Journal of Microbiology, Immunology and Infection 55 (2022) 812—819

Available online at www.sciencedirect.com

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journal homepage: www.e-jmii.com

Original Article

Epidemiological changes in cytomegalovirus end-organ diseases in a developed country: A nationwide, general-population-based study

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Received 28 March 2021; received in revised form 29 June 2021; accepted 5 August 2021
Available online 26 August 2021

KEYWORDS
Cytomegalovirus;
End-organ disease;
Incidence;
Mortality

Abstract *Background:* Cytomegalovirus (CMV) can cause tissue-invasive diseases in various organs after primary infection or through reactivation of latent-to-lytic switch over a lifetime. The number of individuals who are at risk of CMV diseases, such as elderly or immunocompromised patients, is constantly increasing; however, recent epidemiological changes associated with CMV disease have not been fully evaluated.
Methods: We used claims data of about 50 million individuals between 2010 and 2015 from the Korean Health Insurance Review and Assessment Service nationwide database. The code for CMV end-organ diseases in the 'Relieved Co-payment Policy' program matches the ICD-10 code of B25, except for congenital CMV infection and mononucleosis. A 628 cases of CMV and 3140 controls (without CMV disease), matched for age and sex, were selected from this dataset in order to evaluate the effect of adult CMV diseases on all-cause death.
Results: The overall unadjusted incidence rate (IR) of CMV end-organ diseases was 0.52/100,000 individuals. The standardized IR, adjusted for age and sex, have continuously increased from 0.32/100,000 in 2010 to 0.75/100,000 in 2015. The overall unadjusted IR in adult population was highest in 70—79 years for six years (0.96/100,000). In the model adjusted for age, sex, immunocompromised status including solid-organ or hematopoietic stem cell transplant recipients, hematologic malignancies, and human immunodeficiency virus diseases,

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https://doi.org/10.1016/j.jmii.2021.08.004

the hazard ratio of case group was 5.2 (95% confidence interval, 3.6—7.4) for all-cause mortality.
Conclusion: Nationwide data indicates that CMV end-organ disease has steadily increased in the past six years and is associated with higher mortality.

Introduction

Cytomegalovirus (CMV) is acquired without symptoms at an early age in most healthy individuals and is maintained as a latent infection with continuous latency-associated proteins synthesis and intermittent viral replication throughout an individual's lifespan via various mechanisms including immune evasion and suppression of genes encoding immediate early protein.[1—4] This phenomenon can cause a wide range of CMV indirect effects, including chronic inflammation as well as chronic vascular diseases or immunosenescence or immune exhaustion, even in immunocompetent populations.[5—8] The lytic reactivation of CMV can result in life-threatening tissue-invasive end-organ diseases affecting several organs including the lungs, retina, and gastrointestinal tract, particularly in severely immunocompromised patients, including those who have undergone solid organ transplantation (SOT) and hematopoietic stem cell transplantation (HSCT), or those with acquired immunodeficiency syndrome.[9]

Recently, active CMV production in critically ill non-immunocompromised patients, especially those receiving intensive care unit (ICU) care, has received increased attention and a randomized control study was performed to evaluate the efficiency of CMV prophylaxis for clinical outcome in this population.[10,11] Another critical issue of CMV is intrauterine fetal or congenital CMV infection through vertical transmission from the primary or non-primary (reinfection and reactivation) CMV-infected mother as it can result in irreversible sequelae including neurological abnormalities such as microcephaly or hearing loss and premature birth or intrauterine growth retardation.[12] These detrimental effects of CMV infection or reactivation have prompted the development of well-tailored post-transplantation preventive strategies in SOT and HSCT recipients as well as regular maternal screening for CMV serologic status.[13—15] Till date, a number of studies on CMV vaccine development have been performed in clinical settings, without any promising results.[16]

Unlike well-assessed epidemiologic features including the transmission rate to the fetus in congenital CMV infection, the global incidence trend for CMV end-organ diseases in the general population encompassing severely immunocompromised and immunocompetent individuals has not been fully evaluated.[12,17] Several studies analyzing anti-CMV-immunoglobulin G tests have shown that CMV seroprevalence rates varied from 20 to 100% according to region, race, socioeconomic status, sex, and age.[9,18] However, nearly all of these reports were published prior to 1990 and did not examine the incidence of CMV end-organ tissue-invasive diseases.[18] Knowledge of the large-scale epidemiology of CMV diseases rather than seropositivity in the general population has clinical importance to identify disease burden and the associated long-term inflammatory diseases associated with CMV.[7,8] In addition, the most recent trends will provide significant clinical or public information because the public health service and sanitation have improved while the number of patients at high risk for CMV replication has increased continuously in recent decades. In this context, we performed an epidemiological analysis of CMV end-organ disease based on a nationwide general-population large database in South Korea, a nation in which CMV seropositivity rate is relatively high.[19,20]

