Cytomegalovirus Seroprevalence and Titres in Solid Organ Transplant Recipients and Non-transplant Individuals in Seoul, South Korea

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Abstract

Background: Cytomegalovirus (CMV) can cause poor outcomes in solid organ transplant (SOT) recipients and have relation to cardiovascular diseases (CVD) in general population. The anti-CMV immunoglobulin G (IgG) seroepidemiology is useful for identifying the risk of post-SOT CMV infection or disease as well as immunosenescence or CVD. However, recent CMV seroprevalence and titre have not been fully evaluated with respect to age distribution and comparison between SOT recipients and non-transplant individuals. Methods: We retrospectively retrieved all anti-CMV IgG results from 12658 individuals aged of > one years screened between July 2006 and Nov. 2017 at the Severance Hospital at Seoul. The cohort excluding hematopoietic stem cell transplant recipients and subjects with equivocal values included 2184 SOT recipients and 9738 non-transplant individuals. All IgG results in SOT recipients were measured at pre-transplant period, and only first values among subjects with repeated tests were included in the analyses. Results: The overall IgG seroprevalence and titres were significantly higher among SOT recipients relative to non-transplant individuals (98.7% vs. 94.8%, p < 0.001 and 64.7 ± 44.3 vs. 54.7 ± 38.9 arbitrary units aU/mL, p < 0.001, respectively). The lowest seropositive rates were observed among both SOT recipients and non-transplant individuals aged 11-15 years (70.6% and 70.2%, respectively). The frequency of seropositivity among adults aged ≥ 41 years increased to ≥ 99% in both groups. Age and SOT group were independently associated factors with higher CMV seroprevalence (OR, 1.12, 95% CI, 1.11-1.12, p < 0.001 and OR 2.43, 95% CI, 1.65-3.59, p < 0.001, respectively). Although liver (99.7%, 80.1 ± 54.5 aU/mL) and lung (100%, 84.3 ± 68.3 aU/mL) transplants had significantly higher seropositive rates and titres compared to kidney (98.3%, 59.4 ± 36.1 aU/mL) and heart (97.0%, 58.1 ± 46.9 aU/mL) transplant (overall p = 0.024 and < 0.001, respectively), the different transplant organs did not affect the seroprevalence in multivariate regression analysis. Conclusions: CMV seropositivity was lowest among school-aged children. IgG testing revealed that most adult SOT recipients in South Korea faced an intermediate serostatus risk of post-transplant CMV infection and disease.

Introduction

The genomic DNA of cytomegalovirus (CMV) is incorporated into the host chromosome after primary
infection (usually during early life) and is retained throughout life in a latent status [1-4]. Various mechanisms can induce temporary or sustained CMV replication, leading to acute cytolytic inflammation [1, 5, 6]. In both immunocompetent and immunocompromised patients, reactivation of latent CMV can result in direct tissue damage that causes end-organ diseases [1, 7-10]. The indirect immunomodulatory effects by CMV may cause serious problems such as increased mortality, graft dysfunction or failure, and rejection in recipients of highly immunosuppressive solid organ transplantation (SOT) and hematopoietic stem cell transplantation (HSCT) [8, 11, 12]. The CMV-specific immune activation in the non-immunocompromised general population could predispose individuals to chronic inflammatory diseases such as cardiovascular diseases and diabetes [13-15]. Therefore, surveillance for CMV IgG seropositivity may be epidemiologically important as a means of predicting CMV reactivation and various related chronic diseases in this era of population aging. Additionally, such surveillance could provide useful information regarding individually tailored anti-CMV preventive strategies for SOT recipients [1, 3, 16, 17].

The CMV serostatus, which is assessed using an anti-CMV immunoglobulin G (IgG) test, is an important pre-transplant analysis used to predict the risk of post-transplant CMV infection and disease [12, 16]. The anti-CMV IgG positivity rate has varied widely by era, geographic distribution, age group, and population characteristics [18-21]. Therefore, in CMV vaccine-absent era, the regular analyses of CMV seroprevalence by age group in the general population may be needed to obtain information about the epidemiology of CMV, which has various long-term effects on public health. However, no recent report has evaluated CMV seroepidemiology across all ages in South Korea, which has experienced rapid socioeconomic development and advances in public health. In addition, the patterns of pre-transplant CMV IgG seroprevalence and titres in SOT recipients have not been compared to those of non-transplant individuals to identify differences, particularly according to age. Therefore, this study aimed to evaluate the recent CMV serostatus distributions among SOT recipients and non-transplant individuals.

