Human cytomegalovirus is the cause of essential hypertension

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Abstract

Objective: To our knowledge, no study has provided strict evidence of a clear relationship between a human cytomegalovirus (HCMV) infection and human essential hypertension (EH).

Methods: To examine the possible role of HCMV in the etiology of EH, a literature searched through the electronic database PubMed was performed. Data were accurately assessed and re-analyzed by new statistical methods.

Results: The meta-analysis results of this study provide evidence that HCMV infection and essential hypertension are connected.

Conclusions: Without HCMV infection no EH.

Keywords: ***Human cytomegalovirus, essential hypertension, causal relationship.***

1. Introduction

Human cytomegalovirus as a large dsDNA virus belonging to the ß-herpes virus family (Dolan et al., 2004) is ranked among one of the most common infections in adults globally (Bate, Dollard, & Cannon, 2010) with the seropositive rates ranging from 60–99% (Cannon, Schmid, & Hyde, 2010). Once acquired, HCMV establishes lifelong latency (Crough & Khanna, 2009) and may periodically reactivate without causing symptoms in healthy individuals. Theoretically, a common widespread virus, such as HCMV, might initiate hypertension too. Cheng et al. (Cheng et al., 2009) found that mouse cytomegalovirus infection caused a significant increase of blood pressure in mice independent of a high cholesterol diet. Previous research documented repeatedly that HCMV seropositivity (Firth et al., 2016) is associated with hypertension (S. Li et al., 2011). Meanwhile, HCMV is identified as one of several predisposing factors for hypertension (Hui et al., 2016) and it is widely accepted that HCMV plays an important part in the pathogenesis of essential hypertension. Moreover, some studies found that HCMV IgG titers are associated with high blood pressure (Haarala et al., 2012; Jeong et al., 2016; Tang et al., 2014). HCMV IgG titers may indirectly represent the cumulative viral burden and HCMV itself remains in the human host throughout lifetime (Gandhi, Wills, Sissons, & Carmichael, 2003). Reactivation of latent HCMV infection, recurrent HCMV infection may result changes and in higher HCMV IgG antibody concentrations. In point of fact, most of the aforementioned studies demonstrated a positive relationship between HCMV infection and hypertension but the cause of essential hypertension is still not identified. To the best of our knowledge, this study is the first to comprehensively report on the causal relationship between HCMV IgG titers and essential hypertension.

2. Material and methods

HCMV is a double-stranded DNA virus of the β-herpesvirus family genome and persists in certain human host cells for life after primary infection (Dolan et al., 2004), HCMV is never cleared by human host. Reactivation and latency are defining characteristics of HCMV infection. A reactivation from latency (Sinclair & Sissons, 2006) even in non-immunocompromised individuals can results in serious disease. HCMV IgG indicates HCMV positivity or latency while changes of HCMV IgG during HCMV latency (Mehta, Stowe, Feiveson, Tyring, & Pierson, 2000) might point to recent or frequent HCMV reactivation. Reactivations or superinfections may result in higher titers of HCMV immunoglobulin G (IgG) antibodies but of increased levels of pro-inflammatory markers too. HCMV-specific IgG is used as an indicator for long-term HCMV infection. HCMV IgG titers are measured while using different kits. The cutoff value for HCMV positivity was different. The sensitivity and specificity of these kits is different which might have impact on the results achieved.

2.1. Material

2.1.1. Search Strategy

Meta-analysis can be a very useful tool to combine information from different sources but is as such not free of errors and may result in misleading results. In general, one of the main problems of meta-analysis is how to evaluate the presence of publication bias. Still, for the questions addressed in this paper, the electronic database PubMed was searched for appropriate studies (published later than 1.1.2015) conducted in any country which investigated the relationship between HCMV and EH i. e. sero-epidemiologically or by polymerase chain reaction (PCR) et cetera. The search in PubMed was performed while using some medical key words like “cytomegalovirus and atherosclerosis” or “cytomegalovirus and atherosclerosis”. Those articles were considered for a re-view where data were available without significant access barrier. Additionally, the reference list of identified articles was used as a potential source of articles appropriate for this study.

