Association of cytomegalovirus diseases with newly developed myocardial infarction and congestive heart failure: data from a national population-based cohort

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Abstract

Introduction: Anti-cytomegalovirus (CMV) IgG seropositive and/or titer are associated with a higher risk of cardiovascular diseases (CVD). However, it is not clear whether CMV end-organ disease may have a relation with development of CVD or chronic heart diseases.

Material and methods: In matched cohort study, the National Health Insurance Database covering 50 million people was used to identify 667 patients with CMV diseases and aged ≥ 20 years between 2010 and 2014. 6,670 control subjects without CMV diseases were matched by age, sex, type 2 diabetes mellitus (DM), hypertension, dyslipidemia, and cohort entry year. Data on CMV disease and heart disease events of myocardial infarction (MI), congestive heart failure (CHF), and atrial fibrillation (AF) were retrieved. Previous events before CMV disease or cohort entry were excluded until January 2006. Subjects were followed until December 2015 in subjects without events and until date of events in subjects with events.

Results: The multivariate regression model adjusted by age, sex, low-income status, type 2 DM, hypertension, dyslipidemia, solid organ transplantation, and hematopoietic stem cell transplantation showed a significantly higher incidence rate of MI (odds ratio (OR) = 2.1, 95% confidence intervals (CI): 1.0–4.5) and CHF (OR = 3.8, 95% CI: 2.1–6.8) but not AF (OR = 1.9, 95% CI: 0.9–4.0) in patients with CMV disease. The age group of 40–64 years with CMV disease had the highest risk for new-onset CHF in this regression model (OR = 9.4, 95% CI: 4.12–21.44, p = 0.029).

Conclusions: Symptomatic CMV tissue-invasive diseases were associated with a higher risk of new-onset MI and CHF.

Key words: cytomegalovirus, end-organ disease, myocardial infarction, heart failure, atrial fibrillation.

Introduction

In most cases, cytomegalovirus (CMV) infection is asymptomatically acquired in infancy and early childhood via breast milk or saliva and subsequently maintained in a latent status throughout the lifespan [1–3]. However, lytic replication through reactivation of latent CMV can result in diverse symptomatic tissue-invasive diseases with end-organ involvement, particularly fatal pneumonia or retinitis in severe immunocom-
promised patients [1, 4]. In addition, CMV-sero-
positive individuals without CMV diseases can have chronically significant CMV-specific CD8+ T-cell-mediated immune responses (CMV-CMI), indicating intermittent asymptomatic CMV reactivation and immune boosting [5–7]. Therefore, per-
sistent inflation of CMV-CMI due to latent CMV infec-
tion can promote various chronic inflammatory diseases such as atherosclerosis, autoimmune dis-
orders, and inflammatory bowel diseases [8–12]. The overt inflammatory necrotic CMV tissue-inva-
sive diseases could lead to these chronic diseases through noteworthy intensification of the CMV-
CMI [1, 3, 8].

Despite concerted efforts to control traditionally accepted modifiable risk factors including hy-
pertension, type 2 non-insulin dependent dia-
betes mellitus (NIDDM), dyslipidemia, obesity, and smoking, the incidences of cardiovascular dis-
eses (CVD), such as coronary heart disease (CHD), myocardial infarction (MI), and ischemic cerebral infarction, have been consistently increasing [13, 14]. Immune-mediated vascular endothelial dam-
age in relation to currently unmodifiable con-
tributors such as CMV or other unknown factors could be a possible cause of this epidemiologic phenomenon. Several studies suggest that the risk and mortality of heart diseases may increase with CMV infection due to chronic inflammation accompanied by T-cell associated immune senes-
cence, endothelial cell injury, altered lipid profile, and vascular smooth muscle cell proliferation [6, 8, 9, 15–23]. Conversely, some studies have reported that CMV infection was irrelevant to atheroscle-
rosis and/or CVD [24–27]. Recent meta-analyses have demonstrated an association between CMV and heart diseases [28]. However, these results originated from seropositive status and/or titers in anti-CMV IgG tests, indicating previous CMV ac-
quision and humoral immunity [28]. It was not found that the tissue-invasive end-organ disease by active lytic replication of CMV may be related to higher incidence of CVD [9, 28]. Thus, it would be worthwhile to determine whether symptomat-
ic CMV tissue-invasive end-organ diseases, which are more relevant to overt inflammatory boosting, rather than silent CMV latent status by anti-CMV IgG serology, may increase the risk of heart dis-
eseves.

