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RESEARCH ARTICLE

Prevalence of cerebral amyloid angiopathy and its correlation with Alzheimer's disease and cognition in an autopsy-confirmed cohort from China

Xiang-Sha Yin[1,2] | **Jianru Sun**[1] | **Xue Wang**[1,2] | **Wei Wu**[1,2] | **Zhen Chen**[1,2] | **Di Zhang**[1,2] | **Yuanyuan Xu**[1] | **Yongmei Chen**[1] | **Wenying Qiu**[1,2] | **Xiaojing Qian**[1,2] | **Jun Ni**[3] | **Chao Ma**[1,2,4]

[1]Department of Human Anatomy, Histology and Embryology, Institute of Basic Medical Sciences, Neuroscience Center, Joint Laboratory of Anesthesia and Pain, Chinese Academy of Medical Sciences, Peking Union Medical College, Beijing, China

[2]National Human Brain Bank for Development and Function, Beijing, China

[3]Department of Neurology, State Key Laboratory of Complex Severe and Rare Diseases, Peking Union Medical College Hospital, Chinese Academy of Medical Science and Peking Union Medical College, Beijing, China

[4]Chinese Institute for Brain Research, Beijing, China

Correspondence
Chao Ma, Wenying Qiu and Xiaojing Qian, Department of Human Anatomy, Histology and Embryology, Institute of Basic Medical Sciences, Chinese Academy of Medical Sciences, Peking Union Medical College, No. 5 Dongdansantiao, Dongcheng District, Beijing 100005, Beijing, China.
Email: machao@ibms.cams.cn; qiuwy73@126.com; qianxj72@sina.com

Jun Ni, Department of Neurology, State Key Laboratory of Complex Severe and Rare Diseases, Peking Union Medical College Hospital, Chinese Academy of Medical Science and Peking Union Medical College, No.1 Shuaifuyuan, Dongcheng District, Beijing 100032, China.
Email: pumchnijun@163.com

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Abstract

BACKGROUND: We aimed to investigate the prevalence of cerebral amyloid angiopathy (CAA) and its correlations with Alzheimer's disease (AD) and cognitive impairment in an autopsy-confirmed cohort donated to a human brain bank in Beijing, China.

METHODS: A total of 483 subjects were neuropathologically evaluated based on standardized protocols. Descriptive statistics and ordinal logistic regression models were used to estimate the correlation between CAA, AD, apolipoprotein E (*APOE*) genotyping, and cognitive function proximal to death.

RESULTS: Neuropathological assessment revealed that 53 of 483 subjects (11%) had CAA without AD, 78 of 483 (16%) had AD without CAA, 98 of 483 (20%) had both CAA and AD, and 254 of 483 (53%) had neither condition. A significant correlation was confirmed between CAA severity and AD. Subjects with both CAA and AD exhibited aggravated cognitive impairment.

DISCUSSION: Our results indicate a substantial prevalence of CAA that is frequently comorbid with AD and may exacerbate cognitive decline in the elderly population in China.

KEYWORDS
Alzheimer's disease, Alzheimer's disease neuropathologic change, cerebral amyloid angiopathy, cognitive function, human brain bank

Xiang-Sha Yin and Jianru Sun contributed equally to this work.

Highlights

- First reporting of cerebral amyloid angiopathy (CAA) based on an autopsy-confirmed cohort from China.
- The prevalence of CAA was high in the elderly Chinese sample.
- Age and apolipoprotein E (*APOE*) ε4 allele were related to the prevalence of CAA.
- CAA and Alzheimer's disease (AD) were frequently co-occurred and significantly associated.
- Subjects with both CAA and AD exhibited aggravated cognitive impairment.

1 | BACKGROUND

Cerebral amyloid angiopathy (CAA) is an age-related disease characterized by the deposition of the amyloid beta (Aβ) protein in the walls of cerebral vessels.[1–3] The apolipoprotein E (*APOE*) ε4 allele is a major risk factor for both Alzheimer's disease (AD) and CAA, whereas *APOE* ε2 is a risk factor for hemorrhagic CAA.[4–7] There are three stages of pathologic development according to the distribution of CAA among brain regions.[8–10] Although a set of clinical and radiological criteria have been developed and validated,[11–15] a definitive diagnosis of CAA requires brain tissue histopathologic evaluation. Autopsy studies have shown that the prevalence of CAA varies among different countries and regions.[16–18] The majority of published CAA epidemiological studies based on autopsy have focused predominantly on non-Hispanic White decedents. For example, in an American study including 1113 community-based elderly subjects, CAA was present in 78.9% of participants and exhibited a moderate association with AD pathology.[19] A recent study encompassing 848 elderly participants from the Kaiser Permanente Washington database revealed that CAA was present in 38.0% of the participants and that 53.7% of those with CAA exhibited dementia.[20] However, the incidence of CAA in Chinese individuals has not yet been reported. Therefore, it is imperative to investigate the prevalence and characteristics of CAA in elderly Chinese individuals.

