Incidence and associated factors of major VCI in first-ever ischemic stroke patients with mild VCI: a five-year prospective cohort study

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Summary

Background Long-term outcomes of ischemic stroke patients having mild vascular cognitive impairment (VCI) are not well-known. The aim of this study was to investigate the five-year outcomes of ischemic stroke patients with mild VCI.

Methods This study analyzed data from the Korean Stroke Cohort for Functioning and Rehabilitation study. Patients were recruited from August 2012 through May 2015. We included patients who survived five-year after stroke onset and were classified as having mild VCI at six-month post-onset. Assessments were performed serially from six-month to five-year post-onset. Cognition was assessed by Korean version of Mini-Mental Status Examination (K-MMSE). Functional Independence Measure (FIM) was used to assess activities of daily living (ADL) of the participants. Vascular Impairment of Cognition Classification Consensus Study (VICCCS) guideline was used to define VCI condition. Longitudinal trajectories of VCI condition and K-MMSE, including the specific domains, were identified. Multivariable logistic regression analysis was performed, to demonstrated factors associated with progression to major VCI condition.

Findings A total of 998 patients were included. At five-year post-onset, 136 (13·6%) patients progressed to major VCI condition. Older age (OR 1·09, 95% CI 1·06∼1·12), presence of diabetes (OR 1·83, 95% CI 1·15∼2·88) and atrial fibrillation (OR 2·47, 95% CI 1·25∼4·79), high level of education (OR 0·32, 95% CI 0·10∼0·90), etiology of small vessel occlusion (OR 1·95, 95% CI 1·18∼3·22), higher FIM score at six-month (OR 0·90, 95% CI 0·85∼0·96), impairment in the attention and calculation domain of the K-MMSE at six-month (OR 2·10, 95% CI 1·25∼3·61), and longer hospitalization (OR 1·04, 95% CI 1·02∼1·05) were associated with the risk of being classified as having major VCI at five-year.

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Interpretation This study investigated the incidence and associated factors of major VCI in patients with mild VCI. The results provide insights into cognitive decline trajectories in this population, enabling the development of targeted management strategies to mitigate disease progression.

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Keywords: Vascular cognitive impairment; Ischemic stroke; Longitudinal outcomes

Research in context

Evidence before this study

We searched PubMed for articles published in English with the keywords ("vascular cognitive impairment" or "post-stroke dementia") AND ("outcome" or "trajectory"), from database inception to December 31, 2024, to identify relevant studies. Most studies focused on incidence, biomarkers, outcome predictors, or narrative review (including pathophysiology, management, or treatment strategies) of cognitive impairment. Some studies assessed the long-term incidence or outcomes regarding vascular cognitive impairment. However, no studies have revealed the actual longitudinal trajectories of ischemic stroke patients having mild VCI. In addition, no studies to date have characterized the longitudinal trajectories of ischemic stroke patients diagnosed with mild VCI, particularly through concurrent evaluation of both cognitive function and activities of daily living (ADL). This dual-domain assessment remains absent in existing literature, despite its clinical relevance for understanding the actual natural course of stroke patients suffering from cognitive impairment.

Added value of this study

To the best of our knowledge, this study is the first to provide longitudinal serial outcomes in ischemic stroke patients classified as having mild VCI at six-month post-onset, incorporating both cognition (using Korean version of Mini-Mental Status Examination, K-MMSE) and ADL (using Functional Independence Measure, FIM).

We found that 13·6% mild VCI patients progressed to major VCI condition at five years after onset. In addition, cognitive trajectory was different between the mild and major VCI patients classified at five-year post-onset. Regarding the specific domains of K-MMSE, attention and calculation domain and recall domain were the most commonly reported problems. In addition, this study identified associated factors of progression to major VCI in patients with mild VCI. Those included older age, presence of diabetes and atrial fibrillation, low level of education, stroke etiology of small vessel occlusion, lower FIM score at six-month, impairment in the attention and calculation domain of the K-MMSE at six-month, and prolonged hospitalization. While prior studies on post-stroke dementia have reported similar risk factors, our findings provide novel insights by exclusively focusing on mild VCI patients without normal cognition. This distinction may explain observed discrepancies in predictors across studies, highlighting population-specific risk factor heterogeneity.

Implications of all the available evidence

Long-term outcomes in ischemic stroke patients offer critical insights into residual disabilities and functional prognosis. While the incidence of major VCI or post-stroke dementia has been relatively well-documented, the longitudinal trajectories of mild VCI patients, specifically those excluding individuals with normal cognition, remain uncharacterized. This study addresses this gap by identifying progression patterns to major VCI in mild VCI patients, thereby guiding the development of targeted management strategies. Furthermore, by incorporating dual assessments of cognitive function and ADL, the findings establish a foundation for future research to adopt more comprehensive and clinically relevant assessment frameworks in VCI populations.

Introduction

Cognitive impairment after stroke is a common condition, with prevalence rates varying between 8·2–78·7%, depending on type of stroke, diagnostic criteria, race, or assessment timing.[1,2] This cognitive deficit after stroke is a major contributor to disability, resulting in a significant global health burden and associated costs.[3] In recent years, diagnostic consensus regarding post-stroke cognitive impairment or vascular cognitive impairment (VCI) has been relatively well established. VCI without significant disturbance in activities of daily living (ADL) is considered mild VCI. In contrast, VCI with disturbance in ADL is classified as major VCI or post-stroke dementia.[4] In addition, recent studies have focused on the global cognitive trajectory or risk factors associated with post-stroke dementia, demonstrating significant results. These studies have revealed a decline in global cognition, and risk factors including older age, clinical stroke severity, large artery atherosclerosis, lacunar infarction, cerebral small vessel disease, white matter hyperintensities, education level, presence of diabetes or atrial fibrillation.[1,5–7] However,

the exact natural course of patients with cognitive impairment after stroke is still not fully understood. Specifically, although the recent guidelines defining cognitive impairment after stroke incorporates the level of ADL, no previous studies have focused the cognition along with the ADL. In addition to the level of cognition, it is crucial to provide information regarding the level of ADL in patients suffering VCI. Furthermore, studies focusing on patients with mild VCI following a stroke is sparse. Mild VCI is a condition that could progress in to major VCI, which significantly causes health burden to both patients and caregivers.[8] Providing an understanding of the long-term course of mild VCI patients could be essential for identifying key characteristics and, consequently, guiding future studies aimed at halting progression to major VCI.