Table 1. ***The article selection process of the studies analyzed***

1. Identification of records	Size	Total
Records identified by searching in the databases		
PubMed	139	
Lipid Studies	0	
Immune-suppressive Drug studies	0	
		139
2. Clean-up of search (Screening)		
Records removed after verifying duplication, excluded by title, excluded due to other reasons		130
3. Eligibility		
Articles evaluated for eligibility		9
Articles excluded for various reasons	6	
4. Included		
Articles included in the meta-analysis (**Table**)		3

Adopted from PRISMA 2009 (Moher, Liberati, Tetzlaff, & Altman, 2009).

2.1.2. HCMV IgG-Studies considered for re-analysis

The following HCMV IgG sero-epidemiological studies (Feng et al., 2018; Z. Li et al., 2017; Tang et al., 2014) as presented by **Table 2** were considered for meta-analysis.

Table 2. ***Without*** **HCMV IgG sero-positivity** ***no*** **EH**.

Study	Year	N	Case +	Case Tot	Con +	Con Tot	k	P Value (k)	**p(SINE)**	P Value	X²(SINE|Bt)	p (IOI) + P(IOU)	p(IOU)	p(IOI)
Tang et al.	2014	800	452	467	312	333	0,074	0,016	0,981	0,019	0,482	0,910	0,539	0,371
Tang et al.	2014	800	433	482	288	318	-0,012	0,092	0,939	0,059	4,981	0,803	0,504	0,299
Li et al.	2017	339	146	148	186	191	0,044	0,228	0,994	0,006	0,027	0,959	0,416	0,543
Feng et al.	2018	720	348	360	336	360	0,076	0,017	0,983	0,017	0,400	0,900	0,450	0,450
	Total	2659	1379	1457	1122	1202			0,97067	**0,02891**	**5,89015**	0,893		

Alpha =	0,05	
D. f. =	4	
X²(Critical) =	**9,48773**	
P Value =		**0,2075**

The study design of the most studies was very inappropriate thus that the result of the re-analysis can be biased (p (IOI) + p(IOU) = 0,893).

2.1.3. HCMV and smoking

Table 3. *Without* HCMV IgG sero-positivity *no* smoking.

The study of Li et al. , 2017.

Country: **China**	Smokers YES	NO		
HCMV (IgG) YES	192	355	**547**	
HCMV (IgG) NO	**5**	11	16	
	197	366	**563**	**PMID: 28837559**

Statistical analysis

Causal relationship k =	**+0,013**	95 % CI (k) :	(-0,081	to	0,108)
P value (k | HGD) =	**0,203**	Chi Sq.(k) =	0,101	Z Score (crit val) =	2,000
p(IOI) =	**0,622**	**p(IOU) =**	**0,321**	**p(IOU) + p(IOI) =**	**0,943**
p (SINE) =	**0,991**	**X^2(SINE|Bt) =**	**0,127**	**X^2(SINE|At) =**	**1,563**
P likely (SINE)=	0,991	**P Value (SINE)=**	**0,009**		
p (IMP) =	**0,369**	X^2(IMP| At)) =	230,393	X^2(IMP|Bt) =	344,331
P likely (IMP) =	0,532	P Value (IMP) =	0,468		
p (SINE ^ IMP) =	**0,361**	X^2(SINE^IMP|At) =	344,458	X^2(SINE^IMP|Bt) =	344,458
p likely (SINE^IMP)=	0,528	p Value (SINE^IMP)=	0,472		
p (EXCL) =	**0,659**	X^2(EXCL| At)=	67,393	X^2(EXCL|Bt)=	187,127
P (Likely EXCL)=	0,711	P Value (EXCL)=	0,289		
Odds ratio (OR) =	1,190	95 % CI (OR) :	(0,407	to	3,475)

2.1.3. HCMV and alcohol consumption

Table 4. *Without* HCMV IgG sero-positivity *no* alcohol consumtion.

The study of Li et al., 2017. .