Methods
Study design and population
For this retrospective cohort study, we retrieved the anti-CMV IgG results of 13146 individuals who underwent this screening irrespective of the testing purpose between July 2006 and November 2017 from the electric medical records of Severance Hospital, a university-affiliated tertiary care centre in Seoul, South Korea. We excluded the 488 infants under one year of age, because infants could have maternal anti-CMV IgG for a year [22]. The cohort with total 11922 individuals after further exclusion of 34 subjects with equivocal result and 702 HSCT recipients was stratified into two groups of 2184 SOT recipients and 9738 non-transplant individuals (5982 out-patients and 3756 in-patients at CMV IgG measurements) who did not receive any transplantation (SOT or HSCT). Our cohort did not have the SOT recipients who received HSCT before and after SOT or human immunodeficiency virus-infected individuals. If the subject had the repeated anti-CMV IgG tests, we only included the first value in the analyses. For all of SOT recipients, anti-CMV IgG values were evaluated at the pre-transplantation within three months of transplantation. The ages at the time of first testing and anti-CMV IgG titres were also recorded. Ages were grouped in five-year intervals up to 40 years and then in 20-year intervals. For these patients, the age, sex and result/titre at the time of the first test were included in the analysis. The study was approved by our institution review board, which waived the requirement for informed consent.

Measurement of anti-human cytomegalovirus IgG antibody

Serum samples were automatically subjected to quantitative anti-CMV IgG testing using an enzyme-linked fluorescent immunoassay (VIDAS®, bioMérieux Cop., Marcy-l’Etoile, Lyon, France). Antigens from the CMV AD169 laboratory strain were used as the positive control. The antibody titre was expressed in arbitrary units (aU)/mL. Qualitatively, the results were reported as positive, equivocal and negative if the titres were ≥ 6, 4 to < 6 and < 4 aU/mL, respectively. The results of anti-CMV IgG tests in the analyses were just categorised as positive and negative.

Statistical analyses

We used the independent two-sample T-test and the chi-square test or Fisher’s exact test, respectively, to examine differences in continuous and nominal variables between SOT recipients and non-transplant individuals. The post-hoc analyses in nominal variables were performed by adjusted
standardized residuals to control for type I error inflation (adjusted $p$ value). An analysis of variance (ANOVA) with the Bonferroni post-hoc test was used for multiple comparisons of IgG titres between transplant organs. The multivariate logistic regression analyses were performed to identify the effect of age, sex and SOT on CMV seroprevalence. Data are expressed as numbers (percentages) or means ± standard deviations (SD) or odds ratio (OR) (95% confidence interval [CI]). SAS version 9.3 (SAS Institute Inc., Cary, NC, USA) was used for the statistical analyses. A two-tailed $p$ value of $\leq 0.05$ was considered statistically significant.

Results

**CMV IgG results from SOT recipients and non-SOT individuals**

The overall anti-CMV IgG positivity rate was 95.5% in total subjects. The CMV seropositivity of male was not significantly different compared to female in total subjects (95.2% [n=6634] vs. 95.8% [n=5288], $p = 0.093$) and SOT recipients (99.8% [n=1354] vs. 98.4% [n=830], $p = 0.564$). However, male in non-transplant group had the significantly lower CMV seropositive rate (94.2% [n=5280] vs. 95.3% [n=4458], $p = 0.016$). The frequency of anti-CMV IgG negativity was significantly lower among SOT recipients than among non-transplant recipients (1.33% vs. 5.23%, $p < 0.001$) (Table 1). Among total subjects, the repeated anti-CMV IgG test results were available for 816 of 276 SOT recipients and 540 non-transplant individuals. Almost all individuals remained positive (96.4%) and only seven subjects (0.86%) switched from a positive to negative serostatus, indicating the disappearance of humoral immunity against CMV.

**CMV seroprevalence according to age group**

The proportion of anti-CMV IgG negativity was nearly zero among SOT recipients aged ≥ 31 years, and among non-transplant individuals aged ≥ 41 years. CMV seronegative rates were highest among those aged 11–15 years (29.4% and 29.8 in SOT recipients and non-transplant individuals, respectively). Among those aged 16–20 (93.2% vs. 77.6%, $p = 0.018$), 26-30 (96.6% vs. 92.1%, $p = 0.046$), 31-35 (99.3% vs. 95.4%, $p = 0.037$), 36-40 (99.1% vs. 96.9%, $p = 0.048$) and 41-60 years (99.8% vs. 99.3%, $p = 0.038$), SOT recipients had significantly higher rates of seropositivity, compared to non-transplant individuals (Table 1). The adult SOT recipients aged > 18 years had
significantly lower seronegative rate than non-transplant individuals aged > 18 years (0.8% vs. 3.7%, 
P < 0.001), but the seroprevalence was similar between two groups aged ≤ 18 years (Table 1).