Materials and methods

Data source and processing

The South Korean National Health Insurance Service (NHIS) is operated by the government as a single insurer to ensure universal public health care at the national level and extended its coverage to the entire nation with mandatory registration in 1989.[21] All types of hospitals, clinics, pharmacies, and community health centers electronically submit health insurance claims to the Korean Health Insurance Review and Assessment Service (HIRA), which is a non-profit organization that reviews incurred expense and determines reimbursement for healthcare services.[22—24] For claims processing, the HIRA has systematically developed and managed a comprehensive database of healthcare utilization information such as inpatient and outpatient care, medical/surgical procedures, pharmaceutical services including prescriptions, and the demographic or socioeconomical characteristics of the beneficiaries.[22—24] The detailed process of the generation and structure of the HIRA database was reviewed previously.[22,24] The HIRA claims database contains information from the entire Korean population because the ratio of beneficiaries to the total population in South Korea in the HIRA registry consistently exceeds one.[22] We used the HIRA claims database from individuals of all ages to perform nationwide general-population-based analyses. The study was approved by the Institutional Review Board of Gangnam Severance Hospital, Yonsei University College of Medicine (IRB No. 3-2017-0341), and allowed by the National Health Insurance Sharing Service.

Reliability and accuracy of subjects' identification

The Korean NHIS implemented a policy to extend the health insurance benefit coverage to lower the out-of-pocket

expenses of patients with rare intractable diseases (RID) in 2006. This 'Relieved Co-payment Policy' uses the specific diagnostic codes for RID to register and manage the program.[21] To provide benefits and ensure the rigorous application of 'Relieved Co-payment Policy', healthcare providers are requested to submit the exact diagnosis with specific codes based on the strict criteria distributed by the NHIS to the HIRA.[21,25] This procedure guarantees the reliability and accuracy of the information about each RID in the HIRA claims registry.[21,25,26]

To register the CMV end-organ diseases as RID, the physicians should report the V104 code with the specific form, which is comprised of histopathologic findings as well as the results of CMV polymerase chain reaction (PCR) and/or pp65 antigen test and/or virus culture with appropriate clinical symptoms and/or signs except asymptomatic CMV DNAemia and/or pp65 antigenemia. The approved commercial qualitative and/or quantitative real-time PCR targeting CMV UL83 has been performed without national change for availability or policy of CMV PCR test during study period. The commercial PCR tests are fully available to all hospitals. The highly stringent unique V104 code for CMV tissue-invasive end-organ diseases in the 'Relieved Co-payment Policy' program matches code B25 in the online 2016 International Statistical Classification of Diseases and Related-Health Problems 10th Revision (ICD-10) from the World Health Organization (WHO).[27] The B25 code includes all types of CMV end-organ diseases except for congenital CMV infection (P35.1) and cytomegaloviral mononucleosis (B27.1).[27] We confirmed that there were no CMV end-organ diseases cases the same patient had additional coding for the respective event.

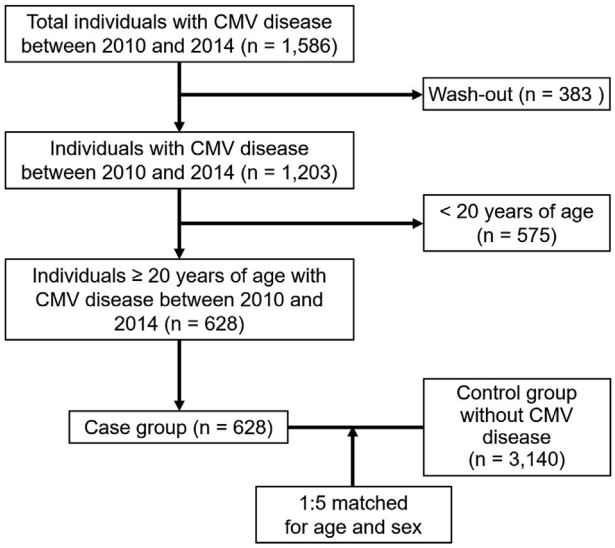

Figure 1. Flow chart of the selection of the case and control groups.

Study design and information acquisition

This study included two datasets; (1) a nationwide cohort study from HIRA claims data in accordance with the V104 code between 2010 and 2015 in the entire Korean population to analyze the incidence rates (IRs) of CMV disease and (2) a retrospective matched case—control study extracted from HIRA claims data to verify the effect of adult CMV disease on all-cause death. To clarify the cause-and-effect

Table 1 Incidence rates of cytomegalovirus diseases between 2010 and 2015.

