Long-Term Follow-Up of Cerebral Amyloid Angiopathy-Associated Intracranial Hemorrhage Reveals a High Prevalence of Atrial Fibrillation

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Goal: Cerebral amyloid angiopathy (CAA) is the second-most common cause of nontraumatic intracerebral hemorrhages (ICH), surpassed only by uncontrolled hypertension. We characterized the percentage, risk factors, and comorbidities of patients suffering from CAA-related ICH in relation to long-term outcomes. *Material and Methods*: We performed retrospective analyses and clinical follow-ups of individuals suffering from ICH who were directly admitted to neurosurgery between 2002 and 2016. *Findings*: Seventy-four of 174 (42%) spontaneous nontraumatic lobar ICH cases leastwise satisfied the modified Boston criteria definition for at least "possible CAA." Females suffered a higher risk of CAA-caused ICH (42 of 74, 56.8%, *P*= .035). Atrial fibrillation as a major comorbidity was observed in 19 patients (25.7%). Recovery (decrease of modified Rankin scale [mRS]) was highest during hospitalization in the acute clinic. One-year mortality was as follows: 14 of 25 patients (56%) with probable CAA without supporting pathology, 6 of 18, and 8 of 31 patients with supporting pathology and possible CAA, respectively. Only 10 of 74 (13.6%) had favorable long-term outcomes (mRS ≤2). Increasing numbers of lobar hemorrhages, low initial Glasgow Coma Scale, and subarachnoid hemorrhage were significantly associated with poor survivability, whereas statins, antithrombotic agents, an intraventricular hemorrhage, and midline shift played seemingly minor roles. *Conclusions*: Symptomatic ICH is a serious stage in CAA progression with high mortality. The high incidence of concurrent atrial fibrillation in these patients may support data on more widespread vascular pathology in CAA.

Key Words: Cerebral amyloid angiopathy—intracerebral bleeding—atrial fibrillation—long-term outcome—computer tomography—magnetic resonance tomography

Introduction

Cerebral amyloid angiopathy (CAA) is a type 2 small-vessel disease responsible for up to 20% of nontraumatic intracerebral hemorrhages (ICH)—the second-most common cause following hypertension.[1-5] CAA has a mortality rate of up to 50%, with less than half of the patients regaining independence.[2,3,6-8] Factors detectable on cerebral imaging in connection with CAA-caused ICH leading to a poorer outcome include: increasing volumes of ICH, suffering

Abbreviations: CAA, cerebral amyloid angiopathy; cMBs, cerebral microbleeds; CNS, central nervous system; Css, cortical superficial siderosis; GCS, Glasgow Coma Scale; ICH, intracerebral hemorrhage; IVH, intraventricular hemorrhage; OAC, oral anticoagulation/oral anticoagulants; mBC, modified Boston criteria; mRS, modified Rankin Score; SAH, subarachnoid hemorrhages; TIA, transitory ischemic attack

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from an intraventricular hemorrhage (IVH), midline shift, multiple cerebral microbleeds (cMBs), and postoperative ICH.[2,3,8-10] Increasing age, dementia, cognitive impairment, antiplatelet agents, low initial Glasgow Coma Scale (GCS), and (potentially) gender carry a higher individual risk for facing severe disability or death.[2,3,5,9]

Similar studies also including ICH with other causes partially support these findings, further proving large volumes of ICH, IVH, and high volumes of white matter hyperintensities to be ICH-related risk factors for poor outcome.[7,11-15] Age, low GCS at admission, oral anticoagulation, and low initial body weight also factor in as individual negative prognostic determinants.[7,11-13,16,17] The role of antiplatelet agents and statins remains ambiguous because of a sparsity of data concerning individuals affected solely by CAA-related ICH.[2-4,12,18-30]

In CAA, accumulation of amyloid β primarily in leptomeningeal, cortical, and subcortical arterioles and capillaries causes vessels to become fragile and brittle, leading to ICH, cortical subarachnoid hemorrhages, cMBs, dementia, rapid progressive cognitive and neurological decline, transient focal neurological episodes resulting from cortical superficial siderosis (cSS), ischemic, and white matter lesions.[2-4]

ApolipoproteinE ε2 and ε4 alleles are the only currently established genetic risk factors for CAA.[2-4,8,31-35] Increasing age (which poses a general risk for the development of CAA), gender, cSS, cMBs, minor head trauma, and hypertension all heighten the risk of ICH.[3,4,16,21,36-40] Secondary preventative measures against recurrent ICH are nonspecific and include strict treatment of hypertension as well as the avoidance of other cerebrovascular risk factors whenever possible.[3,4,19,32,40]

Inconsistent research results and the general sparsity of data focusing on the long-term follow-up of CAA patients were the primary motivating factors for this study. To this end, we analyzed patients admitted and treated for CAA-related ICH at the neurosurgical ward of the University Hospital Regensburg to reveal any suspected risk and prognostic factors and their influence on determining short- and long-term follow-up.

