Patients with rIA had higher mean ACI, 25.93 (SD 22.7 95% CI 18.6–21.8) than matched controls, 18.0 (SD 22.7, 95% CI 16.2–19.9, $p < 0.001$). Fewer rIA patients had total calcification free aorta (8.8% *vs.* 25.7%, $p < 0.001$) compared to matched controls. Hypertension was more common in the rIA group (73.2% *vs.* 62.7%). There was less hypercholesterolemia (27.8% *vs.* 37.7%) and alcohol abuse (15.5% vs 32.0%) in the rIA patient group. Markers of coronary artery disease, including previous percutaneous coronary interventions (PCI) and coronary artery bypass grafting surgery (CABG), were also less common among rIA patients than in matched control patients.

Results of multivariate logistic regression analyses are shown in Fig. 2. Comparison of rIA patients and matched controls showed that hypercholesterolemia (OR 0.42, 95% CI 0.22–0.787), older age (OR 0.96 per year, 95% CI 0.93–0.99), prior PCI (OR 0.30 95% CI 0.10–0.86) and alcohol abuse (OR 0.41, 95% CI 0.19–0.86) reduced the odds for rIA, and hypertension (OR 2.65, 95% CI 1.35–5.23), having calcification in the aorta (OR 3.35, 95% CI 1.42–7.87) and ACI (OR 1.02, 95% CI 1.00–1.03 per increment) increased odds for rIA. ACI >3 increased risk for rupture with OR 5.77, 95% CI 3.29–10.11.

3.2. UIAs vs. matched controls

Mean ACI for unruptured intracranial aneurysm (UIA) patients was 23.4 (SD 24.2, 95% CI 20.3–26.4) and was significantly higher than for matched controls (mean ACI 17.8, 95% CI 16.1–19.5). Compared to matched controls, UIA patients had more prior myocardial infarctions (15.6% *vs.* 10.3%), chronic-obstructive pulmonary disease (COPD) (20.3% *vs.* 12.9 and hypertension (75.8% *vs.* 63.1%). Matched controls had significantly more type I diabetes, history of alcohol abuse, asthma and dialysis treatment than UIA patients.

Comparison of UIA patients and matched controls showed that alcohol abuse (OR 0.56 95% CI 0.31-0,99) was a negative predictor of UIA, and total aortic calcification (OR 2.10 95% CI 1.11–4,01), dialysis treatment (3.29 95% CI 1.46–7.45) and previous myocardial infarction (OR 1.87 95% CI 1.01–3.48) showed increased odds for UIA. ACI was not associated with odds for UIA when compared to matched controls. ACI >3 increased odds for UIA with OR 2.10, 95% CI 1.34–3.30.

3.3. rIA vs. UIA

There was no statistically significant difference in mean ACI between UIA and rIA patients although mean ACI was numerically higher for rIA patients (25.9 95% CI 22.9–29.0 *vs.* 23.4 95% CI 20.3–26.4) Comparison of rIA patients and UIA patients showed that ACI (OR 1.02 95% CI 1.00–1.03 per increment) increased odds for rIA, and dialysis treatment (OR 0.26 95% CI 0.08–0.86), hypercholesterolemia (OR 0.47, 95% CI

