Association of cytomegalovirus infection with hypertension risk: a meta-analysis

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Summary
Background Information regarding association between cytomegalovirus (CMV) infection and essential hypertension (EH) risk is not consistent across studies. Therefore, we conducted a meta-analysis to investigate the association in detail.

Methods We comprehensively searched the published literature from the PubMed and Embase databases for any study analyzing the association between CMV and EH risk. A random-effects model was used to calculate the pooled odds ratio (OR) with 95% confidence interval (CI).

Results Three studies involving 9657 patients were included in the meta-analysis, and the results showed a significantly increased risk of EH in patients with CMV infection. Overall, 79.3% of the hypertension patients were CMV-positive, which was significantly higher than the percentage for controls (OR = 1.39, 95% CI = 0.95–2.05, P = 0.017). There was significant heterogeneity among the studies included (I² = 70.5%). The funnel plot and Egger’s test also indicated no publication bias.

Conclusions The results showed a significant association between CMV and EH, which indicates that CMV infection is a possible cause of EH.

Keywords Cytomegalovirus · Essential hypertension · Meta-analysis

Background
Essential hypertension (EH) is the most common form of hypertension [1] and is a major risk factor for cardiovascular, cerebrovascular, and renal diseases. Hypertension is a multifactorial disease [2], and its development involves both genetic and environmental factors; however, the specific mechanism and risk factors remain unclear.

As a member of the human Herpesviridae family, cytomegalovirus (CMV) contains double-stranded DNA [3] and establishes a latent infection that can persist for the lifetime of the host. Despite being nearly ubiquitous in the population [4], overt human CMV disease in adults is typically restricted to immunocompromised individuals [5–7]. In healthy individuals, both primary infection and the reactivation of latent virus rarely cause any significant clinical symptoms owing to the robust immune response of the host.

CMV infection is associated with various chronic inflammatory diseases, including cardiovascular diseases (CVDs) [8] such as myocarditis, atherosclerosis, and coronary artery disease [9–11]. Hypertension is an important cause of CVDs, and recent studies [12–18] have shown that patients with a CMV infection have an increased risk of EH; however, the association between CMV and EH remains unclear, and thus the effect of CMV infection on blood pressure is controversial. Therefore, we performed the present meta-analysis to more com-
pre comprehensively investigate the association between CMV and EH.

**Materials and methods**

**Literature search and selection**

We comprehensively searched the PubMed and Embase databases up to July 2015. The search key words used included “EH or hypertension”, “blood pressure”, and “CMV”. Relevant articles in the reference lists of the published literature were also searched manually for other potential studies.

**Inclusion and exclusion criteria**

Studies were included in the meta-analysis if they met the following criteria (1) case-control study, (2) investigated the positive rate of CMV in hypertension patients and controls, (3) hypertension is defined as systolic blood pressure (SBP) or diastolic blood pressure (DBP) of 140 or 90 mmHg, respectively, (4) not an animal study. Studies were excluded if insufficient details were reported to be able to perform the meta-analysis.

**Data extraction**

Two authors (JH and Y-YQ) extracted the data independently. In cases where any data were lacking from an article, the authors of selected studies were contacted directly for the missing data. The two reviewers came to an agreement before the final analysis. The following information was extracted from each study: first author’s name, year of publication, country, ethnicity, CMV detection method, patient characteristics, the sample sizes of cases and controls, and the relationship between CMV and EH.

**Statistical analysis**

We performed statistical analyses using Stata statistical software ver.12.0. (Stata Corporation, College Station, TX, USA). Meta-analysis was conducted by combining odds ratios (ORs) with corresponding 95% confidence intervals (CIs) for the association between the CMV-positive rate of hypertension patients and controls. Heterogeneity across all selected studies was evaluated using the Q-test and the I² statistic (range 0–100%) [19] and was judged to be significant when \( P < 0.1 \) or \( I^2 > 50\% \), respectively. We select the random-effects model in the analysis if significant heterogeneity was observed across studies; otherwise, the fixed-effects model was used. Sensitivity analysis was performed with the random-effects model to evaluate the stability of the crude results by removing one study at a time. The Begg’s funnel plot and Egger’s linear regression test were performed to determine the level of potential publication bias [20, 21]. A P-value lower than 0.05 was considered statistically significant.