Material and Methods

The study was approved by the Ethical Review Board of the University of Regensburg (reference: 16-101-0050/16-050-101). We searched the neurosurgical database between 2002 and 2016 for the term "atypical intracerebral hemorrhage" and the ICD Code I61. Informed consent was obtained from individuals participating in a long-term follow-up via the patients or their legal guardians. In Regensburg, patients may be either admitted directly to the stroke unit that is located in a separate facility nearby (Bezirksklinikum Regensburg) or to the general emergency wards at University Hospital. In order to identify as many patients with histological work-up as possible only patients admitted to the neurosurgery ward were included. During the study period, 46 patients per year with an ICH were treated primary in our neurological ward, thus almost one third of patients were primarily treated in the Department of Neurosurgery and included into this analysis.

The following information was extracted from medical records of all patients suffering from ICH: date of birth, gender, age at admission, date of admission, cause, and location of ICH, whether surgery (extraventricular drainage, craniotomy, craniectomy) was performed and in-hospital mortality.

We analyzed the records of 74 patients suffering from CAA-related ICH to account for risk and prognostic factors, basic characteristics, and mortality at discharge. The following parameters were included: ICH volume, preoperative and maximal midline shift, existence of IVH, SAH, GCS at admission or prior to sedation (according to Sternbach et al), modified Rankin Score (mRS) at admission and discharge, performed operations, and medication administered on arrival (including statins, antiplatelet, and anticoagulating agents).[41,42] In addition, comorbidities such as hypertension, diabetes mellitus, and cardiovascular diseases (including atrial fibrillation) were evaluated (Supplemental Material Table 5: vessel diseases). GCS scores were subdivided into 3 subgroups as published by Mendelow et al: 3-8 (group 1), 9-12 (group 2), and greater than 12 scoring points (group 3).[6]

Hypertension was defined as "taking any antihypertensive medication" or having blood pressure values according to the ESC guidelines.[43] A mRS score of $\leq$2 was defined as "favorable" and $\geq$3 as "unfavorable."[44]

ICH volumes were calculated using the ACB/2 formula.[45] In order to classify patients according to the mBC, we examined all available MRIs for cMBs using the MARS criteria and cSS where appropriate (any cSS detected in postoperative MRIs were excluded).[36,46] In addition, we searched for recent ischemic lesions, white matter hyperintensities (classified using the Fazekas score), residual lesions caused by previous cerebral ischemia and ICHs, and cerebral edemas (Supplemental Material Table 6: MRI analysis).[47]

We obtained each individuals mortality rate after 14 and 30 days as well as after 1, 2, and 5 years whenever appropriate information was available, excluding 2 individuals who could not provide sufficient data and those not exceeding the required minimum time. Consequently, we included 70 patients for 1-year mortality rates, 66 for 2 years, and 45 for 5 years, respectively.

The estimated mRS was, whenever possible, recorded for the follow-up at the time of discharge from the neurosurgical ward, neurological rehabilitation, and in 2017.

Despite being supplied with an accompanying mRS of each patient's discharge from the acute clinic, we were only able to assess 37 patients on their discharge from neurological rehabilitation. An interview was held with most patients or their relatives in the subsequent spring and

Table 1. *Causes of ICH and basic characteristics of all ICH patients*

Number of patients	Percentage	Cause of ICH	Age—median	Age—average	Age—standard deviation	Female gender		Operation		Death upon discharge	
						n	%	n	%	n	%
18	5.5	Probable CAA with supporting pathology	68.50	69.61	6.97	10	55.6	18	100	1	5.6
25	7.6	Probable CAA	71.00	70.60	6.38	15	60.0	14	56.0	7	28.0
31	9.5	Possible CAA	74.00	71.32	7.90	17	54.8	17	54.8	3	9.7
74	22.6	CAA as defined in modified Boston criteria	72.00	70.66	7.13	42	56.8	49	66.2	11	14.9
26	7.9	Possible CAA, too little information to exclude other causes of ICH accurately	76.50	74.46	7.79	16	61.5	15	57.7	12	46.2
20	6.1	Traumatic ICH	60.00	61.00	14.67	9	45.0	10	50.0	2	10.0
14	4.3	Central nervous system tumor	64.00	60.43	14.24	10	71.4	14	100.0	0	0.0
1	.3	Cerebral lymphoma	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.
3	.9	Infection of CNS	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.
27	8.3	Vascular malformation	57.00	55.22	15.88	8	29.6	22	81.5	4	14.8
2	.6	Hemorrhagic transformation after ischemic stroke	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.
2	.6	Cerebral vein thrombosis	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.
8	2.4	Coagulopathy	55.50	51.88	20.14	2	25.0	3	37.5	3	37.5
8	2.4	Tumor-associated (except primary CNS tumor)	54.00	60.75	14.94	1	12.5	6	75.0	3	37.5
7	2.1	CAA possible, but patient is too young (<55 years)	42.00	39.29	9.34	3	42.9	6	85.7	0	0.0
1	.3	CAA possible, but patient under 55 years and too little information to exclude other causes than CAA	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.
134	40.9	Deep ICH	65.50	64.19	14.46	50	37.3	85	63.4	29	21.6
327	100.0	All ICH	67.00	64.33	14.43	147	44.8	218	66.5	68	20.7

Abbreviation: n.a., not available.