CAA is a common neuropathologic finding in elderly adults (over 65 years of age), especially among those with AD, which is characterized by neuropathologic changes comprising Aβ plaques, neuritic plaques, and neurofibrillary tangles.[18,21–23] Given the shared role of Aβ deposition in CAA and AD, it is important to understand the relationship between these two diseases. Studies have reported that CAA and AD are frequently comorbid and significantly associated, but sometimes CAA can exist independently.[10,16,19,22,24–26] Hence, it is notable that CAA holds importance beyond being a mere adjunct to AD.

CAA is an important risk factor for cognitive impairment in the elderly adults. Due to the limitations of clinical diagnosis, it is of great value to investigate the association between CAA with or without AD and cognition by using human brain pathology studies. The presence of CAA in patients with AD may lead to a greater cognitive impairment than AD alone.[27,28] Although CAA appears to independently contribute to cognitive deficits beyond AD in some studies,[19,29] this association may disappear after adjusting for AD in other studies.[16] Further comprehensive investigations are warranted to explore the intricate relationships among CAA, AD, and cognitive impairment, particularly in elderly Chinese individuals.

Pathological diagnoses of AD or CAA at autopsy are relatively common in cognitively impaired individuals. However, these changes are also observed in individuals with normal cognitive function prior to death. A systematic review of clinicopathological studies has shown that the prevalence of CAA is 20% to 40% in people with normal cognition and 50% to 60% in people with dementia.[30] The prevalence is higher in individuals who died with both dementia and AD pathology.[31,32] Many databases for the study of AD and CAA pathology, such as the National Alzheimer's Coordinating Center (NACC), lack sufficient data on preclinical AD/CAA or non-AD/CAA individuals, which limits generalizability due to selection bias.[33] Therefore, more bias-reducing pathologic autopsy studies are needed to elucidate the epidemiology of CAA.

This study focused on the relationships among CAA pathology, Alzheimer's disease neuropathologic change (ADNC), and cognitive conditions using 483 human brain samples and data from the National Human Brain Bank for Development and Function at Chinese Academy of Medical Sciences/Peking Union Medical College (CAMS/PUMC). The primary objectives of this study were to describe (1) the prevalence and characteristics of CAA in an autopsy-confirmed cohort from China; (2) the co-occurrence of CAA and AD; and (3) the association between CAA, AD, and cognitive status.

2 | METHODS

2.1 | Human brain samples and data sources

Human brain samples and demographic data for this study were obtained from National Human Brain Bank for Development and Function in Beijing, China. The National Human Brain Bank for Development and Function, relying on the Willed Body Donation Registration Station of CAMS/PUMC, conducts standardized collection of postmortem whole brain tissue based on a natural population. The subjects of this study were individuals who voluntarily donated their bodies to the National Human Brain Bank for Development and Function between 2012 and 2023. Participants were recruited based on voluntary dona-

RESEARCH IN CONTEXT

1. **Systematic review:** Previous studies have reported that cerebral amyloid angiopathy (CAA) is an important risk factor for cognitive decline in elderly populations, especially among those with Alzheimer's disease (AD). However, the incidence of CAA in a Chinese population has not been reported and more data are required from large datasets in different regions to better characterize the relationship among CAA, AD, and cognition.
2. **Interpretation:** This study was the first to report that the prevalence of CAA confirmed by pathology is high in a Chinese elderly sample; age and apolipoprotein E (*APOE*) ε4 allele were related to the prevalence. CAA and AD frequently co-occurred and were significantly associated, which might lead to more severe cognitive impairment.
3. **Future directions**: Large sample sizes and longitudinal data are needed to explore the intricate relationships among CAA, AD, and cognitive impairment.