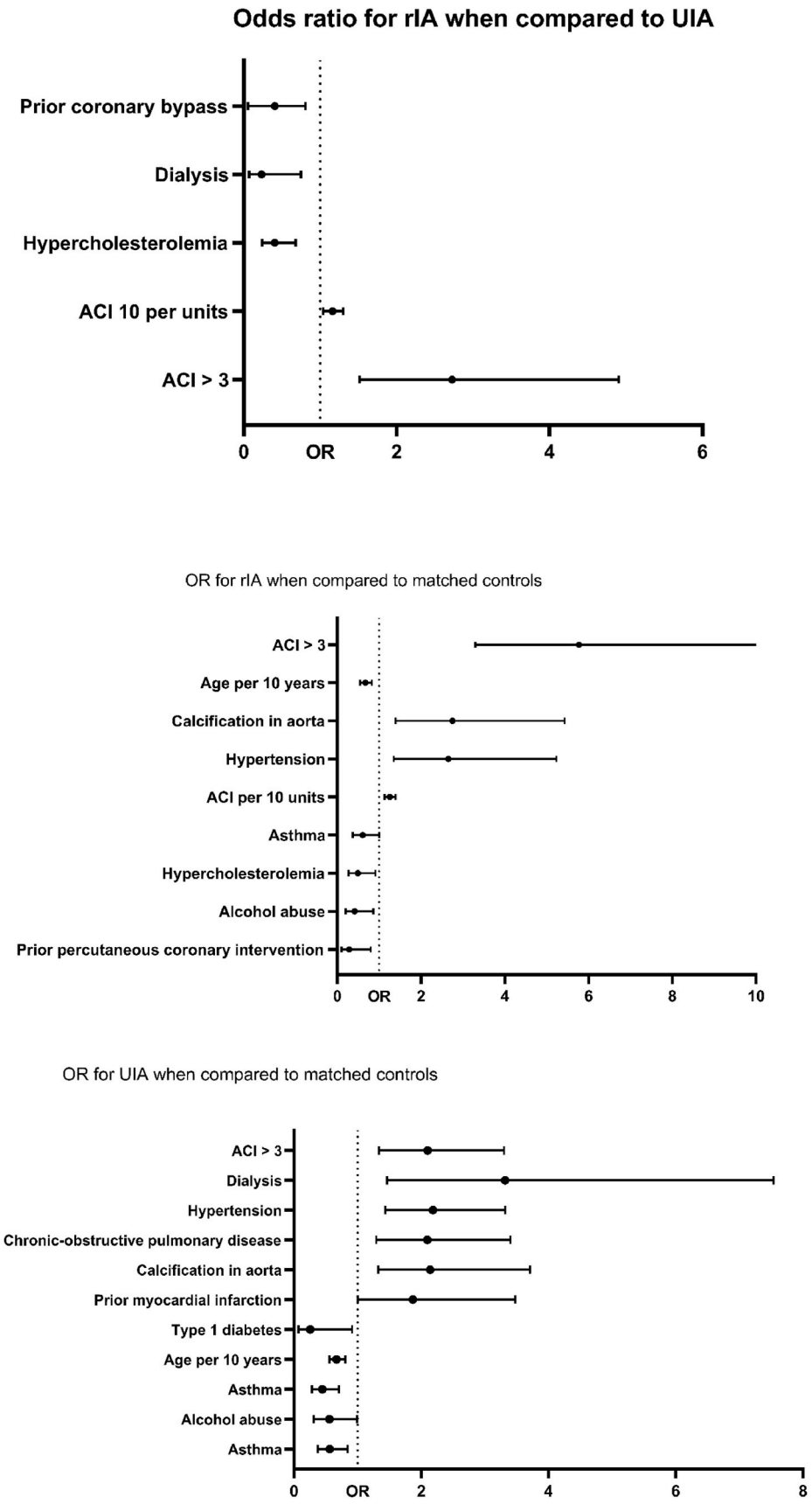

Fig. 2. Diseases, risk factors and ACI: odds ratios for rIA and UIA.

0.28–0.78) and previous CABG (OR 0.12, 95% CI 0.05–0.77) reduced odds for rIA. ACI >3 increased risk for rupture with OR 2.73 95% CI 1.51–4.91. Patients with UIA and rIA patients were not matched to each others.

3.4. Decision-tree and ROC

CART-analysis on the entire study population revealed that ACI over 3.1 (range from 0 to 134.0, mean 19.8) was associated with a two-fold risk of IA. Ruptured aneurysms were more prevalent in patients who had ACI over 3.1, diagnose of hypertension and age over 63. CART-analysis on only IA patients revealed that ACI over 3.3 was associated with rIAs. 49.6% of patients with ACI over 3.3 were rIA patients, whereas in patients with ACI under 3.3 only 34.6% had rIA. Decision tree is shown in Fig. 3.

ROC analysis of ACI in rIA, UIA and matched control patients as well as between rIA and UIA patients showed a biggest AUC (0.63 95% CI 0.59–0.67 $p \leq 0.0001$) in rIA patients compared to matched controls. Cut-off value of 3 in ACI showed sensitivity of 0.83 and 1-specificity was 0.61. Comparison of rIA and UIA patients AUC was 0.62 (95% CI 0.58–0.67, $p < 0.0001$) and a cut-off value of 3 yielded a sensitivity of 0.83 and 1-specificity was 0.62. UIA patients *vs*. their matched controls AUC was 0.58 (95% CI 0.54–0.62, $p = 0.0002$). At the cut-off of 3, sensitivity was 0.73 and 1-specificity was 0.60.

3.5. Inter-rater reliability

ACI measurements inter-rater reliability was excellent when comparing ratings against board-certified neuroradiologist ratings (ICC value of 0.99, 95% CI 0.96–1.00).