In this study, we analyzed nationwide data per-
taining to the entire population with CMV invasive diseases during a five-year period. We sought to
determine whether cytopathic CMV replication that causes overt symptomatic organ disease is associated with the development of heart disease. Our results may constitute powerful evidence for supporting a relationship between CMV and heart diseases.

Material and methods

The origin of data

The South Korean National Health Insurance Service (KNHIS) is a mandatory state-operated system that was instituted to ensure universal healthcare. The KNHIS covers the entire South Ko-
orean population and provides health coverage by employment status. The low income group which accounts for about 2.8% of the total population is the beneficiary of the Medical Aid program, and the remaining population is divided into insurance for industrial workers and self-employed individu-
als [31]. Healthcare providers are required to submit all information pertaining to medical prac-
tice to the Health Insurance Review and Assess-
ment (HIRA) to claim reimbursement of costs. The HIRA has systematically founded and managed a comprehensive data warehouse of beneficiaries, which is referred to as the National Health Insur-
ance Database (NHID), for regularizing the Nation-
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From 2005 onward, the KNHIS has imple-
mented a policy to extend healthcare service to people experiencing economic difficulties due to excessive medical expenses related to RID and to help lower out-of-pocket expenses [32]. All CMV end-organ diseases are strictly registered as RID with specific codes and information sheets us-
ing predefined diagnostic criteria by the HIRA. We accessed the NHID for data from 2010 to 2014 as submitted to the National Health Insur-
ance Sharing Service (NHISS) to analyze medical information pertaining to the entire Korean pop-
ulation [33–35]. This study was approved by the Institutional Review Board of the Gangnam Sev-
erance Hospital, Yonsei University College of Med-
icine, and relevant permission forms have been obtained from the NHISS.

Definitions

The diagnosis of CMV tissue-invasive end-organ diseases is based on several findings either in combination or separately as follows: 1) histopa-
thologic features upon immunohistochemical staining for CMV, 2) measurement of pp65 antigen and/or detection of CMV in sterile body fluid or tissue using antigenemia test, culture, or nucleic acid amplification test [3, 4]. The unique V104 code for CMV diseases used in the enrollment of RID and submission to the HIRA completely corre-
sponds with the B25 code within the International
Statistical Classification of Diseases and Related Health Problems 10th Revision (ICD-10) codes, as presented in the 2016 online version by the World Health Organization (WHO) [36]. The B25 code includes all types of CMV end-organ diseases except for congenital CMV infection (P35.1) and cytomegaloviral mononucleosis (B27.1) [36].

The CHA2DS2-VASc score for risk stratification in atrial fibrillation (AF) was calculated using congestive heart failure, hypertension, age, DM, vascular disease, sex, and stroke/transient ischemic attack/thromboembolic events according to the American Heart Association guidelines [37]. We defined low-income status as the lower 25% percentile according to the annual household income based on results of the 2010 South Korea Population and Housing Census [35].

In this cohort study, events were defined as MI and/or congestive heart failure (CHF) and/or AF. The diseases were identified by ICD-10 diagnosis codes: acute or subsequent MI (I21, I22), CHF (I50), AF (I48.0, I48.1, I48.2, I48.9), hypertension (I10-I13, I15), type 2 NIDDM (E11), and dyslipidemia (E78 including E78.0-E78.9). The solid organ transplant (SOT) or hematopoietic stem cell transplant (HSCT) recipients of the high-risk group for CMV disease could have various underlying conditions attributing MI or CHF or AF. Therefore, we identified the SOT and HSCT recipients, who had received transplantation within 3 years from the index date, using unique codes for RID such as CMV disease, to adjust the confounding effects of CMV disease on development of heart diseases. We applied the RID codes of V084-V088 for kidney, liver, pancreas, heart, and lung transplantation, respectively. The V081-V083 codes were used for umbilical cord, autologous, and allogeneic HSCT, respectively. The point of cohort entry was assigned to the V104 code submission date for individuals without CMV disease. The index date for patients with CMV disease and to the matched case group, and the occurrence of newly developed heart disease may affect the correlation between CMV and heart diseases. Finally, 667 patients with CMV invasive diseases were included in the case group, and the occurrence of newly developed heart disease was analyzed. The control group comprising 6,670 patients without CMV diseases (during the entire follow-up period and including any previous events during the wash-out period) was randomly selected at a 1 : 10 ratio matched by age, sex, type 2 NIDDM, hypertension, dyslipidemia and year of cohort entry (Figure 1 A). Therefore, our matched cohort enabled reliable identification of new-onset MI, CHF, and AF events. The follow-up was continued until occurrence of newly developed events in patients with events or until the cohort end date in patients without events in both groups. If the patients died after the occurrence of events, they were included in the event analyses and censored at date of death (Figure 1 B).