Anti-CMV IgG titres in SOT recipients and non-transplant individuals

The overall CMV IgG titre was significantly higher among SOT recipients than among non-transplant 
individuals (64.7 ± 44.3 vs. 54.7 ± 38.9 aU/mL, P < 0.001). Additionally, SOT recipients had 
significantly higher IgG titres relative to non-transplant individuals in the all age groups except 1-5, 6-
10 and 11-15-year-old. The subject aged ≤ 18 years had similar IgG titres between SOT recipients 
and non-transplant individuals (P = 0.847), but, SOT recipients aged > 18 years had significantly 
higher IgG titres compared to non-transplant individuals aged > 18 years (66.1 ± 44.7 vs. 52.3 ± 37.9 
aU/mL, P < 0.001) (Table 2)

CMV seroprevalence and titres according to transplant organs

The kidney (1436, 65.8%) was most common transplant organ in this cohort. The liver (LT) and lung 
(LTx) transplant recipients had significantly higher mean ages compared to kidney (KT) and heart 
transplant (HT) recipients (P < 0.001). In all age groups, overall anti-CMV IgG titres among LT (80.1 ± 
54.5 aU/mL) and LTx (84.3 ± 68.3 aU/mL) recipients were significantly higher than among KT (59.4 ± 
36.1 aU/mL) and HT (58.1 ± 46.9 aU/mL) recipients (P < 0.001). In addition, seropositive rates in all 
age groups were significantly higher in LT (99.7%) and LTx (100%) recipients than in KT (98.3%) and 
HT (97.0%) recipients (P = 0.024). However, CMV IgG positive rate and titres were similar between 
four-transplant organs among SOT recipients aged ≤ 40 years (Table 3)

Regression analyses for the effect of age and SOT on CMV seropositivity

The older age (OR: 1.12, 95% CI: 1.11-1.12, P < 0.001) and SOT (OR: 2.43, 95% CI: 1.65-3.59, P < 
0.001) were independent factors associated with higher CMV IgG positive rate. However, sex did not 
have the independent effect on CMV seroprevalence. Another regression model showed that the 
transplant organs were not related to CMV seropositive rate (Table 4).

Discussion

Our data demonstrate very high recent CMV seroprevalence (up to 95%) in South Korea, a developed 
country with a high socioeconomic status and well-organised public health system. As a result, our
data may suggest high proportions of both seropositive donors and recipients (D+/R+), which is considered a usual intermediate serostatus risk for CMV infection and disease after SOT through reactivation of latent virus [16, 23]. Our IgG seropositive rate is higher than 83% (or 88% of upper level in 95% uncertainty interval) of general CMV seroprevalence worldwide in recent meta-regression-based estimation [24]. Seronegative people were rare among those aged ≥ 41 years in non-transplant individuals and extremely rare among those aged ≥ 31 years in SOT recipients. In general, CMV seropositive rates were proportional to age except at teenagers. The lowest seroprevalence observed in subjects aged 11-15 years could be attributed to primary acquisition of CMV at adolescents owing to improved hygiene.

In addition, this analyses reveal high CMV IgG titres even in elderly population. A high CMV IgG titre and persistent immune reactivation caused by an inflation in the population of long-lived, non-classical CMV-specific effector memory CD8+ T lymphocytes have been associated with chronic inflammatory diseases, including atherosclerosis, stroke and coronary artery disease [3, 4, 14, 15, 25-28]. Therefore, this report showing fairly high seropositivity and IgG titres at old age might suggest further evaluation for prevention of CMV reactivation in specific population regardless of their immunocompromised status, as this approach could reduce the morbidity and mortality associated with inflammatory vascular diseases in rapidly aging societies.

