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Meta-analysis of cytomegalovirus seroprevalence in volunteer blood donors and healthy subjects in Iran from 1992 to 2013

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ABSTRACT

Objective(s): Human cytomegalovirus (CMV), a double-strand DNA herpesvirus, can be transmitted via blood transfusion which is especially important for immunocompromised recipients and can cause a fatal infection. CMV seroprevalence in Iran was studied on blood donors, healthy subjects, and some patients. Highly variable rates were detected. The purpose of this study was to review CMV seroprevalence in blood donors and apparently healthy individuals, in Iran.

Materials and Methods: One hundred and fifty-eight electronic and paper-based resources and databases including published articles in internal and external journals, seminars, dissertations, and theses available in the database and different websites were used to be systematically reviewed as a meta-analysis. Less related articles to the issue, papers of specific high risk population, and articles with not enough information, were excluded. Eventually 22 articles that satisfied our selection criteria were systematically reviewed and analyzed. To explore heterogeneity between studies the I square (I^2) index was used. Data were analyzed using the statistical software package (STATA) 11.

Results: The heterogeneity between selected studies was 97% with an I^2 statistic. In this study a random effects model was used for meta-analysis. The prevalence of CMV IgG and CMV IgM antibodies in the country were estimated to be 92% (95% CI: 90-94) and 2.6% (95% CI: 1.7-3.6), respectively.

***Conclusion*:** Given high rate of CMV seropositivity in Iran, it seems that CMVAbs screening would not be a reasonable and affordable approach to prevent CMV infection via transfusion especially for immune compromised recipients, so alternative strategies should be considered.

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Introduction

Cytomegalovirus (CMV) a double-strand DNA herpes virus (1) is very common infection and can lead to major disability and mortality for an immune compromised host. Transfusion of infected blood is one of human cytomegalovirus (HCMV) transmission routes. Primary infection in immunocompetent hosts usually is asymptomatic and mostly occurs in childhood and adolescence but can also be seen in adults. CMV causes severe disease with high mortality in immunocompromised individuals including solid organ transplant recipients, hematopoietic cell transplant recipients, HIV-infected patients, and patients treated with immunomodulating drugs.

The virus may hide in white cells and have a latent status after primary infection and reactivation of infection may occur whenever immune status changes, in immunocompromised and immunocompetent patients. Clinical manifestations often mimic infectious mononucleosis or severe influenza. CMV disease can be identified by finding the evidence of CMV infection with attributable symptoms or signs that may be manifest either as a viral syndrome such as fever, malaise, leukopenia, thrombocytopenia or as evidence of tissue invasion such as neurological, pulmonary, gastrointestinal, ocular, cardiovascular, and hepatic manifestations (2-5). Transmission of CMV during pregnancy can be as high as 40% and in first trimester of gestation and may lead to severe fetal developmental abnormalities (1, 4-6).

The diagnosis of CMV infection can be relied on different techniques including: electron microscopic detection of typical CMV virion, histologic or cytologic detection of typical CMV cytopathology, isolation of virus, detection of CMV antigen in blood and tissues, detection of CMV genome in tissues, DNA

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amplification, and serology techniques based on CMV antibodies detection. The diagnosis of CMV infection in immunocompromised patients can be difficult as it requires virus detection and determination of CMV as the cause of the disease. Several other tests are available including: DNA probe techniques, polymerase chain reaction (PCR), and immunofluorescence technique for detection of CMV early antigen (pp65) in circulating leucocytes (7). One of the most common available serologic tests to detect CMV IgG and CMV IgM antibodies is based on enzyme-linked immunosorbent assay (ELISA). IgG positive result is indicative of a person infected by CMV during his or her life. This test is not able to determine the exact time of infection. CMV IgM presence could be interpreted as new infection, acute infection or re-activation of CMV. It has been reported that CMV infection rate increases with blood donor age (3, 4). There are many articles on CMV antibody prevalence in blood donors, healthy people, pregnant women, HIV positive subjects, and patients' candidate for renal transplantation in Iran (8-33), which reflect highly variable rates among different populations in different provinces.

The purpose of this study was to conduct a meta-analysis in order to define the rate of CMV seropositivity among the blood donors and healthy subjects and suggest a better way to limit transfusion transmission CMV, especially for immunocompromised recipients.

