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Occurrence of Intracranial Hemorrhage and Associated Risk Factors in Cerebral Autosomal Dominant Arteriopathy With Subcortical Infarcts and Leukoencephalopathy: A Systematic Review and Meta-Analysis

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Background and Purpose Intracranial hemorrhage (ICH) is thought to be a rare but probably underestimated presentation of cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL). We conducted a systematic review and meta-analysis with the aim of comprehensively revealing the occurrence of ICH in patients with CADASIL.

Methods English-language studies published up to September 30, 2021 were searched for in the MEDLINE (PubMed), Web of Science, and Cochrane Library databases. The design, patient characteristics, occurrence rate of ICH, and associated risk factors were retrieved for each identified relevant study.

Results We enrolled 13 studies in the final meta-analysis, which included 1,310 patients with CADASIL. The probability of ICH occurrence in patients with CADASIL was 10.1% (95% confidence interval [CI]=5.6%−18.0%, I^2=85.1%). When stratified by geographic region, the occurrence rate of ICH was much higher in Asians (17.7%; 95% CI=11.0%−28.5%, I^2=76.3%) than in Europeans (2.0%; 95% CI=0.4%−10.8%, I^2=82.8%). A higher burden of cerebral microbleeds (CMBs) and a history of hypertension were the most commonly recorded risk factors for ICH, which were available for three and two of the included studies, respectively.

Conclusions Our study suggests that ICH is an important clinical manifestation of CADASIL, especially in Asians. A higher burden of CMBs and the existence of hypertension were found to be associated with a higher probability of ICH occurrence in patients with CADASIL.

Keywords intracranial hemorrhage; CADASIL; cerebral microbleed; hypertension.

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INTRODUCTION

Cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL) is a monogenic hereditary cerebral small-vessel disease (SVD) caused by mutations in the NOTCH3 gene. CADASIL was initially thought to be a rare disorder, but the identification of increasing numbers of families worldwide has made it the most common heritable SVD.[1] Typical clinical characteristics of CADASIL include migraine with aura, recurrent cerebral ischemic stroke, psychiatric symptoms, cognitive impairment, and dementia in different disease stages.[2] On neuroimaging, CADASIL manifests with various combinations of white-matter hyperintensities (WMH), lacunes, cerebral microbleeds (CMBs), and brain atrophy.[3] Diagnosing CADASIL depends on detecting mutations in the NOTCH3 gene and/or the accumulation of granular osmiophilic material (GOM) in vascular smooth-

muscle cells.[2]

Early studies showed that intracranial hemorrhage (ICH) rarely occurred in patients with CADASIL.[4-6] However, recent increases in reported cases series of ICH in CADASIL indicate that ICH might be an underestimated clinical manifestation of CADASIL.[7-9] ICH was thought to be associated with higher mortality and long-term disability compared with ischemic stroke,[10] and fatal ICH has been reported in patients with CADASIL,[11,12] indicating that more attention needs to be paid to this condition. Nevertheless, the occurrence rate of ICH in CADASIL patients has remained undetermined. In the present study, we performed a systematic review and meta-analysis with the aim of determining the probability of ICH occurrence in patients diagnosed with CADASIL.

METHODS

Study selection

We followed the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) Statement guidelines and Meta-analysis Of Observational Studies in Epidemiology (MOOSE) guidelines for conducting a systematic review.[13,14] Two of the authors (Q.L.L. and Y.X.Z.) independently searched for relevant articles in the MEDLINE (PubMed), Web of Science, and Cochrane Library databases published up to September 30, 2021. The search was limited to English-language studies involving humans identified using the following search expression: ("cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy" OR "CADASIL") AND ("hemorrhage" OR "haemorrhage" OR "bleed" OR "microbleed"). We retrieved all of the identified articles and searched their reference lists to find as many relevant studies as possible. No ethical approval or patient consents were required since all analyses were based on previously reported studies.