Despite the international distribution of CMV, seropositivity rates around the world vary widely from 18% to 100%, according to geographical location, ethnicity and specific subpopulation features [24, 29-32]. In recent study of Li et al, stratification of serological profiles by age group revealed a very high IgG positive rate (97%) even among young individuals (0–14 years), in contrast to our data, that may be associated with high rate of breastfeeding or regional hygienic status [17]. The Netherlands study in 2006–2007 reported that non-Western individuals (76.7%) had a considerably higher seroprevalence than did native Dutch and Western individuals (41.5%) [31]. In general, the very high CMV seroprevalence of South Korea was similar to that of World Health Organization Eastern Mediterranean region, rather than European region or region of the Americas [24, 29, 31, 32]. The different breastfeeding rates and CMV IgM or IgG seropositive rates at women of reproductive age
could attribute to various CMV seroprevalence between countries or regions, because mother-to-infant CMV transmission may have a major impact on global epidemiology of CMV [24, 33, 34].

In a SOT setting reported in Hungary, living organ donors were found to have a CMV seroprevalence of 85% [35]. However, a detailed analysis of the pre-transplant CMV IgG seropositivity rates and titres among SOT recipients according to age groups or transplant organs as well as contrast to non-transplant individuals had not been fully reported. In our study, adult SOT recipients aged ≥ 18 years had a higher IgG seropositive rate and titres relative to non-SOT individuals. The SOT was the independent factor associated with high CMV seroprevalence in multivariate regression analysis. It would be informative to reveal that patients received SOT in end-stage organ disease state have the higher CMV IgG seropositive rates and titres compared to non-transplant individuals. This finding might have any association with asymptptomatically intermittently CMV replication and immune boosting against CMV by chronic end-stage medical diseases as well as polyclonal immune activation through pro-inflammatory cytokine release by fulminant acute organ failure leading to SOT [36-39].

Characteristically, the sub-analyses by transplant organs showed LT and LTx recipients have higher CMV IgG seroprevalence and titres compared to KT and HT recipients. But, multivariate regression model did not show the independent effect of transplant organs on higher seroprevalence. The older mean age in LT and LTx recipients seems to have a relation to their higher CMV IgG seropositive rates and titres.

This study was mainly limited by the retrospective large-scale data extraction. Accordingly, we could not perform further subgroup analyses according to healthy individuals, various underlying morbidities, and other immunosuppressive conditions except SOT and HSCT in non-transplant group. In addition, the purpose of CMV IgG measurement would be heterogeneous and was hard to obtain this information. But, 38.6% of in-patient test among non-transplant individuals may suggest that the substantial portion of non-transplant group did not receive CMV IgG test for routine health check-up without any illness. Therefore, our non-transplant group may be relevant to compare with IgG values of SOT recipients. In addition, this design did not allow the serial testing of anti-CMV IgG titres in all individuals with initial negative results. However, this study is the first to report a difference in the
qualitative and quantitative anti-CMV IgG findings between SOT recipients and non-transplant individuals according to serial age groups as well as transplant organs in SOT recipients.

**Conclusion**

The overall CMV seropositive rate in South Korea was as high as 95% among both SOT recipients and non-transplant individuals, and the frequency of seronegativity decreased to less than one percentage among adults aged ≥ 41 years. Furthermore, compared to non-transplant individuals, SOT recipients had higher CMV IgG titres. The wide range of prospective serosurveillance could be helpful in the general population, as well as among immunocompromised patients who harbour high risks of CMV infection and life-threatening end-organ diseases.

**List Of Abbreviations**

aU: Arbitrary unit  
CMV: Cytomegalovirus  
CVD: Cerebrovascular disease  
HSCT: Hematopoietic stem cell transplantation  
HT: Heart transplantation  
Ig: Immunoglobulin  
KT: Kidney transplantation  
LT: Liver transplantation  
LTx: Lung transplantation  
SOT: Solid organ transplantation

**Declarations**

Ethics approval and consent to participate: The study was approved by the institution review board in Gangnam Severance Hospital, which waived the requirement for informed consent.

Consent for publication: Not available

Availability of data and material: The datasets used and/or analyzed during the current study available from the corresponding author on reasonable request.

Competing interests: None of the authors declare conflicts of interest associated with this manuscript.

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Authors' contributions: YL performed the data collection, preparation, statistical analyses, interpretation of results, and wrote the manuscript. DEK, SGY and KHL involved in the review and revision of original draft. SHH provided project administration, intellectual comments about data interpretation and revised the manuscript. All authors read and approved the final manuscript.