**Statistical analysis**

Categorical data were expressed as numbers (percent), and continuous data were presented as means ± standard deviation. Comparison between the matched groups was performed using the McNemar test and the paired t-test. Kaplan-Meier curves were constructed to analyze the incidence and probability of heart diseases according to the presence of CMV diseases. Multivariate logistic regression analyses using model 1 (M1, non-adjusted), model 2 (M2, adjusted by age and sex), model 3 (M3, adjusted by age, sex, low-income status, NIDDM, hypertension, and dyslipidemia), and model 4 (M4, adjusted by age, sex, low-income status, NIDDM, hypertension, dyslipidemia, SOT, and HSCT) were performed to evaluate the impact of CMV diseases on new-onset heart diseases. Statistical analyses were performed using the SAS program (version 9.2; SAS Institute, Cary, NC) and GraphPad Prism V6 (GraphPad Software, La Jolla, CA). A two-tailed p-value < 0.05 was considered statistically significant.

**Results**

**Clinical characteristics of patients in the matched cohort**

The control group had significantly higher percentages of MI (control group vs. case group: 1.5% vs. 0.7%, p = 0.035) and CHF (2.6% vs. 0.8%, p < 0.001). The frequencies of SOT (20.4% vs. 0.04%, p < 0.001) or HSCT (2.6% vs. 0%, p < 0.001) recipients in the case group were significantly higher compared to the control group. The CHA2DS2-VASc score was also significantly higher in the case group than it was in the control group (case group vs. control group: 1.8 ±1.5 vs. 1.5 ±1.4, p < 0.001). However, the frequency
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**Figure 1.** Schematic flow charts of study design and selection or follow-up of patients in case and control groups. A – Study design and patient selection. B – Schematic diagram of follow-up and exclusion of previous events in both groups.

AF – atrial fibrillation, CHF – congestive heart failure, CMV – cytomegalovirus, DM – diabetes mellitus, F/U – follow-up, ICD-10 – the International Statistical Classification of Diseases and Related Health Problems 10th Revision, MI – myocardial infarction, NHID – the National Health Insurance Database.
of AF was not significantly different between the two groups (case group vs. control group: 1.4% vs. 0.9%, \( p = 0.214 \)). The overall mean follow-up duration for each event was approximately 3 years in both groups (Table I).

### CMV disease and risk of newly developed MI, CHF, and AF

The IR/1,000 patients of MI in the case group was approximately two-fold higher than that in the control group as per M3 with an odds ratio (OR) of 2.2 (95% confidence interval (CI): 1.1–4.2) and as per M4 with an OR of 2.1 (95% CI: 1.0–4.5). The IR/1,000 patients of CHF in the case group was also up to three-fold higher than that in the control group (M3, 2.1–6.3 and M4, 3.8 (2.1–6.8)) (Table II). During the maximal 6-year follow-up period, the incidence probabilities of MI (\( p = 0.023 \)) and CHF (\( p < 0.001 \)) were significantly higher in the case group than those in the control group (Figures 2 A, B).

In contrast, the IR of AF showed a lower OR (1.6–1.9) than that of MI or CHF; the IR of AF was not significantly different between the case and the control groups (95% CI: M3, 0.8–3.3 and M4, 0.9–4.0) (Table II). The incidence probability of newly developed AF was similar between the two groups as per Kaplan-Meier curve analysis (\( p = 0.169 \)) (Figure 2 C).

### The risk difference of newly developed heart diseases in age and sex subgroup analysis

The ORs for MI were higher in men than in women (M4, 2.3 vs. 1.7), and the OR was also higher in the 40–64 years age group compared to that in the ≥ 65 years age group (M4, 2.6 vs. 2.0). In the case of CHF, the ORs were higher in women than in men (M4, 4.2 vs. 3.4), and higher in the 40–64 years age group than in the ≥ 65 years age group (M4, 9.4 vs. 1.7). The middle-aged (40–64-year-old) patients in the case group had the higher ORs and statistically significant 95% CIs for CHF (\( p \)-values for subgroup interaction = 0.029). However, there were no statistically significant differences in the IRs of MI, CHF, and AF associated with CMV disease in the overall sex and age subgroup analysis except CHF in age group (Table III).