		Year					
		2010	2011	2012	2013	2014	2015
Total	Total population	50,165,317	50,443,562	50,761,374	51,011,717	51,279,732	51,571,506
	Cases	159	206	205	259	359	398
	Unadjusted IR[a]	0.32 (0.27—0.37)	0.41 (0.35—0.46)	0.40 (0.35—0.46)	0.51 (0.45—0.57)	0.70 (0.63—0.77)	0.77 (0.70—0.85)
	Standardized IR[a,b]	0.32 (0.27—0.37)	0.41 (0.35—0.47)	0.40 (0.35—0.46)	0.50 (0.44—0.56)	0.68 (0.61—0.76)	0.75 (0.68—0.82)
Male	Total population	25,150,418	25,282,308	25,434,189	25,538,756	25,665,697	25,812,116
	Cases	81	113	109	146	191	228
	Unadjusted IR[a]	0.32 (0.25—0.39)	0.45 (0.36—0.53)	0.43 (0.35—0.51)	0.57 (0.48—0.66)	0.74 (0.64—0.85)	0.88 (0.77—1.00)
	Standardized IR[a,b]	0.33 (0.26—0.40)	0.45 (0.37—0.53)	0.42 (0.34—0.50)	0.56 (0.47—0.65)	0.73 (0.62—0.83)	0.86 (0.74—0.97)
Female	Total population	25,014,899	25,161,254	25,327,185	25,472,961	25,614,035	25,759,390
	Cases	78	93	96	113	168	170
	Unadjusted IR[a]	0.31 (0.24—0.38)	0.37 (0.29—0.44)	0.38 (0.30—0.45)	0.44 (0.36—0.53)	0.66 (0.56—0.76)	0.66 (0.56—0.76)
	Standardized IR[a,b]	0.32 (0.25—0.39)	0.37 (0.30—0.45)	0.38 (0.30—0.45)	0.44 (0.36—0.52)	0.64 (0.54—0.74)	0.65 (0.55—0.74)

[a] Per 100,000 individuals.
[b] Standardized rate adjusted for age and sex based on the results of the 2010 South Korea Population and Housing Census per 100,000 individuals.
Data are expressed as numbers or rates (95% CI). Abbreviation: IR, incidence rate.

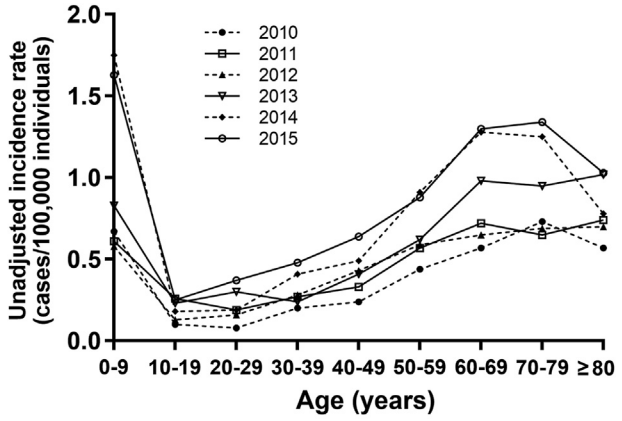

Figure 2. Incidence rates of cytomegalovirus disease according to age groups between 2010 and 2015.

relationships with CMV disease in the case group, we applied conservative and strict selection criteria with a sufficiently long wash-out period of 6 months. The control group without CMV disease (n = 3140) was selected by matching for age and sex with the case group (n = 628) in a 5:1 ratio. Fig. 1 shows the detailed process for the selection of the case and control groups. To evaluate the recurrence rate of CMV disease in the total population, we utilized the re-implementation status of anti-CMV therapy with ganciclovir and/or valganciclovir. Recurrence was defined as a case of repeated anti-CMV therapy between one month and one year after the first CMV disease event.[28] The annual household income was categorized as either lowest quintile or the remaining quintiles.[29,30] We clearly confined the immunocompromised status to SOT (Z94.0, Z94.1, Z94.2, Z94.3 and Z94.4)/HSCT (Z94.81 and Z94.84) recipients, hematologic malignancies (C81–C96), and Human immunodeficiency virus (HIV) disease (B20–B24) to stringently find those conditions by ICD-10 code.[27]

Statistical analyses

Data were expressed as numbers (percent) or means ± standard deviation (SD) or as rates (95% confidence interval [CI]). The IRs per 100,000 individuals were expressed as unadjusted or standardized rates adjusted for

Table 2 Incidence rates of cytomegalovirus disease according age groups between 2010 and 2015 in all population.