Materials and Methods

This study is a meta-analysis to define the seroprevalence of CMV infection in Iran among apparently healthy people and blood donors based on review of all published papers and theses documents from January1992 up to December 2013. Electronic and paper-based resources and databases were used, including published articles in internal and external journals, seminars, dissertations, and theses available in the databases and different websites (e.g: Index Copenicus, PubMed, academic journals database, free medical journals, Google scholar, SID, Magiran, Iran Docs, Medlib, Google, Bing, webcrawler, scientific journal of Iranian blood organization (IBTO) and IBTO research information booklet, dissertations) or theses in the above databases and the ones that were available in the libraries of Medical Faculty of the Universities of Tehran, Iran, Shahid Beheshti, and Tarbiat Modarres in Tehran. The literature search was performed using the dedicated keywords including CMV IgG, CMV IgM, blood donors, Iran, CMV infection, blood donors, CMV seroprevalence, meta-analysis, in reports published in both English and Persian.

To limit the different articles and records in different data bases , a combination of keywords was used in the different electronic resources or search engines (e.g: CMV + Iran + blood donors + IgG + IgM, in Google Scholar and Iran + CMV + IgG in PubMed). The registered cases about CMV in the libraries were studied. Totally nearly 800 different sources or records (including published articles in internal and external journals, seminars, and dissertations) were found, most relevant records were saved in Endnote software and duplicated (or repeated) papers or records were deleted.

Selection criteria

Initially all articles and dissertations that reported CMV were reviewed separately. Only those that specifically referred to the estimated prevalence of CMV antibodies in Iranian population were enrolled and unrelated reviews and studies with no reports of prevalence or insufficient data were excluded from the study, after critical evaluation by the authors. Based on the above steps a total of 158 records were found about CMV infection on groups of post kidney/liver, and hematopoietic stem cell transplantation (HSCT), pregnant women and their neonates after exchange blood transfusion, thalassemic patients, neurological patients, Iranian blood donors of some provinces, patients with heart diseases, HIV positive patients, healthy subjects as control groups of different ages, and army force pilots. Initially 45 articles were selected. Subsequently, 12 less relevant articles, 6 papers about high risk population, and 5 articles without enough informative data were excluded. Eventually 22 articles that satisfied our selection criteria were systematically analyzed.

Data extraction

The 22 statistically analyzed. The percentage of IgG and IgM positivity, were transcribed into a table that included place of study, study time, sample size, percentage of CMV IgG and CMV IgM antibodies positivity, and general characteristics of the samples (Table 1).

The antibodies were tested by ELISA method (based on colorimetry) using different kits prepared from different manufactures like: Dia-Pro (Italy), Diagnostica EIA-Gen (Italy), Biochem (Germany), Pishtaz-reb (Iran), Trinity Biotech Captia™ (USA), Radim SPA (Italy), Euroimmune (Germany), Sigma Diagnostica, IBL International, Biotest (Germany). CMV antibodies were evaluated with Minineph kit based on nephelometry in one study (20).

Statistical analysis

The prevalence rate of CMV antibodies (IgG and IgM) was collected from descriptive studies in this field. In this review a random effects model was used for meta-analysis, the heterogeneity between selected studies was tested using I square (I^2) statistic. The test significance level was set at 0.05. Data were analyzed using the statistical software package (STATA) 11.

Table 1. Characteristics of selected studies (including: year/population/detection method/sample size/ results). -: Not reported

% IgM positivity	% IgG positivity	Detection method	N	Population	Year	Place	Reference
-	96	ELISA	180	Blood bags (as controls)	1991	Tehran	18
0.4	89.6	ELISA	1040	Blood donors (as controls)	2004	Tehran	7
3.4	89.2	ELISA	500	Blood donors	2004	Zanjan	11
2.3	-	ELISA	600	Blood donors	2004	Kashan	14
0	100	ELISA	30	Blood donors (as controls)	2004	Tehran	9
-	94	ELISA	250	Urmia residents	2005	Urmia	24
2.8	100	ELISA	180	Blood donors (as controls)	2006	Urmia	21
-	92.8	ELISA	1754	Bushehr residents	2007	Bushehr	25
4.9	-	ELISA	225	Healthy subjects <15Y	2007	Ardebil/ Tehran	27
4.4	98.9	ELISA	364	Blood donors	2007	Shiraz	17
13.5	88.6	ELISA	37	Blood donors (as controls)	2008	Urmia	10
-	100	ELISA	925	Kidney donors (as controls)	2009	Tehran	28
-	96.7	ELISA	96	Healthy subjects	2009	Ahvaz	29
1.1	94.4	ELISA	360	Female university students	2009	Kazeroon	30
6.2	95.4	ELISA	65	Healthy subjects	2010	Tehran	19
0	75	ELISA	200	Healthy Women (as controls)	2010	Jahrom Hormozgan	31
6.5	49	Minineph	123	Blood donors (as controls)	2011	Zabol	20
-	98.2	ELISA	595	Province residents	2011	Isfahan	16
0.4	55	ELISA	270	Blood donors (as controls)	2012	Khoramabad	12
0.28	69.6	ELISA	20	Healthy Men	2013	Tehran	32
-	93	ELISA	100	Healthy people	2013	Tehran	22
1.6	99.2	ELISA	1008	Blood donors	2013	Mashhad	13

