Journal of Acute Disease

Systematic Review and Meta−analysis

doi: 10.4103/2221-6189.276076 jadweb.org

Global study of viral myocarditis: A systematic review and meta−analysis

Masoud Dadashi[1,2#], Taher Azimi[3,4#], Ebrahim Faghihloo[5]✉

[1]*Department of Microbiology, School of Medicine, Alborz University of Medical Sciences, Karaj, Iran*

[2]*Non Communicable Diseases Research Center, Alborz University of Medical Sciences, Karaj, Iran*

[3]*Department of Pathobiology, School of Public Health, Tehran University of Medical Sciences, Tehran, Iran*

[4]*Students Scientific Research Center, Tehran University of Medical Sciences, Tehran, Iran*

[5]*Department of Microbiology, School of Medicine, Shahid Beheshti University of Medical Sciences, Tehran, Iran*

ABSTRACT

Objective: To investigate the prevalence of viral myocarditis worldwide.

Methods: We conducted a systematic search for the prevalence of the most common viruses in myocarditis and 75 studies were included for statistical analysis of the prevalence of adenovirus, hepatitis C virus, cytomegalovirus, Ebola virus, human herpesvirus 6, influenza virus, parvovirus, and non-polio enteroviruses.

Results: The highest prevalence was related to B19 (25.0%) and non-polio enteroviruses (18%). The prevalence of human herpesvirus 6, cytomegalovirus, and Ebola virus was12.8%, 5.5%, and 3.1%, respectively. Hepatitis C virus accounted for 6.1% of the disease, the adenoviruses contributed to 5.2% of viral myocarditis. The lowest incidence was related to the influenza virus with 2.0%.

Conclusions: Treatment of myocarditis is still problematic and may depend on the etiologic diagnosis. So it is important to know the commonly occurring viral factors in myocarditis and timely diagnosis and treatment are also imperative.

KEYWORDS: Virus; Myocarditis; Meta-analysis; B19; Non-polio enteroviruses

1. Introduction

Myocarditis is a multi-factorial disease of the myocardium with a large number of risk factors that are particularly attributed to multiple infectious and non-infectious agents[1,2]. Globally, the occurrence of myocarditis is around 1.5 million cases annually, and the incidence of myocarditis was 10 to 20 per 100 000 worldwide[3]. Moreover, it is the main reason for the severe heart failure among all age groups, especially children and adults aged <40 years[4]. The clinical symptoms of myocarditis are variable, including asymptomatic courses, chest pain, congestive heart failure, syncope, cardiogenic shock, cardiac arrest and even sudden death, and other severe illness with the necessity of intensive care therapy[2,5,6]. According to the immunohistological evaluation of endomyocardial biopsies, clinicopathological and clinical criteria, the diagnosis and classification of myocarditis have been conducted[7-9]. Several autoimmune disorders such as Wegener's granulomatosis, systemic lupus erythematosus, and giant cell arteritis belong to non-infectious causes of myocarditis[5,10]. However, among infectious causes, viral infections are the main reasons for inflammatory dilated cardiomyopathy and myocarditis. In the different parts of the world, especially in Europe and North America, myocarditis is caused predominantly by viral infections[1,4,11]. Moreover, it is predicted that 35% to 50% of dilated cardiomyopathy has been caused by viral myocarditis (VMC)[1,2,11]. The finding of several studies indicated that molecular pathological analyses, such as polymerase chain reaction and *in situ* hybridization, as well as serological analyses, could be applied for fast and comprehensive identification of viral myocardial infection[1,6,12,13]. Generally, the occurrence and prevalence of VMC is principally based on 3 types of evidence: (1) Detection rate of VMC at immunohistological evaluation of endomyocardial biopsies as the gold standard method; (2) High prevalence of myocarditis disease during the

#Both of the authors contributed equally to this work.

✉To whom cerrespondence may be addressed. faghihloo@gmail.com; faghihloo@sbmu.ac.ir

How to cite this article: Dadashi M, Azimi T, Faghihloo E. Global study of viral myocarditis: A systematic review and meta-analysis. J Acute Dis 2020; 9(1): 1-13.

Article history: Received 7 December 2019; Revision 27 December 2019; Accepted 8 January 2020; Available online 24 January 2020

period of virus infection outbreaks; (3) Percentage of VMC out of all infection diseases in a definite province and a particular population[2]. Viral infections include adenovirus, enteroviruses, particularly coxsackievirus B, as well as parvovirus (B19) and human herpesvirus 6 (HHV-6) are related to VMC[4,11]. Previously published studies revealed that viral nucleic acids in the myocardium in patients with myocarditis were high[14,15], while information from distinct studies regarding the interaction between different viral family and myocarditis is not entirely consistent. For this purpose, we focused on the relationship of viral infection and myocarditis and we conducted a systematic review and meta-analysis with no language restriction.

2. Materials and methods

2.1. Literature search

We conducted a systematic search for the prevalence of the most common viruses in myocarditis including adenovirus, hepatitis C virus (HCV), herpesviruses including cytomegalovirus (CMV), Ebola virus (EBV), and human herpes virus (HHV) 6, influenza virus, B19 and non-polio enteroviruses based on scientific keywords “Myocarditis” or “Heart disease” and “Viral infection” or “Viral myocarditis” and their synonyms by using three main electronic databases of Medline (*via* PubMed), Embase, and Web of Science from October 1973 to September 2017. The search was limited to the original articles published in English that indicated the prevalence or incidence of mentioned viruses in different parts of the world. We also searched the bibliographies for any retrieved articles for additional references.

