Association Between Cytomegalovirus Disease and Dementia: A Population-Based Cohort Study

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Abstract

Background

The association between human cytomegalovirus (CMV) and dementia remains controversial. Previous studies have suggested that CMV serostatus assessed by serum immunoglobulin G plays a role in neurodegeneration with cognitive impairment. We aimed to evaluate the association between CMV tissue-invasive diseases and vascular dementia (VD) and Alzheimer's disease (AD).

Methods

The International Classification of Diseases (ICD) 10th revision codes from the National Health Insurance Database covering entire people in Republic of Korea were used to classify patients: case group (n = 687), age ≥ 40 years with CMV tissue-invasive end-organ disease and control group (n = 3,435), without CMV disease, matched by age and sex (ratio, 1:5). The case and control subjects selected during 2010–2014 with a washout period of the previous 4 years were followed-up until December 2016.

Results

The multivariate regression model adjusted for age and sex showed a significantly higher incidence of dementia (odds ratio [OR], 2.1; 95% confidence interval [CI], 1.5–3.1) in the case group. The risk of VD (OR, 3.3; 95% CI, 1.3–8.4) was higher than that of AD (OR, 1.7; 95% CI, 1.1–2.8) in the case group. In age subgroup analysis adjusted for sex, patients aged 40–59 years with CMV disease had a significantly higher risk of all kinds of dementia than those aged 60–79 and ≥ 80 years (OR, 12.6; 95% CI, 3.3–48.8 vs. OR, 2.1; 95% CI, 1.3–3.4 vs. OR, 1.4; 95% CI, 0.7–2.9; $P=0.021$).

Conclusions

CMV disease may be associated with the risk of VD.

Background

Dementia is a neurologic disease defined as a gradual decline in memory and cognitive function [1]. The worldwide dementia burden, estimated to be 47 million cases in 2015, is expected to double every 20 years [1, 2]. Although the aetiology and pathogenesis of dementia are not yet clear, it could be caused by brain damage due to vascular ischemia and hereditary, sporadic, or age-related factors. Moreover, the hypothesis that infection may be a risk factor for Alzheimer's disease (AD) has been supported by neuroinflammation and disease pathology [3–5]. In vascular dementia (VD), the second most common cause of dementia, neurogenic inflammation due to vascular damage could develop into cognitive dysfunction [6–8].

Past ubiquitous human cytomegalovirus (CMV) infection can present in several forms, from life-long asymptomatic latency to tissue-invasive end-organ disease [9]. Because CMV is associated with several

chronic inflammatory diseases, particularly vascular disorders and immunodysfunction, an association between CMV and dementia has been suggested [8, 10–12]. CMV is associated with AD development and declining global cognition [10, 11]. CMV deoxyribonucleic acid was more dominant in the brain tissue of case group subjects (with VD) than in the control group subjects [12]. However, several studies on CMV and dementia were based on seroprevalence or the serostatus of latent CMV, assessed using serum CMV immunoglobulin G (IgG). Serum CMV IgG was suggested to play a role in neurodegeneration with cognitive impairment [8, 10, 11], but a significant association between CMV and dementia was not observed in a recent meta-analysis [13, 14]. The Republic of Korea has high rates of CMV seropositivity [15–17]. The Republic of Korea strictly applies the registration of CMV tissue-invasive disease diagnosis using the national health insurance system. Therefore, a confirmation of the association between dementia and CMV tissue-invasive end-organ diseases would indicate active replication of the whole virus in patients, not latent past infection status; this can provide clearer evidence than that from previous studies based on the known seroprevalence. This study aimed to evaluate the association between CMV tissue-invasive end-organ diseases and type of dementia.