From left to right: number of patients and their share of the defined causes of ICH; median and average ages of the included patients as well as standard deviation of age, number, and percentage of patients with female gender, patients who needed an operation and patients who died).

summer of 2017, excluding 4 who were lost to follow-up (mean follow-up period: 5.1 years (SD ± 3.4 years, minimum .4 years, maximum 13.2 years). Patients in whom neurological examination was not feasible (eg, remoteness from the hospital or for medical reasons) were sent a detailed questionnaire. For the remaining patients, we recalculated the mRS based on a telephone interview (in cases where the individual could not be contacted, their relatives or primary caretakers were questioned instead).

Statistical analyses were carried out using SPSS 25 using chi-square tests, CramerV tests, Spearman's correlation, and binary regression models (where appropriate) with a significance of $P \leq .05$.

Results

Classification of Atypical ICH

In this nonselected collective of patients, 327 individuals suffered from any ICH and were treated in the Department of Neurosurgery at the University Hospital Regensburg. Of those patients, 134 were classified as "typical" ("hypertensive") ICH and 20 had traumatic ICH. Table 1 illustrates the classifications of ICH excluding 10 misclassified individuals (these did not suffer from acute ICH). The following causes of lobar (cortical and subcortical) ICH other than CAA were detected: 15 primary CNS tumors, 27 vascular malformations, 8 coagulopathies, and 8 likely tumor-associated ICH (excluding primary CNS tumors) caused by an impaired clotting behavior induced by systemic tumors (excluding primary CNS tumors). Infrequent causes of lobar bleeding encompassed: 3 CNS infections, 2 hemorrhagic transformations following an ischemic stroke, and 2 cerebral vein thromboses.

Seventy-five cases of ICH first matched the mBC (as defined by Linn et al), and only a single participant had to be excluded post hoc due to a previously unknown trauma prior to ICH.[48] The remaining 74 patients satisfied the requirements for being classified as at least "possible CAA." Patients not meeting these criteria were either too young (8 patients) or had insufficient examinations and anamneses to rule out other causes of atypical ICH besides possible CAA, commonly trauma (26 patients). A subclassification of the 74 CAA patients according the mBC showed that no patients met the status "definite

CAA" (as no autopsy showing histopathological evidence was performed) (subgroup 0), 18 patients were classified as having a probable CAA with supporting pathology (subgroup 1), 25 as probable CAA without supporting pathology (subgroup 2), and 31 as possible CAA (subgroup 3).

In summary, 74 of all 307 ICH (24.1%) and 74 of the 173 lobar bleedings (42.8%) identified in our cohort (after excluding traumatic subtypes) were precipitated by CAA. The average age of patients with CAA was 70.7 years (range 55-88 years), 56.8% of these being females. The diagnostic process revealed that MRI was performed on 35 of 74 (47%) patients, all but 1 receiving iron-sensitive sequences. Neurosurgical operations were performed on all 18 patients in subgroup 1, 14 of 25 patients from subgroup 2, and 17 of 31 in subgroup 3. Cerebral MRI was available for 7 patients in subgroup 1 (39%), 20 patients in subgroup 2 (80%), and 8 patients in subgroup 3 (26%) (Table 2: basic characteristics of CAA patients; including medication, comorbidities, therapy, and location of ICH).

Risk Factors for CAA-Related ICH

The female gender was a statistically significant risk factor for CAA-related ICH when compared to deep ICH (P = .007). These findings remain statistically significant (P = .035) when compared to all other precisely defined causes of lobar ICH (Table 1).

The cumulative average incidence of atrial fibrillation in CAA patients reached 25.7% with notable differences between the mBC-defined subgroups: 6 of 18 (33.3%) patients in subgroup 1, 12 of 31 (38.7%) in subgroup 3 but only a single patient of 25 (4%) in subgroup 2 (Table 2). These disparities reached statistical significance with P = .009. A total of 86.5% of our cohort suffered from hypertension. At least 50% of our cohort (excluding atrial fibrillation) were affected by cardiovascular diseases, the most common being cardiac arrhythmia (7 patients), coronary heart disease (9 patients), prior cerebral ischemia(s) (9 patients), and ICH/SAH (10 patients). For an exact subgroup classification, refer to the Supplemental Material Table 5: vessel diseases. Superficial white matter lesions of at least second degree (according to the Fazekas score) detected on MRI were present in 26 of 34 patients, deep lesions in 24 of 33.[47]

Short- and Long-Term Outcome

Mortality rates for both genders were largely similar in univariant analyses (P> .6 for 14 days, 30 days, 1 year, 2, and 5 years), despite the female individuals in this cohort being younger in average (70.1 ± SD 7.36 versus 71.4 ± SD 6.85) than their male counterparts. In addition, there was no statistically significant relationship in the regression analyses (P > .4 for 14 days, 30 days, and 5 years, P > .15 at 1 year and 2 years).