4. Discussion

The main finding of this study was that higher abdominal aortic

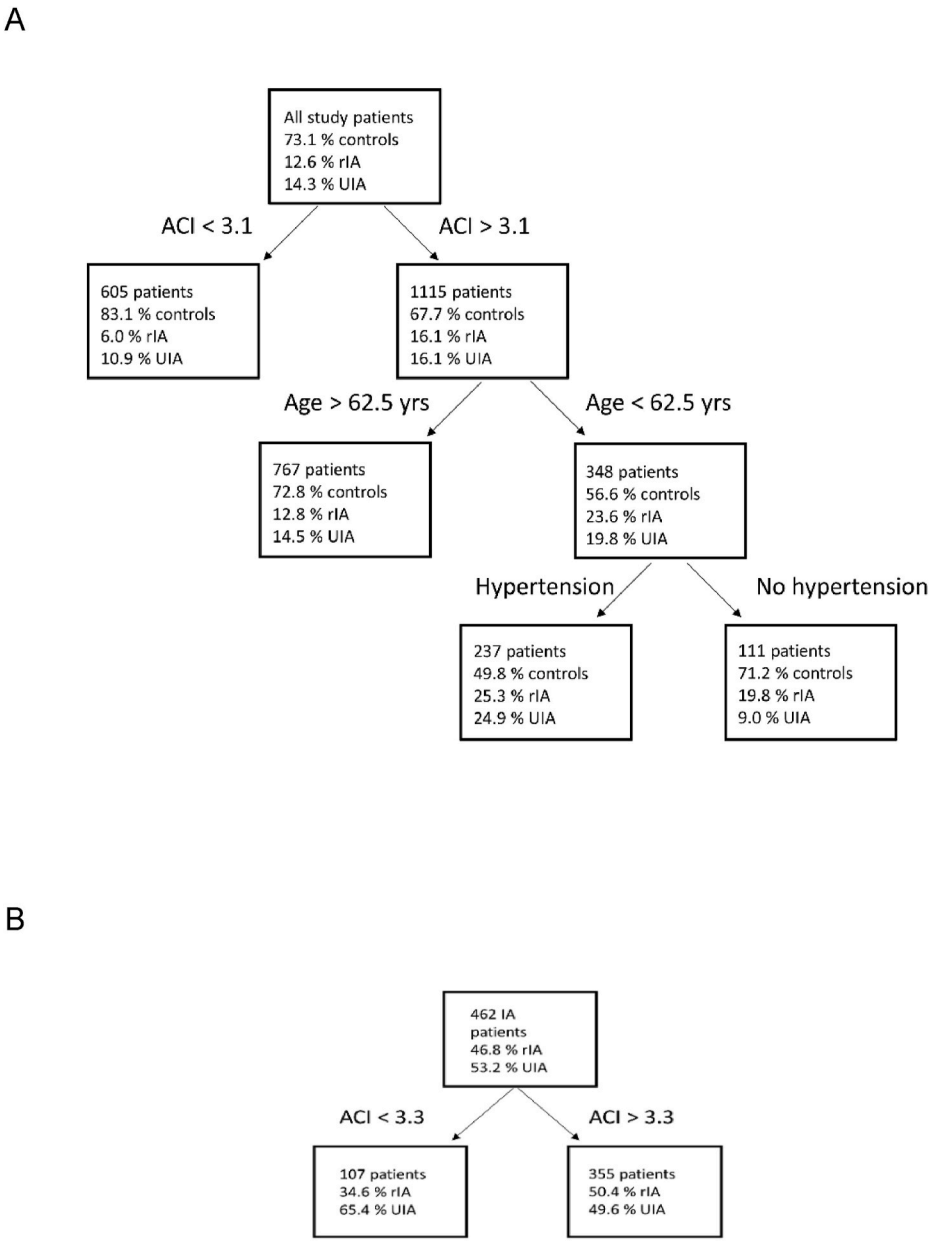

Fig. 3. CART-analysis decision tree.
(A) All study patients, including rIA, UIA and control patients. (B) CART-analysis of only rIA and UIA patients.

calcification was associated with a higher risk of intracranial aneurysms overall. Mean ACI was significantly higher in rIA (ruptured intracranial aneurysm) patients than matched controls and the risk for rIA increased with higher ACI when compared to matched controls. On the other hand, ACI did not increase odds for incidental intracranial aneurysms (UIA) when compared to matched controls even though mean ACI was significantly higher in UIA patients. CART-analysis confirmed that ACI is independently associated with IAs and especially with rIAs. Highest risk for IA was overall in patients with an ACI over 3.1 and who had hypertension and were older than 63 years. ACI over 3 was associated with increased risk of rIA and UIA when compared to matched controls, as well as with risk for rIA when rIA patients were compared to unmatched UIA patients.

Aortic calcification index is plausible, easily measurable and a relatively unbiased marker for systemic atherosclerosis: calcified plaques represent an arterial wall that is affected by atherosclerosis [19]. ACI reveals atherosclerosis regardless of recorded risk factors and it has been previously linked to increased carotid intima-media thickness, incidence and severity of coronary artery disease and cardiovascular events in patients with coronary artery disease [14,20–22]. Our results suggest that ACI indicates an increased risk for IAs, both rIAs and UIAs.