Therefore, the aim of this study was to investigate the outcomes of mild VCI patients surviving first-ever ischemic stroke over a five-year follow-up period. The outcome was the longitudinal trajectory of cognitive function and its associated factors.

Methods

Selection of KOSCO participants with mild VCI patients surviving first-ever ischemic stroke

This study analyzed data of mild VCI patients surviving first-ever ischemic stroke patients from the Korean Stroke Cohort for Functioning and Rehabilitation (KOSCO) study.[9] Mild VCI patients were defined by using the Vascular Impairment of Cognition Classification Consensus Study (VICCCS) guidelines.[4] Ischemic stroke was diagnosed by using the definition from the American Heart Association/American Stroke Association.[10] The inclusion criteria were as follows: 1) patients with ischemic stroke confirmed by brain imaging, using magnetic resonance imaging (MRI) or computed tomography (CT) scans, and 2) classified as mild VCI at six-months post-onset. The exclusion criteria were: 1) premorbid cognitive impairment, 2) death before five-year post-onset, and 3) loss to follow-up or inability to complete assessments due to neurological deficits (such as mental change, aphasia, and so on) at six-month and five-year assessments.

In this study, we used the VICCCS guidelines to define VCI in stroke patients.[4] Accordingly, patients with mild VCI exhibited cognitive impairment with mild to no disruption in ADL, whereas those with major VCI demonstrated cognitive impairment accompanied by disruption in ADL. For cognitive evaluation, we utilized the Korean version of Mini-Mental Status Examination (K-MMSE) and categorized cognitive domains as follows: orientation to time and place, registration, attention and calculation, working memory (recall), and language.[11] The K-MMSE domains and their reference scores were considered as follows: Orientation to time (five points; reference 4∼5), orientation to place (five points; reference 4∼5), registration (three points; reference 3), attention and calculation (five points; reference 4∼5), recall (three points; reference 3), and language (nine points; reference 8∼9).[11] Cognitive impairment was defined as having deficits in at least one K-MMSE domain. For the evaluation of ADL, we utilized the Functional Independence Measure (FIM). A score below six in any of the 18 FIM subcategories was classified as indicative of disruption in ADL, as a score of six or seven indicates independence.[12]

As a result, 6253 (79·6%) had ischemic stroke among the 7858 of participants. At six-month post-onset, 1333 (21·3%) ischemic stroke patients were classified as having mild VCI. After excluding those who did not complete the assessments, 998 (74·9%) patients were included in the final analyses (Fig. 1 and Supplemental Table S1).

Data collection

Data were collected from the KOSCO study, which is a prospective multi-center cohort study of patients with first-ever stroke. Patients were recruited from nine tertiary hospitals in South Korea, between August 2012 and May 2015.[9] Among the screened patients, 7858 patients agreed to participate in the study. All the participants provided written informed consent, and the study protocol was approved by the institutional review board of each participating hospital.

Baseline clinical characteristics and demographic information were documented, which included age, sex, body mass index, smoking and alcohol consumption, medical history and comorbidities, pre-stroke functional level, and education level. The medical history included hypertension, diabetes, dyslipidemia, atrial fibrillation, and coronary heart disease. Comorbidities were assessed using Charlson's weighted index of comorbidities (WIC). Pre-stroke disability was assessed by using modified Rankin Scale (mRS). Education level of the participants was documented and we categorized those into no education, elementary (<6 years), middle (6∼12 years), and high level (>12 years). Details of the stroke lesion, including side, location, and etiology, were recorded. Etiology was classified using the TOAST classification.[13] Initial clinical severity was assessed using the National Institute of Health Stroke Scale (NIHSS) at the time of hospital arrival. Additionally, baseline clinical assessments were conducted at six-month post-onset, including clinical severity (NIHSS), disability (mRS), ADL (FIM), and cognition (K-MMSE). Over the five-year follow-up period, ADL and cognition were assessed. All assessments were performed face-to-face by licensed occupational and physical therapists who had completed designated training programs, following predefined follow-up time points.[9] The duration of hospitalization, records of neurological symptoms progression or recurrence of