Only 2 of 74 patients (2.7%) suffering from CAA-related ICH achieved a good performance (defined as mRS ≤2) at admission to the acute clinic, while 8 of 74 (10.8%) attained a favorable outcome (mRS ≤2) on discharge from neurosurgery. Further 55 of 74 faced a poor outcome (mRS 3-5) on discharge, and 11 patients died during their hospitalization in the acute clinic. Of the 37 known outcomes of neurological rehabilitation, 6 patients (14%) regained independence/mRS ≤2, 29 (67.5%) were discharged with a severe disability (mRS 3-5), and 2 (4.7%) died (Table 3: clinical presentation, prognostic factors measured by cCT, and follow-up).

The long-term follow-up of all participants (excluding 4 who were lost to follow-up) using the mRS was investigated after a mean of 5.1 years (SD ± 3.4 years, minimum .4 years, maximum 13.2 years) with 60.8% of the data collated for more than 5 years. Ten patients had a favorable outcome, 26 had an unfavorable one, and an additional 34 had died (Table 3).

The number of lobar hemorrhages was the most substantial risk factor for a patients' long-term outcome, as these gain statistical significance as a predictor for mortality at 1 and 2 years (P = .005 and P = .004). Binary regression analyses did not yield a statistically significant result for short- and 5-year outcomes. Additionally, increasing numbers of macrobleedings were statistically significantly higher in individuals dying within 1-2 years in a univariant analysis (P = .016, P = .016; eta = .423, eta = .436, respectively). Nonsignificant mortality rate were found for 5-year mortalities (P = .23 and eta = .461). After 1 year, the mortality rate of patients with probable CAA exceeded 55% (14 individuals died)—which nearly doubled that of patients with supporting pathology (33.3%, 6 of 18) and the 1 in the group of possible CAA (25.8%, 8 of 31). We observed an insignificant trend toward higher 1-year mortality rates in subgroup 2 in univariant analyses when compared to the remainder (P = .068), reaching statistical significance at 2-year mortalities (P = .023). However, no significance was found for very short (14- and 30-day mortalities) and long 5-year mortalities (P = .67, P = .36, and P = .60, respectively).

Low GCS scores at admission were the second-best item predicting long-term mortality. Those with the worst performances had a high risk of dying within 1 or 2 years (P = .021 for 1-year mortalities and P = .037 for 2-year mortalities) and trended toward higher mortality rates at 30 days (P = .066) in our regression analyses.

With respect for short-term mortalities, the presence of cortical subarachnoid hemorrhages was a significant predictor of 30-day mortalities (P = .019), while other prognostic determinants such as statins, atrial fibrillation, growing age (increasing), ICH volume, presence of IVH, enlarging midline shifts, antiplatelet-, and anticoagulant agent were largely unreliable predicting long- and short-term mortalities. These determinants were also less frequent in cases of probable CAA without supporting pathology.

Table 2. *Basic characteristics of CAA patients; including medication, comorbidities, therapy, and location of ICH*