Pathophysiology of arterial calcification is multifactorial, including genetic and environmental risk factors [23], which could be also related to IA pathophysiology. Earlier studies suggest that inflammation has an important role in the pathophysiology of IA formation and rupture [9]. Also in atherosclerosis, the role of inflammation is well established [24]. Hence there could be several mechanisms explaining ACI association with intracranial aneurysms. Similarities in the inflammatory profile could be one of them, even though morphological devastation is different in IAs, and atherosclerotic plaques and inflammatory cascade is initiated by different triggers: accumulated oxidized low-density lipoprotein in atherosclerosis and mechanical shear stress and hemodynamic disturbance in IAs, according to current understanding.

Endothelial dysfunction is a systemic disorder related to pathophysiology of atherosclerosis and IA formation, and endothelial dysfunction severity correlates with arterial calcifications [8,25]. Connection between these two clinical entities is under investigation. A recent study found out that atherosclerotic lesions and immunohistochemical signs of inflammation in intracranial aneurysms were associated with aneurysm wall enhancement in imaging [26]. Intracranial aneurysms and atherosclerotic plaques harbor T-helper lymphocytes and macrophages, and the same types of cytokines (IL-1b, TNF-a) are found in both [7,9,11,24,27–29]. In IA, VSMCs phenotype is changed from contractile type to ECM-synthetizing type, and cells become pro-inflammatory, as in atherosclerotic plaques [30–32]. Markers of inflammation are more prominent in rupturing aneurysm: they harbor more pro-inflammatory cells, polarization of macrophage types is skewed towards type 1 pro-inflammatory macrophages and overall, rIAs harbor more inflammatory cells than UIAs [33–35].

Similarly to our results, lower prevalence of cardiovascular diseases in rIA patients was reported by Kang et al. earlier [36]. However, as Huhtakangas et al. revealed in their follow-up study [37], IA patients have excess mortality due to cardiovascular and cerebrovascular diseases at younger age than matched controls. They also found multiple IAs to be related to IA patients long-term mortality – perhaps describing more wide-spread inflammation of cerebral arteries. Even though markers of coronary artery disease were indeed fewest in rIA patients, within each IA patient group (rIA, UIA) and control patients, mean ACI was higher in those who had coronary artery disease or history of coronary interventions than those who had no coronary artery disease or intervention in history (see Supplementary Table). Thus our results give credence to the idea of IAs being related to atherosclerotic diseases - we used ACI to expose the subject's atherosclerotic status and found an association between IAs and atherosclerotic burden, even though other specific, heart-related atherosclerotic end-points were not present.

Our results did not show increased risk for IAs with hypercholesterolemia (OR 0.42, 95% CI 0.27–0.91 for rIA) or alcohol abuse (OR 0.41, 95% CI 0.20–0.86 for rIA), which were previously associated with rIAs [38,39]. Also, in our study population smoking was not associated with increased risk for IAs, even though smoking is a well-established risk factor for IAs [40]. Several factors might explain these findings: first, these risk factors may be insufficiently reported in patient records, and thus such register-based data is susceptible to bias. Second, IA patient's risk profile might have improved (reduction of risk behavior, lipid profile improvement) after diagnosis, but our data is not able to visualize this possible phenomenon. Third, in our data ex-smokers and current smokers are reported together.

It is noteworthy that smoking was not infrequent in our study population – 67.5% of all subjects were categorized as ex-smokers or current smokers. As our data on smoking relies on patient records, it is difficult to interpret findings with it. Our method does not allow us to classify smokers according to the smoking intensity. Reporting heavy smokers with those who barely are identifiable as smokers introduces perhaps a falsely increased number of smokers in our data. Still, separating smokers from ex-smokers could produce in the same way biased information on smoking. An earlier study reports that duration and intensity of smoking increase risk of aneurysm rupture but cessation and duration since cessation do not reduce the risk [40]. Thus we saw it most fit to report ex- and current smokers together. Retrospective setting does not allow us to reliably assess the intensity of smoking or duration since cessation. Most importantly, these inverse findings with recorded risk factors underline the relevance of ACI measurements. ACI is not dependent on reported vices but rather it summarizes individual's atherosclerotic vascular disease burden.