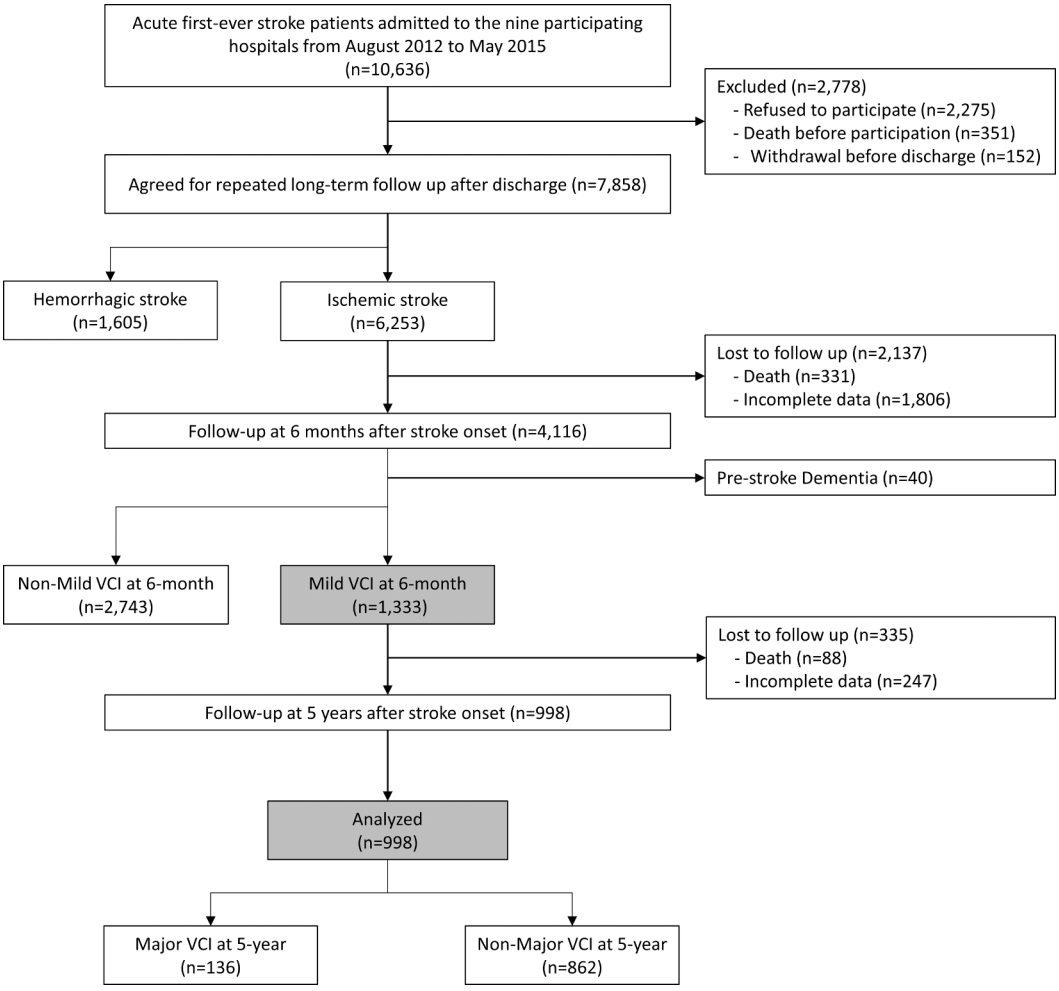

Fig. 1: **Inclusion flowchart**.

stroke, and receiving inpatient rehabilitation, were documented during the first hospitalization.

Statistical analysis

Demographic and clinical characteristics were reported as frequencies and percentages for categorical variables and as means with standard deviations (SD) for numerical variables. The participants were dichotomized into two groups: major VCI group, and non-major VCI group. The major VCI group consisted of patients classified as major VCI, while the non-major VCI group consisted of patients classified as normal or minor VCI at five-year assessment. To compare the characteristics between the groups, Fisher's exact test and independent t-test were used for categorical and numerical variables, respectively.

To analyze the covariates and identify the associated factors with progression to major VCI at five-year, we used multivariable binomial logistic regression analysis. Covariates included in the analysis were selected based on pre-performed univariable logistic analyses that showed significance with a p-value of <0·1, as well as clinically important variables, even if they were not statistically significant.[14] To assess multicollinearity among the variables, the variance inflation factor (VIF) was calculated. Additionally, mixed-effects analysis was used to analyze longitudinal trajectory between the two groups.

Missing data were present during the follow-up period, and analyses were conducted using complete cases only. Details regarding the missing data are provided in the Supplemental Table S2. Statistical significance was set at a two-sided p-value of <0·05 for all analyses. Statistical analyses were conducted using R version 4.4.2 (R Foundation for Statistical Computing, Vienna, Austria).

Role of the funding source

The funder had no role during conduct of the study, including study design, data collection, analysis,

interpretation, writing of the manuscript, or the decision to submit for publication.

Results

Clinical characteristics and demographics

Among the 998 patients included, the mean (±SD) age was 65·1 ± 10·5 and 617 (61·8%) were male. The proportion of patients with hypertension, diabetes, dyslipidemia, atrial fibrillation, and coronary heart disease was 55·7%, 25·3%, 14·2%, 10·1%, and 6·3%, respectively. Premorbid disability, as measured by the mRS was 0·7 ± 1·2, indicating that no significant disabilities were present before stroke onset. Regarding the education level, 8·5% of patients had no formal education, and 14·2% of patients had a high level of education. The etiology of ischemic stroke revealed that large artery atherosclerosis (49·4%) was the most common underlying cause, followed by small vessel occlusion (23·4%). The mean (±SD) K-MMSE score was 26·0 ± 2·9 at six months after onset. Specifically, at the six-month, 6·5% of patients showed impairment in orientation to time domain of the K-MMSE, 0·6% in orientation to place, 0·7% in registration, 60·2% in attention and calculation, 75·8% in recall, and 16·4% in language.

Five-year trajectory of cognition among mild VCI patients

Among the 998 patients classified with mild VCI at six-month, 862 (86·4%) patients were classified as non-major VCI at five-year post-onset. In contrast, 136 (13·6%) patients progressed into major VCI condition over the five-year follow-up period. Specifically, 9·4% of mild VCI patients were classified as major VCI at one-year, 12·9% at three-year, and 13·6% at five-year post-onset (Fig. 2).

K-MMSE score for the total patients were 26·0 ± 2·9 at six months, and reached a plateau at two years after onset (26·7 ± 3·5, $p < 0·05$). Among the two classified groups, significant differences regarding K-MMSE score were identified. In major VCI patients, K-MMSE score declined significantly over the follow-up period. K-MMSE scores were 23·9 ± 3·8, 22·7 ± 5·9, 21·6 ± 6·0, and 20·6 ± 5·7, at six-month, three-year, four-year, and five-year post-onset, respectively ($p < 0·05$). In non-major VCI patients, K-MMSE score significantly improved from six months (26·3 ± 2·6) to two years (27·1 ± 3·0) after onset and then remained plateau ($p < 0·05$) (Supplemental Table S3 and Fig. 3). In addition, mixed-effects analysis revealed significantly different trajectories of K-MMSE scores between the two groups, demonstrating a significant decline in patients with major VCI over the five-year follow-up period (Supplemental Table S4).