(n = number, p = percentage)			All patients n	All patients p	Patients with probable CAA and supporting pathology n	Patients with probable CAA and supporting pathology p	Patients with probable CAA n	Patients with probable CAA p	Patients with possible CAA n	Patients with possible CAA p
Age	Average		70.66	n.a.	68.5	n.a.	71	n.a.	74	n.a.
	Median		72	n.a.	69.61	n.a.	70.6	n.a.	71.32	n.a.
	Standard deviation		7.13	n.a.	6.97	n.a.	6.38	n.a.	7.9	n.a.
sex	Female		42	56.8	10	55.6	15	60.0	17	54.8
	Male		32	43.2	8	44.4	10	40.0	14	45.2
Therapy	Operation	Yes	49	66.2	18	100.0	14	56.0	17	54.8
		No	25	33.8	0	0.0	11	44.0	14	45.2
	Solely extraventricular drainage		4	8.2	0	0.0	3	21.4	1	5.9
	Craniotomy		44	89.8	18	100.0	11	78.6	15	88.2
	Craniectomy		6	12.2	5	27.8	1	7.1	0	0.0
MRI		Yes	35	47.3	7	38.9	20	80.0	8	25.8
		No	39	52.7	11	61.1	5	20.0	23	74.2
Vascular comorbidities	Hypertension	Yes	64	86.5	15	83.3	19	76.0	30	96.8
		No	10	13.5	3	16.7	6	24.0	1	3.2
	Atrial fibrillation	Yes	19	25.7	6	33.3	1	4.0	12	38.7
		No	55	74.3	12	66.7	24	96.0	19	61.3
	Vessel diseases except atrial fibrillation	Yes	39	52.7	9	50.0	14	56.0	16	51.6
		No	35	47.3	9	50.0	11	44.0	15	48.4
Medication	Statins	Yes	21	28.4/32.3	4	22.2/25.0	10	40.0/45.5	7	22.6/25.9
		No	44	59.5/67.7	12	66.7/75.0	12	48.0/54.5	20	64.5/74.1
		Unknown	9	12.2	2	11.1	3	12.0	4	12.9
	Antiplatelet therapy on admission	Yes	23	31.3/38.3	7	38.9/46.7	9	36.0/42.9	7	22.6/29.2
		No	37	50.0/61.7	8	44.4/53.3	12	48.0/57.1	17	54.8/70.8
		Unknown	14	18.9	3	16.7	4	16.0	7	22.6
	OACs at admission (including phenprocoumon and NOACs)	Yes	13	17.6/21.7	2	11.1/13.3	1	4.0/4.8	10	32.3/41.7
		No	47	63.5/78.3	13	72.2/86.7	20	80.0/95.2	14	45.2/58.3
		Unknown	14	18.9	3	16.7	4	16.0	7	22.6

(*Continued*)

Table 2 (*Continued*)

(n = number, p = percentage)		All patients n	All patients p	Patients with probable CAA and supporting pathology n	Patients with probable CAA and supporting pathology p	Patients with probable CAA n	Patients with probable CAA p	Patients with possible CAA n	Patients with possible CAA p
Low molecular weight heparin on admission	Yes	2	2.7/2.9	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.
	No	68	91.9/97.1	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.
	Unknown	4	5.4	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.
lysis imminent to ICH	Yes	2	2.7	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.
	No	50	78.4	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.
	Unknown	14	18.9	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.
Death prior to discharge	Yes	11	14.9	1	5.6	7	28.0	3	9.7
	No	63	85.1	17	94.4	18	72.0	28	90.3
Location of ICH	Right	37	50.0	11	61.1	11	44.0	15	48.4
	Left	33	44.6	6	33.3	11	44.0	16	51.6
	Bilateral	4	5.4	1	5.6	3	12.0	0	0.0
	Frontal	19	25.7	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.
	Parietal	17	23.0	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.
	Temporal	15	20.3	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.
	Occipital	6	8.1	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.
	Multiple spontaneous ICH	17	23.0	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.

Abbreviation: n.a., not available.

Percentages like XX/YY meaning XX% in all cases, YY% in patients excluding cases where appropriate information was not available.

Table 3. *Clinical presentation, prognostic factors measured by cCT and follow-up*

		(n = number, p = percentage)	All patients n	All patients p	Patients with probable CAA and supporting pathology n	Patients with probable CAA and supporting pathology p	Patients with probable CAA n	Patients with probable CAA p	Patients with possible CAA n	Patients with possible CAA p
Clinical presentation	mRS at admission	0-2	2	2.7	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.
		3-5	72	97.3	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.
	Sedation	Yes	6	8.1	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.
		No	14	18.9	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.
		Unknown	54	73	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.
	GCS at admission	3-8	21	28.4	6	33.3	5	20.0	10	32.3
		9-12	11	14.9	3	16.7	3	12.0	5	16.1
		>12	42	56.8	9	50.0	17	68.0	16	51.6
CCT criteria	Intraventricular hemorrhage	Yes	31	41.9/42.5	4	22.2	13	52.0	14	45.2/46.7
		No	42	56.8/57.5	14	77.8	12	48.0	16	51.6/53.3
		Unknown	1	1.4	0	0.0	0	0.0	1	3.2
	SAH	Yes	29	39.2/40.8	6	33.3	13	52.0/54.2	10	32.3/34.5
		No	42	56.8/59.2	12	66.7	11	44.0/45.8	19	61.3/65.5
		Unknown	3	4.1	0	0.0	1	4.0	2	6.4
	Preoperative midline shift (cm)	Average	.500		1.050	n.a.	.400	n.a.	.500	n.a.
		Median	.638		1.044	n.a.	.458	n.a.	.561	n.a.
		Standard deviation	.522		.574	n.a.	.340	n.a.	.513	n.a.
	Maximum of midline shift (cm)	Average	.500		1.050	n.a.	.450	n.a.	.500	n.a.
		Median	.663		1.022	n.a.	.533	n.a.	.546	n.a.
		Standard deviation	.557		.626	n.a.	.455	n.a.	.508	n.a.
	Volume of ICH (cm^3)	Average	42.000		59.220	n.a.	36.410	n.a.	40.190	n.a.
		Median	45.803		61.259	n.a.	36.173	n.a.	45.246	n.a.
		Standard deviation	30.716		33.962	n.a.	19.169	n.a.	33.988	n.a.
		Minimum	1.13		4.93	n.a.	9.84	n.a.	1.13	n.a.
		Maximum	157.30		119.00	n.a.	82.37	n.a.	157.30	n.a.
Neurological development since ICH	Asymptomatic: no secondary bleeding, ischemic stroke, recurrent ICH	Yes	27	36.5/54.0	5	27.8/35.7	8	32.0/50.0	14	45.2/70.0
		No	23	31.1/46.0	9	50.0/64.3	8	32.0/50.0	6	19.4/30.0
		Unknown	24	32.4	4	22.2	9	36.0	11	35.4
	Postoperative ICH	Yes	5	6.8	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.
		No	69	93.2	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.
	Recurrent ICH	Yes	16	21.6/28.6	6	33.3/37.5	7	28.0/38.9	3	9.7/13.6