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**Table I:** Comparison of clinical characteristics between adult individuals with and without CMV disease in a matched cohort

| Characteristics                  | CMV disease | \( p \)-value |
|----------------------------------|-------------|--------------|
|                                 | Yes (n = 667) | No (n = 6,670) |
| Sex, male                        | 368 (55.17)  | 3,680 (55.17)  | > 0.999*          |
| Age [years]:                     |             |              |
| 20–39                            | 50.58 ±15.34 | 50.58 ±15.33  | > 0.999’          |
| 40–64                            | 381 (57.12)  | 3,810 (57.12) | > 0.999*          |
| ≥ 65                             | 121 (18.14)  | 1,210 (18.14) | > 0.999*          |
| Low income status                | 179 (26.84)  | 1,553 (23.28) | 0.039*            |
| Type 2 NIDDM                     | 146 (21.89)  | 1,460 (21.89) | > 0.999*          |
| Hypertension                     | 260 (38.98)  | 2,600 (38.98) | > 0.999*          |
| Dyslipidemia                     | 164 (24.59)  | 1,640 (24.59) | > 0.999*          |
| SOT                              | 136 (20.39)  | 3 (0.04)      | < 0.001*          |
| HSCT                             | 17 (2.55)    | 0 (0.00)      | < 0.001*          |
| CHA2DS2-VASc Score               | 1.80 ±1.46   | 1.51 ±1.39    | < 0.001’          |
| Acute or subsequent MI           | 10 (1.50)    | 49 (0.73)     | 0.035*            |
| Congestive heart failure         | 17 (2.55)    | 52 (0.78)     | < 0.001*          |
| Atrial fibrillation              | 9 (1.35)     | 58 (0.87)     | 0.214*            |
| Death                            | 66 (9.9)     | 165 (2.47)    | < 0.001*          |
| Follow-up duration [years]:      |             |              |
| Myocardial infarction            | 3.07 ±1.60   | 3.25 ±1.52    | 0.005’            |
| Congestive heart failure         | 3.06 ±1.62   | 3.25 ±1.52    | 0.002’            |
| Atrial fibrillation              | 3.07 ±1.61   | 3.24 ±1.52    | 0.007’            |
| Death                            | 3.09 ±1.60   | 3.26 ±1.52    | 0.005’            |

Data are expressed as number (percent) or mean ± SD. McNemar test, *Paired t-test,* ‘Between cohort entry point and development of each event in patients with new-onset MI, CHF, AE or death, or between cohort entry point and cohort end date in patients without development of each event. CMV – cytomegalovirus, HSCT – hematopoietic stem cell transplantation, NIDDM – non-insulin dependent diabetes mellitus, MI – myocardial infarction, SOT – solid organ transplantation.
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**Table II. Multivariate logistic regression models to examine the effect of cytomegalovirus (CMV) disease in adults**

| Outcomes | CMV disease | No. | Events | Total follow-up duration [years] | IR* | Odds ratio (95% CI) |
|----------|-------------|-----|--------|-------------------------------|-----|-------------------|
|          |             |     |        |                               |     | Model 1 | Model 2 | Model 3 | Model 4 |
| MI       | No          | 6,670 | 49 | 21,644.42 | 2.264 | 1 (Ref.) | 1 (Ref.) | 1 (Ref.) | 1 (Ref.) |
|          | Yes         | 667  | 10 | 2,048.02  | 4.883 | 2.16     | 2.21     | 2.23     | 2.14     |
|          |             |    |     |                               |     | (1.03–4.08) | (1.05–4.17) | (1.07–4.22) | (1.01–4.52) |
| CHF      | No          | 6,670 | 52 | 21,681.55 | 2.400 | 1 (Ref.) | 1 (Ref.) | 1 (Ref.) | 1 (Ref.) |
|          | Yes         | 667  | 17 | 2,040.14  | 8.333 | 3.47     | 3.62     | 3.73     | 3.79     |
|          |             |    |     |                               |     | (1.95–5.87) | (2.03–6.12) | (2.09–6.31) | (2.10–6.84) |
| AF       | No          | 6,670 | 58 | 21,605.37 | 2.685 | 1 (Ref.) | 1 (Ref.) | 1 (Ref.) | 1 (Ref.) |
|          | Yes         | 667  | 9  | 2,048.60  | 4.393 | 1.63     | 1.69     | 1.70     | 1.89     |
|          |             |    |     |                               |     | (1.07–3.12) | (1.07–3.24) | (1.07–3.26) | (0.90–3.96) |