Regarding the domains of K-MMSE, the majority of patients showed impairment in attention and calculation (60·2%), and recall (75·8%) at six-month assessment. At five-year, patients showing impairment in those domains decreased to 42·2% and 51·5%, respectively. The proportion of impairment in other domains

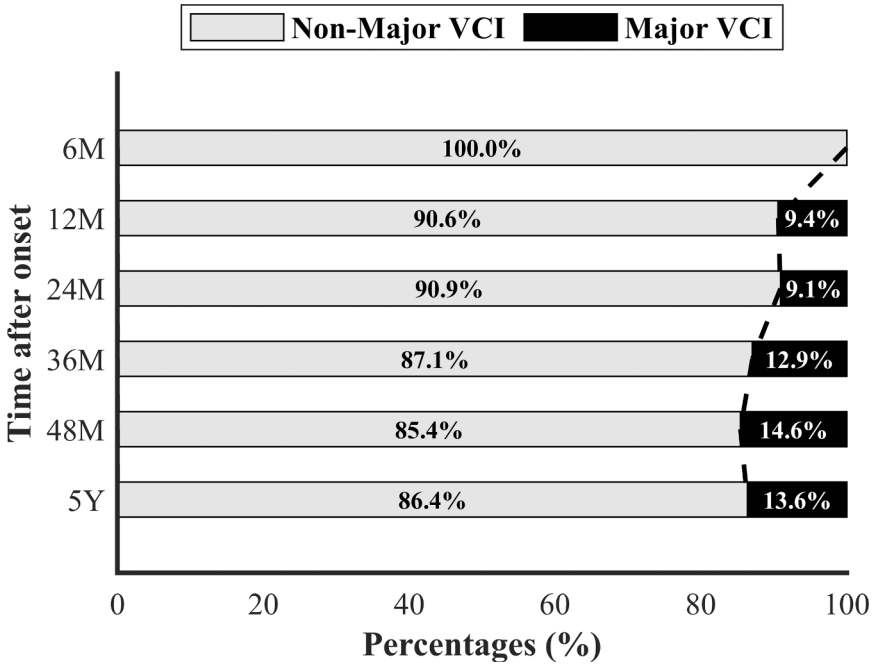

Fig. 2: **VCI classification over five-year follow-up period of mild VCI patients.** VCI, Vascular Cognitive Impairment.

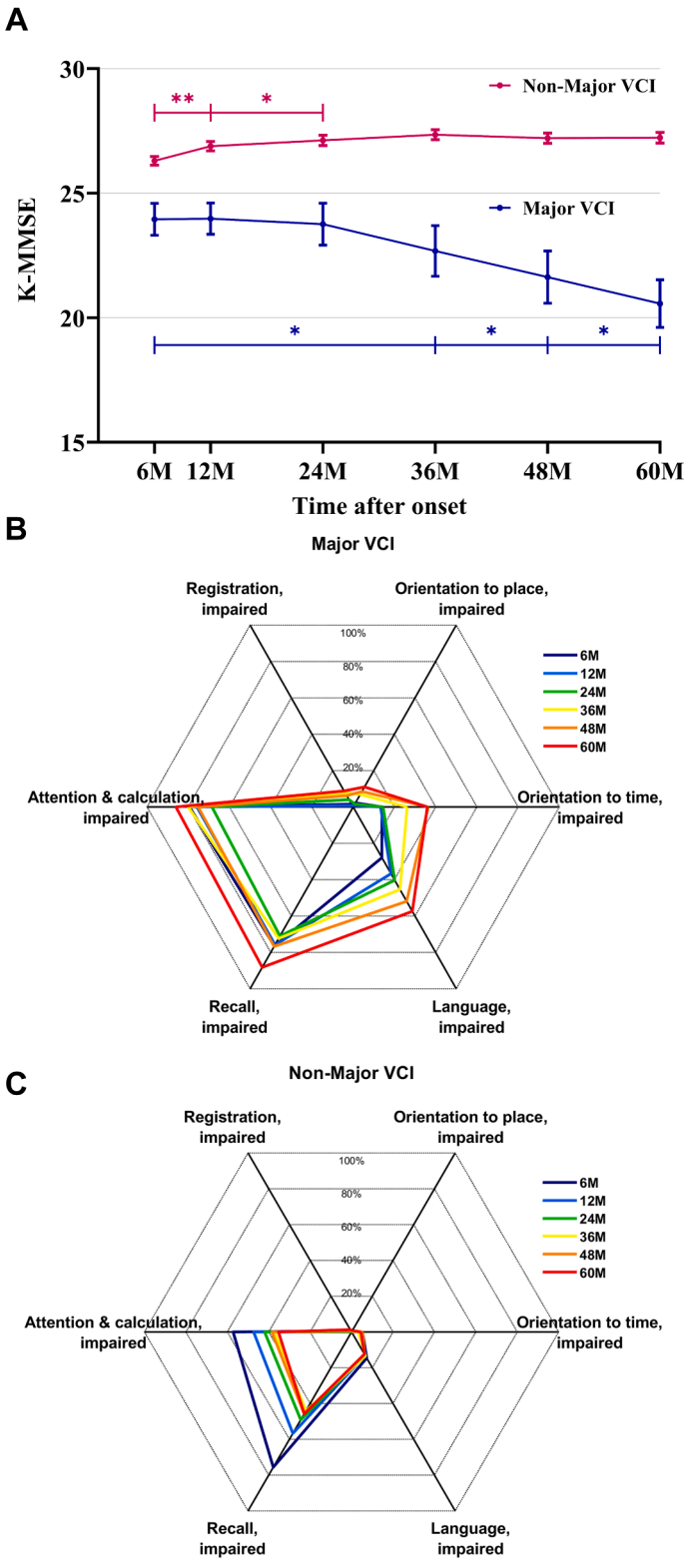

***Fig. 3:* K-MMSE of mild VCI patients over five-year follow-up period. A)** Longitudinal trajectory of total K-MMSE score, **B)** Domain-specific impairments on the K-MMSE in Major VCI patients at five-year, **C)** Domain-specific impairments on the K-MMSE in Non-Major VCI patients at five-year. K-MMSE, Korean version of Mini-Mental Status Examination; VCI, Vascular Cognitive Impairment. *$p < 0.05$, **$p < 0.001$, compared between each time point using paired t-test with Bonferroni correction.