(*Continued*)

Table 3 (*Continued*)

		(n = number, p = percentage)	All patients n	All patients p	Patients with probable CAA and supporting pathology n	Patients with probable CAA and supporting pathology p	Patients with probable CAA n	Patients with probable CAA p	Patients with possible CAA n	Patients with possible CAA p
		No	40	54.1/71.4	10	55.6/62.5	11	44.0/61.1	19	61.3/86.4
		Unknown	18	24.3	2	11.1	7	28.0	9	29.0
	Ischemic stroke since ICH	Yes	4	5.4/8.9	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.
		No	41	55.4/91.1	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.
		Unknown	29	39.2	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.
Follow-up	mRS at discharge from neurosurgery /at admission to neurological rehabilitation	0-2	8	10.8	3	16.7	1	4.0	4	12.9
		3-5	55	74.3	14	77.8	17	68.0	24	77.4
		6	11	14.9	1	5.6	7	28.0	3	9.7
	mRS at discharge from neurological rehabilitation	0-2	6	8.1/14.0	2	11.1/14.3	3	12.0/37.5	1	3.2/4.8
		3-5	29	39.2/67.5	9	50.0/64.3	4	16.0/50.0	16	51.6/76.2
		6	2	2.7/4.7	0	0.0	0	0.0	2	6.5/9.5
		Unknown or no mRS available	37	50.0	7	38.9	18	72.0	12	38.7
	mRS at follow-up	0-2	10	13.6/13.9	3	16.7	3	12.0/12.5	4	12.9/13.3
		3-5	26	35.2/36.2	7	38.9	6	24.0/25.0	13	41.9/43.4
		6	34	45.9/47.2	8	44.4	15	60.0/62.5	11	35.5/36.7
		Unknown	4	5.4	0	0.0	1	4.0	3	9.7
	Mortality	14-day mortality	10	13.5/13.9	1	5.6	5	20/20.8	4	12.9/13.3
		30-day mortality	13	17.6/18.1	2	11.1	5	20/20.8	6	19.4/20.0
		1-year mortality	28	37.8/40.0	6	33.3/35.3	14	56.0/58.3	8	25.8/27.6
		2-year mortality	29	39.2/43.9	7	38.9/43.8	14	56.0/66.7	8	25.8/27.6
		5-year mortality	32	43.2/71.1	7	38.9/63.6	15	60.0/78.9	10	32.3/66.7
	Survival	14 days	62	83.8/86.1	17	94.4	19	76/79.2	26	83.9/86.7
		30 days	59	79.7/81.9	16	88.9	19	76/79.2	24	77.4/80.0
		1 year	42	56.8/60.0	11	61.1/64.7	10	40.0/41.7	21	67.7/72.4
		2 years	37	50.2/56.1	9	50.0/56.3	7	28.0/33.0	21	67.7/72.4
		5 years	13	17.6/28.9	4	22.2/36.4	4	16.0/21.1	5	16.1/33.3
	Survival/mortality unknown or too early for	14 days	2	2.7	0	0.0	1	4.0	1	3.2
		30 days	2	2.7	0	0.0	1	4.0	1	3.2
		1 year	4	5.4	1	5.6	1	4.0	2	6.5

Table 3 (*Continued*)

		All patients n	All patients p	Patients with probable CAA and supporting pathology n	Patients with probable CAA and supporting pathology p	Patients with probable CAA n	Patients with probable CAA p	Patients with possible CAA n	Patients with possible CAA p
	(n = number, p = percentage)								
follow-up (time passed since ICH <1/2/5 years)	2 years	8	10.8	2	11.1	4	16.0	2	6.5
	5 years	29	39.2	7	38.9	6	24.0	16	51.6
Total number of ICHs	1	48	64.9/67.6	12	66.7	10	40.0/43.5	26	83.9/86.7
	2	16	21.6/22.5	3	16.7	9	36.0/39.1	4	12.9/13.3
	3	5	6.8/7.0	3	16.7	2	8.0/8.7	0	0.0
	≥4	2	2.8/2.7	0	0.0	2	8.0/8.7	0	0.0
	Unknown	3	4.1	0	0.0	2	8.0	1	3.2

Abbreviation: n.a., not available.
Percentages like XX/YY meaning XX% in all cases, YY% in patients excluding cases where appropriate information was not available.