Results

Twenty two articles estimated the prevalence of CMV IgG and 15 articles evaluated the prevalence of CMV IgM antibodies were analyzed (Table 1). The studies were conducted in the time period of 1992 to 2013.

Total number of subjects in all articles was 8913, in average 405 people. In these studies, the highest rate of CMV IgG prevalence was reported as high as 100% in 180 blood donors of Urmia in 2006 (21), 30 blood donors of Tehran in 2004 (9), and 925 kidney donors of Tehran in 2009 (28). The lowest prevalence of CMV IgG was found as 49% among 123 blood donors in Zabol (20) and 55% (95% CI: 49-60) in 2012 among 270 blood donors from Khoramabad (12).

As the purpose of this study was to estimate the pooled prevalence of CMV IgG and CMV IgM antibodies in the Iranian blood donors and healthy subjects, based on the heterogeneity test (I square=%97) a random effects model was considered.

The prevalence of CMV IgG using the random effects model in Iranian blood donors and healthy individuals was 92% (95% CI: 90-94) (Figure 1).

In some articles listed in Table 1, IgM prevalence was not studied so the sample size for meta-analysis of IgM prevalence was 15 out of 22 articles. The heterogeneity between these 15 reviewed studies was tested using I square (I^2) statistic. Based on the heterogeneity test (I^2=%83) a random effect model was considered.

The prevalence of CMV IgM using the random effect model in Iranian population was 2.6% (95%CI: 1.7-3.6) (Figure 2).

The highest rate of CMV IgM prevalence was eported 13.5% in 37 blood donors of Urmia in 2008 (10), and the lowest prevalence of CMV IgM was reported as 0.28% and 0.4% among healthy and blood donors individuals in Tehran (7, 32) and blood donors in Khoramabad (12), respectively.

Discussion

Using our criteria and analysis the prevalence of CMV IgG and CMV IgM antibodies in blood donors and healthy subjects were found to be 92% and 2.6%, respectively. The high seroprevalence of CMV IgG reflects the endemic state of CMV infection in Iran.

There are many studies about the prevalence of CMV antibody in adult population who live in different parts of the world; however the results may not be comparable because of different diagnostic methods,

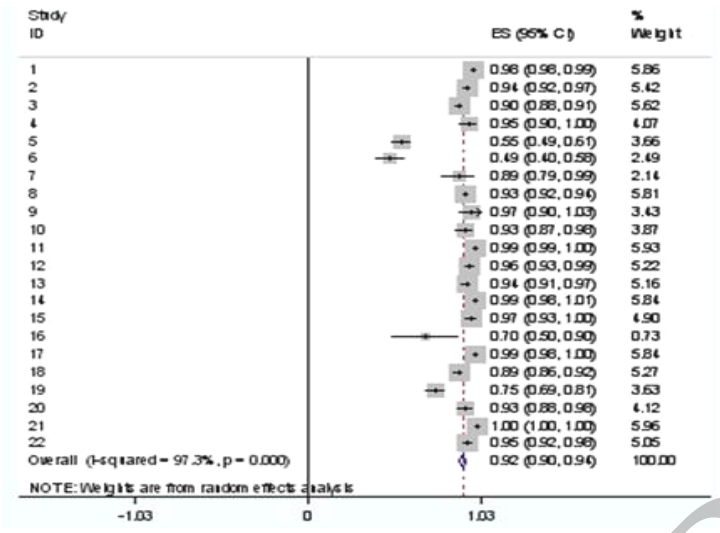

Figure 1. Forest plot of cytomegalovirus IgG antibody prevalence for random effects meta-analysis. Confidence interval (CI)

tools, and sample sizes. The results of several articles with available abstracts or full texts focused on CMV antibodies prevalence in blood donors or healthy subjects from different countries are summarized in Table 2. Articles with no information about method of antibody detection were excluded. The highest CMV IgG prevalence (97.2%) was reported in Turkey (39), while the lowest rate (64%) was reported in Brazil (35). The highest CMV IgM prevalence (19.5%) was reported in Lagos (41), while the lowest rate (0.071%) was reported in India (49).