tion in Beijing without any disease predisposition. Exclusion criteria of brain donation included the presence of infectious diseases and postmortem delay (PMD) exceeding 48 h. Missing data on CAA severity or AD-related neuropathological evaluations was the only sample exclusion criteria in this study. The final sample included 483 autopsied subjects. The demographic characteristics of this sample are consistent with the Beijing census standards, indicating that it represents a typical community-sourced cohort. Individual information, including age, gender, education level, medical history, PMD, and Everyday Cognitive (ECog) scores, was routinely collected for each donor. Cognitive function was recorded using Ecog scores provided by the next-of-kin of donors. The brain tissues were collected following the published standard human brain banking procedures.[34,35] All the brain samples were subjected to neuropathological evaluation for neurodegenerative diseases such as AD, Lewy body disease (LBD), frontotemporal lobar degeneration (FTLD) and so on, and cerebrovascular diseases such as CAA, infarction, and hemorrhage. The research protocol was approved by the institutional review board of the Institute of Basic Medical Sciences of the Chinese Academy of Medical Sciences, China (Approval Number: 009-2014, 031-2017, and 2022125). All antemortem written informed consent forms were received from both the potential donor and his/her next of kin to ensure that the donation was completely voluntary and that ethically approved use of the brain tissues in future scientific research was permitted.

2.2 | Neuropathological evaluation of AD

According to the National Institute on Aging and Alzheimer's Association (NIA-AA) guidelines,[36] the brain tissues all underwent identical neuropathological analysis using the ABC score, which was conducted by professionals at the brain bank. The ABC score was utilized to assess the presence of Aβ deposits (A score), neurofibrillary tangles (B score), and neuritic plaques (C score). The general ABC score was divided into four distinct categories: None (N), Low (L), Intermediate (I), and High (H). "N/L" suggests that it is unlikely for the donor to have AD. In this case, we can consider the donors to be normal elderly individuals. On the other hand, the ADNC diagnosis of the "I/H" group indicates a high probability of AD in the donor.

2.3 | Neuropathological evaluation of CAA

The anatomic distribution of vessels involved in the CAA allows for its severity to be categorized into three stages. In Stage 1, the CAA is confined to leptomeningeal or parenchymal vessels of the neocortex (frontal cortex, parietal cortex, temporal cortex, and occipital cortex). In Stage 2, involvement extends to vessels of the allocortex (cingulate gyrus, entorhinal cortex, and hippocampus), cerebellum, and midbrain. Stage 3 encompasses all areas already affected in Stage 2, as well as the lower brainstem, basal ganglia, and thalamus.[9] Examples of CAA pathological assessments are given in Figure S1. For analytic purposes, CAA was also categorized as present (any CAA) or absent (no CAA) in the study.

2.4 | Cognitive function assessment

Clinical cognitive status was determined using the Ecog Questionnaire.[37] Face-to-face or phone interviews with the next-of-kin of donors were conducted for all subjects recruited from the National Human Brain Bank for Development and Function. A 39-question assessment was used to evaluate the antemortem daily cognitive function of brain donors. Ratings for each question were based on a four-point scale: (1) no significant change or better; (2) questionable problems; (3) consistently worse to a small extent; and (4) consistently worse to a large extent. The related items were marked "unknown" if the informant could not recall or respond. If more than half of the items were marked "unknown," the average score was not calculated. The global Ecog score was calculated by averaging all questions. The Ecog scores were finally categorized as cognitively normal (≤1.0), mild cognitive impairment (1.0–2.0), or dementia (>2.0) for further analysis.[38–40]

2.5 | *APOE* genotyping

The prefrontal cortex was subjected to DNA extraction using a tissue DNA extraction kit (GeneOn BioTech GO-BTCD-400), followed by polymerase chain reaction (PCR) restriction fragment length polymorphism analysis for detection. The genotyping process involved the utilization of second-generation sequencing technology and was con-

ducted by Beijing Zixi Bio Tech Co., Ltd. The above methods were used to detect the alleles of rs7412 and rs429358, the haplotype of which ultimately determined the *APOE* alleles including *APOE* ε2, *APOE* ε3, and *APOE* ε4.

2.6 | Statistical analysis

Normally distributed continuous variables are presented as the means and standard deviations (SDs), and categorical variables are presented as frequencies and percentages. The Pearson chi-square test was used to compare categorical measures, analysis of variance (ANOVA) was used to compare continuous measures, and the Mann–Whitney *U* test (two groups) or Kruskal–Wallis *H* test (three or more groups) was used to compare ordinal variables. Spearman correlation coefficients were calculated to evaluate correlations among CAA pathological changes, ADNC, clinical cognitive status, and demographic variables (age, gender, education, and PMD). Age was found to influence both pathological changes and cognition. Therefore, age was used as a control factor in the analysis of CAA stage, ABC score, and global Ecog score. Because CAA stage (Stages 0, 1, 2, and 3) and cognitive status (normal, MCI, and dementia) were ordinal variables, ordinal logistic regression (OLR) models were used. Age was first analyzed separately using a univariate OLR model. Then, multivariate OLR analysis was conducted. Statistical analyses were performed using SPSS 25.0. $p < .05$ was regarded as statistically significant.