**Results**

**Characteristics of studies included**

A total of three articles [12, 13, 16] were included in the meta-analysis, comprising 2347 cases and 7310 controls. All of the studies used enzyme-linked immunosorbent assay (ELISA), and one study [12] used a combination of ELISA and polymerase chain reaction (PCR). ELISA was used to determine the titer of anti-HCMV IgG antibodies, and quantitative PCR was used to test the HCMV DNA copy number. The flow diagram for the search process is shown in Fig. 1. The characteristics of the selected studies are given in Table 1.

**Meta-analysis results**

We pooled data from all studies included and analyzed the association between CMV and EH risk. A total of 79.3% of the hypertension patients were CMV-positive compared with 64.2% of the controls. The pooled OR was 1.39 (95% CI = 0.95–2.05, \( P = 0.017 \)). We used a random-effects model, given the significant heterogeneity (\( I^2 = 70.5\% \)) observed across studies. The overall result of the meta-analysis is shown as a forest plot in Fig. 2.

**Sensitivity analysis**

Sensitivity analysis was conducted to evaluate the stability of the crude results. The results showed that no single study substantially affected the stability of the crude results, given the lack of change in the ORs after exclusion of one study at a time (Fig. 3). Therefore, the results of this meta-analysis were deemed to be reliable.

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**Fig. 1** Flow diagram of the study selection process
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When a human is first infected, CMV replicates in many different cells. The virus can remain a latent state for the life of its host. In most immunocompetent individuals, the CMV infection is mild or even asymptomatic. Viruses modulate the intracellular environment so that it is optimized to support the viral life cycle. With heightened stress or immunosuppression, however, latent CMV can be reactivated reinitiating productive replication and causing clinical problems, especially in immunosuppressed or immunocompromised patients. Moreover, CMV infection has been shown to be associated with the increased arterial blood pressure via stimulation with renin and cytokine production in mice [23].

Recently, several previous studies have investigated the role of CMV seropositivity as a risk factor for hypertension. In a Chinese cohort, Tang et al. [12], showed that CMV seropositivity was significantly associated with hypertension after adjustment for age in Kazakh males but not in females. However, in another study cohort [13], CMV seropositivity was associated with hypertension in females before, but not after, adjusting for age. By con-
Reactive oxygen species (ROS) have been shown to be generated in response to CMV infection [26] and are also directly involved in vasoconstriction [27–30] and vascular inflammation [31]. CMV infection can induce an inflammatory reaction through modulation of inflammatory mediators that evoke vasoconstriction, such as cytokines, chemokines, and adhesion molecules [32–34]. Second, CMV might influence hypertension via regulation of the renin-angiotensin system. CMV infection has been shown to induce the generation of angiotensin II (AngII) [25], which reacts with endothelial nitric oxide synthase to promote vasoconstriction; this may also enhance the production of ROS [35, 36]. An in vivo experimental study showed that CMV infection increased arterial pressure and further stimulated the expression of renin and increased AngII levels in the blood and arterial tissues [23], which can lead to arterial constriction. Third, the immune response triggered by CMV infection could itself lead to hypertension. Indeed, suppression of the immune system has been shown to depress blood pressure in both experimental animals and humans [37]. Finally, genomic-related changes could be involved in the mechanism. In particular, DNA methylation of gene promoter region [38–40] and the corresponding changes in mRNA expression [14] are also involved in regulating blood pressure. The studies included there are not enough, so we need more prospective studies to prove the link.

The results of the present meta-analysis suggest that CMV may be a contributing factor to the development of EH. However, there are limitations to the meta-analysis that should be acknowledged. First, although the pooled sample size of the studies included was sufficiently large to carry out the meta-analysis, the number of studies included is not as large as we had hoped for in order to perform a comprehensive analysis. In particular, this limited our ability to conduct a subgroup analysis to explore the influence of sample size, ethnicity, age, or other factors and to explore the nature of the observed heterogeneity. Therefore, these findings should be interpreted with caution, and more studies are needed to confirm the results of this meta-analysis.

Conclusions

The results showed a significant association between CMV and EH, which indicates that CMV infection is a possible cause of EH.

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Compliance with ethical standards

Conflicts of interest
J. Hui, Y.-y. Qu, N. Tang, Y.-m. Liu, H. Zhong, L.-m. Wang, Q. Feng, Z. Li, and F. He declare that there are no actual or potential conflicts of interest in relation to this article.

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