Eligibility criteria

Each article was read in its entirety to assess the appropriateness of including the study in the analysis. Studies were included if they met the following criteria: 1) original data obtained in clinical studies; 2) CADASIL diagnosed by a genetic test or skin biopsy; 3) availability of the occurrence rate of ICH in patients with CADASIL; and 4) meeting at least four items of the standardized assessment tool (Supplemental Table 1 in the online-only Data Supplement), which was an eight-item scoring instrument proposed by Boyle[15] and was previously used in a systematic review of the incidence and prevalence of comorbidity in multiple sclerosis.[16] Case report and case series were excluded from the meta-analysis. When patient data overlapped in multiple articles, as identified based on the sample origin and period, only the article with the most-complete information was included.

Data extraction

All of the studies were evaluated and examined carefully by two authors (Q.L.L. and Y.X.Z.), with discrepancies resolved by discussions involving a third author (J.J.W.). The following data were retrieved for each study: first author, publication year, study design, study period, sample origin, sample size, sex, age, mutation type of the NOTCH3 gene, diagnostic criteria for ICH, location of ICH, and occurrence rate of ICH and associated risk factors.

Data analysis

The pooled estimates were reported with 95% confidence intervals (CIs). A representative forest plot showing the ratios of the individual studies and the combined effect was generated to provide an overview of the results. Between-study heterogeneity was assessed using the I^2 statistical test, with $p<0.10$ or $I^2>0.50$ considered indicative of heterogeneity. The analysis was performed using a random-effects model with the DerSimonian and Laird method if substantial heterogeneity was detected; otherwise a fixed-effects model was used.

Sensitivity analysis was conducted by excluding each study individually and recalculating the combined estimates for the remaining studies to assess the influence of the excluded study on the pooled estimates. Begg's test and the trim-and-fill method were applied to evaluate publication bias, with $p<0.05$ considered as indicative of significant publication bias. All of the data analyses were performed using Stata software (version SE 16.0, StataCorp, College Station, TX, USA).

RESULTS

Study characteristics

Thirteen studies[6,12,17-27] were included in the final meta-analysis (Fig. 1). Together the studies collectively included 1,310 patients diagnosed with CADASIL. The mean age of the patients ranged from 42.4 to 62.6 years, and the male-to-female ratio ranged from 8:15 to 16:5. The 13 included studies comprised 6 prospective observational studies[6,19-21,23,26] and 7 retrospective studies.[12,17,18,22,24,25,27] Eight studies were conducted in Asia,[17-19,22,24-27] 4 in Europe,[6,20,21,23] and 1 in South America.[12] A quality assessment indicated that all of the included studies achieved a moderate quality score of 4 or 5 on a scale of up to 8, as indicated in Table 1. The diagnostic criteria, number, and location of ICH in each study are listed in Table 2.

Occurrence of ICH in CADASIL

Given the underlying heterogeneity, we evaluated the prob-

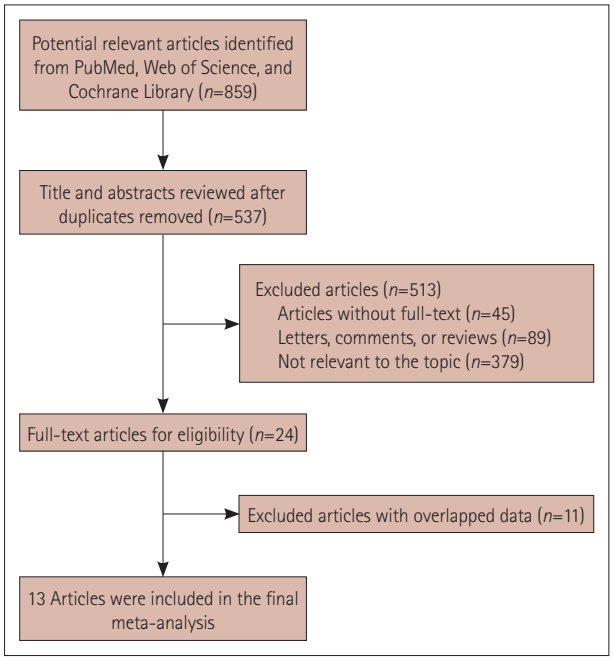

Fig. 1. Study selection flow diagram.