3 | RESULTS

3.1 | The prevalence and characteristics of CAA

A total of 483 autopsy subjects were included in the analyses. Clinical and pathologic characteristics classified by CAA status are shown in Table 1. The mean (SD) age at death was 78.8 (13.8) years; 285 of 483 subjects (59%) were men, and 198 of 483 (41%) were women. Ninety-one percent (425/483) of subjects had a middle school education or above. Ninety-nine percent (475/483) of samples were collected within 24 h and 319/483 (66%) were collected within 12 h. Seventy-seven of 483 subjects (16%) had at least one *APOE* ε4 allele.

CAA was observed in 151 of 483 subjects (31%); 89 of 483 (18%), 57 of 483 (12%), and 5 of 483 (1%) subjects were in Stage 1, 2, and 3, separately. Univariate analysis revealed that subjects with CAA were more likely to be older. The severity of CAA pathology correlated positively with age in a graded fashion ($p < .001$) (Figure S2A). In addition, subjects with CAA were more likely to have an *APOE* ε4 allele. There was no significant difference in gender, education level, or PMD between subjects with or without CAA. There were no significant differences in comorbidity with LBD or FTLD, or in the occurrence of large hemorrhage or microhemorrhage, between subjects with and without CAA (Table 1).

3.2 | The prevalence and characteristics of AD

The demographic and clinical characteristics of the subjects according to the ADNC levels were also analyzed (Table S1). According to the general ABC score, 220 of 483 (46%), 87 of 483 (18%), 141 of 483 (29%), and 35 of 483 (7%) subjects had None, Low, Intermediate, and High score. Therefore, 307 of 483 subjects (64%) were assessed as normal ("N/L" score), whereas 176 of 483 (36%) were considered to have AD ("I/H" score). The group with AD was significantly older than the normal group (Table S1). Both the general ABC score and each of the ABC component scores were positively correlated with age in a graded fashion ($p < .001$) (Figure S2B-E). In addition, the presence of the *APOE* ε4 allele was more likely among subjects with AD.

3.3 | The comorbidity of CAA and AD

Subjects with CAA had higher general ABC scores and A, B, and C component scores (Table 1), and both the general ABC score and each of the ABC component scores correlated positively with the severity of CAA ($p < .001$) (Figure S3). According to the general ABC score, 98 of 151 (65%) of subjects with CAA had AD, whereas 78 of 330 (24%) of subjects without CAA had AD. At the same time, subjects with higher ABC scores were more likely to have greater CAA severity ($p < .001$) (Figure S3). In addition, 98 of 176 (56%) of subjects with AD had CAA pathology, whereas 53 of 307 (17%) of subjects without AD had CAA. In general, among 483 subjects, 53 of 483 (11%) had only CAA, 78 of 483 (16%) had only AD, 78 of 483 (16%) had both CAA and AD, and 254 of 483 (53%) had neither CAA nor AD (Figure 1).

Furthermore, we analyzed the clinical characteristics of the subjects according to whether they had co-occurring CAA and AD (Table 2). It turned out that age and *APOE* ε4 allele findings of the subjects differed. Subjects with AD with or without CAA were more likely to be older than those with CAA only or those without AD or CAA. Compared to those in the other three groups, subjects with co-occurring AD and CAA tended to have a higher proportion of the *APOE* ε4 allele.

3.4 | The correlation between CAA and AD

Spearman correlation analysis was used to further confirm the relationships among CAA stage, ABC scores, and demographic variables first (Table S2). The results showed that age and *APOE* ε4 allele were positively related to CAA and AD. Then partial correlation analysis was applied to CAA stage, general ABC score, and A score, B score, and C score after adjusting for age and *APOE* ε4 allele (Table S3). CAA severity was more strongly correlated with the general ABC score and A score than with the B score or C score. Using the OLR model to analyze the impact of the ABC score on CAA stage, we found that the odds ratios (ORs) for a worse CAA stage in the "L," "I," and "H" ABC score groups were 5.960, 10.881, and 50.300 ($p < .001$), respectively, compared to

TABLE 1 Clinical and pathologic characteristics of subjects classified by CAA status.