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**Tables**

Table 1. Comparison of CMV IgG seroprevalence between solid organ transplantation recipients and non-transplant individuals according to age distribution

| Age (years) | Anti-CMV IgG | SOT recipients (n=2184) | Non-transplant individualsa (n=9738) | p value |
|-------------|--------------|-------------------------|--------------------------------------|---------|
| 1-5         | Positive     | 12 (80.0)               | 136 (81.0)                           | >0.999  |
|             | Negative     | 3 (20.0)                | 32 (19.0)                            |         |
| 6-10        | Positive     | 9 (75.0)                | 82 (81.2)                            | 0.700   |
|             | Negative     | 3 (25.0)                | 19 (18.8)                            |         |
| 11-15       | Positive     | 12 (70.6)               | 153 (70.2)                           | >0.999  |
|             | Negative     | 5 (29.4)                | 65 (29.8)                            |         |
| 16-20       | Positive     | 41 (93.2)               | 339 (77.6)                           | 0.018   |
|             | Negative     | 3 (6.8)                 | 98 (22.4)                            |         |
| 21-25       | Positive     | 54 (90.0)               | 655 (86.5)                           | 0.555   |
|             | Negative     | 6 (10.0)                | 102 (13.5)                           |         |
| 26-30       | Positive     | 114 (96.6)              | 987 (92.1)                           | 0.046   |
|             | Negative     | 4 (3.4)                 | 85 (7.9)                             |         |
| 31-35       | Positive     | 133 (99.3)              | 1129 (95.4)                          | 0.037   |
|             | Negative     | 1 (0.7)                 | 54 (4.6)                             |         |
| 36-40       | Positive     | 215 (99.1)              | 901 (96.9)                           | 0.048   |
|             | Negative     | 2 (0.9)                 | 29 (3.1)                             |         |
| 41-60       | Positive     | 1287 (99.8)             | 3358 (99.3)                          | 0.038   |
|             | Negative     | 2 (0.2)                 | 22 (0.7)                             |         |
| ≥ 61        | Positive     | 278 (100)               | 1489 (99.8)                          | 0.599   |
|             | Negative     | 0 (0)                   | 3 (0.2)                              |         |
| Total       | Positive     | 2155 (98.7)             | 9229 (94.8)                          | <0.001  |
|             | Negative     | 29 (1.3)                | 509 (5.2)                            |         |

**Adult vs. paediatric**

|         | Anti-CMV IgG | SOT recipients (n=2184) | Non-transplant individualsa (n=9738) | p value |
|---------|--------------|-------------------------|--------------------------------------|---------|
| ≤ 18    | Positive     | 59 (81.9)               | 527 (75.4)                           | 0.248   |
|         | Negative     | 13 (18.1)               | 172 (24.6)                           |         |
| > 18    | Positive     | 2096 (99.2)             | 8702 (96.3)                          | <0.001  |
|         | Negative     | 16 (0.8)                | 337 (3.7)                            |         |
Data are expressed as number (percent). aNon-transplant group included subjects who did not receive SOT or HSCT. Aberrations: CMV, cytomegalovirus; HSCT, hematopoietic stem cell transplantation; IgG, immunoglobulin G; SOT, solid organ transplantation

Table 2. Difference of anti-CMV IgG titre (aU/mL) between individuals who did not receive transplantation and solid organ transplantation recipients with seropositivity according to age distribution

| Age (years) | SOT recipients | Non-transplant individuals | p value |
|------------|----------------|-----------------------------|---------|
| 1-5        | 43.5 ± 16.6    | 46.2 ± 24.2                 | 0.707   |
| 6-10       | 48.1 ± 33.0    | 41.0 ± 32.6                 | 0.627   |
| 11-15      | 39.9 ± 14.0    | 51.1 ± 44.9                 | 0.391   |
| 16-20      | 56.9 ± 35.6    | 41.3 ± 27.7                 | 0.001   |
| 21-25      | 60.1 ± 43.9    | 45.8 ± 36.3                 | 0.008   |
| 26-30      | 55.0 ± 38.8    | 45.2 ± 30.7                 | 0.002   |
| 31-35      | 54.6 ± 27.8    | 47.4 ± 30.2                 | 0.010   |
| 36-40      | 64.7 ± 37.1    | 50.7 ± 33.9                 | <0.001  |
| 41-60      | 67.8 ± 45.3    | 55.9 ± 37.7                 | <0.001  |
| ≥ 61       | 70.4 ± 52.5    | 58.1 ± 48.8                 | <0.001  |
| Total      | 64.7 ± 44.3    | 54.7 ± 38.9                 | <0.001  |