An inverse relation between rIA and cardiovascular diseases can be explained by rIA patients being asymptomatic until IA rupture and having not been diagnosed with cardiovascular diseases whereas patients with incidental aneurysms have been evaluated for intracranial aneurysms in part due to known risk factors and cardiovascular diseases. Coronary artery disease and other atherosclerotic diseases may not emerge as comorbidities in rIA patients because the aneurysmal rupture and subarachnoidal hemorrhage could be the first presentation of atherosclerotic disease. Also, in our study setting patients are categorized as rIA patients by having a diagnosed ruptured IA. This introduces a potential survivor bias, as some of the patients could have later developed further atherosclerotic burden, or they have not been evaluated for their cardiovascular comorbidities due to thus far being asymptomatic.

Other potential explanation is that patients with diagnosed coronary artery disease, cerebrovascular disease or peripheral vascular disease are more likely to have on-going pharmacotherapy with statins, antithrombotic medication (aspirin or clopidogrel) and antihypertensive medication for secondary prevention. Consequently, the lower prevalence of cardiovascular diseases in rIA patients is most likely a surrogate marker for lacking optimal preventive pharmacotherapy. Some UIA patients may be future rIA patients, and some UIA patient's aneurysms are treated electively before rupture. Thus, some patients with atherosclerotic burden and inflammation possibly leading to aneurysm rupture are categorized as UIA patients due to an early diagnosis rather than being diagnosed with a different disease entity. This is plausible as it is already established that inflammation extinguishing medication such as aspirin and statins reduces IA rupture risk and growth [39,41,42].

There are few limitations to this study. Some demographic variables (smoking, alcohol abuse, cardiovascular diseases) revealed controversial findings as discussed above. In addition, our method and retrospective approach is susceptible to selection bias: IA and control patients are hospitalized patients, admittedly in part due their risk profile. However, IA patients abdominal imaging is not performed due to IAs, and control patients are selected from emergency departments patients who had undergone abdominal imaging at their emergency visit. Selection bias therefore is presumably present, but we claim it has minor effect on our hypothesis, because abdominal imaging rarely has much to

do with atherosclerotic and/or IA events. Even further, abdominal imaging is not performed with the intention to find out the atherosclerotic status of an individual. The inflammatory mechanism of atherosclerosis is based on earlier research, and we did not have results on subjects pro-inflammatory markers. We think that it is not needed in this study, mainly because ACI index is cumulative in nature, i.e. it summarizes the results of an individual atherosclerotic process regardless of other kind of measurements.

Abdominal aortic calcification is more common in patients with IAs compared to matched controls. In addition, higher abdominal aortic calcification could be associated with ruptured IAs. Our results suggest that IA and especially rIA could be a marker and a result of increased atherosclerotic burden, and careful consideration for primary prevention in IA patients would be reasonable.

Author contributions

Conceptualization: Dan Laukka, Jarmo Gunn, Methodology: Ville Rantasalo, Dan Laukka, Formal analysis: Ville Rantasalo, Dan Laukka, Jarmo Gunn, Writing – original draft: Ville Rantasalo, Dan Laukka, Jarmo Gunn, Writing – review & editing: Ville Rantasalo, Dan Laukka, Jarmo Gunn, Tuomas Kiviniemi, Ilkka Saarenpää, Juri Kivelev, Melissa Rahi, Elli Lassila, Jaakko Rinne, Visualization: Ville Rantasalo, Validation, inter-rater reliability: Jussi Hirvonen.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.atherosclerosis.2021.08.027.

References

[1] M.H.M. Vlak, A. Algra, R. Brandenburg, G.J.E. Rinkel, Prevalence of unruptured intracranial aneurysms, with emphasis on sex, age, comorbidity, country, and time period: a systematic review and meta-analysis, Lancet Neurol. 10 (7) (2011) 626–636, https://doi.org/10.1016/S1474-4422(11)70109-0.

[2] K.C. Kent, R.M. Zwolak, N.N. Egorova, T.S. Riles, A. Manganaro, A.J. Moskowitz, A.C. Gelijns, G. Greco, Analysis of risk factors for abdominal aortic aneurysm in a cohort of more than 3 million individuals, J. Vasc. Surg. 52 (3) (2010) 539–548, https://doi.org/10.1016/j.jvs.2010.05.090.

[3] B.G. Thompson, R.D. Brown, S. Amin-hanjani, J.P. Broderick, K.M. Cockroft, E. S. Connolly, G.R. Duckwiler, C.C. Harris, V.J. Howard, S.C.C. Johnston, et al., AHA/ASA Guideline Guidelines for the Management of Patients with Unruptured Intracranial Aneurysms, 2015, https://doi.org/10.1161/STR.0000000000000070.