ability of ICH occurrence using the random-effects model, which revealed that ICH had occurred in 10.1% patients with CADASIL (95% CI=5.6%–18.0%, I^2=85.1%) (Fig. 2). Sensitivity analyses performed by successively removing each study in turn and reanalyzing indicated that no studies significantly affected the pooled probability or heterogeneity (ranging from 8.7% [95% CI=4.8%–15.9%, I^2=82.1%] to 12.8% [95% CI=7.6%–21.4%, I^2=80.4%]), which confirmed the stability of our results. There was a certain degree of publication bias suggested from the result of Begg's test (p=0.024) and the asymmetric funnel plot. We then applied the trim-and-fill method, but no trimming was performed and the summary estimate remained unchanged, indicating that the funnel-plot asymmetry might not have been solely caused by the publication bias.

Subgroup analyses

When subgroup analyses were performed by geographic region (Asia vs. Europe), study design (prospective vs. retrospective), and mean age (<50 vs. ≥50 years), the heterogeneity was still present. When stratified by geographic region, the probability of ICH occurrence was much higher in CADASIL patients from Asia (17.7%; 95% CI=11.0%–28.5%, I^2=76.3%) than in those from Europe (2.0%; 95% CI=0.4%–10.8%, I^2=82.8%). When stratified by study design, the probability of ICH occurrence was 4.8% (95% CI=1.0%–22.7%, I^2=92.1%) in the prospective studies and 15.5% (95% CI=9.7%–24.8%, I^2=65.4%) in the retrospective studies. When grouped by mean age, the probability of ICH occurrence was 3.4%

Table 1. Characteristics of the studies included in the final meta-analysis

Study	Sample origin	Study design	Period	Sample size	Males/females	Age (yr), mean±SD	Mutation type	Quality score
Liao et al.[17]	Taipei Veterans General Hospital, Taipei, Taiwan, China	Retrospective	Jan 2010 to Dec 2019	127	61/66	60.1±9.2	R544C for 77.2%	4
Kim et al.[18]	Seoul National University Hospital, Seoul, Korea	Retrospective	2005 to 2015	34	12/22	52.5±9.4	Various	4
Chen et al.[19]	12 Hospitals in Taiwan, China	Prospective	Since 2006	67	42/25	58.3±9.1	R544C	4
Nannucci et al.[20]	Two centers in Florence, Italy, and London, United Kingdom	Prospective	NA	125	56/69	50.6±14.2	Various	4
Bersano et al.[21]	18 Centers of the Lombardia GeNetics of Stroke project, Italy	Prospective	2009 to 2016	16	9/7	52.9±11.5	Various	4
Chen et al.[22]	Second Affiliated Hospital of Zhejiang University School of Medicine, Huashan Hospital of Fudan University, and First Affiliated Hospital of Fujian Medical University, China	Retrospective	May 2009 to Mar 2016	169	NA	45.0±9.0	Various	4
Puy et al.[23]	Lariboisière, Paris, France, and Munich, Germany	Prospective	Nov 2003 to Apr 2011	369	165/204	46.0±9.7	NA	5
Lee et al.[24]	Jeju National University Hospital, Jeju, Korea	Retrospective	Mar 2012 to Jan 2015	94	52/42	62.6±12.5	R544C for 95%	4
Hawkes et al.[12]	Neurological Research Institute Raúl Carrea, Buenos Aires, Argentina	Retrospective	NA	13	7/6	48.0±9.0	NA	4
Tan et al.[25]	General Hospital of the People's Liberation Army, Beijing, China	Retrospective	Jan 2002 to Mar 2013	52	28/24	42.4±8.9	Various	4
Noh et al.[26]	Asan Medical Center, Seoul, Korea	Prospective	Jan 2000 to Aug 2012	23	8/15	55.0±12.5	NA	4
Adib-Samii et al.[6]	CADASIL National Referral Service, United Kingdom	Prospective	NA	200	86/114	47.7±11.4	Various	4
Lee et al.[27]	Taichung Veterans General Hospital, Taichung, Taiwan, China	Retrospective	NA	21	16/5	54.1±12.2	Various	4

CADASIL, cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy; NA, not available; SD, standard deviation.