Methods

Extraction of nationwide population data

In the Republic of Korea, the national health insurance service involves mandatory registration for the entire population. These compulsory subscribers pay for health insurance based on their income level. All medical institution present claims through the diseases diagnosed using the International Statistical Classification of Diseases and Related Health Problems 10th Revision (ICD-10) codes [18]. Rare incurable disorders (RIDs), such as human immunodeficiency virus infection, other specific viral diseases including CMV disease, and cancer, are considered special disorders by the Korean National Health Insurance Service [19]. Patients with RID receive significant health coverage by paying 5% of their healthcare costs. Therefore, the process of diagnosing RID and receiving medical claims should be based on strict and accurate data. The Korean Health Insurance Review and Assessment (HIRA) plays an important inspector role in this process. We used a medical dataset extracted from the National Health Insurance Database (NHID), which was submitted to the HIRA. The NHID includes big data consisting of 1.3 trillion records with information regarding medical diagnosis, treatment results, long-term care insurance for elderly patients, registration information on cancer or RIDs, and status of medical institutions [20, 21]. Health information-related data of the total population of the Republic of Korea were collected. This study was approved by the Institutional Review Board of the Gangnam Severance Hospital, Yonsei University College of Medicine, with the waiver of the informed consent as well as the relevant permission forms have been obtained from the NHI Sharing Service.

Study population and design

From January 2010 to December 2014, data of 1,557 patients diagnosed with CMV tissue-invasive end-organ diseases and enrolled with RID were extracted from the NHID. A 4-year washout period was

considered (between January 2006 and December 2009) to evaluate the effect of CMV on new-onset dementia. Forty-five patients diagnosed with dementia during the washout period were excluded. Among the remaining 1,512, 687 with CMV tissue-invasive diseases and age ≥ 40 years were selected for the case group with CMV disease. For the case-control study, 3,435 age- and sex-matched controls with no CMV tissue-invasive diseases were selected at a 1:5 ratio. Participants from both groups were followed-up until December 2016. The incidence rate (IR) per 1,000 individuals was calculated by dividing the number of events (new-onset dementia) with the total follow-up duration.

Definition

The criterion for diagnosing CMV disease as RID is 'tissue invasion'. The diagnosis of CMV tissue-invasive end-organ diseases can be established if the following are observed: (1) histopathologic features during immunohistochemical staining for CMV and the presence of inclusion bodies, (2) pp65 antigen measurement, and (3) detection and quantification of CMV or CMV-related genes in body fluids or tissue using the antigenemia test, culture test, or nucleic acid amplification test.

CMV tissue-invasive diseases are given a unique V104 code for RID registration. The V104 code is consistent with the specific B25 codes in the ICD-10 provided by the World Health Organization, including all types of CMV tissue-invasive end-organ diseases, such as cytomegaloviral pneumonitis (B25.0), cytomegaloviral hepatitis (B25.1), cytomegaloviral pancreatitis (B25.2), other cytomegaloviral diseases (B25.8), and cytomegaloviral diseases, unspecified (B25.9). This did not include congenital CMV infection (P35.1) or cytomegaloviral mononucleosis (B27.1). Furthermore, dementia diagnosis for RID registration was consistent with the ICD-10 codes: AD (F00 and G30), VD (F01.0-F01.3 and F01.8-F01.9), and unspecified or other dementia (F02, F03, G23.1, G31.0-G31.1, G31.82-G31.83, G31.88, and F10.7). Other diseases, hypertension (I10-I13, I15), type 2 non-insulin-dependent diabetes mellitus (NIDDM) (E11), and dyslipidaemia (E78), were identified using ICD-10 codes [18].

Statistical analysis

Categorical and continuous data were presented as numbers (percent) and mean $\pm$ standard deviation, respectively. Matched groups were compared using the McNemar and paired t-tests. Kaplan-Meier curves adjusted for age and sex, were established to analyse the incidence and probability of dementia according to the presence of CMV diseases. Multivariate logistic regression analyses using model 1 (M1, non-adjusted), model 2 (M2, adjusted for age and sex), and model 3 (M3, adjusted for age, sex, low-income status, NIDDM, hypertension, and dyslipidaemia) were performed to evaluate the impact of CMV diseases on dementia development. Statistical analyses were performed using the Statistical Analysis System (SAS) program (version 9.2; SAS Institute, Cary, NC). Two-tailed P values < 0.05 were considered significant.