Adult vs. paediatric

|                   | Adults | ≤ 18 | > 18  | p value |
|-------------------|--------|------|-------|---------|
| Anti-CMV IgG titre (aU/mL) |        |      |       |         |
|                   |        |      |       |         |
|                   | 47.7 ± 28.2 | 46.7 ± 37.4 | 0.847 |
| ≥ 18              | 66.1 ± 44.7 | 52.3 ± 37.9 | <0.001 |

Data are expressed as mean ± standard deviation. aNon-transplant group included subjects who did not receive SOT or HSCT. Aberrations: aU, arbitrary unit; CMV, cytomegalovirus; HSCT, hematopoietic stem cell transplantation; IgG, immunoglobulin G; SOT, solid organ transplantation

Table 3. Comparison of CMV seropositive rates and anti-CMV IgG titre (aU/mL) according to transplant organs in solid organ transplant recipients
| Age (years) | Kidney (n=1436) | Liver (n=579) | Lung (n=69) | Heart (n=100) | p value |
|------------|----------------|--------------|-------------|---------------|--------|
| ≤ 40       |                |              |             |               |        |
| Seropositive | 478 (95.2)    | 57 (98.3)    | 15 (100)    | 34 (94.4)     | 0.716  |
| Titre (aU/mL) | 57.7 ± 36.6  | 65.3 ± 42.6  | 69.5 ± 44.4 | 51.1 ± 27.0   | 0.184  |
| 41-60      |                |              |             |               |        |
| Seropositive | 801 (100)     | 400 (99.8)   | 33 (100)    | 47 (97.9)     | 0.073  |
| Titre (aU/mL) | 60.7 ± 34.6*† | 81.3 ± 55.5* | 88.5 ± 72.3† | 66.4 ± 60.7   | 0.001  |
| ≥ 61       |                |              |             |               |        |
| Seropositive | 133 (100)     | 120 (100)    | 21 (100)    | 16 (100)      | —      |
| Titre (aU/mL) | 59.9 ± 44.2*  | 82.9 ± 56.3* | 90.3 ± 80.5 | 48.8 ± 27.4   | 0.001  |
| Total      |                |              |             |               |        |
| Age, year  | 44.9 ± 12.4*† | 52.3 ± 12.0*‡| 50.2 ± 13.0†§| 44.3 ± 17.3†§| <0.001 |
| Seropositive | 1412 (98.3)   | 577 (99.7)a  | 69 (100.0)a | 97 (97.0)     | 0.024  |
| Titre (aU/mL) | 59.4 ± 36.1*† | 80.1 ± 54.5*‡| 84.3 ± 68.3†§| 58.1 ± 46.9†§| <0.001 |

Data are expressed as mean ± standard deviation. *†‡§p-value < 0.05 between two groups in post-hoc tests by Bonferroni correction after ANOVA. aadjusted p < 0.05 between two groups using post-hoc analyses based on adjusted standardized residuals. Aberrations: aU, arbitrary unit; CMV, cytomegalovirus; IgG, immunoglobulin G

Table 4. Logistic regression analyses to evaluate the effect of age and sex on CMV IgG positive rate in all subjects except hematopoietic stem cell transplant recipients

| Variables                              | OR  | 95% CI          | p value |
|----------------------------------------|-----|-----------------|--------|
| **Model 1**                            |     |                 |        |
| Age, yearsa                            | 1.117 | 1.111-1.124     | <0.001 |
| Sex, male                              | 1.174 | 0.975-1.414     | 0.090  |
| Solid organ transplantation, yes        | 2.432 | 1.648-3.589     | <0.001 |
| **Model 2**                            |     |                 |        |
| Age, yearsa                            | 1.376 | 1.346-1.407     | <0.001 |
| Sex, male                              | 1.155 | 0.528-2.530     | 0.718  |
| Transplant organ                       |     |                 |        |
| Kidney                                 | 1.415 | 0.371-5.400     | 0.611  |
| Liver                                  | 1.162 | 0.023-2.135     | 0.067  |
| Heart                                  | 1.541 | 0.163-3.793     | 0.315  |
| Lung                                   | 1.118 | 0.128-1.788     | 0.997  |
a per one-year increase. Aberrations: CI, confidence interval; CMV, cytomegalovirus; IgG, immunoglobulin G; OR, odds ratio, Ref, reference.