Previous systematic review and meta-analysis regarding CMV seroprevalence in healthy or blood donors has not been conducted in Iran, therefore we were not able to compare the results with another similar study in the country. Blood donation is voluntary and unpaid in Iran, with age range between 18 to 65 years old. More than 90% of donors are men. Blood donors are selected as test group in some studies, or as control group in a couple of studied articles (34, 38). According to information written in some articles (Table 1) healthy controls were selected from healthy relatives of patients included in the studies, female students, province population. (22, 24, 27, 28, 30).

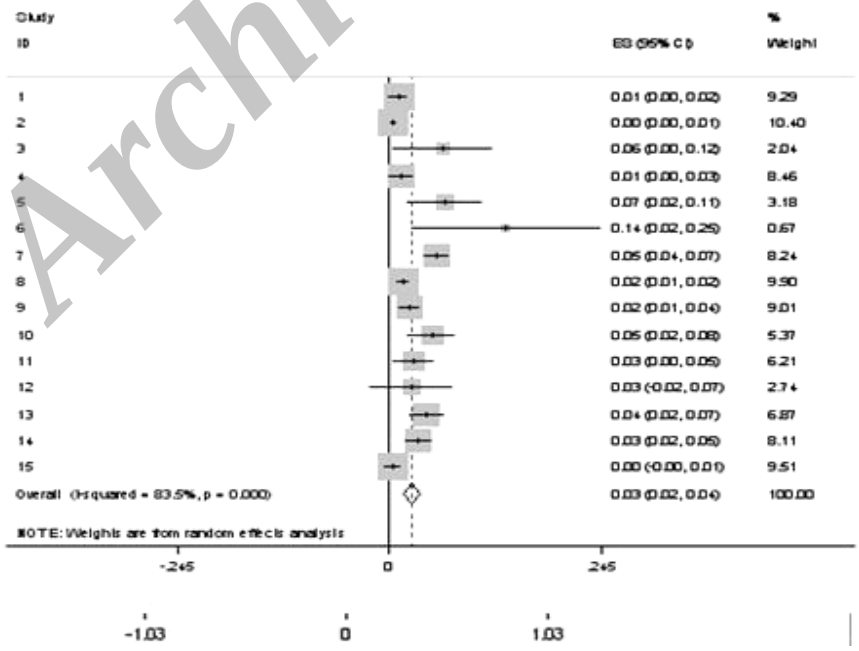

Figure 2. Forest plot of cytomegalovirus IgM antibody prevalence for random effects meta-analysis. Confidence interval (CI)

Table 2. Characteristics and results of studies reporting cytomegalovirus IgG and IgM antibodies prevalence

Country	Year	N	population	% IgG positivity	% IgM positivity	References
India	2002	200	Blood donors	95	4.5	36
Thailand	2001	441	Blood donors	52.23	9.52	37
Germany	2004	24,260	Blood donors	45.8		38
USA	2006	16,040 >20Y	Normal USA Population	68	-	2
Turkey	2008	1,264	Blood donors	97.2	-	39
India	2008	5,600	Blood donors	-	0.071	40
Lagos	2009	122	Blood donors	96	19.5	41
Sudan	2009	150	Blood donors	77	-	42
Bangladesh	2010	100	donors, staffs	94	2	43
Brazil	2010	1,045	Blood donors	64	2.3	35
Iraq	2011	90	Blood donors	-	3	44
Nigeria	2012	200	Blood donors	92	-	45
Nigeria	2012	192	Blood donors	95.8	3.1	46
Saudi Arabia	2012	316	Female students	76	-	47
Jordan	2012	2,000	Blood donors	90	-	48
Japan	2013	2,400	Blood donors	76.6	-	49

The seropositivity rate of CMV in people over 40 years of age in the world is 60 to 100%, due to different factors and spreading through contacts in public places (34). Nearly 90% of population more than 6 years of age in developing countries are infected to CMV (30). It is suggested that CMV antibodies presence is related to different factors such as socioeconomic level, and environmental and climatic factors. Souza *et al* (35) and Staras *et al* (2) declared there was no correlation between the presence of CMV antibodies and the socioeconomic characteristics of donors in the USA and Brazil. In one of the included studies (7), that serum samples were collected in spring and summer time, there was not any significance difference according to age, socioeconomical, and gender of blood donors (unpublished results).