Country: **China**		Alcohol YES	NO		
HCMV (IgG)	YES	135	412	**547**	
	NO	**4**	12	16	
		139	424	**563**	**PMID: 28837559**

Statistical analysis

Causal relationship k =	**-0,001**	95 % CI (k) :	(-0,095	to	0,093)
P value (k | HGD) =	**0,228**	Chi Sq.(k) =	0,001	Z Score (crit val) =	2,000
p(IOI) =	**0,725**	**p(IOU) =**	**0,218**	**p(IOU) + p(IOI) =**	**0,943**
p (SINE) =	**0,993**	**X^2(SINE|Bt) =**	**0,115**	**X^2(SINE|At) =**	**1,000**
P likely (SINE)=	0,993	**P Value (SINE)=**	**0,007**		
p (IMP) =	**0,268**	X^2(IMP| At)) =	310,318	X^2(IMP|Bt) =	400,340
P likely (IMP) =	0,481	P Value (IMP) =	0,519		
p (SINE ^ IMP) =	**0,261**	X^2(SINE^IMP|At) =	400,455	X^2(SINE^IMP|Bt) =	400,455
p likely (SINE^IMP)=	0,478	p Value (SINE^IMP)=	0,522		
p (EXCL) =	**0,760**	X^2(EXCL| At)=	33,318	X^2(EXCL|Bt)=	131,115
P (Likely EXCL)=	0,787	P Value (EXCL)=	0,213		
Odds ratio (OR) =	0,983	95 % CI (OR) :	(0,312	to	3,099)

2.2. Methods

2.2.1. Definitions

Definition 1. (The 2x2 Table)

Karl Pearson (K. Pearson, 1904) introduced in 1904 the notion of a contingency table (I. Barukčić, 2019a, 2019d) or two by two table. Especially the relationships between Bernoulli (i. e. Binomial) distributed random variables can be examined by contingency tables. Thus far, let a Bernoulli distributed random variable A_t occur/exist et cetera with the probability $p(A_t)$ at the Bernoulli trial (period of time) t. Furthermore, let another Bernoulli distributed random variable B_t occur/exist et cetera with the probability $p(B_t)$ at the same Bernoulli trial (period of time) t. Let $p(a_t)= p(A_t \cap B_t)$ denote the joint probability distribution of A_t and B_t at the same Bernoulli trial (period of time) t. The following table (**Table 7**) may show the relationships in more details.

Table 5. The probabitlities of a contingency table

		Conditioned B		
		Yes = +1	**No = +0**	**Total**
Condition A	Yes =+1	$p(a_t)$	$p(b_t)$	$p(A_t)$
	No = +0	$p(c_t)$	$p(d_t)$	$p(\underline{A}_t)$
	Total	$p(B_t)$	$p(\underline{B}_t)$	**1**

In this context, it is *per definitionem*

$$
\begin{array}{ccccc}
p(A_t) & \equiv & p(a_t)+p(b_t) & = & 1-p(\underline{A}_t) \\
p(B_t) & \equiv & p(a_t)+p(c_t) & = & 1-p(\underline{B}_t) \\
p(a_t) & \equiv & p(A_t \cap B_t) & = & 1-p(b_t)-p(c_t)-p(a \\
+1 & \equiv & p(A_t)+p(\underline{A}_t) & = & p(B_t)+p(\underline{B}_t) \\
+1 & \equiv & p(a_t)+p(b_t) & + & p(c_t)+p(d_t) \\
p(B_t)+p(\Lambda_t) & \equiv & p(A_t) & = & 1-p(\underline{B}_t)+p(\Lambda_t) \\
p(\underline{A}_t) & = & 1-\left(1-p(\underline{B}_t)+p(\Lambda_t)\right) & = & p(\underline{B}_t)-p(\Lambda_t) \\
p(\Lambda_t) & = & p(A_t)-p(B_t) & = & p(b_t)-p(c_t) \\
p(b_t)+p(c_t) & = & \left(2\times p(c_t)\right)+p(\Lambda_t) & = & 1-p(a_t)-p(d_t)
\end{array}
\qquad (1)
$$

while +1 may denote *the normalized sample space* of A_t and B_t. Under circumstances were *the probability of an event is* ***constant*** *from trial to trial* (i. e. Binomial distribution), the relationships above simplifies. It is *per definitionem*