Model 1 – non-adjusted, Model 2 – age- and sex-adjusted, Model 3 – age-, sex-, low income status-, type 2 NIDDM-, hypertension- and dyslipidemia-adjusted, Model 4 – age-, sex-, low income status-, type 2 NIDDM-, hypertension-, dyslipidemia-, SOT- and HSCT-adjusted. *per 1,000 patients. AF – atrial fibrillation, CHF – congestive heart failure, CI – confidence interval, CMV – cytomegalovirus, HSCT – hematopoietic stem cell transplantation, IR – incidence rate, MI – myocardial infarction, NIDDM – non-insulin dependent diabetes mellitus, No. – number, Ref. – reference, SOT – solid organ transplantation.

**Figure 2.** Kaplan-Meier curves for incidence probability of heart diseases according to tissue-invasive end-organ disease caused by cytomegalovirus. A – Myocardial infarction. B – Congestive heart failure. C – Atrial fibrillation

**CMV** – cytomegalovirus.

**Discussion**

This nationwide study aimed to clarify the relationship between CMV tissue-invasive end-organ diseases and new-onset heart diseases during a 6-year follow-up period. Previous studies with various study designs and participant characteristics have evaluated different aspects of asso-
Table III. Multivariate logistic regression models to examine the effect according to sex and age distribution

| Outcome | Subgroup | CMV disease | No. Events | Total f/u duration [years] | IR* | Odds ratio (95% CI) | P-value for interaction |
|---------|----------|-------------|------------|---------------------------|-----|---------------------|-------------------------|
|         |          |             |            |                           |     | Model 1             | Model 2                 | Model 3                 | Model 4                 |           |
| MI      | Sex:     |             |            |                           |     |                     |                         |                         |                         | 0.962      |
|         | Male     | No          | 3680       | 33                        | 11945 | 2.76 (1 Ref.)      | 1 (Ref.)                | 1 (Ref.)                | 1 (Ref.)                |                     |
|         |          | Yes         | 368        | 7                         | 1142  | 6.13                | 2.22 (0.90–4.72)        | 2.23 (0.90–4.74)        | 2.26 (0.92–4.81)        | 2.30 (0.96–5.49)        |
|         | Female   | No          | 2990       | 16                        | 9699  | 1.65 (1 Ref.)      | 1 (Ref.)                | 1 (Ref.)                | 1 (Ref.)                |                     |
|         |          | Yes         | 299        | 3                         | 906   | 3.31                | 1.99 (0.46–5.98)        | 2.14 (0.50–6.44)        | 2.13 (0.49–6.40)        | 1.73 (0.40–7.52)        |
| Age [years]: |               |             |            |                           |     |                     |                         |                         |                         |           |
|         | 20–39    | No          | 1650       | 2                         | 5695  | 0.35 (1 Ref.)      | 1 (Ref.)                | 1 (Ref.)                | 1 (Ref.)                |                     |
|         |          | Yes         | 165        | 0                         | 557   | 0.00               | –                      | –                      | –                      | –                      |
|         | 40–64    | No          | 3810       | 23                        | 12474 | 1.84 (1 Ref.)      | 1 (Ref.)                | 1 (Ref.)                | 1 (Ref.)                |                     |
|         |          | Yes         | 381        | 6                         | 1182  | 5.07                | 2.79 (1.03–6.43)        | 2.80 (1.04–6.46)        | 2.77 (1.02–6.39)        | 2.58 (0.89–7.51)        |
|         | ≥ 65     | No          | 1210       | 24                        | 3476  | 6.91                | 1 (Ref.)                | 1 (Ref.)                | 1 (Ref.)                |                     |
|         |          | Yes         | 121        | 4                         | 307   | 12.99               | 1.86 (0.55–4.82)        | 1.87 (0.55–4.85)        | 1.81 (0.53–4.70)        | 1.95 (0.68–5.64)        |
| CHF     | Sex:     |             |            |                           |     |                     |                         |                         |                         | 0.565      |
|         | Male     | No          | 3680       | 27                        | 11982 | 2.25 (1 Ref.)      | 1 (Ref.)                | 1 (Ref.)                | 1 (Ref.)                |                     |
|         |          | Yes         | 368        | 8                         | 1139  | 7.02                | 3.11 (1.32–6.55)        | 3.14 (1.33–6.59)        | 3.08 (1.30–6.48)        | 3.37 (1.46–7.76)        |
|         | Female   | No          | 2990       | 25                        | 9700  | 2.58 (1 Ref.)      | 1 (Ref.)                | 1 (Ref.)                | 1 (Ref.)                |                     |
|         |          | Yes         | 299        | 9                         | 900   | 10.00               | 3.85 (1.70–7.95)        | 4.21 (1.86–8.71)        | 4.34 (1.91–9.01)        | 4.17 (1.80–9.67)        |
| Age [years]: |               |             |            |                           |     |                     |                         |                         |                         | 0.029      |
|         | 20–39    | No          | 1650       | 5                         | 5693  | 0.88 (1 Ref.)      | 1 (Ref.)                | 1 (Ref.)                | 1 (Ref.)                |                     |
|         |          | Yes         | 165        | 2                         | 553   | 3.62                | 4.08 (0.59–18.93)        | 4.08 (0.58–18.91)        | 4.76 (0.68–22.39)        | 5.15 (0.57–46.51)        |
|         | 40–64    | No          | 3810       | 16                        | 12488 | 1.28 (1 Ref.)      | 1 (Ref.)                | 1 (Ref.)                | 1 (Ref.)                |                     |
|         |          | Yes         | 381        | 11                        | 1176  | 9.35                | 7.29 (3.29–15.57)        | 7.47 (3.37–15.95)        | 7.77 (3.50–16.63)        | 9.40 (4.12–21.44)        |
|         | ≥ 65     | No          | 1210       | 31                        | 3500  | 8.86                | 1.46 (0.44–3.70)        | 1.49 (0.44–3.76)        | 1.59 (0.47–4.03)        | 1.66 (0.59–4.73)        |
|         |          | Yes         | 121        | 4                         | 310   | 12.88               | 1.94 (0.44–3.70)        | 1.94 (0.44–3.76)        | 1.94 (0.47–4.03)        | 1.94 (0.59–4.73)        |
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Table III.