Characteristics	Number of Participants (% of total)			
	Total sample	Cerebral amyloid angiopathy		
	(*n* = 483)	No (*n* = 332)	Yes (*n* = 151)	*p* value
Age at death, mean [SD], y	78.8 [13.8]	76.2 [14.6]	84.6 [9.8]	<0.001
Gender				
Male	285 (59.0)	200 (60.2)	85 (56.3)	.41
Female	198 (41.0)	132 (39.8)	66 (43.7)	
Educational level[a]				
Primary school or less	40 (8.6)	25 (7.8)	15 (10.5)	.6
Middle or high school	199 (42.8)	145 (45.0)	54 (37.8)	
College or above	226 (48.6)	152 (47.2)	74 (51.7)	
Post-mortem delay[a]				
<12 h	319 (66.3)	211 (63.9)	108 (71.5)	.11
12–24 h	156 (32.4)	115 (34.8)	41 (27.2)	
>24 h	6 (1.2)	4 (1.2)	2 (1.3)	
Comorbidity				
Lewy body disease with dementia	25 (5.2)	16 (4.8)	9 (6.0)	.60
Frontotemporal lobar degeneration	7 (1.4)	4 (1.2)	3 (2.0)	.80
Cerebral hemorrhage				
Large hemorrhage	12 (2.5)	10 (3.0)	2 (1.3)	.43
Microhemorrhage	37 (7.7)	24 (7.2)	13 (8.6)	.60
APOE ε4 allele[a]	77 (16.1)	39 (11.9)	38 (25.2)	<0.001
APOE ε2 allele[a]	73 (15.1)	50 (15.1)	23 (15.2)	.961
General ABC score				
None	220 (45.5)	200 (60.2)	20 (13.2)	<0.001
Low	87 (18.0)	54 (16.3)	33 (21.9)	
Intermediate	141 (29.2)	69 (20.8)	72 (47.7)	
High	35 (7.2)	9 (2.7)	26 (17.2)	
A score				
0	219 (45.3)	199 (59.9)	20 (13.2)	<0.001
1	117 (24.2)	71 (21.4)	46 (30.5)	
2	78 (16.1)	37 (11.1)	41 (27.2)	
3	70 (14.3)	25 (7.5)	44 (29.1)	
B score				
0	39 (8.1)	37 (11.1)	2 (1.3)	<0.001
1	117 (24.2)	98 (29.5)	19 (12.6)	
2	265 (54.7)	181 (54.5)	83 (55.0)	
3	63 (13.0)	16 (4.8)	47 (31.1)	
C score				
0	255 (52.8)	225 (67.8)	30 (19.9)	<0.001
1	53 (11.0)	30 (9.0)	23 (15.2)	
2	146 (30.0)	65 (19.6)	80 (53.0)	
3	30 (6.2)	12 (3.6)	18 (11.9)	

(Continues)

TABLE 1 (Continued)

Characteristics	Number of Participants (% of total)			
	Total sample	Cerebral amyloid angiopathy		
	(*n* = 483)	No (*n* = 332)	Yes (*n* = 151)	*p* value
Global ECog score				
≤ 1	399 (82.6)	289 (87.0)	110 (72.8)	<0.001
1–2	21 (4.3)	15 (4.5)	6 (4.0)	
> 2	63 (13.0)	28 (8.4)	35 (23.2)	

[a]Missing data: educational level = 18 (3.7%), post-mortem delay = 2 (0.4%), *APOE* allele = 4 (1.2%). Abbreviation: SD, Standard Deviation.