[4] S. Kaptoge, S.R.K. Seshasai, P. Gao, D.F. Freitag, A.S. Butterworth, A. Borglykke, E. Di Angelantonio, V. Gudnason, A. Rumley, G.D.O. Lowe, et al., Inflammatory cytokines and risk of coronary heart disease: new prospective study and updated meta-analysis, Eur. Heart J. 35 (9) (2014) 578–589, https://doi.org/10.1093/eurheartj/eht367.

[5] N. Etminan, G.J. Rinkel, Unruptured intracranial aneurysms: development, rupture and preventive management, Nat. Rev. Neurol. 12 (12) (2016) 699–713, https://doi.org/10.1038/nrneurol.2016.150.

[6] D. Wolf, K. Ley, Immunity and inflammation in atherosclerosis, Circ. Res. 124 (2) (2019) 315–327, https://doi.org/10.1161/CIRCRESAHA.118.313591.

[7] D. Hasan, N. Chalouhi, P. Jabbour, A.S. Dumont, D.K. Kung, V.A. Magnotta, W. L. Young, T. Hashimoto, H.R. Winn, D. Heistad, Early change in ferumoxytol-enhanced magnetic resonance imaging signal suggests unstable human cerebral aneurysm, Stroke 43 (2012) 3258–3265, https://doi.org/10.1161/STROKEAHA.112.673400.

[8] R. Tulamo, J. Frösen, J. Hernesniemi, M. Niemelä, Inflammatory changes in the aneurysm wall: a review, J. Neurointerventional Surg. 10 (2018) i58–i67, https://doi.org/10.1136/neurintsurg-2018-014090.

[9] N. Chalouhi, M.S. Ali, P.M. Jabbour, S.I. Tjoumakaris, L.F. Gonzalez, R. H. Rosenwasser, W.J. Koch, A.S. Dumont, Biology of intracranial aneurysms : role of inflammation, J. Cerebr. Blood Flow Metabol. 32 (9) (2012) 1659–1676, https://doi.org/10.1038/jcbfm.2012.84.

[10] B.H. Cho, J.H. Kim, S.H. Suh, S.J. Baik, H.S. Lee, J. Kim, K.Y. Lee, Characteristics of intracranial aneurysms according to levels of coronary artery calcium, Stroke 50 (6) (2019) 1403–1408, https://doi.org/10.1161/STROKEAHA.119.024726.

[11] J. Moriya, Critical roles of inflammation in atherosclerosis, J. Cardiol. 73 (1) (2019) 22–27, https://doi.org/10.1016/j.jjcc.2018.05.010.

[12] M.D. Philip Greenland, Michael J. Blah, M.D. MPH, J. Matthew, M.D. Budoff, M. D. Raimund Erbel, Karol E. Watson, Coronary calcium score and cardiovascular risk, ADepartments, J. Am. Coll. Cardiol. 72 (4) (2018) 434–447, https://doi.org/10.1016/j.jacc.2018.05.027. Coronary.

[13] F. Kushiya, H. Wada, M. Sakakura, Y. Mori, E.C. Gabazza, M. Nishikawa, T. Nobori, M. Noguchi, K. Izumi, T. Nakasaki, et al., Prognostic impact of aortic calcification index and ankle-arm blood pressure index in patients under hemodialysis, Clin. Appl. Thromb. Hemost. 11 (2) (2005) 161–169, https://doi.org/10.1177/107602960501100205.

[14] M. Tsushima, Y. Terayama, A. Momose, T. Funyu, C. Ohyama, R. Hada, Carotid intima media thickness and aortic calcification index closely relate to cerebro- and cardiovascular disorders in hemodialysis patients, Int. J. Urol. 15 (1) (2008) 48–51, https://doi.org/10.1111/j.1442-2042.2007.01925.x.

[15] X. Feng, P. Qi, L. Wang, J. Lu, H.F. Wang, J. Wang, S. Hu, D. Wang, Relationship between cerebrovascular atherosclerotic stenosis and rupture risk of unruptured intracranial aneurysm: a single-center retrospective study, Clin. Neurol. Neurosurg. 186 (1) (2019) 105543, https://doi.org/10.1016/j.clineuro.2019.105543.

[16] D. Yamamoto, S. Suzuki, H. Ishii, K. Hirayama, K. Harada, T. Aoki, Y. Shibata, Y. Negishi, Y. Tatami, T. Sumi, et al., Predictors of abdominal aortic calcification progression in patients with chronic kidney disease without hemodialysis, Atherosclerosis 253 (2016) 15–21, https://doi.org/10.1016/j.atherosclerosis.2016.08.004.

[17] J.W. Roh, B.J. Kwon, S.H. Ihm, S. Lim, C.S. Park, K. Chang, W.S. Chung, D Bin Kim, S.R. Kim, H.Y. Kim, Predictors of significant coronary artery disease in patients with cerebral artery atherosclerosis, Cerebrovasc. Dis. 48 (2019) 226–235, https://doi.org/10.1159/000504927.