$$
\begin{array}{ccccc}
A & \equiv & n\times p(a_t)+n\times p(b_t) & = & n\times p(A_t) \\
B & \equiv & n\times p(a_t)+n\times p(c_t) & = & n\times p(B_t) \\
a & \equiv & n\times p(a_t) & = & n\times p(A_t \cap B_t) \\
b & & n\times p(b_t) & & \\
c & & n\times p(c_t) & & \\
d & & n\times p(d_t) & & \\
n & \equiv & n\times p(a_t)+n\times p(b_t) & + & n\times p(c_t)+n\times p(d_t) \\
n & \equiv & n\times p(A_t)+n\times p(\underline{A}_t) & = & n\times p(B_t)+n\times p(\underline{B}_t)
\end{array}
\qquad (2)
$$

The meaning of the abbreviations a, b, c, d, n et cetera are explained by following 2 by 2-table (**Table 8**). The relationships are valid even under conditions where n = 1.

Table 6. The sample space of a contingency table

		Conditioned B (Outcome)		
		Yes = +1	**No = +0**	**Total**
Condition A	Yes =+1	a	b	A
(risk factor)	No = +0	c	d	$\underline{A}$
	Total	B	$\underline{B}$	*n*

Definition 2. (Index of unfairness)

The index of unfairness (IOU) is defined (I. Barukčić, 2019c) as

$$IOU \equiv \left(\left(\frac{A \quad + B}{n}\right) - 1\right) \tag{3}$$

The range of A is $0 \leq A \leq n$, while the range of B is $0 \leq B \leq n$. A study design based on A=B=0 leads to an index of unfairness of IOU = (((0+0)/n)-1) = -1. A study design which demands that A=B=n leads to an index of unfairness of IOU = (((n+n)/n)-1) = +1. In particular, the range of the index of unfairness is [-1;+1].

Definition 3. (The probability of an index of unfairness)

The probability of an unfairness p(IOU) is defined as

$$p(IOU) \equiv Absolute\left(\left(\frac{A \quad + B}{n}\right) - 1\right) \tag{4}$$

Definition 4. Index of independence (IOI)

The index of independence (IOI) is defined (I. Barukčić, 2019b) as

$$IOI \equiv \left(\left(\frac{A \quad + \underline{B}}{n}\right) - 1\right) \tag{5}$$

Definition 5. (The probability of an index of independence)

The probability of an index of independence p(IOI) is defined (I. Barukčić, 2019b) as

$$p(IOI) \equiv Absolute\left(\left(\frac{A \quad + \underline{B}}{n}\right) - 1\right) \tag{6}$$

Definition 6. Sufficient Condition (Conditio per Quam)

The *sufficient* condition (I. Barukčić, 2018d, 1989, 1997, 2017, 2018a, 2018b, 2019d; K. Barukčić & Barukčić, 2016, 2016) relationship (*conditio per quam*) of a population is defined (I. Barukčić, 2019a, 2019d) as

$$\begin{aligned} p(A_t \rightarrow B_t) &\equiv \frac{(a_t) + (c_t) + (d_t)}{N_t} = 1 \\ &\equiv p(a_t) + p(c_t) + p(d_t) \\ &\equiv p(B_t) + p(d_t) \\ &\equiv p(a_t) + p(\underline{A}_t) \\ &\equiv +1. \end{aligned} \tag{7}$$

and is used to prove the hypothesis: *if* A_t *then* B_t or is taken to express that *the occurrence of an event* A_t *is a sufficient condition for existence or occurrence of an event* B_t. Sufficient and necessary conditions are converse relations (I. Barukčić, 2019a, 2019d).