Table 2. Detailed information of ICH in patients with CADASIL

Study	Diagnostic criteria for ICH	Number of ICHs (%)	Location of ICH (detailed position)	Associated risk factors
Liao et al.[17]	ICH lesions were identified by brain MRI/CT. ICH lesions with a clinical event were defined as symptomatic ICH. Hemosiderin deposits with a diameter >10 mm on SWI or T2*-GRE imaging without a clinical event were defined as asymptomatic ICH	27 (21.3)	Intracerebral (including lobar, deep, brainstem, and cerebellum)	CMBs in brainstem; total CMB count >10
Kim et al.[18]	NA	6 (17.6)	Intracerebral (all located deep)	Mutations in exon 3 (R75P), exon 9 (Y465C), exon 11 (R587C), and exon 22 (R1175W)
Chen et al.[19]	NA	28 (41.8)	Intracerebral (NA)	Family history of stroke, severe white-matter changes on neuroimaging
Nannucci et al.[20]	NA	3 (2.4)	Intracerebral (including deep and cerebellum) and extracerebral (subarachnoid)	Larger total number of CMBs
Bersano et al.[21]	NA	3 (18.8)	NA	NA
Chen et al.[22]	NA	5 (3.0)	Intracranial (NA)	NA
Puy et al.[23]	NA	2 (0.5)	Intracerebral (NA)	NA
Lee et al.[24]	ICH was defined as spontaneous nontraumatic bleeding into the brain parenchyma, based on CT/MRI. Asymptomatic ICH were defined as MRI (including SWI)-documented hemorrhage without associated symptoms	16 (17.0)	Intracerebral (including lobar, deep, brainstem, and cerebellum)	Higher CMB count (≥9)
Hawkes et al.[12]	NA	2 (15.4)	Intracranial (NA)	NA
Tan et al.[25]	NA	12 (23.1)	Intracerebral (NA)	Hypertension
Noh et al.[26]	NA	3 (13.0)	Intracerebral (NA)	NA
Adib-Samii et al.[6]	NA	1 (0.5)	Intracerebral (brainstem)	NA
Lee et al.[27]	NA	5 (23.8)	Intracerebral (including lobar and deep)	Hypertension, R544C in exon 11

CADASIL, cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy; CMB, cerebral microbleed; CT, computed tomography; ICH, intracranial hemorrhage; MRI, magnetic resonance imaging; NA, not available; SWI, susceptibility-weighted imaging; T2*-GRE, T2*-weighted gradient-recalled echo.

(95% CI=0.7%−16.1%, I^2=89.6%) in younger patients (<50 years old) and 17.6% (95% CI=10.9%−28.5%, I^2=71.4%) in older patients (≥50 years old). The pooled results of subgroup analyses are presented in Table 3.

Associated risk factors for ICH in CADASIL

Risk factors for ICH in CADASIL patients were reported for only 7 of the 13 included studies (Table 2).[17-20,24,25,27] A higher burden of CMBs[17,20,24] and a history of hypertension[26,27] were the most commonly recorded risk factors, which were available for three and two of the included studies, respectively. Furthermore, the presence of CMBs in the brainstem[17] was found to be a risk factor for ICH in one study. With regard to mutations of the NOTCH3 gene, R544C in exon 11,[27] and R75P in exon 3, Y465C in exon 9, R587C in exon 11, and R1175W in exon 22[18] were reported as predisposing factors for one study each. Finally, a family history of stroke as well as severe WMH on neuroimaging were regarded as hazard factors for ICH in one study. [19]