Results

Clinical characteristics according to CMV disease

Mean age and percentage of subjects aged ≥ 60 years in the study cohort were 58 years and 40.9%, respectively. The follow-up duration was significantly longer in the control group (4.1 ± 1.6 vs. 3.7 ± 1.8 years, $P < 0.001$), but the case group had significantly higher rates of NIDDM (29.8% vs. 11.2%), hypertension (47.7% vs. 28.4%), and dyslipidaemia (29.3% vs. 17.7%) ($P < 0.001$). The incidence of all dementia types was significantly higher in the case group (5.5% vs. 3.1%, $P = 0.001$). The incidence of VD (1.0% vs. 0.4%, $P = 0.018$) but not AD (3.4% vs. 2.2%, $P = 0.085$) was significantly higher in the case group (Table 1).

Effect of CMV disease on dementia development

The case group (14.8/1,000 individuals) had twofold higher IRs for all types of dementia than the control group (7.5/1,000) per M1 with an odds ratio (OR) of 2.0 (95% confidence intervals [CI], 1.4–2.9), per M2 with an OR of 2.1 (95% CI, 1.5–3.1), and per M3 with an OR of 2.0 (95% CI, 1.4–3.0). In the subgroup analysis based on dementia type, the IR of AD in the case group (9.0/1,000) was 1.7 times higher than that in the control group (5.5/1,000) with an OR of 1.7 (95% CI, 1.1–2.8) in M2. The IR of VD in the case group (2.7/1,000) was up to threefold higher than that in the control group (0.9/1,000) with an OR of 3.3 (95% CI, 1.3–8.4) in M2. The IR of other dementia except AD and VD in the case group (3.1/1,000) was 2.8 times higher than that in the control group (1.1/1,000) (Table 2).

Incidence probability of new-onset dementia

During the 7-year follow-up, the incidence probability of all types of dementia ($P < 0.001$) was significantly higher in the case group (Figure 1A). The incidence probabilities of AD ($P = 0.034$) and VD ($P = 0.011$) were also significantly higher in the case group (Figure 1B, 1C). The slope of the Kaplan-Meier curves indicates that the incidence probability of AD was fairly different between the groups 5 years after follow-up initiation. Contrastingly, VD mostly occurred within 3 years of CMV tissue-invasive end-organ disease diagnosis (Figure 1B, 1C).

Effect of CMV diseases on dementia according to sex and age

The IRs of all dementia types in the case and control groups were not significantly different between men and women (OR in M2, 2.3 vs. 2.0, $P = 0.635$). The OR for IRs of all dementia types and AD in the two groups were significantly highest in subjects aged 40–59 years than in those aged 60–79 and ≥ 80 years (OR in M2, 12.6 vs. 2.1 vs. 1.4, $P = 0.021$ and OR in M2, 10.8 vs. 1.9 vs. 1.0, $P = 0.033$, respectively). Contrastingly, the IR of VD was not significantly different among subjects aged 40–59, 60–79 and ≥ 60 years ($P = 0.718$) (Table 3).

Discussion

This study showed that the new-onset incidence of all types of dementia and each type of AD or VD were significantly higher in subjects with CMV tissue-invasive end-organ disease. After adjusting for age, sex, low-income status, NIDDM, hypertension, and dyslipidaemia which can be the risk factors of dementia [5,