| Outcome Subgroup | Sex | CMV disease | No. Events | Total f/u duration [years] | IR* | Odds ratio (95% CI) | P-value for interaction |
|------------------|-----|-------------|------------|---------------------------|-----|---------------------|------------------------|
| AF              | Male | No            | 3680       | 11921                     | 2.68 | 1 (Ref.)            | 1 (Ref.)               |
|                 |      | Yes           | 368        | 11921                     | 2.49 | 0.87 (0.39–2.11)   | 0.67 (0.24–1.81)       |
|                 | Female | No            | 2990       | 9685                      | 2.69 | 1 (Ref.)            | 1 (Ref.)               |
|                 |      | Yes           | 299        | 9685                      | 2.69 | 0.87 (0.39–2.11)   | 0.67 (0.24–1.81)       |
| Age, years     | 20–39 | No            | 1650       | 5991                      | 0.70 | 1 (Ref.)            | 1 (Ref.)               |
|                 |      | Yes           | 165        | 5991                      | 0.70 | 1 (Ref.)            | 1 (Ref.)               |
|                 | ≥65  | No            | 1210       | 303                      | 4.04 | 1 (Ref.)            | 1 (Ref.)               |
|                 |      | Yes           | 121        | 303                      | 4.04 | 1 (Ref.)            | 1 (Ref.)               |

Model 1 – non-adjusted, Model 2 – age- and sex-adjusted, Model 3 – age-, sex-, low income status-, type 2 NIDDM-, hypertension-, and dyslipidemia-adjusted, Model 4 – age-, sex-, low income status-, type 2 NIDDM-, hypertension-, dyslipidemia-, SOT- and HSCT-adjusted. *per 1,000 patients. AF – atrial fibrillation, CHF – congestive heart failure, CI – confidence interval, CMV – cytomegalovirus, f/u – follow-up, HSCT – hematopoietic stem cell transplantation, ICD-10 code-based detection, MI – myocardial infarction, NIDDM – non-insulin dependent diabetes mellitus, No. – number, Ref. – reference, SOT – solid organ transplantation.