Definition 7. The X² Test of Goodness of Fit of a Sufficient Condition

A observed value base on sample distribution must not be identical with a theoretical or hypothetical value of the population. However, if there is no discrepancy, then the difference between observed sample data and expected population data should equal zero in the case of perfect fit. A set of observations can fit very well a certain theoretical distribution but must not. *The chi square goodness of fit test* which requires a sufficient sample size in order for the chi-

square approximation to be valid is sometimes confused with *the chi-square test for independence*, but both are quite different. Both tests use the chi-square distribution and statistic. However, the chi-square test for independence is used to test a set of data to see if there is a relationship while the chi square goodness of fit test does not. Under certain circumstances, the X^2 test of goodness-of-fit is an appropriate method for testing the null hypothesis that a random sample of observations comes from a specific distribution (i.e. the distribution of a sufficient condition) against the alternative hypothesis that the data have some other distribution (I. Barukčić, 2019a, 2019d). The additive property of X^2 distribution is of special importance in this context. The applicability of using the Pearson chi-squared statistic including Yate's continuity correction (I. Barukčić, 2019a, 2019d) are widely discussed in literature. Especially, the need of incorporating Yate's continuity correction into the calculation of the X^2 value is very controversial. Thus far, only due to formal reasons, in the following, the use of *the continuity correction* is assured. The chi-square value of a conditio per quam relationship is derived (I. Barukčić, 2019a, 2019d) as

$$X^2\left(\left(A \quad \rightarrow B \quad\right)|A \quad\right) \equiv \frac{\left(\left(b \quad\right) - \left({}^{1}/_{2}\right)\right)^2}{A} + 0 = 0 \tag{8}$$

or alternatively as

$$X^2\left(\left(A \quad \rightarrow B \quad\right)|\underline{B} \quad\right) \equiv \frac{\left(\left(b \quad\right) - \left({}^{1}/_{2}\right)\right)^2}{\underline{B}} + 0 = 0 \tag{9}$$

Definition 8. Necessary Condition (Conditio Sine Qua Non)

The self-organization of matter is governed by view basic natural laws among those is the necessary condition (conditio sine qua non) too. An event A_t which is necessary (or an essential) for some other event B_t to occur must be satisfied in order to obtain B_t (I. Barukčić, 2019a, 2019d). In this respect, let an event A_t with its own probability $p(A_t)$ at the (period of) time *t* be a necessary condition for another event B_t with its own probability $p(B_t)$. This is equivalent to say that it is impossible to have B_t without A_t. In other words, *without* A_t *no* B_t or the absence of A_t must guarantee the absence of B_t. The mathematical formula of the *necessary* condition (I. Barukčić, 2018d, 1989, 1997, 2017, 2018a, 2018b, 2019d; K. Barukčić & Barukčić, 2016,

2016) relationship (conditio sine qua non) of a population is defined (I. Barukčić, 2019a, 2019d) as

$$\begin{aligned} p(A_t \leftarrow B_t) &\equiv \frac{(a_t) + (b_t) + (d_t)}{N_t} = 1 \\ &\equiv p(a_t) + p(b_t) + p(d_t) \\ &\equiv p(A_t) + p(d_t) \\ &\equiv p(a_t) + p(\underline{B_t}) = p(a_t) + \left(1 - p(B_t)\right) \\ &\equiv +1. \end{aligned} \tag{10}$$

Definition 9. The X² Test of Goodness of Fit of a Necessary Condition

The chi-square value of a *conditio sine qua non* distribution (I. Barukčić, 2019a, 2019d) before changes to

$$X^2\left((A \leftarrow B)|B\right) \equiv \frac{\left((c) - (1/2)\right)^2}{B} + 0 = 0 \tag{11}$$

Depending upon the study design, another alternative and equivalent method to calculate the chi-square value of a *conditio sine qua non* distribution (while using *the continuity correction*) is defined as

$$X^2\left((A \leftarrow B)|\underline{A}\right) \equiv \frac{\left((c) - (1/2)\right)^2}{\underline{A}} + 0 = 0 \tag{12}$$

Definition 10. Exclusion (A_t Excludes B_t and Vice Versa Relationship)