6], patients diagnosed with CMV disease had a higher risk for VD than for AD (OR, 3.3 vs. 1.7). Previous studies suggested that *Helicobacter pylori*, *Chlamydia pneumoniae*, and human T-lymphotropic virus-1 infection could be associated with VD [22-24]. The chronic infection of murine CMV (MCMV) in blood vessel could progress atherosclerotic plaque, and then VD could be induced by atherosclerosis pathogenesis in mouse model [25]. However, it is difficult to simulate the pathogenesis of HCMV disease in a MCMV infection mouse model because human CMV and MCMV are genetically different, and mice could not be infected with HCMV [26]. Even though the relevant infectious agents of VD have not been studied more than those of AD, the stronger association of CMV disease with VD than AD in this study will be interesting finding. This result suggests that CMV may play a possible role in complex VD pathogenesis because active recurrent intermittent CMV replication and/or latent CMV infection status is associated with chronic inflammatory atherosclerosis, vascular damage, and ultimately, cerebrovascular/cardiovascular diseases (CVDs) [27, 28].

Apolipoprotein E (APOE), produced in the kidney, liver, and brain, is involved in lipid transport and uptake [3, 29, 30]. The $\epsilon 4$ allele of APOE, a genetic risk factor for AD and CVD, induces oxidative damage in the central nervous system in herpes simplex virus infection. Neurotoxicity and neuroinflammation by APOE ultimately results in neurodegeneration and dementia [3, 30, 31]. When APOE $\epsilon 4$ is expressed, β -amyloid is aggregated in the brain, and amyloid plaques can cause cerebral amyloid angiopathy [32]. CMV and β -herpesviridae might also be associated with APOE. Further studies are required to evaluate the expression of the APOE genotype in dementia patients with CMV tissue-invasive disease. Generally, persistent systemic infection and inflammation can cause chronic neurodegeneration. Particularly, decreased CD8+ T lymphocyte counts and cognitive dysfunction due to CMV infection are characteristic features of AD [33-35].

Because AD is also associated with aging, age matching was essential for determining the association between the case and control groups. The IR of AD in the case group was higher in those aged 40–59 years than in those aged ≥ 60 years. Early-onset dementia in individuals aged < 65 years was associated with head trauma, alcohol abuse, and human immunodeficiency virus-1 infection [36]. The association between CMV serostatus or disease and new-onset dementia has not been studied yet. However, one study revealed that cognitive impairment was six-times higher in patients with three risk factors of low educational level, APOE $\epsilon 4$ allele, and *Herpesviridae* including CMV infection [37]. Moreover, the APOE $\epsilon 4$ allele was associated with new-onset AD or a decline in cognition in the earlier clinical stages [38-41].

Since VD and AD have different pathogeneses, their time of onset may differ. According to the Kaplan-Meier curves adjusted by age and sex, AD occurs in a relatively later clinical stage after the diagnosis of CMV disease than VD. The possible pathogenesis of AD arising from deposition of amyloid plaques as a result of chronic CMV infection could explain that AD occurs in the later clinical stage [32].

This study could have the potential bias associated with the registry-based data and the heterogeneous case population that may present with neurobehavioral disturbances mimicking dementia (e.g. long-term metabolic encephalopathy in the immunocompromised patients and non-immunocompromised critically

ill patients). The patients at risk of CMV reactivation may also have reactivation of other herpes virus. In addition, our report has some limitations. It was conducted using retrospective data from the NHID; thus, information on standard global measurements of cognitive function, such as the Mini-Mental Status Examination, Clinical Dementia Rating, or Activities of Daily Living, was unavailable. Inflammation markers (interferon-gamma, tumour necrosis factor-alpha, and interleukin-6) could not be analysed. Future prospective analyses can significantly support the investigation of pathogenic mechanisms of CMV infection or diseases affecting the development of each dementia type. The incidence or causes of dementia may differ by race, but we only identified the characteristics of dementia in the Republic of Korean subjects. Finally, the incidence of other types of dementia, frontotemporal dementia or Lewy body dementia, was significantly low to be included in the analysis.