Oral anticoagulation was especially rare in patients in both subgroups 1 and 2—with only 3 of the 43 patients being on phenprocoumon treatment (Tables 2 and 3).

Discussion

This study reveals a high cumulative incidence of concurrent atrial fibrillation as well as a high mortality rate in symptomatic ICH in CAA, which may support data of a more systemic and widespread vascular pathology in CAA.

This is, to the best of our knowledge, the second largest published cohort of patients with CAA-caused ICH treated in a neurosurgical ward. The largest study, released by Petrides et al, included 99 patients treated in a neurosurgical ward, focusing on risk factors determining mortality and severe disability: increasing age and therefore age-linked comorbidities like hypertension and chronic ischemic heart disease were poor prognostic determinants.[49] In contrast to our study, the follow-up time of the paper mentioned above was short, demonstrating the outcome of these patients at discharge from the neurosurgery only. Furthermore, this study did not reveal any information about atrial fibrillation. A Chinese study containing 367 patients suffering from ICH treated in a neurosurgical ward revealed more patients with deep ICH (135/367 patients = 36.7%) and patients younger than 55 years were included. Interestingly, all individuals showed at least mild degrees of CAA in histopathological analysis.[50] Differences in ethics may have contributed to these substantial differences to our studies that make comparison difficult and racial differences of the influence of ApoE in lobar ICH have been recently shown.[51]

A substantial part of patients suffering from ICH were CAA-related and reached 24% (excluding traumatic ICH; 42.5% when excluding these and deep ICH), therefore partly exceeding former studies gravely with 7%-40% (Table 4). This may be explained by the differing base populations and classification types, as some studies used the SMASH-U-criteria (S = structural cerebral lesions, M = medication (including anticoagulation), A = CAA, S = systemic disease (including liver cirrhosis, thrombocytopenia, etc), H = hypertensive angiopathy, and U = undetermined) while others used histopathological criteria.[52]

Atrial fibrillation was frequent in our CAA cohort (19 of 74 individuals, 25.7% of all CAA patients), but rare in our patients with probable CAA (4% compared to 33% [subgroup 1] and 38% [subgroup 3]). Contrary, the cumulative incidence of atrial fibrillation in other age-matched populations was found to be approximately only 10%-16%.[54,55] Prior studies found atrial fibrillation to be reliable in predicting the poor outcomes of primary ICH (present as typical bleedings and atypical ones including CAA). Masotti et al found Odds ratios of 3.18 (95% confidence interval 1.12-9.05, P = .03) linking this type of cardiac arrhythmia to worse outcomes, while D'Amore et al reported mortality rates of 29.4% versus 23.3% (with versus without atrial

Table 4. *Frequency of CAA in previously published ICH collectives and classification criteria applied*

Author	Criteria used for classifications	Share of CAA
Petrides et al[49]	Histopathological evidence of CAA	7%
Yeh et al[5]	SMASH-U	12.2%
Meretoja et al[52]	SMASH-U	20 %
Charidimou et al[32]	Sever CAA in autopsy studies	7-40%
Charidimou et al[3]	Clinicopathological studies	5-20%
Mehndiratta et al[2]	No further information given	12-15%
Reijmer et al[53]	Severe CAA in autopsy studies	15-30%

fibrillation; $P = .04$).[56,57] The highest 1-year mortality in our study collective was found in subgroup 2 with 14 of 25 (56%) patients compared to 6 of 18 (33%) in subgroup 1 and 8 of 31 (26%) in subgroup 3. Yet those patients with probable CAA (subgroup 2) had the least occurrences of atrial fibrillation despite having the highest 1-year mortality. This contrasts with the data shown above, demonstrating that atrial fibrillation is a poor prognostic marker, but this finding may result from our limited cohort.