To explore the causes underlying the probability of ICH being higher among Asians, the occurrence rates of common vascular risk factors were analyzed and compared between studies from Asia and Europe. The median mean age in eight studies for patients from Asia was 54.6 years, which was older than for the four studies from Europe (49.1 years). The occurrence rate of hypertension was higher in CADASIL pa-

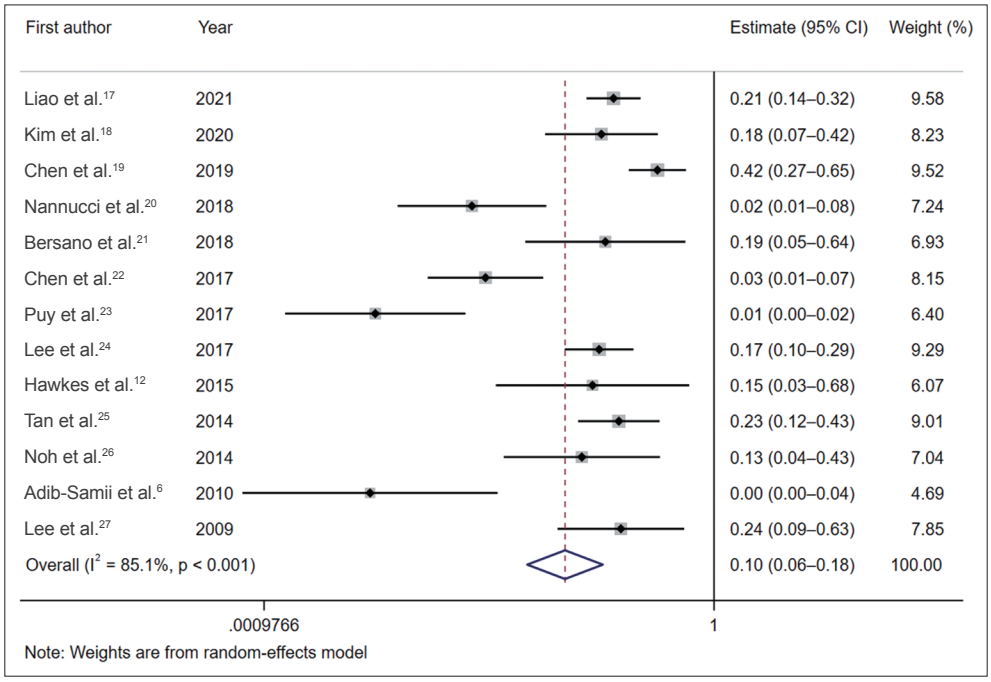

Fig. 2. Forest plot of the probability of intracranial hemorrhage occurrence in cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy. CI, confidence interval.

Table 3. Subgroup analyses of the probability of ICH occurrence in patients with CADASIL

Subgroup	Number of studies	Number of patients	Fixed-effects model	Random-effects model	Heterogeneity test	
					I^2 (%)	*p*
Overall	13	1,310	0.174 (0.142–0.213)	0.101 (0.056–0.180)	85.1	<0.001
Region						
Asia	8	587	0.212 (0.171–0.263)	0.177 (0.110–0.285)	76.3	<0.001
Europe	4	710	0.026 (0.013–0.051)	0.020 (0.004–0.108)	82.8	0.001
Study design						
Prospective	6	800	0.177 (0.124–0.252)	0.048 (0.010–0.227)	92.1	<0.001
Retrospective	7	510	0.172 (0.134–0.221)	0.155 (0.097–0.248)	65.4	0.008
Mean age						
<50 years	5	803	0.074 (0.047–0.116)	0.034 (0.007–0.161)	89.6	<0.001
≥50 years	8	507	0.218 (0.173–0.274)	0.176 (0.109–0.285)	71.4	0.001