However, this study had some strengths. First, only patients diagnosed with tissue-invasive end-organ diseases were included in the case group, regardless of CMV serostatus. This is a major distinctive characteristic of this study. The serum CMV IgG titre can vary at different time-points in each individual, and a positive/negative result only represents latent status caused by past CMV infection instead of representing active CMV replication. Second, we employed a nationwide population-based study using a huge database to analyse the effect of CMV on new-onset dementia after CMV diagnosis through the washout period. Third, previous studies did not include the time of dementia occurring during the follow-up. However, we analysed the onset time for dementia after CMV disease diagnosis for a relatively long duration of 7 years.

Conclusion

Patients with CMV disease had a higher risk of dementia than those without CMV tissue-invasive end-organ disease. Even though the causes of dementia are multifactorial and complex and may be genetic, educational, and environmental in nature, active replication of CMV could have the association with development of dementia, particularly VD in middle age group with 40-59-year-old.

Abbreviations

AD, Alzheimer's disease; CI, confidence interval; CMV, cytomegalovirus; CVD, cerebrovascular/cardiovascular diseases; HIRA, The Korean Health Insurance Review and Assessment; ICD, The International Statistical Classification of Diseases; IgG, immunoglobulin G; IR, incidence rate; NHID; National Health Insurance Database; NIDDM, type 2 non-insulin-dependent diabetes mellitus; OR odds ratio; RID, Rare incurable disorder; VD, vascular dementia.

Declarations

Ethics approval and consent to participate: This study was approved by the Institutional Review Board of the Gangnam Severance Hospital, Yonsei University College of Medicine, with the waiver of the informed consent as well as the relevant permission forms have been obtained from the NHI Sharing Service.

Consent for publication: Not applicable.

Availability of data and materials: The authors are not allowed to share the analysis datasets of the current study due to data regulations.

Competing interests: The authors declare that they have no competing interests.

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Author Contributions: K.H.L, D.E.K. K.D.H, Y.L. and S.H.H. were involved in the design and methodology of the study, the analysis and interpretation of data. K.D.H. was involved in original draft preparation. K.H.L. and S.H.H. were involved in the writing the manuscript. K.H.L, D.E.K. K.D.H, Y.L. and S.H.H. were involved in the review and editing of the final manuscript.

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Tables

Table 1. Comparison of clinical characteristics between the case group with CMV disease and matched control group without CMV disease.

Characteristics	CMV disease		P-value	Data are expressed as number (percentage) and median ± standard deviation. ^a Lower 25th percentile of
	No (n = 3,435)	Yes (n = 687)		
Sex, male	1,950 (56.77)	390 (56.77)	> 0.999	
Age, years	57.98 ± 11.41	57.98 ± 11.42	> 0.999	
≥ 60 years	1,405 (40.9)	281 (40.9)	> 0.999	
Duration of total follow-up, years	4.10 ± 1.58	3.73 ± 1.80	< 0.001	
Low income status ^a	824 (23.99)	181 (26.35)	0.189	
NIDDM	386 (11.24)	205 (29.84)	< 0.001	
Hypertension	974 (28.36)	328 (47.74)	< 0.001	
Dyslipidaemia	607 (17.67)	201 (29.26)	< 0.001	
Dementia				
All	105 (3.06)	38 (5.53)	0.001	
Alzheimer's	77 (2.24)	23 (3.35)	0.085	
Vascular	12 (0.35)	7 (1.02)	0.018	
Other	16 (0.47)	8 (1.16)	0.028	

socioeconomic status. Abbreviations: CMV, cytomegalovirus; NIDDM, non-insulin-dependent diabetes mellitus

Table 2. Multivariate logistic regression analyses to examine the effect of cytomegalovirus disease on the development of dementia.