The mathematical formula of the *exclusion* (I. Barukčić, 2018d, 1989, 1997, 2017, 2018a, 2018b, 2019d; K. Barukčić & Barukčić, 2016, 2016) relationship (A_t excludes B_t and vice versa) of a population is defined (I. Barukčić, 2019a, 2019d) as

$$
\begin{aligned}
p(A_t \mid B_t) \quad &\equiv \quad \frac{(b_t) + (c_t) + (d_t)}{N_t} = 1 \\
&\equiv \quad p(b_t) + p(c_t) + p(d_t) \\
&\equiv \quad p(b_t) + p(\underline{A}_t) = p(b_t) + \left(1 - p(A_t)\right) \\
&\equiv \quad p(c_t) + p(\underline{B}_t) = p(c_t) + \left(1 - p(B_t)\right) \\
&\equiv \quad +1.
\end{aligned}
\tag{13}
$$

and used to prove the hypothesis: A_t *excludes* B_t and vice versa. Under which conditions does A_t exclude B_t and vice versa and what are the consequences? The relationship A_t excludes B_t and vice versa is of outstanding importance especially in human medicine because the same relationship allows researchers to identify among other an *antidote against a certain factor*.

Definition 11. The X² Test of Goodness of Fit of the Exclusion Relationship

The chi square value with degree of freedom 2-1=1of the exclusion relationship with a *continuity correction* can be calculated (I. Barukčić, 2019a, 2019d) as

$$
X^2\left((A \mid B)\mid A\right) \equiv \frac{\left((a) - (1/2)\right)^2}{A} + 0 = 0 \tag{14}
$$

Another equivalent method to calculate the chi-square value of a *conditio sine qua non* distribution is defined (I. Barukčić, 2019a, 2019d) as

$$
X^2\left((A \mid B)\mid B\right) \equiv \frac{\left((a) - (1/2)\right)^2}{B} + 0 = 0 \tag{15}
$$

In particular, the chi square Goodness of Fit Test of the exclusion relationship provides evidence how well observed data compare with the expected theoretical distribution of an exclusion relationship (I. Barukčić, 2019a, 2019d).

Definition 12. Independence

In the case of independence (Kolmogoroff, 1933; Moivre, 1718) of A_t and B_t it is generally valid that

$$p(A_t \cap B_t) \equiv p(A_t) \times p(B_t) \tag{16}$$

Definition 13. The Mathematical Formula of the Causal Relationship k

The causal relationship k (I. Barukčić, 2016a, 2018b, 2018a, 2019d; K. Barukčić & Barukčić, 2016; K. Barukčić, Barukčić, & Barukčić, 2018) is defined *at every single event, at every single Bernoulli trial t,* as

$$k(A_t, B_t) \equiv \frac{p(A_t \cap B_t) - \left(p(A_t) \times p(B_t)\right)}{\sqrt[2]{p(A_t) \times \left(1 - p(A_t)\right) \times p(B_t) \times \left(1 - p(B_t)\right)}} \tag{17}$$

where A_t denotes the cause and B_t denotes the effect. The significance of causal relationship k can be tested by several methods. Under some certain circumstances, the chi-square distribution can be applied too. However, it is necessary to point out again that the mathematical formula of the causal relationship k has nothing to do *neither* with Pearson's concept of correlation *nor* with Pearson's concept of ϕ. Pearson's correlation methods are not identical with causation or correlation and causation must be distinguished, this has been proved (Sober, 2001) many times by different publications.

Definition 14. The 95% Confidence Interval of the Causal Relationship k

The approximate 95% interval for the causal relationship k can be estimated by the formula

$$\left\{ k(A_t, B_t) - \sqrt[2]{\frac{5}{n}} \;;\; k(A_t, B_t) + \sqrt[2]{\frac{5}{n}} \right\} \tag{18}$$

Definition 15. The z-score goodness of fit test

Let X_t denote the observed value of a random variable which is obtained from a sample distribution, i. e. the real value. Let $E(X_t)$ denote the theoretical or expected value of a random variable which is obtained from a hypothetical or theoretical distribution. Let $\sigma(X_t)$ denote the standard deviation of a random variable. The z-score goodness of fit test can be used to determine whether sample data are consistent with a theoretical/hypothesized distribution. If there is no discrepancy between observed and expected value, then z-score should be equal to zero. In this case, the probability of the agreement between the sample distribution and the hypothetical (theoretical) distribution should equal 1. The z-score goodness of fit test, or **the probability of the disagreement between a sample distribution and a hypothetical (theoretical) distribution** is defined as

$$1 - \big(2 \times p(z)\big) \quad = \quad 1 - \left(2 \times p\left(\frac{(X_t \quad - \quad E(X_t))}{\sigma(X_t)}\right)\right) \tag{19}$$

Proof.