improved from six-month to five-year assessment (Orientation to time 6·5% to 8·8%; Orientation to place 0·6% to 2·1%; Registration 0·7% to 2·3%; Language 16·4% to 18·5%). In major VCI patients, the impairment in attention and calculation domain was the most commonly reported problem (79·4%) at six-month post-onset. At five-year, the proportion of patients demonstrating impairment in K-MMSE domains were as follows: 36·0% for orientation to time, 11·0% for orientation to place, 8·8% for registration, 86·0% for attention and calculation, 88·2% for recall, and 57·4% for language (Supplemental Table S3 and Fig. 3).

Factors associated with progression from mild VCI to major VCI

At five years after onset, 136 (13·6%) patients progressed into major VCI. Compared with others, those patients were older (71·4 ± 8·7 vs 64·1 ± 10·4, $p < 0·001$). The proportion of male was lower (44·1% vs 64·6%, $p < 0·0001$), and current alcohol consumption also significantly differed (28·7% vs 39·9%, $p = 0·016$). Regarding medical history, a higher frequency of having hypertension (66·2% vs 54·1%, $p = 0·011$), diabetes (33·1% vs 24·0%, $p = 0·031$), and atrial fibrillation (15·4% vs 9·3%, $p = 0·039$) was observed in the major VCI patients. Education level revealed significant differences between the two groups, with major VCI patients having a lower level of education (No education 13·4% vs 7·7%, elementary 45·5% vs 23·3%, middle 35·8% vs 53·3%, and high level 5·2% vs 15·6%, $p < 0·0001$). Etiology showed no significant difference, although the major VCI patients had a higher proportion of small vessel occlusion (30·1% vs 22·4%, $p = 0·061$). Clinical severity, and functional measurements, including cognitive function, showed significantly lower levels in the major VCI patients. Regarding the specific K-MMSE domains, the major VCI patients showed a higher proportion of impairment in the domain of orientation to time (14·0% vs 5·3%, $p = 0·0006$), orientation to place (2·2% vs 0·3%, $p = 0·036$), attention and calculation (79·4% vs 57·2%, $p < 0·0001$), and language (27·9% vs 14·6%, $p = 0·0003$). The domain of registration and recall showed did not show significant difference. Details are provided in Table 1.

Multivariable logistic regression analysis was performed to identify factors associated with major VCI at five years after onset. Older age (OR 1·09, 95% CI 1·06~1·12), presence of diabetes (OR 1·83, 95% CI 1·15~2·88) and atrial fibrillation (OR 2·47, 95% CI 1·25~4·79), high level of education (OR 0·32, 95% CI

0·10∼0·90), etiology of small vessel occlusion (OR 1·95, 95% CI 1·18∼3·22), higher FIM score at six-month (OR 0·90, 95% CI 0·85∼0·96), impairment in the attention and calculation domain of the K-MMSE at six-month (OR 2·10, 95% CI 1·25∼3·61), and longer hospitalization (OR 1·04, 95% CI 1·02∼1·05) were associated with the risk of being classified as having major VCI at five-year (Table 2).

Discussion

This study examined the five-year trajectory of patients classified with mild VCI at six-month post-onset, based on the VCI classification guidelines. Among 998 mild VCI patients, 136 (13·6%) patients were classified as having major VCI at five years after onset. On the other hand, 862 (86·4%) patients were classified as non-major VCI. The factors associated with progression from mild VCI to major VCI included older age, presence of diabetes and atrial fibrillation, lower educational level, stroke etiology of small vessel occlusion, lower ADL level at six-month assessment, impaired attention and calculation domain of K-MMSE at six-month assessment, and longer duration of hospitalization.

Natural course of cognition in mild VCI patients

In previous literature, demonstrating the natural course regarding cognition in stroke patients with mild VCI are sparse. In contrast, there are several longitudinal studies have reported on the natural course in patients with mild cognitive impairment (MCI). It is widely accepted that individuals with MCI are at significantly higher risk of progressing to Alzheimer's disease (AD) compared to cognitively normal individual.[15,16] Prior studies have suggested that the annual progression rate from MCI to AD ranges from 7·1 to 16·5% per year.[17–19] Regarding cumulative conversion, the conversion rates were reported between 21·8∼28·7% over average of 2·4∼5·1 years of follow-up period.[15,17,20] In this study, we demonstrated that 13·6% of ischemic stroke patients classified as having mild VCI at six-month post-onset progressed to major VCI over the five-year follow-up. The rate of cognitive decline in mild VCI patients appears to be lower than that in MCI patients. The annual progression rate from mild VCI to major VCI in this study was 3.0% per year, which is also lower than the previously reported progression rates from MCI to dementia. These findings suggest that the natural course of mild VCI may differ from that of MCI, with a slower progression toward dementia. Further studies with longer follow-up and detailed assessments of specific cognitive domains are needed.