Type	CMV diseases	No.	Event	Total follow-up duration (person-years)	IR ^a	OR (95% CI)		
						Model 1	Model 2	Model 3
All	No	3,435	105	14,083	7.46	1 (Ref.)	1 (Ref.)	1 (Ref.)
	Yes	687	38	2,564	14.82	1.99 (1.37–2.88)	2.10 (1.45–3.05)	2.03 (1.39–2.97)
AD	No	3,435	77	14,083	5.47	1 (Ref.)	1 (Ref.)	1 (Ref.)
	Yes	687	23	2,564	8.97	1.65 (1.04–2.63)	1.74 (1.09–2.78)	1.73 (1.08–2.78)
VD	No	3,435	12	14,083	0.85	1 (Ref.)	1 (Ref.)	1 (Ref.)
	Yes	687	7	2,564	2.73	3.14 (1.24–7.98)	3.31 (1.30–8.41)	2.90 (1.11–7.56)
Others	No	3,435	16	14,083	1.14	1 (Ref.)	1 (Ref.)	1 (Ref.)
	Yes	687	8	2,564	3.12	2.71 (1.16–6.34)	2.85 (1.22–6.67)	2.76 (1.16–6.57)

Data are expressed as number or OR (95% CI). Model 1, non-adjusted; Model 2, age- and sex-adjusted; Model 3, age-, sex-, low income status-, NIDDM-, hypertension-, and dyslipidaemia-adjusted. ^aper 1,000 individuals. Abbreviations: AD, Alzheimer's dementia; CI, confidence interval; CMV, cytomegalovirus; IR, incidence rate; NIDDM, non-insulin-dependent diabetes mellitus; No., number of patients; OR, odds ratio; Ref., reference; VD, vascular dementia

Table 3. Multivariate logistic regression models to examine the effect of cytomegalovirus disease on the development of dementia according to sex and age distribution.