Age group (years)	2010			2011			2012			2013		
	Total Pop.	Cases	Unadjusted IR[a]	Total Pop.	Cases	Unadjusted IR[a]	Total Pop.	Cases	Unadjusted IR[a]	Total Pop.	Cases	Unadjusted IR[a]
0–9	4,924,127	33	0.67 (0.44–0.90)	4,755,614	29	0.61 (0.39–0.83)	4,677,614	27	0.58 (0.36–0.79)	4,671,563	39	0.83 (0.57–1.10)
10–19	6,814,533	7	0.10 (0.03–0.18)	6,811,530	18	0.26 (0.14–0.39)	6,667,836	9	0.13 (0.05–0.22)	6,435,911	15	0.23 (0.12–0.35)
20–29	7,176,284	6	0.08 (0.02–0.15)	6,989,849	13	0.19 (0.08–0.29)	6,869,401	11	0.16 (0.07–0.25)	6,779,226	20	0.30 (0.17–0.42)
30–39	8,497,742	17	0.20 (0.10–0.30)	8,423,176	23	0.27 (0.16–0.38)	8,331,091	23	0.28 (0.16–0.39)	8,246,955	20	0.24 (0.14–0.35)
40–49	8,785,772	21	0.24 (0.14–0.34)	8,773,798	29	0.33 (0.21–0.45)	8,806,783	38	0.43 (0.29–0.57)	8,805,022	36	0.41 (0.28–0.54)
50–59	6,547,095	29	0.44 (0.28–0.60)	6,995,445	40	0.57 (0.39–0.75)	7,471,688	44	0.59 (0.41–0.76)	7,746,646	48	0.62 (0.44–0.79)
60–69	4,059,789	23	0.57 (0.34–0.80)	4,153,412	30	0.72 (0.46–0.98)	4,183,478	27	0.65 (0.40–0.89)	4,299,039	42	0.98 (0.68–1.27)
70–79	2,481,017	18	0.73 (0.39–1.06)	2,599,811	17	0.65 (0.34–0.96)	2,751,906	19	0.69 (0.38–1.00)	2,949,845	28	0.95 (0.60–1.30)
≥80	878,958	5	0.57 (0.07–1.07)	940,927	7	0.74 (0.19–1.30)	1,001,577	7	0.70 (0.18–1.22)	107,7510	11	1.02 (0.42–1.62)

Age group (years)	2014			2015			Overall unadjusted IR[a] between 2010 and 2015
	Total Pop.	Cases	Unadjusted IR[a]	Total Pop.	Cases	Unadjusted IR[a]	
0–9	4,630,322	81	1.75 (1.37–2.13)	4,605,020	75	1.63 (1.26–2.00)	1.00
10–19	6,219,961	11	0.18 (0.07–0.28)	5,980,148	15	0.25 (0.12–0.38)	0.19
20–29	6,753,600	13	0.19 (0.09–0.30)	6,821,767	25	0.37 (0.22–0.51)	0.21
30–39	8,118,984	33	0.41 (0.27–0.55)	7,945,736	38	0.48 (0.33–0.63)	0.31
40–49	8,903,636	44	0.49 (0.35–0.64)	8,934,200	57	0.64 (0.47–0.80)	0.42
50–59	7,994,509	73	0.91 (0.70–1.12)	8,209,851	72	0.88 (0.67–1.08)	0.68
60–69	4,448,266	57	1.28 (0.95–1.61)	4,691,332	61	1.30 (0.97–1.63)	0.93
70–79	3,051,814	38	1.25 (0.85–1.64)	3,124,524	42	1.34 (0.94–1.75)	0.96
≥80	1,158,640	9	0.78 (0.27–1.28)	1,258,928	13	1.03 (0.47–1.59)	0.82

[a] Per 100,000 individuals. Data were expressed as number or rate (95% CI). Aberration. IR, incidence rate; Pop., population.

age and sex based on the results of the 2010 South Korea Population and Housing Census.[31] The IRs were analyzed by age groups, sex, and year. The age groups were categorized as ten-year intervals ranging from the 0's to the 80's. The 80's group comprised individuals ≥80 years of age. The differences between the matched case and control groups were analyzed by Mantel-Haenszel Chi-square test and paired t-tests. We performed Cox proportional hazard regression analysis adjusted for age, sex, and immunocompromised status to obtain the hazard ratio (HR) of adult CMV end-organ disease for all-cause death. Statistical analyses were performed using SAS version 9.4 (SAS Institute, Cary, NC) and GraphPad Prism V6 (GraphPad Software, La Jolla, CA). Two-tailed $P < 0.05$ were considered statistically significant.

Results

Incidence and recurrence rates of CMV disease in six years

The overall unadjusted IR of CMV end-organ diseases was 0.52/100,000 individuals. Male population had the higher overall unadjusted IR compared to that in female (0.57 vs. 0.47/100,000). The total number of individuals with CMV disease increased 2.5-fold from 2010 to 2015. The annual standardized IRs in the total population increased every year from 2010 (0.32/100,000) to 2015 (0.75/100,000) as well as in both men (from 0.33 to 0.86) and women (from 0.32 to 0.65). The increase range of standardized IR over six years was larger in men (0.53/100,000) than that in women (0.33/100,000). The IR in men was higher than that in women every year for six years (Table 1). The medical aid beneficiaries from the Korean NHIS had higher standardized IR (3.9 [2.3–5.4]/100,000) in 2015 compared to those in all individuals with any other income status. The total recurrence rate over six years was 17.5%, with the highest rate of 23.4% in 2015. According to each ICD-10 code, the majority cases (1379 of 1586, 86.9%) had B25.8 (other cytomegaloviral disease) or B25.9 (cytomegaloviral disease, unspecified) (Supplementary Table 1).