Factors associated with progression to major VCI

The older age, and baseline cognitive level are widely known factors associated with post-stroke dementia demonstrated from previous studies.[1,2,7] Although

	Total (n = 998)	Major VCI (n = 136)	Non-Major VCI (n = 862)	p-value[a]
Age	65·1 ± 10·5	71·4 ± 8·7	64·1 ± 10·4	<0·0001
Sex				<0·0001
female	381 (38·2%)	76 (55·9%)	305 (35·4%)	
male	617 (61·8%)	60 (44·1%)	557 (64·6%)	
Body mass index	23·9 ± 3·0	23·4 ± 3·5	24·0 ± 2·9	0·068
Smoking, current	274 (27·5%)	28 (20·6%)	246 (28·5%)	0·068
Alcohol, current	383 (38·4%)	39 (28·7%)	344 (39·9%)	0·016
Medical history				
Hypertension	556 (55·7%)	90 (66·2%)	466 (54·1%)	0·011
Diabetes	252 (25·3%)	45 (33·1%)	207 (24·0%)	0·031
Dyslipidemia	142 (14·2%)	20 (14·7%)	122 (14·2%)	0·97
Atrial fibrillation	101 (10·1%)	21 (15·4%)	80 (9·3%)	0·039
Coronary heart disease	63 (6·3%)	10 (7·4%)	53 (6·1%)	0·73
WIC	0·7 ± 0·9	0·6 ± 0·8	0·7 ± 0·9	0·22
Premorbid disability, mRS	0 [0–1]	0 [0–1]	0 [0–1]	0·26
0, mRS score	735 (73·7%)	108 (79·4%)	627 (72·7%)	
1, mRS score	174 (17·4%)	19 (14·0%)	155 (18·0%)	
2, mRS score	89 (8·9%)	9 (6·6%)	80 (9·3%)	
Education level				<0·0001
No education	83 (8·5%)	18 (13·4%)	65 (7·7%)	
Elementary (<6 years)	258 (26·4%)	61 (45·5%)	197 (23·3%)	
Middle (6–12 years)	498 (50·9%)	48 (35·8%)	450 (53·3%)	
High (>12 years)	139 (14·2%)	7 (5·2%)	132 (15·6%)	
Side of the lesion				0·13
Right	456 (45·7%)	56 (41·2%)	400 (46·4%)	0·30
Left	463 (46·4%)	73 (53·7%)	390 (45·2%)	0·082
Bilateral	79 (7·9%)	7 (5·1%)	72 (8·4%)	0·26
Location of the lesion				0·74
Cortex	333 (33·4%)	51 (37·5%)	282 (32·7%)	0·32
Subcortex	334 (33·5%)	43 (31·6%)	291 (33·8%)	0·69
Infratentorial	226 (22·6%)	28 (20·6%)	198 (23·0%)	0·61
Multiple	105 (10·5%)	14 (10·3%)	91 (10·6%)	1
Etiology				0·11
LAA	493 (49·4%)	65 (47·8%)	428 (49·7%)	0·76
SVO	234 (23·4%)	41 (30·1%)	193 (22·4%)	0·061
CE	121 (12·1%)	17 (12·5%)	104 (12·1%)	0·99
Other determined	49 (4·9%)	2 (1·5%)	47 (5·5%)	0·074
Undetermined	101 (10·1%)	11 (8·1%)	90 (10·4%)	0·49
Initial clinical severity, NIHSS	3·1 ± 3·4	3·7 ± 3·5	3·0 ± 3·4	0·021
Initial treatment				0·80
Antiplatelet agent or Anticoagulant	828 (83·0%)	111 (81·6%)	717 (83·3%)	
Intra-venous thrombolysis	92 (9·2%)	14 (10·3%)	78 (9·1%)	
Intra-arterial thrombolysis	8 (0·8%)	2 (1·5%)	6 (0·7%)	
Mechanical thrombectomy	6 (0·6%)	1 (0·7%)	5 (0·6%)	
Intra-venous heparin	60 (6·0%)	7 (5·1%)	53 (6·2%)	
Stent insertion	3 (0·3%)	1 (0·7%)	2 (0·2%)	
Assessments, baseline at six-month				
Disability (mRS)	1 [0–1]	1 [1-1]	1 [0–1]	<0·0001
0, mRS score	390 (39·1%)	28 (20·6%)	362 (42·0%)	
1, mRS score	525 (52·6%)	90 (66·2%)	435 (50·5%)	

(Table 1 continues on next page)

	Total (n = 998)	Major VCI (n = 136)	Non-Major VCI (n = 862)	p-value[a]
(Continued from previous page)				
2, mRS score	80 (8·0%)	17 (12·5%)	63 (7·3%)	
3, mRS score	3 (0·3%)	1 (0·7%)	2 (0·2%)	
Level of ADL (FIM)	124·6 ± 3·0	123·3 ± 4·1	124·9 ± 2·7	<0·0001
Cognition (K-MMSE)	26·0 ± 2·9	23·9 ± 3·8	26·3 ± 2·6	<0·0001
Orientation to time, impaired	65 (6·5%)	19 (14·0%)	46 (5·3%)	0·0006
Orientation to place, impaired	6 (0·6%)	3 (2·2%)	3 (0·3%)	0·036
Registration, impaired	7 (0·7%)	2 (1·5%)	5 (0·6%)	0·25
Attention and calculation, impaired	601 (60·2%)	108 (79·4%)	493 (57·2%)	<0·0001
Recall, impaired	756 (75·8%)	104 (76·5%)	652 (75·6%)	0·91
Language, impaired	164 (16·4%)	38 (27·9%)	126 (14·6%)	0·0003
Duration of 1st hospitalization, days	9·9 ± 11·4	12·6 ± 15·2	9·4 ± 10·7	0·0027
Inpatient rehabilitation during the 1st hospitalization	433 (43·4%)	60 (44·1%)	373 (43·3%)	0·72
Neurologic progression during the 1st hospitalization	30 (3·0%)	2 (1·5%)	28 (3·2%)	0·39
Recurrence of stroke	5 (0·5%)	0 (0%)	5 (0·6%)	0·81

WIC, Charson's weighted index of comorbidities; mRS, modified Rankin Scale; LAA, Large Artery Atherosclerosis; SVO, Small Vessel Occlusion; CE, Cardioembolism; NIHSS, National Institutes of Health Stroke Scale; FIM, Functional Independence Measure; K-MMSE, Korean version of Mini-Mental Status Examination. Values are mean ± standard deviations, median [IQR], or frequency(percentage). [a]Compared between the major VCI and non-major VCI patients classified at five-year after the onset, using Fisher' Exact test or independent t-test.