Mostafavi *et al* in his study on the residents of Isfahan province showed high prevalence of CMV infection (nearly 96%) in children under 9 years old and reported that there were no difference or no relationship between CMV prevalence and age groups of 6-9, 10-19, and above 19 years of age; this reflects the fact that most infections in Iran may acquire at early ages. With regard to the reported high rate of CMV seropositivity in children under five years of age, Mostafavi *et al* concluded that the role of congenital, perinatal, and breast feeding transmission of CMV may have a greater effect than childhood contact in kindergartens and schools (16).

Safabakhsh (13) did not report any relationship between CMV seropositivity with gender and age.

The rate of CMV IgG and IgM positivity is reported in range between 52.23% in Thailand (37) to 97.2% in Turkey (39) and 0.071% in India (40) to 19.5% in Lagos (41), respectively (Table 2). The ranges of IgG and IgM seropositivity in Iran look as the same as other developing countries.

Although CMV infection in healthy subjects is mostly asymptomatic, transfusion transmitted CMV infection might be risky in immunocompromised patients (38) such as pregnant women, newborns and such as pregnant women, newborns and immunocompromised patients. Seronegative subjects and infants acquire CMV through infected blood products or direct contact with

infected people (39). Although CMV transmission by non-leukoreduced blood products from seropositive donors occurs undoubtedly, detection rate of viable CMV is very low. It is reported that blood donation from small groups of donors can cause transmission of CMV. There are no data about the infectious dose of CMV, however low concentrations might be assumed infectious for immunocompromised patients. Low concentration of CMV in peripheral blood of immunocompetent subjects causes limitation to detect the virus in their sera (50). Several different strategies have been suggested to reduce the risk of transfusion transmitted CMV.

A possible strategy for immunocompromised patients is to remove leukocytes to decrease latent virus, but due to window period of CMV infections and seroconversion, some apparently seronegative donors with transient viremia (increasing CMV DNA in plasma) may be able to transfer CMV (38).

Providing seronegative blood units is another strategy, but because of high prevalence of CMV (>90%) in some countries, and the need for screening of a great number of blood donations (39), providing of seronegative donors strategy may not be practically affordable. Bowden reported that "the incidence rate of CMV transmission in patients receiving seronegative blood products is 1.3% while it is 2.4% in patients receiving leukodepleted blood products". In this regard using leukodepleted blood products will not be able to significantly reduce CMV transmission. NAT testing may be a useful option, however it is challenging and there are limitations in identifying infected donors during seroconversion; it is reported that CMV DNA is rarely detectable in donors with long term CMV infection. Other strategies to identify infectious donors including testing of urine due to higher viral load in the urine and testing for rising IgM antibody titres are also suggested (50). The rate of CMV DNA positivity is reported as 75-80% in seroconverting individuals (38). Wu and colleagues reported probable transmission of CMV in seronegative patients during transfusion of leukoreduced, CMV-untested cellular blood products (50). Amini *et al* reported CMVDNA positivity in 6 out of 450 blood donors in Tehran blood center, in 2009, who all were CMV IgG positive and CMV IgM negative (51).

Ziemann and Hennig proposed that investigation of the interval between blood donation and transfusion might be useful because CMV stability could be affected by the conditions and duration of blood products storage prior to transfusion (50).

Due to high rate of CMV seropositivity in our country (nearly 92%) CMV antibody screening is not an efficient practical and financial option to identify CMV seronegative blood donors. CMV seronegative blood units should be made available for neonates and immunosuppressed patients or chronic users of blood products. There is no evidence of neonatal transfusion transmitted infection in Iran which might be due to high seroprevalence rate of mothers and passive IgG transfer to newborns.

In brief due to high rate of CMV seropositivity in Iran, it seems that CMV antibody screening is not an efficient or affordable strategy to prevent transfusion transmitted CMV of susceptible recipients, so alternative strategies, (e.g: leukoreduction filtration, saline-washed RBCs, and irradiation) might be helpful to minimize the transmission of CMV through transfusion.

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