Type	Subgroups		CMV	No.	Events	IR ^a	OR (95% CI)			P-value
							Model 1	Model 2	Model 3	
All	Sex	M	No	1,950	42	5.20	1 (Ref.)	1 (Ref.)	1 (Ref.)	0.635
			Yes	390	17	11.45	2.19 (1.25-3.85)	2.31 (1.32-4.06)	2.12 (1.20-3.76)	
		F	No	1,485	63	10.50	1 (Ref.)	1 (Ref.)	1 (Ref.)	
			Yes	297	21	19.46	1.86 (1.13-3.04)	1.97 (1.20-3.23)	1.98 (1.19-3.28)	
	Age	40-59	No	2,030	3	0.35	1 (Ref.)	1 (Ref.)	1 (Ref.)	0.021
			Yes	406	7	4.28	12.31 (3.18-47.60)	12.63 (3.26-48.84)	12.17 (2.95-50.11)	
		60-79	No	1,260	62	12.47	1 (Ref.)	1 (Ref.)	1 (Ref.)	
			Yes	252	21	24.48	1.97 (1.20-3.24)	2.09 (1.27-3.44)	1.99 (1.21-3.30)	
		≥ 80	No	145	40	86.74	1 (Ref.)	1 (Ref.)	1 (Ref.)	
			Yes	29	10	145.71	1.62 (0.81-3.24)	1.44 (0.71-2.91)	1.39 (0.65-2.95)	
		AD	No	1,950	29	3.59	1 (Ref.)	1 (Ref.)	1 (Ref.)	
			Yes	390	13	8.76	2.44 (1.27-4.69)	2.54 (1.32-4.89)	2.41 (1.24-4.69)	
AD	Sex	M	No	1,950	29	3.59	1 (Ref.)	1 (Ref.)	1 (Ref.)	0.133
			Yes	390	13	8.76	2.44 (1.27-4.69)	2.54 (1.32-4.89)	2.41 (1.24-4.69)	
		F	No	1,485	48	8.00	1 (Ref.)	1 (Ref.)	1 (Ref.)	
			Yes	297	10	9.27	1.17 (0.59-2.31)	1.25 (0.63-2.48)	1.31 (0.65-2.62)	
	Age	40-59	No	2,030	2	0.23	1 (Ref.)	1 (Ref.)	1 (Ref.)	0.033
			Yes	406	4	2.44	10.57 (1.94-57.69)	10.78 (1.98-58.90)	15.60 (2.66-91.55)	
		60-79	No	1,260	46	9.25	1 (Ref.)	1 (Ref.)	1 (Ref.)	
			Yes	252	14	16.32	1.80 (0.99-3.27)	1.93 (1.06-3.51)	1.86 (1.02-3.42)	
		≥ 80	No	145	29	62.89	1 (Ref.)	1 (Ref.)	1 (Ref.)	
			Yes	29	5	72.85	1.14 (0.44-2.96)	1.04 (0.40-2.75)	1.02 (0.36-2.83)	
		VD	No	1,950	7	0.87	1 (Ref.)	1 (Ref.)	1 (Ref.)	
			Yes	390	2	1.35	1.52 (0.32-7.32)	1.65 (0.34-7.93)	1.33 (0.27-6.66)	
VD	Sex	M	No	1,950	7	0.87	1 (Ref.)	1 (Ref.)	1 (Ref.)	0.200
			Yes	390	2	1.35	1.52 (0.32-7.32)	1.65 (0.34-7.93)	1.33 (0.27-6.66)	
		F	No	1,485	5	0.83	1 (Ref.)	1 (Ref.)	1 (Ref.)	
			Yes	297	5	4.63	5.47 (1.58-18.88)	5.66 (1.64-19.55)	4.51 (1.22-16.64)	
	Age	40-59	No	2,030	1	0.12	1 (Ref.)	1 (Ref.)	1 (Ref.)	0.718
			Yes	406	1	0.61	5.21 (0.33-83.36)	5.34 (0.33-85.36)	1.20 (0.06-23.37)	
		60-79	No	1,260	7	1.41	1 (Ref.)	1 (Ref.)	1 (Ref.)	
			Yes	252	3	3.50	2.40 (0.62-9.26)	2.47 (0.64-9.54)	1.95 (0.49-7.82)	
		≥ 80	No	145	4	8.67	1 (Ref.)	1 (Ref.)	1 (Ref.)	
			Yes	29	3	43.71	4.66 (1.04-20.90)	4.49 (0.99-20.29)	5.64 (0.93-34.44)	
		Others	No	1,950	6	0.74	1 (Ref.)	1 (Ref.)	1 (Ref.)	
			Yes	390	2	1.35	1.80 (0.36-8.92)	1.95 (0.39-9.66)	1.75 (0.35-8.88)	
Others	Sex	M	No	1,950	6	0.74	1 (Ref.)	1 (Ref.)	1 (Ref.)	0.583
			Yes	390	2	1.35	1.80 (0.36-8.92)	1.95 (0.39-9.66)	1.75 (0.35-8.88)	
		F	No	1,485	10	1.67	1 (Ref.)	1 (Ref.)	1 (Ref.)	
			Yes	297	6	5.56	3.28 (1.19-	3.37 (1.22-	3.41 (1.20-	

						9.03)	9.28)	9.69)	
Age	40-59	No	2,030	0	0.0	—	—	—	—
		Yes	406	2	1.22	—	—	—	
	60-79	No	1,260	9	1.81	1 (Ref.)	1 (Ref.)	1 (Ref.)	
		Yes	252	4	4.66	2.52 (0.77-8.17)	2.62 (0.80-8.53)	2.58 (0.78-8.51)	
	≥ 80	No	145	7	15.18	1 (Ref.)	1 (Ref.)	1 (Ref.)	
		Yes	29	2	29.14	1.74 (0.36-8.41)	1.29 (0.26-6.28)	1.34 (0.25-7.11)	

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Figures

(A) All types of dementia

(B) Alzheimer's dementia

(C) Vascular dementia

Figure 1

Kaplan-Meier curves for incidence probability of dementia in patients with cytomegalovirus (CMV) disease and controls without CMV disease adjusted by age and sex.