Table 1: **Demographic and clinical characteristics.**

clinical severity was not identified as a significant factor, despite being established in previous literature, the duration of hospitalization could indirectly reflect patient severity and was therefore identified as a significant factor. The presence of diabetes and atrial fibrillation were found to be risk factors of progressing to major VCI condition at five years after onset. Previous studies also demonstrated diabetes and atrial fibrillation as risk factors associated with post-stroke dementia.[7] In addition, small vessel occlusion as the etiology of stroke was identified as a significant risk factor. Regarding the etiology of stroke, results from previous studies vary. Large artery atherosclerosis, small vessel occlusion, and cardioembolism have been reported as significant risk factors associated with post-stroke VCI.[5,6] However, these findings differ across studies, which have assessed the prevalence of post-stroke cognitive impairment among all stroke patients. In this study, we assessed patients with mild VCI six months after onset. Based on this specific inclusion criteria, the identified small vessel etiology as a risk factor may have important implications, suggesting that patients with mild cognitive impairment are those having small vessel disease as a risk factor for progression to major VCI or post-stroke dementia condition. The finding that diabetes and atrial fibrillation have been identified as significant factors further support this finding, as they are well-known to increase the burden of brain damage caused by small vessel disease.[21] Therefore, mild VCI patients should receive special attention to control and manage risk factors that could exacerbate the underlying small vessel disease and ultimately progress to major VCI. In addition, impaired ADL level, and attention and calculation domain of K-MMSE at six-month assessment were associated with major VCI at five-year post-onset. The finding that lower ADL level is associated with the risk of major VCI is clearly obvious. In previous studies, specific cognitive domains such as attention and executive function were shown to be impaired in stroke patients with cognitive decline.[21,22] Although the MMSE has been criticized for its lower sensitivity in detecting executive dysfunction, some studies still suggest that it is marginally favorable and shows agreement with specific neuropsychological battery tests.[23,24] Moreover, one study reported that patients with cerebral microbleeds showed lower scores in attention and calculation domain of MMSE. Cerebral microbleeds are thought to be associated with small vessel disease, potentially leading to cognitive impairment, particularly affecting executive function.[24] The finding that the attention and calculation domain of the K-MMSE is a significant factor associated with major VCI aligns with previous research. This finding could serve as an important clinical cue for both physicians and patients, highlighting that impairment in this specific domain requires focus due to the risk of cognitive worsening in patients with mild VCI. It is noteworthy that a high level of education was found to be a significant protective factor against progression to major VCI. Previous study has reported that education serves as an important buffer against cognitive impairment following stroke.[25] Our findings further suggest that education level may contribute to cognitive reserve, thereby reducing the likelihood of progression to major VCI.

K-MMSE in mild VCI patients

K-MMSE scores improved over the follow-up period in both total and mild VCI patients, plateauing at two years post-onset without reaching the minimal clinically important difference (MCID) threshold.[26] Major VCI patients exhibited significant cognitive decline at three-year post-onset, surpassing the MCID. However, given the absence of substantial alterations in K-MMSE scores up to the two-year post-onset stage, it was concluded that alterations in total MMSE scores may not be adequate for the early prediction of progression to major VCI. These findings suggest the importance of prioritizing mild VCI patients in clinical monitoring, as they represent a population at risk for progressive cognitive deterioration over time. Early

Variable	Univariable		VIF	Multivariable	
	OR (95% CI)	*p*-value		OR (95% CI)	*p*-value
Age	1·09 (1·06~1·11)	<0·0001	1·35	1·09 (1·06~1·12)	<0·0001
Sex, male	0·43 (0·3~0·62)	<0·0001	1·97	0·58 (0·33~1·03)	0·065
Body mass index	0·94 (0·88~1)	0·037	1·10	0·98 (0·91~1·05)	0·55
Smoking, current	0·65 (0·41~1)	0·055	1·40	1·36 (0·75~2·45)	0·31
Alcohol, current	0·61 (0·4~0·89)	0·013	1·50	1·21 (0·70~2·10)	0·50
Medical history					
Hypertension	1·66 (1·14~2·45)	0·0087	1·13	1·09 (0·69~1·72)	0·72
Diabetes	1·56 (1·05~2·30)	0·024	1·07	1·83 (1·15~2·88)	0·0096
Atrial fibrillation	1·78 (1·04~2·95)	0·029	1·35	2·47 (1·25~4·79)	0·0080
Education level, reference No education			1·53		
Elementary (<6 years)	1·12 (0·16~0·46)	0·71		1·05 (0·54~2·08)	0·89
Middle (6–12 years)	0·39 (0·21~0·72)	0·0018		0·67 (0·33~1·41)	0·28
High (>12 years)	0·19 (0·07~0·46)	0·0004		0·32 (0·10~0·90)	0·036
Etiology, reference LAA			1·49		
SVO	1·40 (0·91~2·13)	0·12		1·95 (1·18~3·22)	0·0087
CE	1·08 (0·59~1·87)	0·80		0·86 (0·41~1·73)	0·68
Other determined	0·28 (0·05~0·94)	0·083		0·35 (0·05~1·33)	0·18
Undetermined	0·80 (0·39~1·53)	0·53		1·01 (0·46~2·08)	0·98
Initial clinical severity, NIHSS	1·05 (1·01~1·10)	0·024	1·24	1·04 (0·98~1·10)	0·15
Baseline assessments, at six-month					
Level of ADL (FIM)	0·89 (0·85~0·93)	<0·0001	1·09	0·90 (0·85~0·96)	0·0005
Cognition, K-MMSE					
Orientation to time, impaired	2·88 (1·60~5·02)	0·0003	1·56	1·00 (0·47~2·05)	1·00
Orientation to place, impaired	6·46 (1·18–35·21)	0·023	1·15	5·92 (0·64~62·72)	0·12
Registration, impaired	2·56 (0·36~12)	0·26	1·10	1·70 (0·14~16·38)	0·66
Attention and calculation, impaired	2·89 (1·89~4·55)	<0·0001	1·98	2·10 (1·25~3·61)	0·0059
Recall, impaired	1·05 (0·69~1·62)	0·83	1·46	1·04 (0·62~1·75)	0·89
Language, impaired	2·26 (1·48~3·42)	0·0001	2·20	0·83 (0·48~1·40)	0·49
Duration of 1st hospitalization, days	1·02 (1·01~1·03)	0·0056	1·27	1·04 (1·02~1·05)	<0·0001