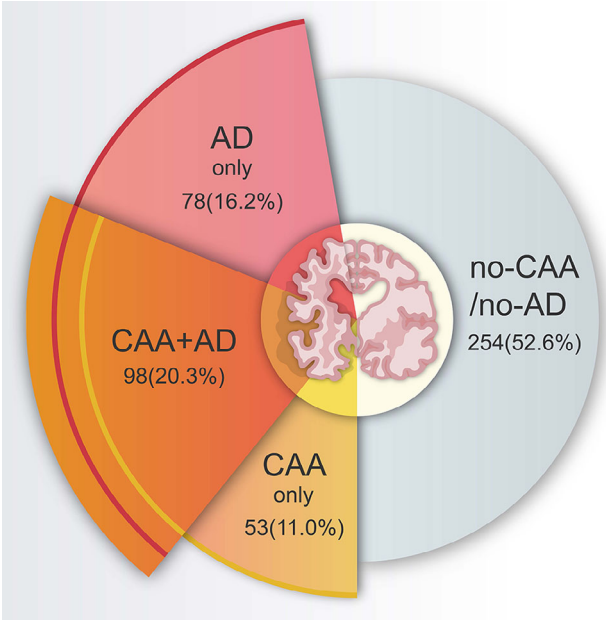

FIGURE 1 The distribution of CAA and AD in the CAMS/PUMC Human Brain Bank. The number and proportion of cases with CAA only, AD only, CAA+AD, and no- CAA/no-AD in the Human Brain Bank. CAA+AD, brains with both CAA and AD pathology; no-CAA/no-AD, brains with neither CAA nor AD pathology.

the None score group. After adjusting for age, the ORs were 5.371, 8.012, and 37.226, respectively ($p < .001$). Furthermore, after adjusting for both age and *APOE ε4* allele, the ORs remained significant at 5.238, 7.323, and 32.884 ($p < .001$) (Table 3). This demonstrated that the general ABC score has a significant positive impact on the CAA stage.

3.5 | The correlations among CAA, AD, and cognition

Among all the subjects, 399 of 483 (83%), 21 of 483 (4%), and 63 of 483 (13%) had normal cognition, mild cognitive impairment (MCI), and dementia, respectively (Table S4). Among 399 individuals with normal cognition, 225 of 399 (56%) had neither AD nor CAA, 46 of 399 (12%) had only CAA, 63 of 399 (16%) had only AD, and 65 of 399 (16%) had both AD and CAA (Table 1). Univariate analysis revealed that the dementia group was older and with more obvious CAA pathology and ADNC. Subjects with CAA or ADNC had higher global Ecog scores than those without CAA or ADNC (Table 1, Table S1). The average global Ecog scores (SD) for the CAA Stage 0, Stage 1, and Stage 2/3 groups were 1.2 (0.6), 1.4 (0.8), and 1.8 (1.2), respectively, and the global Ecog scores were generally positively correlated with the severity of CAA ($p < .001$) (Figure S4A). In addition, the average global Ecog scores for the Intermediate and High groups were 1.4 (0.8) and 2.4 (1.4), respectively, whereas those for the None and Low groups were 1.1 (0.5) and 1.2 (0.6), respectively ($p < .001$) (Figure S4B). Furthermore, compared to subjects without AD and subjects only with AD, subjects with co-occurring AD and CAA tended to have more severe cognitive impairment ($p < .001$) (Figure S4C). However, there was no significant difference in cognition between subjects with CAA only and normal subjects (Figure S4C). Table 2 also showed that among individuals without AD, the proportion in the ECoG category "≤1" is similar for those with and without CAA (86.8% vs 88.6%). In contrast, among individuals with AD, a smaller proportion of those with CAA fall into the ECoG category "≤1" (67.0% vs 78.8%), whereas a larger proportion fall into the ECoG category " >2" (29.9% vs 17.5%). Our results indicate that CAA may not be an independent predictor of cognitive impairment; however, CAA can exacerbate cognitive dysfunction in the presence of AD.

Partial correlation analysis showed that CAA was correlated with the cognition (Table S3). Moreover, the OR for a worse cognitive state in the *APOE ε4*-negative CAA Stage 2 and 3 group was 3.494 ($p = .001$) after adjusting for age (Table 4). However, the effect of CAA stage on cognitive state was not significant after adjusting for the general ABC score (Table 4).

Both the general ABC score and each of the ABC component scores were significantly correlated with the global Ecog score after adjusting for age and *APOE ε4* allele (Table S3). Moreover, the OR for a worse cognitive state in the ABC score "High" group was 8.158 relative to that in the ABC score "None" group, after adjusting for age, *APOE ε4* allele, and CAA stage (Table S5).

4 | DISCUSSION

This study was the first to report the prevalence of CAA and its correlation with AD and clinical cognitive function based on a large

TABLE 2 Clinical characteristics of subjects with and without cooccurring CAA and AD.