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correlations between CMV and CVD [18, 22, 24–27], and a recent meta-analysis performed with 10 prospective studies showed that CMV infection significantly increased the risk of CVD with low relative risk (RR) of 1.22 [28]. However, by confining the analysis to three studies of ischemic heart disease (IHD), including coronary artery disease, CHD, and MI, the overall RR of CMV infection was not statistically significant (p = 0.145) [28]. Despite the large number of participants and CVD events, the most important drawback of studies including this meta-analysis was the simplification of CMV infection as just a positive result or a high titer in an anti-CMV IgG serology test [28]. In our first study, we defined CMV status as tissue-invasive organ disease resulting in strong immunologic effects; the results of that study revealed that the development of CMV diseases was associated with a 200–400% higher risk of new-onset MI or CHF. In addition, using a definite cytopathic inflammatory manifestation to define symptomatic CMV disease, this study has several unique strengths, as follows: (1) a long wash-out period to exclude previous heart diseases in groups with and without CMV diseases, which ensured the exploration of a relationship between CMV disease and MI or CHF; (2) precise ICD-10 code-based detection of MI or CHF events, in contrast to CHD or coronary artery disease diagnoses; this allowed for effective evaluation of the clinical impact of active CMV replication on CVD; (3) the retrieval of data on subjects and events from a database covering the entire national population of 50 million; this ensured greater reliability of data and statistics; (4) the relatively small number of events from this well-stratified matched cohort retrieved from a large database; this may have reduced the proportion of misdiagnoses of CMV and heart diseases.

Interestingly, the analysis of our cohort which excluded heart transplantation recipients showed that CMV disease increased the risk of CHF but did not significantly affect AF. CMV replication in heart transplant recipients is one of the major risk factors of graft dysfunction and CHF [4, 17]. However, the epidemiologic association between CMV and CHF or AF in the general population has not been evaluated. IHD is the most important and common cause of and predisposing factor for CHF [38]. Therefore, the chronic or strong inflammatory processes induced by CMV invasive disease may promote CHF caused by IHD-associated systolic dysfunction. In contrast, it is unclear whether any association exists between AF and CD8+ T-cell-mediated CMI [39]. This new finding, in contrast to the association between CMV and AF, would support our hypothesis about the relationship between CMV-induced chronic inflammation and inflammatory heart diseases such as MI and CHF.
In addition to the immunologic mechanisms underlying the impact of CMV-induced inflammation on atherosclerosis [9], subacute CMV infection inhibits \( P53 \) gene product activity and promotes smooth muscle cell proliferation and restenosis in coronary angioplasty patients [40]. Viperin is an interferon-inducible antiviral protein derived from CMV, which promotes inflammatory responses of the host; the activity of this protein may explain the impact of CMV infection on MI and CHF [41, 42]. Viperin interacts with mitochondria to reduce cellular adenosine triphosphate production, inhibits mitochondrial apoptosis, and ultimately induces inflammatory processes [41]. Natural killer cells, nuclear factor \( \kappa B \), and pro-inflammatory cytokines, such as tumor necrosis factor-\( \alpha \) and interleukin-6, also contribute to the development of atherosclerosis [9]. Further studies pertaining to the pathogenesis of atherosclerosis in active CMV replication conditions, including CMV DNAemia or tissue-invasive end-organ diseases, but excluding the non-replicative latent status of seropositivity, will be warranted to verify the following hypothesis: upregulation of inflammation (CMV-CMI) induced by the active production of CMV virions could potentiate the process of CVD development.

This study has some limitations that should be considered: (1) This is a retrospective observational study with a short mean follow-up time of 3 years. In our study, Kaplan-Meier curve analysis showed that the incidence of MI, CHF, and AF increased progressively throughout the follow-up period in the control group without CMV diseases. These findings adequately demonstrate that our cohort was effectively matched. However, the occurrence of CHF increased rapidly within 1 year after the development of CMV diseases. The incidence of new-onset MI varied significantly 3 years after the development of CMV diseases. The incidence of new-onset MI varied significantly 3 years after the development of CMV diseases.