VCI, Vascular Cognitive Impairment; LAA, Large Artery Atherosclerosis; SVO, Small Vessel Occlusion; CE, Cardioembolism; NIHSS, National Institutes of Health Stroke Scale; FIM, Functional Independence Measure; K-MMSE, Korean version of Mini-Mental Status Examination; VIF, Variance Inflation Factor.

Table 2: **Logistic regression analysis demonstrating associated factors with major VCI at five-year.**

identification of individuals within this group who are susceptible to decline, coupled with elucidation of contributing risk factors, may enable timely interventions to mitigate progression to severe cognitive impairment.

Previous studies suggested that the cut-off value of MMSE for classifying cognitive impairment as 27.[23,27] The result of this study aligns with previous studies. The studies reporting conversion of mild VCI to major VCI are sparse. One study reported information on conversion from mild cognitive impairment to vascular dementia, suggesting cut-off points of MMSE as 25, although sensitivity was low.[28] The identified K-MMSE score (23·9 ± 3·8) of mild VCI patients who progressed to major VCI at five years in this study could provide further insights into the conversion from mild cognitive impairment to major VCI or vascular dementia. Regarding specific domain of K-MMSE, recall (88·2%), attention and calculation (86·0%), language (57·4%), and orientation to time (36·0%) were commonly impaired at five years after onset. Compared to six-month assessment, language (27·9%) and orientation to time (14·0%) were the most aggravated domains. Lo et al. have reported that the language domain exhibited significant decline with a relatively large effect size.[29] In addition, we demonstrated that orientation to time also deteriorates over time in patients with mild VCI. These findings could provide insights in managing the cognitive function in the mild VCI patients. Although the MMSE has limitations in evaluating post-stroke cognitive deficits, we utilized it not only for total scores but also to analyze specific cognitive domains. In addition, cognitive impairment was assessed in conjunction with evaluation of ADL. As a result, we could provide meaningful MMSE scores in comparison with previously suggested cut-off values, as well as domain-specific information on impaired cognitive functions.

Strengths and limitations

The strength of this study lies in our classification of patients using the current VICCCS guidelines, along

with actual cognitive and ADL measurements. No previous studies have demonstrated the actual disturbances in ADL of patients to assess cognitive impairment after stroke, using specific measurements such as FIM or BI. In addition, we focused on mild VCI patients, thereby revealing the exact proportions of patients whose cognition remained or worsened over the long-term follow-up.

There are several limitations to this study. First, as this study was based on data from the KOSCO study, we were limited to using the K-MMSE to assess cognitive function. Besides the MMSE, the Montreal Cognitive Assessment (MoCA) is also widely used to evaluate post-stroke cognitive impairments. MoCA has advantages over MMSE in capturing attention and executive function.[23] However, by defining cognitive domains based on previous literature that also used MMSE and combining these with accurate ADL measurements, our results remain meaningful. Future studies may consider using MoCA or other cognitive assessments to demonstrate the cognitive course in this patient population and compare it with the findings of this study. Second, specific radiological features, such as white matter changes or lesion volumes, were not available. Third, although this study was conducted as a multi-center cohort, all participants were exclusively from South Korea. Given that post-stroke outcomes may vary based on race or socioeconomic status, the generalizability of our findings may be limited. Fourth, included patients for this analysis were limited from the initial eligible patients and some patients were missing or lost to follow-up assessments. Therefore, the potential selection bias may exist. Nonetheless, we clearly provided the comparison of the excluded and lost patients to consider this limitation (Supplemental Tables S1 and S2). Lastly, other medical conditions may have influenced patients' functional status. Additionally, some patients may have developed AD, resulting in a classification of mixed dementia. Although these conditions could have impacted the study population, such data were not available in the present study. Based on our findings, these limitations could be addressed through a more precisely structured prospective cohort in the future, which would allow for more comprehensive results and provide valuable insights into post-stroke cognitive impairment.

Contributors

H.S.L did writing of the original draft. H.S.L, D.H.K, and W.H.C did the study design, data interpretation, statistical analysis and visualization of the study. M.K.S, J.L, D.Y.K, Y.-I.S, Y.-S.L, M.C.J, S.Y.L, M.-K.S, Y.-H.K, and W.H.C took part in data collection and supervision of the manuscript. G.-J.O, J.H, J.A, Y.-H.L, and Y.-T.K took part in data curation, data interpretation, and critical review. Y.-H.K, and W.H.C took part in funding acquisition, and project administration. H.S.L and W.H.C had full access to all data in the study and verified the data. H.S.L and W.H.C were responsible for the decision to submit the manuscript.

Data sharing statement

The data that support the findings of this study, including neuropsychological assessments and identified participant data, will be made available from the date of publication, following a reasonable request to e-mail of the corresponding author from any qualified investigator who provides a methodologically sound proposal.

Ethics approval

This study was approved by the Institutional Review Board (IRB) of all participating hospitals: Samsung Medical Center, 2012-06-016; Severance Hospital, 4-2012-0341; Konkuk University Medical Center, 1180-01-700; Chungnam National University Hospital, 2012-06-011; Chonnam National University Hospital, CNUH-2012-127; Pusan National University Yangsan Hospital, 05-2012-057; Kyungpook National University Hospital, 2013-03-029; Wonkwang University Hospital, WKUH-1515; Jeju National University Hospital, 2013-02-001.

Declaration of interests

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Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.lanwpc.2026.101800.

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