Table 3 Comparisons of clinical characteristics between adult individuals with CMV disease (case group) and without CMV disease (control group).

Characteristics	Case group (n = 628)	Control group (n = 3140)	*P*-value
Sex, male	357 (56.9)	1785 (56.9)	1[a]
Age, years	49.4 ± 14.7	49.4 ± 14.7	1[b]
Age group			1[a]
20–39 years	166 (26.4)	830 (26.4)	
40–64 years	373 (59.4)	1865 (59.4)	
≥65 years	89 (14.2)	445 (14.2)	
Lower quintile of yearly income	177 (28.2)	712 (22.7)	.003[a]
Immunocompromised status	366 (58.3)	28 (0.9)	<.001[a]
Solid organ transplant recipients	92 (14.6)	10 (0.3)	<.001[a]
Kidney	71 (11.3)	9 (0.3)	<.001[a]
Liver	15 (2.4)	1 (0.0)	<.001[a]
Heart and/or lung	6 (1.0)	0 (0.0)	<.001[a]
Hematopoietic stem cell transplant recipients	148 (23.6)	7 (0.2)	<.001[a]
Hematologic malignancies	107 (17.0)	11 (0.4)	<.001[a]
HIV disease	19 (3.0)	0 (0.0)	<.001[a]
All-cause death	59 (9.4)	63 (2.0)	<.001[a]
Time interval between matching and all-cause death (years)	3.1 ± 1.6	3.3 ± 1.5	.005[b]

[a] Mantel-Haenszel Chi-square test.
[b] Paired t-test.
Data are expressed as numbers (percent) or means ± SD.
Abbreviation: HIV, human immunodeficiency virus.

Change in CMV disease according to age groups

According to age group, the overall unadjusted IR of CMV end-organ diseases was highest in those ≤9 years of age and lowest in those 10-19-years of age (1.00 and 0.19/100,000 individuals, respectively). Among adult population aged ≥20 years, the 60–69 and 70-79-year age groups had the high IRs with a pattern of steady increase over six years (0.93 and 0.96 overall unadjusted IR, respectively) (Table 2 and Fig. 2). The IR according to age group showed the similar patterns regardless of sex (Supplementary Tables 2 and 3).

Effect of adult CMV disease on all-cause death

The mean age and male percentage were 49 years and 57% in the case and control group. Patients with CMV disease had significantly higher all-cause mortality compared to that in the control group (9.4% vs. 2.0%, $P < .001$). The

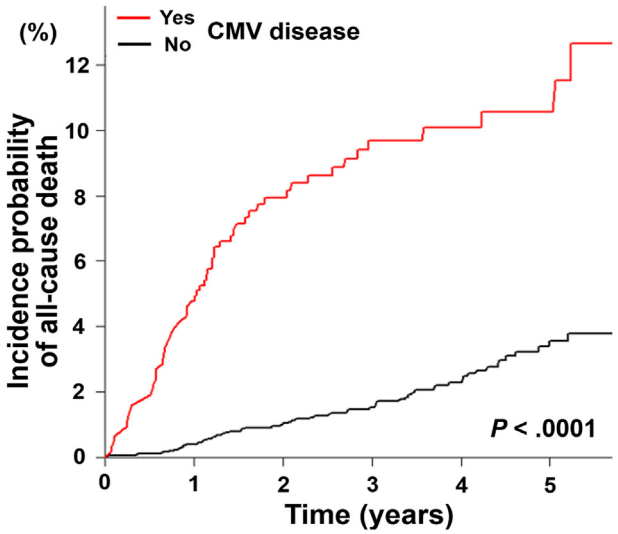

Figure 3. Kaplan–Meier curve of the difference in mortality rates between individuals with and without cytomegalovirus diseases.

Table 4 Cox proportional hazard regression model to examine the effect of adult CMV disease on all-cause death.

Subgroups	CMV end-organ disease	Total individuals	All-cause deaths	Follow-up duration (years)	Mortality rate per 1000 PY	Hazard ratio (95% CI)	*P*-value for Interaction
Total	No	3140	63	10,330	6.10	1 (Ref)	
	Yes	628	59	1948	30.29	5.18 (3.63—7.40)[a]	
Sex							0.016
Male	No	1785	47	5873	8.00	1 (Ref)	
	Yes	357	33	1130	29.22	3.67 (2.34—5.71)	
Female	No	1355	16	4457	3.59	1 (Ref)	
	Yes	271	26	819	31.76	9.98 (5.39—19.05)	
Age (years)							0.463
20-39	No	830	0	2870	0.00	1 (Ref)	
	Yes	166	8	560	14.29	—	
40-64	No	1865	26	6147	4.23	1 (Ref)	
	Yes	373	30	1171	25.63	6.06 (3.59—10.32)	
≥ 65	No	445	37	1314	28.16	1 (Ref)	
	Yes	89	21	218	96.55	3.36 (1.93—5.70)	
Immunocompromised status[b]	No	28	1	97	10.30	1 (Ref)	
	Yes	366	121	1126	107.46	11.03 (6.87—21.94)	