Under conditions where an observed value X_t is identical or equal to an expected value $E(X_t)$, it is

$$X_t \quad = \quad E(X_t) \tag{20}$$

Rearranging we obtain

$$\big(X_t - E(X_t)\big) \quad = \quad 0 \tag{21}$$

or

$$\frac{\big(X_t - E(X_t)\big)}{\sigma(X_t)} \quad = \quad \frac{0}{\sigma(X_t)} = 0 \tag{22}$$

or

$$z = \frac{\left(X_t - E(X_t)\right)}{\sigma(X_t)} = \frac{0}{\sigma(X_t)} = 0 \tag{23}$$

Calculating the probability as associated with the z-score, we obtain

$$p(z) = p\left(\frac{\left(X_t - E(X_t)\right)}{\sigma(X_t)}\right) \tag{24}$$

Multiplying by 2, it is

$$2 \times p(z) = 2 \times p\left(\frac{\left(X_t - E(X_t)\right)}{\sigma(X_t)}\right) \tag{25}$$

Rearranging, it follows that

$$-\left(2 \times p(z)\right) = -\left(2 \times p\left(\frac{\left(X_t - E(X_t)\right)}{\sigma(X_t)}\right)\right) \tag{26}$$

The probability of the disagreement between a sample distribution and a hypothetical (theoretical) distribution follows as

$$1 - \left(2 \times p(z)\right) = 1 - \left(2 \times p\left(\frac{\left(X_t - E(X_t)\right)}{\sigma(X_t)}\right)\right) \tag{27}$$

Quod erat demonstrandum.

2.2.2. Data analysis

The causal relationship k (I. Barukčić, 1989, 1997, 2016a, 2016b, 2017, 2018a, 2019d; K. Barukčić & Barukčić, 2016; Hessen, 1928; Korch, 1965) was used to proof the data for a causal relationship while the significance was tested by the hypergeometric distribution (HGD) and the chi-square distribution (Karl Pearson, 1900). The *conditio sine qua non* (I. Barukčić, 2018d, 1989, 1997, 2017, 2018a, 2018b, 2019d; K. Barukčić & Barukčić, 2016, 2016) relationship (SINE) was used to proof the hypothesis, *without* HCMV infection *no* EH. The *conditio per quam* (I. Barukčić, 2018d, 1989, 1997, 2017, 2018a, 2018b, 2019d; K. Barukčić & Barukčić, 2016, 2016) relationship (IMP) was used to proof the hypothesis, *if* HCMV infection *then* alcohol consumption. The *necessary and sufficient condition* (I. Barukčić, 2018d, 1989, 1997, 2017, 2018a, 2018b, 2019d; K. Barukčić & Barukčić, 2016, 2016) relationship (SINE) was used to proof the hypothesis, (*without* HCMV infection *no* EH) **and** (*if* HCMV infection *then* EH). The index of unfairness (I. Barukčić, 2019c) was used to control publication bias. All statistical analyses were performed with Microsoft® Excel® for Mac® version 16.2 (181208) software (© 2018, Microsoft GmbH, Munich, Germany). The level of significance was set to 0.05.

3. Results

THEOREM 1. WITHOUT HCMV IGG SERO-POSITIVITY NO EH

CLAIM.

Null-Hypothesis: HCMV IgG sero-positivity is a necessary condition of EH.

Alternative Hypothesis: HCMV IgG sero-positivity is not a necessary condition of EH.

PROOF.

The studies which were considered for meta-analysis (**Table 2**) provided an evidence of a conditio sine qua non relationship between HCMV and EH which should not be ignored. One part of the study of Tang et al. provided self-contradictory and should not have considered for re-analysis. However, the same was considered. Besides of this negative effect, the data analysed support the null-hypothesis: **without** a HCMV IgG positivity **no** EH. HCMV IgG positivity is a necessary condition of EH (Alpha = 0,05; degrees of freedom = 4; X^2(Critical) = 9,4877; **X^2(Calculated) = 5,89015**).