The higher cumulative incidence of atrial fibrillation in patients suffering from acute ICH may indicate a deeper relationship with CAA, that is, in the sympathetic brain-heart axis. In a recent study, Krämer et al found basophilic degeneration aggregates, located primarily in the myocardium and atria, which correlated with age, degree of myocardial fibrosis in individuals with arterial hypertension, and the severity of CAA. Especially intracytoplasmic deposition of N-terminal sAPPδ/η fragments found in the myocytes links amyloid-β protein in CAA to myocardiac diseases. However, of the series of autopsies performed, only 9 of 51 patients were reported to have atrial fibrillation, 8 of 54 had ICH without classification, and the majority were male (45 of 62 patients)—thus differing from our studies population.[58]

Most of our patients (86.5%) suffered from hypertension, illustrating the link between common cardiovascular risk factors and β-amyloid diseases. The most frequently discussed explanation for this refers to the relationship between high levels of receptor of advanced glycation end products (RAGE) and the development of Alzheimer's disease, highlighting the possible importance of hypertension and RAGE as targets of pharmacological interventions apart from β-amyloid or alpha synuclein clearance strategies.[59,60]

Our results suggest that the female gender is a substantial risk factor for suffering from CAA-caused ICH, concurring with the study of Petrides et al, which cited a 60% female gender ratio in its cohort of CAA-related ICH, but contrasting with that of Tang et al, which found a male majority (68.4%).[49,50] Despite prior studies revealing contradictory results toward how gender influences the individual outcomes, the univariant- and binary regression statistical analyses we performed showed no visible relationships.[5,9,11,61] Disregarded differences between the Asian and Caucasian base populations of the CAA cohorts may have contributed to the disparate results.

Patients appeared to recover most rapidly during their hospitalization in the acute clinic—a possible indication for rapid or already ongoing neuroplasticity in CAA development. Tang et al obtained similar results by comparing mRS at discharge and after 1 year.[50] Our observation of fewer favorable outcomes after discharge from the acute clinic may be compared cautiously with Petrides et al, but the significant differences between the studies' core data (different patient inclusion criteria, scoring systems, and definitions of favorable outcomes) hindered comparison to other study collectives.[49,62,63] The hypothesis of early or premorbid neuroplasticity is also supported by an overestimation of clinical symptoms in atypical cortical ICH based on the CT-based anatomical estimation.[64] Combining both observations might indicate that the neurological function of preclinical CAA affection appear to shift to neighboring brain structures prior to a lobar hemorrhage, resulting in a less-than-expected loss of neurofunctions and more rapid immediate recovery. This hypothesis needs to be validated in larger prospective cohorts.

When predicting the outcomes of our patients, statins, age, criteria measured in CCT (such ICH volume, presence of IVH, and midline shift), and antithrombotic treatments were insufficient as predictors for patient short- and long-term mortality. The total number of ICHs and the initial GCS were the most substantial risk factors for 1- and 2-year mortalities, whereas any detection of SAH was linked to worse 30-day mortalities. We were unable to show any statistically significant result in 5-year mortalities, which may again stem from our small cohort.

Similar to our findings, a small case study series reported no patient with multiple ICHs having a positive outcome and another study suggested that patients suffering multiple spontaneous ICHs have mortality rates of up to 84%.[63,65] However, some diverging results exist, reporting no differences in mortality rates between spontaneous multiple ICHs and a single ICH.[66] None of the published articles we found examined the relationship between the number of lobar hemorrhages and long-term outcomes (excluding 1 study containing patients suffering from hereditary CAA and therefore representing a different phenotype of CAA).[67]

Overall, 42 of 70 (60%) of the patients with a follow-up in our study survived at least a year after the ICH leading up to their initial admission into the neurosurgical ward, but only 29% (13 of 45 patients from whom a 5-year follow-up could be obtained) survived up to 5 years. Patients have had a better 1-year survival than in the meta-analysis of Poon et al (all types of primary ICHs included), who reported a 46% 1-year survival, but an identical 5-year survival, which could be considered an exemption of CAA-associated ICHs, as they result in better short-term outcomes.[7]

Strengths and Limitations

The strength of our study lies in its follow-up rate of nearly 95% and long period of follow-ups of more than 5 years for 60.8% of our participants. This is, to the best of our knowledge, the longest currently published follow-up period for cases of spontaneous CAA and the second largest published cohort of CAA patients treated in a neurosurgical ward.

A limitation of our study is the primarily retrospective design, as well as our comparatively small cohort with only 74 CAA-affected patients, preventing a subgroup analysis. A potential bias in our study is that we had to exclude several patients who had too little information available for an accurate analysis because they were considered to have an extremely poor outcome (and hence were treated with the best supportive care). The analysis of patients admitted directly to neurosurgery may be considered a selection bias toward more severely affected patients. However, our study population is similar to others in the literature albeit with good diagnostic confidence.

Summary

CAA is an important cause of ICH and is attracting increasing attention, especially as its frequency increases in today's aging population. Our results indicate that the most influential factor on the affected individual's long-term mortality is the number of macrobleedings and the initial GCS score. In addition, our results revealed an overrepresentation of the female gender, and atrial fibrillation in individuals suffering from CAA challenging any antithrombotic treatment and pointing to a more widespread β-amyloid pathology than previously thought. Further studies are needed to support our findings.

Conflicts of Interests

The authors report no conflicts of interests.

Supplementary materials

Supplementary material associated with this article can be found in the online version at doi:10.1016/j.jstrokecerebrovasdis.2019.104342.

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