[a] Age-, sex-, immunocompromised status-adjusted model.
[b] Include solid-organ or hematopoietic stem cell transplant recipients, hematologic malignancies, and HIV disease.
Abbreviations: CI, confidence interval; PY, person-years; Ref, reference.

frequency of patients with immunocompromised status in the case group was the significantly higher than that in the control group (58.3% vs. 0.9%, $P < .001$) (Table 3). The Cox proportional hazard regression model adjusted for age, sex, and immunocompromised status revealed that patients with CMV end-organ disease had an approximately five-fold increased HR for all-cause death (HR [95% CI]; 5.18 [3.63—7.40]). Women with CMV diseases had a 2.7-fold higher HR compared to that in men with CMV diseases (9.98 [5.39—19.05] in women and 3.67 [2.34—5.71] in men, $P = .016$). The age distribution did not result in a significant change in HR ($P = .463$) (Table 4). The Kaplan—Meier curve for all subjects in this case—control study also showed a significantly higher probability of all-cause death in adult patients with CMV disease ($P < .001$) (Fig. 3).

Discussion

The results of this nationwide cohort study including the entire general population indicated that CMV tissue-invasive end-organ diseases have consistently increased in the last six years. This trend was not affected by age group or sex, and the IRs were lowest among those 10—29 years of age and highest among 70—79 years of age in adult population. The consistently homogeneous change in the IRs after adjusting for age and sex offer confidence in the findings of this large cohort-based study using RID code. Our data processing was able to cover CMV end-organ diseases to the exclusion of asymptomatic CMV DNAemia, CMV syndrome, and congenital CMV infection. Two papers using ICD codes from the Taiwan NHIS database among people living with HIV and liver transplant recipients reported cases of CMV end-organ diseases.[32,33] However, despite some nationwide reports on congenital CMV infection,[34,35] there has been no report on the general-population-based incidence of CMV tissue-invasive diseases.

Our data revealed that the incidence of CMV diseases were highest in the youngest population, which may indicate a high incidence of primary infection. Further analysis of this age subgroup confirmed that rate of CMV diseases at a much younger age had the higher with inverse proportion relationship between age and the rate of CMV diseases. The diagnosis of CMV disease in individuals less than 10 years of age would be performed using CMV-specific DNA amplification tests of blood or urine or other samples in patients with infection symptoms and signs as well as histopathologic findings in immunocompromised patients.[9,12] Further study of early postnatal primary CMV disease is warranted.

The severely immunocompromised conditions including transplant recipients, hematologic malignancies, and acquired immunodeficiency syndrome (AIDS) are main risk factors associated with CMV end-organ diseases development. In addition, those critically-ill underlying diseases are major attributing causes for mortality in patients with CMV disease.[36,37] This study showed that CMV end-organ disease had relation to all-cause mortality, as revealed in

the Cox proportional hazard regression model adjusted by immunocompromised status. The HR of mortality was higher in women than in men irrespective of the lower incidence.

This cohort could not explain the main reason for the increment or major risk population of CMV disease. Further analysis did not identify an epidemiologic association between the increase in CMV disease and HIV infection. Despite the increasing proportion of the advanced age population ≥60 years in the aging Korean society,[31] the standardized rate adjusted for age and sex revealed the increasing incidence of CMV end-organ disease. The wide range of immunosuppressive conditions besides transplant recipients and hematologic malignancies, particularly critically-ill patients in ICU care and a recent surge in various new targeted and biological drugs for solid cancers and rheumatic diseases could be attributed the expansion of CMV tissue-invasive diseases.[38,39] The further study is warrant to evaluate whether the groups receiving the specific biologics have the higher risk of CMV diseases. In spite of the Cox proportional hazard analysis, the various comorbidities or disease severity or other opportunistic infections besides age, sex, severe immunocompromised status as well as our study design could not affirm that CMV end-organ disease may be independent risk factor of higher mortality.

Another limitation was that this study was based on diagnostic codes; we did not obtain detailed clinical information on the CMV illnesses such as affected organs and treatment outcomes. In addition, the IR might have been underestimated due to missing RID code data. However, the rigid operating system and direct reduction of medical expenses with the large scale could sufficiently reduce the likelihood of the underestimation. The increasing attention of CMV diseases may also be attributed to the change of IR. Despite these limitations, this first nationwide, population-based report may have a clinical significance by describing the recent epidemiologic characteristics of CMV disease by age group and sex with adjustment for co-variables on a large scale.