Table IV. Distribution for incidence of cytomegalovirus tissue-invasive end-organ disease according to ICD-10 codes in the entire-population database

| ICD-10 codes                      | Year     |
|-----------------------------------|----------|
|                                   | 2010     | 2011 | 2012 | 2013 | 2014 |
| B25 (Cytomegalovirus disease)     | 2        | 0    | 1    | 0    | 0    |
| B25.0 (Cytomegaloviral pneumonitis)| 14       | 14   | 14   | 16   | 17   |
| B25.1 (Cytomegaloviral hepatitis) | 20       | 10   | 10   | 19   | 26   |
| B25.2 (Cytomegaloviral pancreatitis)| 0       | 0    | 0    | 0    | 0    |
| B25.8 (Other cytomegaloviral diseases)| 56      | 77   | 93   | 87   | 123  |
| B25.9 (Cytomegalovirus disease, unspecified) | 67 | 105 | 87 | 137 | 193 |
| Total (N = 1,188)                 | 159      | 206  | 205  | 259  | 359  |

Data are represented as numbers, obtained from the Korean Health Insurance Review and Assessment Service claims data warehouse. 
ICD-10 – International Statistical Classification of Diseases and Related Health Problems 10th Revision.

Table V. Frequencies of solid organ transplantation recipients with cytomegalovirus disease or infection according to ICD-10 codes between 2010 and 2015 in the entire-population database

| ICD-10 codes                      | Total individuals | SOT recipients |
|-----------------------------------|-------------------|----------------|
| B25 (Cytomegalovirus disease)     | 3                 | 0 (0.0)        |
| B25.0 (Cytomegaloviral pneumonitis)| 89                | 6 (6.7)        |
| B25.1 (Cytomegaloviral hepatitis) | 101               | 4 (4.0)        |
| B25.2 (Cytomegaloviral pancreatitis)| 4            | 0 (0.0)        |
| B25.8 (Other cytomegaloviral diseases)| 485       | 80 (16.5)      |
| B25.9 (Cytomegalovirus disease, unspecified) | 621 | 193 (31.1) |
| Total                             | 1,303             | 283 (21.7)     |

Data are presented as number (percent). CMV – cytomegalovirus, ICD-10 – International Statistical Classification of Diseases and Related Health Problems 10th Revision, SOT – solid organ transplantation.
in real clinical practice and confirmatory pathologic-based diagnosis of these conditions is difficult since it is not easy to obtain tissue samples. The majority of CMV diseases (≥ 85%) involved codes B25.8 or B25.9, indicating other organs including the gastrointestinal tract. (3) We analyzed the association of three representative heart diseases – MI, CHF, and AF – with CMV diseases. A future prospective study of the relationship of non-cardiogenic vascular diseases such as peripheral vascular diseases with symptomatic CMV diseases is warranted. Due to relatively high inaccuracy of diagnostic codes, we were unable to perform this type of study. (4) Our entire cohort included approximately 20% of severely immunocompromised solid organ transplantation (SOT) recipients (Table V). The effect of active CMV replication on the outcome of diseases is considered highly significant in SOT [4]. In addition, we could not acquire detailed information about the immunocompromised status or diseases directly associated with CMV end-organ diseases for all the participants. Therefore, it was not possible to adjust for all of the known contributable confounding factors for MI or CHF. (5) There were relatively few events of MI, CHF, and AF in both groups. However, given the low IR of CMV end-organ diseases, it may be difficult to conduct a well-designed prospective study to gather enough CMV and heart disease events. (6) The cohort was constituted almost entirely of participants of South Korean origin, because the data were derived from the Korean medical insurance system. Therefore, ethnic differences could not be analyzed. (7) Our observational cohort study may potentially have informational bias arising from the difference of follow-up loss between two groups.

Despite these limitations, our results are consistent with a recent meta-analysis of 10 prospective studies, and our hypothesis is supported by results from several in-vitro studies. Thus, our study confirms that CMV, regardless of latent non-repllicative, active lytic (tissue-invasive end-organ disease), asymptomatic, or symptomatic status, is a definite risk factor of IHD and atherosclerosis [9, 10, 22, 23, 28, 40, 42]. To additionally reduce the burden of ischemic vascular diseases, tailored preventive or therapeutic strategies with vaccines or anti-CMV drugs in particularly high-risk patients should be explored in the near future. Immune monitoring by QuantiFERON-CMV, intracellular cytokine staining or other similar methods would be helpful to evaluate and stratify patients based on risk of CMV-associated CVD [43].

In conclusion, this whole-population-based matched cohort study suggests that symptomatic CMV invasive organ disease is a contributing factor for new-onset MI or CHF with a high incidence.

Conflict of interest
The authors declare no conflict of interest.

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