	No AD		AD		
	No CAA ($n = 254$)	CAA ($n = 53$)	No CAA ($n = 78$)	CAA ($n = 98$)	*p* value
Age at death, mean [SD], y	73.2 [14.9]	80.7 [12.4]	86.1 [7.6]	86.7 [7.3]	<0.001
Gender					
Male	161 (63.4)	33 (62.3)	39 (50.0)	52 (53.1)	.1
Female	93 (36.6)	20 (37.7)	39 (50.0)	46 (46.9)	
Educational level					
Primary school or less	18 (7.1)	5 (9.4)	7 (9.0)	10 (10.2)	.8
Middle or high school	116 (45.7)	17 (32.1)	29 (37.2)	37 (37.8)	
College or above	112 (44.1)	25 (47.2)	40 (51.3)	49 (50.0)	
Global ECog score					
≤ 1	225 (88.6)	46 (86.8)	63 (78.8)	65 (67.0)	<0.001
1–2	12 (4.7)	4 (7.5)	3 (3.8)	3 (3.1)	
> 2	17 (6.7)	3 (5.7)	14 (17.5)	29 (29.9)	
APOE ε4 allele	25 (10.0)	7 (13.2)	14 (18.2)	31 (31.6)	<0.001
APOE ε2 allele	41 (16.1)	13 (24.5)	9 (11.5)	10 (10.2)	0.090

Abbreviation: SD, Standard Deviation.

TABLE 3 Results of ordinal logistic regression for the general ABC score and CAA stage.

	Univariate model		Multivariate Model 1[a]		Multivariate Model 2[a]	
Variables	Unadjusted OR (95% CI)	*p* value	Adjusted OR (95% CI)	*p* value	Adjusted OR (95% CI)	*p* value
	General ABC score					
None	Reference		Reference		Reference	
Low	5.960 (3.177–11.179)	<0.001	5.371 (2.846–10.135)	<0.001	5.238 (2.773–9.905)	<0.001
Intermediate	10.881 (6.203–19.087)	<0.001	8.012 (4.433–14.483)	<0.001	7.323 (4.019–13.343)	<0.001
High	50.300 (22.488–112.505)	<0.001	37.226 (16.346–84.775)	<0.001	32.884 (14.282–75.717)	<0.001

Note: The dependent variable is CAA stage.
Abbreviations: CI, Confidence Interval; OR, Odds Ratio.
[a]Age was included in multivariate Model 1; age and *APOE* ε4 allele were included in multivariate Model 2.

autopsy pathology dataset in China. The main findings of this study include: (1) the prevalence of CAA confirmed by pathology is high in this autopsy-confirmed cohort from China, and age and *APOE* ε4 allele are related to the prevalence; (2) CAA and AD were frequently comorbid and significantly associated, which might lead to more severe cognitive impairment; (3) CAA severity was associated with lower cognition among those without an *APOE* ε4 allele, but the association disappeared after adjustment for ADNC. These results advance our understanding of the prevalence characteristics of CAA among Chinese elderly individuals and relationships among CAA, AD, and cognition.

CAA is a common neuropathological finding in the elderly population, and the prevalence rates reported from clinical imaging and pathological studies vary across different populations.[1,27,28,41] Previous autopsy studies have revealed that the prevalence of CAA is 2.3% among individuals 65–74 years of age, 8% among those 75–84 years of age, and 12.1% among those 85 years of age or older.[42] Our study reported that 151 of 483 CAA cases (31%) occurred in a sample with an average age of 78.8 in China by using the CAMS/PUMC Human Brain Bank dataset, which is one of the largest high-quality datasets with detailed autopsy information. In our study, we also described the demographic and clinical characteristics of CAA and verified the increased prevalence of CAA with age. In addition, our results also confirmed the association between CAA and the *APOE* ε4 allele. *APOE* is the only susceptibility locus for CAA, and the *APOE* ε4 allele is a major risk factor for CAA.[5] Although the *APOE* ε2 allele was also reported to be associated with CAA and clinical hemorrhages,[7] there was no obvious correlation between the *APOE* ε2 allele and CAA in our study. Further studies should be done to examine the role of the *APOE* ε2 allele in CAA subtypes in a larger sample.

Neuropathological studies have shown that vascular and parenchymal Aβ deposition can occur independently or overlap. Approximately

TABLE 4 Results of ordinal logistic regression for CAA stage and ECog score.

Variable	*APOE ε4* (–)				*APOE ε4* (+)			
	Multivariate Model 1[a]		Multivariate Model 2[a]		Multivariate Model 1[a]		Multivariate Model 2[a]	
CAA	Unadjusted OR	*p value*	Adjusted OR	*p value*	Adjusted OR	*p value*	Adjusted OR	*p value*
Stage	(95% CI)		(95% CI)		(95% CI)		(95% CI)	
0	Reference		Reference		Reference		Reference	
1	1.921 (0.958–3.850)	0.066	1.674 (0.796–3.518)	.163	0.499 (0.117–2.123)	.347	0.454 (0.098–2.111)	.314
2&3	3.494 (1.687–7.236)	0.001	1.852 (0.780–4.393)	.174	1.56 (0.412–5.912)	.512	0.928 (0.200–4.302)	.924

Note: The dependent variable is ECog score.
Abbreviations: CI, Confidence Interval; OR, Odds Ratio.
[a]Age was included in multivariate Model 1; age and general ABC scores were included in multivariate Model 2.