Conclusion

This study revealed the consistent increase in IRs of CMV disease in all age groups and both sexes and that CMV disease is associated with all-cause death. Our result supports that the clinical and public significance of tight application for preventive strategies about CMV end-organ diseases in individuals with risks for CMV replication in the country with a high CMV-seropositivity rate.

Funding

None.

Declaration of competing interest

None of the authors have conflicts of interest associated with this manuscript to declare.

References

1. Zhu D, Pan C, Sheng J, Liang H, Bian Z, Liu Y, et al. Human cytomegalovirus reprogrammes haematopoietic progenitor cells into immunosuppressive monocytes to achieve latency. *Nat Microbiol* 2018;**3**:503—13.
2. Moller R, Schwarz TM, Noriega VM, Panis M, Sachs D, Tortorella D, et al. miRNA-mediated targeting of human cytomegalovirus reveals biological host and viral targets of IE2. *Proc Natl Acad Sci USA* 2018;**115**:1069—74.
3. Poole E, Sinclair J. Sleepless latency of human cytomegalovirus. *Med Microbiol Immunol* 2015;**204**:421—9.
4. Noriega V, Redmann V, Gardner T, Tortorella D. Diverse immune evasion strategies by human cytomegalovirus. *Immunol Res* 2012;**54**:140—51.
5. Varani S, Frascaroli G, Landini MP, Soderberg-Naucler C. Human cytomegalovirus targets different subsets of antigen-presenting cells with pathological consequences for host immunity: implications for immunosuppression, chronic inflammation and autoimmunity. *Rev Med Virol* 2009;**19**:131—45.
6. Nikitskaya E, Lebedeva A, Ivanova O, Maryukhnich E, Shpektor A, Grivel JC, et al. Cytomegalovirus-productive infection is associated with acute coronary syndrome. *J Am Heart Assoc* 2016;**5**.
7. Lee KH, Kwon DE, Do Han K, La Y, Han SH. Association between cytomegalovirus end-organ diseases and moderate-to-severe dementia: a population-based cohort study. *BMC Neurol* 2020;**20**:216.
8. Yoo SG, Han KD, Lee KH, La Y, Kwon DE, Han SH. Impact of cytomegalovirus disease on new-onset type 2 diabetes mellitus: population-based matched case-control cohort study. *Diabetes Metab J* 2019;**43**:815—29.
9. Dioverti MV, Razonable RR. Cytomegalovirus. *Microbiol Spectr* 2016;**4**.
10. Kalil AC, Florescu DF. Prevalence and mortality associated with cytomegalovirus infection in nonimmunosuppressed patients in the intensive care unit. *Crit Care Med* 2009;**37**:2350—8.
11. Limaye AP, Stapleton RD, Peng L, Gunn SR, Kimball LE, Hyzy R, et al. Effect of ganciclovir on IL-6 levels among cytomegalovirus-seropositive adults with critical illness: a randomized clinical trial. *J Am Med Assoc* 2017;**318**:731—40.
12. Lim Y, Lyall H. Congenital cytomegalovirus - who, when, what-with and why to treat? *J Infect* 2017;**74**(Suppl 1):s89—94.
13. Forsgren M. Prevention of congenital and perinatal infections. *Euro Surveill* 2009;**14**:2—4.
14. Kotton CN, Kumar D, Caliendo AM, Asberg A, Chou S, Danziger-Isakov L, et al. Updated international consensus guidelines on the management of cytomegalovirus in solid-organ transplantation. *Transplantation* 2013;**96**:333—60.
15. Marty FM, Ljungman P, Chemaly RF, Maertens J, Dadwal SS, Duarte RF, et al. Letermovir prophylaxis for cytomegalovirus in hematopoietic-cell transplantation. *N Engl J Med* 2017;**377**:2433—44.
16. Anderholm KM, Bierle CJ, Schleiss MR. Cytomegalovirus vaccines: current status and future prospects. *Drugs* 2016;**76**:1625—45.
17. van Zuylen WJ, Hamilton ST, Naing Z, Hall B, Shand A, Rawlinson WD. Congenital cytomegalovirus infection: clinical presentation, epidemiology, diagnosis and prevention. *Obstet Med* 2014;**7**:140—6.
18. Cannon MJ, Schmid DS, Hyde TB. Review of cytomegalovirus seroprevalence and demographic characteristics associated with infection. *Rev Med Virol* 2010;**20**:202—13.
19. Seo S, Cho Y, Park J. Serologic screening of pregnant Korean women for primary human cytomegalovirus infection using IgG avidity test. *Korean J Lab Med* 2009;**29**:557—62.
20. La Y, Kwon DE, Yoo SG, Lee KH, Han SH, Song YG. Human cytomegalovirus seroprevalence and titres in solid organ