Data are estimate and 95% CI values.
CADASIL, cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy; CI, confidence interval; ICH, intracranial hemorrhage.

tients from Asia (53.2%; 95% CI=39.5%–71.7%, I^2=56.9%) than in those from Europe (25.1%; 95% CI=21.3%–29.6%, I^2=0.0%). Similarly, the comorbidity rate of diabetes mellitus was higher in Asians (18.7%; 95% CI=12.9%–27.0%, I^2=35.7%) than in Europeans (5.2%; 95% CI=3.2%–8.5%, I^2=0.0%). The occurrence rates of dyslipidemia and smoking did not differ significantly between Asians and Europeans. The pooled results of vascular risk factors among these two subgroups are listed in Table 4.

DISCUSSION

To the best of our knowledge, this study represents the first systematic review and meta-analysis of the occurrence rate of ICH in patients with CADASIL. The results suggest that the general probability of ICH occurrence is around 10%. Stratifying by geographic region, we found that the occurrence rate of ICH was much higher in CADASIL patients from Asia (17.7%) than in those from Europe (2.0%).

ICH is less common than cerebral ischemic stroke in CADASIL patients. During the past 2 decades, small numbers

Table 4. Comparison of common vascular risk factors between studies from Asia and Europe

Vascular risk factor	Studies from Asia				Studies from Europe			
	No.	Pooled occurrence rate*	I^2 (%)	*p*	No.	Pooled occurrence rate*	I^2 (%)	*p*
Hypertension	5/8	0.532 (0.395–0.717)	56.9	0.055	4/4	0.251 (0.213–0.296)	0.0	0.744
Diabetes mellitus	5/8	0.187 (0.129–0.270)	35.7	0.183	3/4	0.052 (0.032–0.085)	0.0	0.380
Dyslipidemia	5/8	0.368 (0.290–0.468)	21.1	0.280	4/4	0.523 (0.409–0.667)	64.7	0.037
Smoking	5/8	0.272 (0.176–0.420)	65.2	0.022	4/4	0.353 (0.212–0.587)	89.3	<0.001

Data are estimate and 95% CI values.
*The analysis was performed using a random-effects model with the DerSimonian and Laird method if substantial heterogeneity was detected; otherwise a fixed-effects model was used.

of cases of ICH in CADASIL patients have been reported as an atypical presentation of CADASIL.[4-6] Palazzo et al.[28] collected 5 CADASIL patients with ICH from their own medical records and 47 cases from the published literature, with the combined 52 cases being aged 56±11 years (mean±standard deviation) and comprising 69% males. A total of 60 ICHs occurred in those 52 patients, with deep hemorrhages being the most common type (*n*=39, 65%), followed by lobar (*n*=12, 20%) and infratentorial (*n*=60, 15%) hemorrhages. A certain proportion of ICHs were asymptomatic, which could be easily overlooked if susceptibility-weighted images were not available.[17,28]

The present results suggest that ICH in CADASIL is more common in Asians than in Europeans. There are several possible reasons underlying this race-related difference in occurrence rate. Firstly, Asians are well known for being prone to ICH.[29] In a systematic review of 36 population-based epidemiological studies, the incidence rate of ICH was twofold higher in Asians than in white people (51.8 vs. 24.2 per 100,000 person-years).[30] In a multicenter study including 54,334 patients with ischemic stroke, the rate of hemorrhagic complications after intravenous thrombolytic therapy was also higher in Asian patients than in white patients.[31] Secondly, traditional vascular risk factors including age, hypertension, and diabetes mellitus are more common in CADASIL patients from Asia than in those from Europe, which could increase the risk of ICH. Thirdly, a systematic review of all published CADASIL cases with detailed NOTCH3-gene mutations demonstrated that mutation types and phenotypic characteristics differed significantly between Asians and Caucasians.[32] The risk of ICH was as high as 41.8% in Chinese patients with the R544C mutation of the NOTCH3 gene,[19] which is much higher than our pooled estimate. We found that the R544C mutation in exon 11 was reported to be potentially associated with an increased risk of ICH in one of the included studies,[27] whereas another study found no association between the R544C mutation and ICH presence.[17] One of the included studies found that the mutation types of R75P in exon 3, Y465C in exon 9, R587C in exon 11, and R1175W in exon 22 were also predisposing factors for ICH,[18] but this was based on only a small number of cases. Therefore, the correlations between the occurrence of ICH and specific mutations of the NOTCH3 gene need to be further verified by larger-sample multicenter and multirace prospective studies. Lastly, a lack of awareness and underestimation of ICH in CADASIL patients might be another important factor contributing to differences in ICH occurrence.[17]