[18] T.K. Koo, M.Y. Li, A guideline of selecting and reporting intraclass correlation coefficients for reliability research, J Chiropr Med 15 (2) (2016) 155–163, https://doi.org/10.1016/j.jcm.2016.02.012.

[19] S.E.P. New, E. Aikawa, Cardiovascular calcification-an inflammatory disease, Circ. J. 75 (6) (2011) 1305–1313, https://doi.org/10.1253/circj.CJ-11-0395.

[20] Y. Takayama, Y. Yasuda, S. Suzuki, Y. Shibata, Y. Tatami, K. Shibata, M. Niwa, A. Sawai, R. Morimoto, S. Kato, et al., Relationship between abdominal aortic and coronary artery calcification as detected by computed tomography in chronic kidney disease patients, Heart Ves. 31 (7) (2016) 1030–1037, https://doi.org/10.1007/s00380-015-0712-y.

[21] C. An, H.J. Lee, H.S. Lee, S.S. Ahn, B.W. Choi, M.J. Kim, Y.E. Chung, CT-based abdominal aortic calcification score as a surrogate marker for predicting the presence of asymptomatic coronary artery disease, Eur. Radiol. 24 (10) (2014) 2491–2498, https://doi.org/10.1007/s00330-014-3298-3.

[22] Y. Tatami, Y. Yasuda, S. Suzuki, H. Ishii, A. Sawai, Y. Shibata, T. Ota, K. Shibata, M. Niwa, R. Morimoto, et al., Impact of abdominal aortic calcification on long-term cardiovascular outcomes in patients with chronic kidney disease, Atherosclerosis 243 (2) (2015) 349–355, https://doi.org/10.1016/j.atherosclerosis.2015.10.016.

[23] Calcification A F. Rutsch, Y. Nitschke, R. Terkeltaub, Genetics in arterial calcification pieces of a puzzle and cogs in a wheel, 2011, pp. 1381–1391, https://doi.org/10.1161/CIRCRESAHA.111.247965. Published online.

[24] P. Raggi, J. Genest, J.T. Giles, K.J. Rayner, G. Dwivedi, R.S. Beanlands, M. Gupta, Role of inflammation in the pathogenesis of atherosclerosis and therapeutic interventions, Atherosclerosis 276 (2018) 98–108, https://doi.org/10.1016/j.atherosclerosis.2018.07.014.

[25] G. Engstr, S. Frantz, K. Torngren, R. Rylance, J. Bj, U. Malmqvist, D. Erlinge, Association of coronary calcium score with endothelial dysfunction and arterial stiffness, 313, 2020, pp. 70–75, https://doi.org/10.1016/j.atherosclerosis.2020.09.022. September.

[26] W. Zhong, W. Su, T. Li, X. Tan, C. Chen, Q. Wang, D. Wang, W. Su, Y. Wang, Aneurysm wall enhancement in unruptured intracranial aneurysms: a histopathological evaluation, J Am Heart Assoc 10 (2) (2021) 1–10, https://doi.org/10.1161/JAHA.120.018633.

[27] K. Kataoka, M. Taneda, T. Asai, A. Kinoshita, M. Ito, R. Kuroda, Structural fragility and inflammatory response of ruptured cerebral aneurysms A comparative study between ruptured and unruptured cerebral aneurysms, Stroke 30 (1999) 1396–1401, https://doi.org/10.1161/01.STR.30.7.139.

[28] D. Hasan, N. Chalouhi, P. Jabbour, A.S. Dumont, D.K. Kung, V.A. Magnotta, W. L. Young, T. Hashimoto, H.R. Winn, D. Heistad, Early change in ferumoxytol-enhanced magnetic resonance imaging signal suggests unstable human cerebral aneurysm: a pilot study, Stroke 43 (12) (2012) 3258–3265, https://doi.org/10.1161/STROKEAHA.112.673400.

[29] J. Caird, C. Napoli, C. Taggart, M. Farrell, D. Bouchier-Hayes, Matrix metalloproteinases 2 and 9 in human atherosclerotic and non-atherosclerotic cerebral aneurysms, Eur. J. Neurol. 13 (10) (2006) 1098–1105, https://doi.org/10.1111/j.1468-1331.2006.01469.x.

[30] N. Nakajima, S. Nagahiro, T. Sano, J. Satomi, K. Satoh, Phenotypic modulation of smooth muscle cells in human cerebral aneurysmal walls, Acta Neuropathol. 100 (5) (2000) 475–480, https://doi.org/10.1007/s004010000220.