transplant recipients and transplant donors in Seoul, South Korea. *BMC Infect Dis* 2019;**19**:948.
21. Lee WY, Shaw I. The impact of out-of-pocket payments on health care inequity: the case of national health insurance in South Korea. *Int J Environ Res Publ Health* 2014;**11**:7304—18.
22. Kim JA, Yoon S, Kim LY, Kim DS. Towards actualizing the value potential of Korea health insurance review and assessment (HIRA) data as a resource for health research: strengths, limitations, applications, and strategies for optimal use of HIRA data. *J Kor Med Sci* 2017;**32**:718—28.
23. Kim SM, Jang WM, Ahn HA, Park HJ, Ahn HS. Korean National Health Insurance value incentive program: achievements and future directions. *J Prev Med Public Health* 2012;**45**:148—55.
24. Choi NK, Chang Y, Kim JY, Choi YK, Park BJ. Comparison and validation of data-mining indices for signal detection: using the Korean national health insurance claims database. *Pharmacoepidemiol Drug Saf* 2011;**20**:1278—86.
25. Jung YS, Han M, Kim DY, Cheon JH, Park S. Cancer risk in Korean patients with Behcet's disease: a nationwide population-based study. *PloS One* 2017;**12**:e0190182.
26. Na KH, Kim HJ, Kim KH, Han S, Kim P, Hann HJ, et al. Prevalence, age at diagnosis, mortality, and cause of death in retinitis pigmentosa in korea-A nationwide population-based study. *Am J Ophthalmol* 2017;**176**:157—65.
27. World Health Organization (WHO). *International statistical classification of diseases and related health Problems 10th revision (ICD-10)-WHO version for 2016*. 2016. Available at, http://apps.who.int/classifications/icd10/browse/2016/en. [Accessed 10 March 2020].
28. You DM, Johnson MD. Cytomegalovirus infection and the gastrointestinal tract. *Curr Gastroenterol Rep* 2012;**14**:334—42.
29. Choi YJ, Lee DH, Han KD, Kim HS, Yoon H, Shin CM, et al. The relationship between drinking alcohol and esophageal, gastric or colorectal cancer: a nationwide population-based cohort study of South Korea. *PloS One* 2017;**12**:e0185778.
30. Lee JH, Han KD, Kim KM, Park YG, Lee JY, Park YM. Prevalence of atopic dermatitis in Korean children based on data from the 2008-2011 Korean national health and nutrition examination survey. *Allergy Asthma Immunol Res* 2016;**8**:79—83.
31. *Complete enumeration results of the 2010 population and housing Census*. 2011. Available at, http://kostat.go.kr/portal/eng/pressReleases/8/7/index.board?bmode=read&bSeq=&aSeq=273087&pageNo=2&rowNum=10&navCount=10&currPg=&sTarget=title&sTxt=. [Accessed 10 March 2021].
32. Yen YF, Jen I, Chen M, Chuang PH, Liu YL, Sharp GB, et al. Association of cytomegalovirus end-organ disease with stroke in people living with HIV/AIDS: a nationwide population-based cohort study. *PloS One* 2016;**11**:e0151684.
33. Liu PY, Cheng SB, Lin CC, Lin CH, Chang SN, Cheng CY, et al. Cytomegalovirus disease after liver transplantation: a nationwide population-based study. *Transplant Proc* 2014;**46**:832—4.
34. Korndewal MJ, Vossen AC, Cremer J, Vanb RS, Kroes AC, Ma VDS, et al. Disease burden of congenital cytomegalovirus infection at school entry age: study design, participation rate and birth prevalence. *Epidemiol Infect* 2016;**144**:1520—7.
35. Yamada H, Tairaku S, Morioka I, Sonoyama A, Tanimura K, Deguchi M, et al. Nationwide survey of mother-to-child infections in Japan. *J Infect Chemother* 2015;**21**:161—4.
36. Maffini E, Giaccone L, Festuccia M, Brunello L, Busca A, Bruno B. Treatment of CMV infection after allogeneic hematopoietic stem cell transplantation. *Expet Rev Hematol* 2016;**9**:585—96.
37. Kotton CN, Kumar D, Caliendo AM, Huprikar S, Chou S, Danziger-Isakov L, et al. The third international consensus guidelines on the management of cytomegalovirus in solid-organ transplantation. *Transplantation* 2018;**102**:900—31.
38. Takizawa Y, Inokuma S, Tanaka Y, Saito K, Atsumi T, Hirakata M, et al. Clinical characteristics of cytomegalovirus infection in rheumatic diseases: multicentre survey in a large patient population. *Rheumatology* 2008;**47**:1373—8.
39. Mikulska M, Lanini S, Gudiol C, Drgona L, Ippolito G, Fernández-Ruiz M, et al. ESCMID Study Group for Infections in Compromised Hosts (ESGICH) Consensus Document on the safety of targeted and biological therapies: an infectious diseases perspective (Agents targeting lymphoid cells surface antigens [I]: CD19, CD20 and CD52). *Clin Microbiol Infect* 2018;**24**(Suppl 2):s71—82.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jmii.2021.08.004.