QUOD ERAT DEMONSTRANDUM.

THEOREM 2. WITHOUT HCMV IGG SERO-POSITIVITY NO SMOKING

CLAIM.

Null-Hypothesis: HCMV IgG sero-positivity is a necessary condition of smoking.

Alternative Hypothesis: HCMV IgG sero-positivity is not a necessary condition of smoking.

PROOF.

The study of Li et al. provided some data (**Table 3**) on the relationship between HCMV positivity and smoking. The data are very convincing with respect to this relationship (k = +0,013; p (SINE) = 0,991; X^2(SINE|Bt) = 0,127; X^2(SINE|At) = 1,563; P Value (SINE)= 0,009). This data of (p(IOU) = 0,321) the study of Li et al. support the Null-hypothesis: **without** HCMV positivity **no** smoking.

QUOD ERAT DEMONSTRANDUM.

THEOREM 3. WITHOUT HCMV IGG SERO-POSITIVITY NO ALCOHOL CONSUMPTION

CLAIM.

Null-Hypothesis: HCMV IgG sero-positivity is a necessary condition of alcohol consumption.

Alternative Hypothesis: HCMV IgG sero-positivity is not a necessary condition of alcohol consumption.

PROOF.

The study of Li et al. provided some additional data (**Table 4**) on the relationship between HCMV positivity and alcohol consumption. The data are very convincing with respect to this relationship (**p(SINE) = 0,993**; X^2(SINE|Bt) = 0,115; X^2(SINE|At) = 1,000; **P Value (SINE)= 0,007**). This study could be used as a hypothesis-generating study that **without** HCMV positivity **no** alcohol consumption. The consequence could be that within alcohol itself a kind of an antidot against HCMV could be found. However, the data of Li et al. are in this context self-contradictory too. The causal relationship k is negative. Mathematically it is not possible to obtain a highly significant conditions sine qua non relationship (**P Value $_{Likely}$ (SINE)= 0,007**) while the causal relationship k is negative. The study design of Li et al. is not very appropriate to analyze this relationship (p(IOI) = 0,725; p(IOU) = 0,218; p(IOU) + p(IOI) = 0,943). This fact is not going to do anything to reduce the problems with the analysis of this data of Li et al. However, **p(IOU) = 0,218** and allow us to use the chi square distribution while **p(IOI) = 0,725** does not allow us to take the causal relationship k into consideration. Under these circumstances, we are allowed to deduce, with some limitations and uncertainty: **without** HCMV positivity **no** alcohol consumption (**p(SINE) = 0,993**; X^2(SINE|Bt) = 0,115; X^2(SINE|At) = 1,000; **P Value (SINE)= 0,007**).

QUOD ERAT DEMONSTRANDUM.

4. Discussion

It remains an important investigational subject to define the role of HCMV in essential hypertension. This review may serve as a hypothesis generating approach which justifies a very systematical approach to this relationship. A radical turn will be needed to satisfy the unquenchable thirst for a satisfactory treatment of essential hypertension. This paper has the potential to lead to new treatments for essential hypertension directed at the antiviral therapy of HCMV or prevention by a vaccine against HCMV. Furthermore, there is some evidence the HCMV is responsible for alcohol consumption and for smoking with all the consequences which might develop. At this point, the point at issue isn't about the “chicken or the egg” question but to find medical answers to serious medical problems. The foremost advantage of this study is the justified HCMV seropositivity determines essential hypertension, smoking and alcohol consumption.

5. Conclusion

This study provides some strategic insights into the mechanisms of HCMV with essential hypertension. In conclusion, **without** HCMV seropositivity **no** EH.

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Author Contributions

The author confirms being the sole contributor of this work and has approved it for publication.

Conflict of Interest Statement

The author declares that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest. There are no conflict of interest exists according to the guidelines of the International Committee of Medical Journal Editors.

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