80%–90% of postmortem examinations of AD-affected subjects have shown signs of CAA.[43] However, CAA can occur independently of AD, with fewer than half of CAA cases meeting the pathologic criteria for AD.[14,44] Our study revealed that among 483 subjects, 98 of 151 (65%) of CAA cases had AD, a higher percentage than in previous studies, whereas 98 of 176 (56%) of AD subjects were positive for CAA, a lower percentage. Analysis confirmed the positive correlation between CAA severity and the ADNC. As the ABC score increased, the probability of more severe CAA pathology also increased after adjusting for age and the *APOE ε4* allele. Specifically, compared to individuals with an ABC score of "N," those with ABC scores of "L," "I," and "H" had 5.238-, 7.323-, and 32.884-fold higher odds, respectively, of progressing to a more severe CAA stage. Although these results suggested a close correlation between CAA and AD, it was worth noting that CAA could occur in the absence of AD. The relationship between CAA and AD is complex, and more data are required to better characterize the relationships between them.

Cognitive dysfunction associated with CAA has been reported extensively in countries other than China. To explore the relationships among CAA, AD, and the cognitive impairment in Chinese elderly individuals, we compared the cognition levels among "normal", "CAA only," "AD only," and "CAA+AD" groups. The results verified that the presence of CAA with AD had a greater clinical impact than AD alone or CAA alone. However, there was no significant difference between the "CAA only" group and the "normal" group. Further OLR analysis showed that CAA severity was associated with lower cognition among individuals without an *APOE ε4* allele, but the association disappeared after adjustment for ADNC, suggesting that the cognitive impairment caused by CAA may be due to the combination of AD. Because only 78 cases of subjects with CAA and without AD were analyzed, another possible explanation is that the sample size was not large enough. In the future, we will collect more data to provide a more definitive analysis and answer to this question.

Notably, many existing databases for studying AD and CAA pathology, such as the NACC, lack sufficient data on preclinical AD/CAA or non-AD/CAA individuals. In our cohort, over half of the participants (254/483, 53%) had neither AD nor CAA pathology. In addition, among the 399 individuals with normal cognition, 109 of 399 (27%) had only CAA or only AD, and 65 of 399 (16%) had both AD and CAA, which suggests that our cohort includes a considerable number of individuals with pre-symptomatic changes. The characteristics of our sample effectively compensate for the data limitations in previous autopsy or clinical cohorts, providing valuable insights into the pathological features of a cohort of elderly Chinese individuals.

This research has certain limitations. First, our research is a cohort study based on autopsy. Such studies are prone to selection bias,[45] which limits generalizability and poses challenges in interpreting prevalence estimates. Scientists have concluded that cohorts with more participants who were cognitively normal at recruitment contained more individuals who had higher rates of cerebrovascular disease by analyzing data from NACC.[33] We must recognize that systematic differences exist between autopsy cohorts that serve dementia research so it is essential to consider the characteristics of autopsy cohorts. Notably, the subjects of our study were recruited based on voluntary donation in Beijing without any disease predisposition. Therefore, our sample design has been optimized to minimize selection bias as much as possible. Second, our study is a cross-sectional study and it is difficult to define the causal relationship between pathological changes and cognitive status. A longitudinal clinical study with more detailed clinical information such as age at diagnosis of CAA, concurrent symptoms, and radiological images is needed. Then, CAA pathology is graded in this study according to the affected brain regions, while another commonly used classification method is based on the severity of amyloid deposits in blood vessels of brain. So we will conduct further analysis and comparison by other pathological classification criteria on all available brain tissues. Finally, it is possible that some associations between CAA and cognition have not been detected due to the limited power, and studies with larger samples are needed in the future.

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CONFLICT OF INTEREST STATEMENT

The authors declare no conflicts of interest. Author disclosures are available in the Supporting Information.

CONSENT STATEMENT

All human subjects provided written informed consent.

ORCID

Chao Ma https://orcid.org/0000-0003-1346-6961

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