A higher burden of CMBs was the most common risk factor for ICH in the included studies. Moreover, presence of CMBs in the brainstem and severe WMH on neuroimaging were also described as independent risk factors for ICH. Brain histopathological studies of CADASIL patients demonstrated that the vascular smooth-muscle cells were destroyed by the pathognomonic accumulation of GOM, which was followed by fibrotic thickening and stenosis of the arterioles in the brain white matter.[33,34] A higher burden of CMBs and severe WMH represented more-serious pathological changes of cerebral SVD. Our results supported the notion that patients with CADASIL have more-fragile small cerebral vessels and hence an increased susceptibility to CMBs and hemorrhagic stroke.[35] Pathologically, the CMBs were hemosiderin deposits caused by minor extravasation of blood from damaged small arterioles.[36] The existence of CMBs was significantly associated with the incidence and recurrence of ICH in non-CADASIL patients, indicating that the CMBs were a hemorrhage-prone microangiopathy.[37,38]

Not surprisingly, a history of hypertension was indicated as a common risk factor for spontaneous ICH in CADASIL patients. Hypertension is the most important risk factor for both nonlobar and lobar ICH in the general population.[39] Similarly, a meta-analysis showed a significant association between hypertension and CMBs in both patients with stroke and healthy populations, while CMBs could subsequently increase the risk of ICH.[40] Hypertension is thought to cause arteriolosclerosis with fibrinoid necrosis, lipohyalinosis, microatheromas, and microaneurysms, mainly in the small, deep, perforating cerebral arteries,[41] which may aggravate the microangiopathy and further increase the probability of vessel rupture in CADASIL patients. Considering the high disability and mortality rates of ICH, strict control of blood pressure

may be important in the management of patients with CADASIL, especially in those with more-severe CMBs.[28,42]

The present study had several limitations. Firstly, all of the data were obtained from the published literature, and the presence of publication bias was suggested by Begg's test and the asymmetric funnel plot. Some relevant studies might not have been included in our analysis, including those for which ICHs were neglected or not reported due to their low or no occurrence. Secondly, there were no population-based studies, which may have reduced the statistical power of our analyses. Thirdly, heterogeneity was observed among the pooled estimates after rational subgroup analyses, and we did not quantitatively and explicitly evaluate all of the factors that could potentially contribute to this heterogeneity, including sex, location of ICH, and combined hypertension, due to insufficient data and the small number of studies.

In summary, ICH is an underrecognized clinical manifestation of CADASIL, and so more attention needs to be paid to this in clinical practice. The occurrence rate of ICH in CADASIL was much higher in Asians than in Europeans, probably due to differences in race, age, and the comorbidities of hypertension and diabetes mellitus. A higher burden of CMBs and the existence of hypertension were the main associated risk factors for ICH in patients with CADASIL. Future prospective population-based studies that focus on incidence and prevalence rate of ICH in CADASIL and relevant risk factors are warranted, particularly to investigate the correlations with specific mutations of the NOTCH3 gene.

Supplementary Materials

The online-only Data Supplement is available with this article at https://doi.org/10.3988/jcn.2022.18.5.499.

Availability of Data and Material

The datasets generated or analyzed during the study are available from the corresponding author on reasonable request.

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Conflicts of Interest

The authors have no potential conflicts of interest to disclose.

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