[31] M.R. Bennett, S. Sinha, G.K. Owens, Vascular smooth muscle cells in atherosclerosis, Circ. Res. 118 (4) (2016) 692–702, https://doi.org/10.1161/CIRCRESAHA.115.306361.

[32] R.M. Starke, N. Chalouhi, D. Ding, D.M.S. Raper, M.S. Mckisic, G.K. Owens, D. M. Hasan, R. Medel, A.S. Dumont, Vascular smooth muscle cells in cerebral

aneurysm pathogenesis, Transl. Stroke Res. 5 (3) (2014) 338–346, https://doi.org/10.1007/s12975-013-0290-1.

[33] J. Frösen, A. Piippo, A. Paetau, M. Kangasniemi, M. Niemelä, J. Hernesniemi, J. Jääskeläinen, Remodeling of saccular cerebral artery aneurysm wall is associated with rupture: histological analysis of 24 unruptured and 42 ruptured cases, Stroke 35 (10) (2004) 2287–2293, https://doi.org/10.1161/01.STR.0000140636.30204.da.

[34] J. Cebral, E. Ollikainen, B.J. Chung, F. Mut, V. Sippola, B.R. Jahromi, R. Tulamo, J. Hernesniemi, M. Niemelä, A. Robertson, et al., Flow conditions in the intracranial aneurysm lumen are associated with inflammation and degenerative changes of the aneurysm wall, Am. J. Neuroradiol. 38 (1) (2017) 119–126, https://doi.org/10.3174/ajnr.A4951.

[35] J. Rodemerk, A. Junker, B. Chen, D. Pierscianek, P. Dammann, M. Darkwah Oppong, A. Radbruch, M. Forsting, S. Maderwald, H.H. Quick, et al., Pathophysiology of intracranial aneurysms: COX-2 expression, iron deposition in aneurysm wall, and correlation with magnetic resonance imaging, Stroke 51 (8) (2020) 2505–2513, https://doi.org/10.1161/STROKEAHA.120.030590.

[36] H.G. Kang, B.J. Kim, J. Lee, M.J. Kim, D.W. Kang, J.S. Kim, S.U. Kwon, Risk factors associated with the presence of unruptured intracranial aneurysms, Stroke 46 (11) (2015) 3093–3098, https://doi.org/10.1161/STROKEAHA.115.011351.

[37] J. Huhtakangas, H. Lehto, K. Seppä, R. Kivisaari, M. Niemelä, J. Hernesniemi, M. Lehecka, Long-term excess mortality after aneurysmal subarachnoid hemorrhage: patients with multiple aneurysms at risk, Stroke 46 (7) (2015) 1813–1818, https://doi.org/10.1161/STROKEAHA.115.009288.

[38] V.L. Feigin, G.J.E. Rinkel, C.M.M. Lawes, A. Algra, D.A. Bennett, J. Van Gijn, C. S. Anderson, Risk factors for subarachnoid hemorrhage: an updated systematic review of epidemiological studies, Stroke 36 (12) (2005) 2773–2780, https://doi.org/10.1161/01.STR.0000190838.02954.e8.

[39] A. Can, V.M. Castro, D. Dligach, S. Finan, S. Yu, V. Gainer, N.A. Shadick, G. Savova, S. Murphy, T. Cai, et al., Lipid-lowering agents and high HDL (High-Density lipoprotein) are inversely associated with intracranial aneurysm rupture, Stroke 49 (5) (2018) 1148–1154, https://doi.org/10.1161/STROKEAHA.117.019972.

[40] A. Can, V.M. Castro, Y.H. Ozdemir, S. Dagen, S. Yu, D. Dligach, S. Finan, V. Gainer, N.A. Shadick, S. Murphy, et al., Association of intracranial aneurysm rupture with smoking duration, intensity, and cessation, Neurology 89 (13) (2017) 1408–1415, https://doi.org/10.1212/WNL.0000000000004419.

[41] D.M. Hasan, K.B. Mahaney, R.D. Brown, I. Meissner, D.G. Piepgras, J. Huston, A. W. Capuano, J.C. Torner, Aspirin as a promising agent for decreasing incidence of cerebral aneurysm rupture, Stroke 42 (11) (2011) 3156–3162, https://doi.org/10.1161/STROKEAHA.111.619411.

[42] W. Cheng, X. Jia, J. Li, W. Cheng, Z. Liu, Z. Lin, C. Yang, Relationships of statin therapy and hyperlipidemia with the incidence, rupture, postrepair mortality, and all-cause mortality of abdominal aortic aneurysm and cerebral aneurysm: a meta-analysis and systematic review, J. Cardiovasc. Pharmacol. 73 (4) (2019) 232–240, https://doi.org/10.1097/FJC.0000000000000653.