2.2. Inclusion and exclusion criteria

All of the original papers presenting cross-sectional studies on the prevalence of the most common viruses were evaluated perspicuously. The selected studies were analyzed based on titles, abstracts, and full texts. The entire recorded studies included in our analysis based on the following criteria: (1) Original articles that provided sufficient data; (2) With standard methods, including serology methods, immunohistochemistry assay, and molecular methods to detect adenovirus, HCV, CMV, EBC, HHV6, Influenza virus, B19, and non-polio enteroviruses. The exclusion criteria were: (1) Articles studying non-human samples; (2) Case reports; (3) reviews (4) Abstracts reported in conferences; (5) Duplicate articles for the same investigation.

2.3. Data extraction and definitions

The author’s first name, the date for the investigation, year of publication, country/continent, number of the most common viruses in myocarditis, detection method and the source of isolates were extracted from included studies. Deliberately, the information on the prevalence of adenovirus, HCV, CMV, EBC, HHV6, influenza virus, B19, and non-polio enteroviruses was extracted; concurrently, two people recorded the data from all articles independently without any bias.

2.4. Quality assessment

All reviewed studies were assessed based on the quality assessment checklist (designed by the Joanna Briggs Institute), and only high-quality investigations were evaluated in the final analysis in this study based on mentioned including criteria.

2.5. Meta–analysis

The analysis was performed using STATA (version 14.0) software. The data were pooled using the fixed-effects model[16] and the random-effects model[17]. Statistical heterogeneity was assessed using Cochran Q and I^2 statistical methods[18].

3. Results

3.1. Characteristics of included studies

In total, we identified a total of 2 152 articles in the mentioned databases search. Based on the title and abstract evaluation, after the secondary screening, 1 992 articles were excluded. Upon a full-text review, 84 out of 160 studies were excluded. Ultimately 75 studies were included for statistical analysis of the prevalence of adenovirus, HCV, CMV, EBC, HHV6, influenza virus, B19, and non-polio enteroviruses respectively, based on the inclusion and exclusion criteria (Supplementary Figure 1). These 75 articles that indicated the prevalence of the most common viruses is shown in Table 1. The majority of studies were from Germany (n=22), USA (n=14), Italy (n=10), Japan (n= 6), and England (n=5), respectively[19-83].

3.2. The prevalence of adenovirus, HCV, CMV, EBC, HHV6, influenza virus, B19, and non-polio enteroviruses

Eloquently, the pooled prevalence of adenovirus, HCV, CMV, EBV, HHV6, influenza virus, B19 and non-polio enteroviruses were 5.2% (95% *CI*: 3.3-7.0) among 1 355 patients, 6.1% (95% *CI*: 1.8-10.4) among 413 patients, 5.5% (95% *CI*: 3.3-7.7) among 1 648 patients, and 3.1% (95% *CI*: 1.7-4.6) among 1 952 patients, 12.8% (95% *CI*: 8.8-16.7) among 3 003 isolate, 2.0% (95% *CI*: 0.5-3.4) among 891 patients, 25.0% (95% *CI*: 20.0-29.0) among 3 840 patients and 18 % (95% *CI*: 4.7-11.1) among 599 patients respectively (Figure 1-8).

Table 1. Studies used in the meta-analysis.

First author	Time of study	Country	*n*	Type (Number of viruses)	Male/female	Type of sample	Detection method
Bowles[19]	2003	USA	624	EBV (3), B19 (142), enterovirus (85), parvovirus (6), CMV (18), influenza A (5), HSV (5), RSV (1)	-	Cardiac samples	PCR
Fujioka[20]	2000	Japan	26	Enterovirus (9)	20/6	Myocardial specimens	PCR
Grün[21]	2012	Germany	203	EBV (2), B19 (113), HHV6 (49)	140/63	Endomyocardial biopsy	Nested-PCR
Nielsen[22]	2016	Denmark	150	Picorena viridae (1)	106/44	Formalin-fixed paraffin embed-ded cardiac tissue specimens	Real-time PCR
Boudjellil[23]	2016	France	18	B19 (1), CMV (2), HSV (2), RSV (1)	15/3	Sera and stools	PCR
Kühl[24]	2014	Germany	1 656	HHV6 (273)	-	Cardiac biopsies	Nested PCR, electron microscopy, and immuno-histochemistry
Ukimura[25]	2010	Japan	15	Influenza A (10)	9/6	Myocardial biopsy or autopsy	Probe-based RT-PCR
Li[26]	2000	England	19	Enterovirus (15)	12/7	Explanted or postmortem myocardial samples	RT-PCR, immunohistochemistry assay
Kühl[27]	2005	Germany	245	EBV (5), adenovirus (4), B19 (126), enterovirus (23), CMV (2), HHV6 (53)	178/67	Ventricular septum and blood sample	Nested PCR, serological analysis (remcomBlot Parvovirus-B19-IgG)
Schowengerdt[28]	1997	USA	360	Parvovirus (3)	-	Right ventricular autopsy samples	PCR
Gaaloul[29]	2014	Tunisia	51	Enterovirus (9), enterovirus (2)	89/13	Blood, pericardial fluid samples	RT PCR, immunohistochemistry assay, cell culture, immunofluorescence assay
Simpson[30]	2016	USA	21	Adenovirus (1), B19 (2), enterovirus (4), HHV6 (2)	10/11	Blood samples	PCR
Pauschinger[31]	1999	Germany	94	Adenovirus (12), enterovirus (12)	65/29	Myocardial Biopsy	Nested PCR
Schmidt[32]	1973	USA	92	Coxsackie B (23)	145/114	Sera samples	Immunodiffusion tests
Gagliardi[33]	2016	Italy	23	EBV (2), B19 (10)	-	Serum sample, biopsy sample	PCR
Mahfoud[1]	2011	Germany	124	EBV (7), adenovirus (3), B19 (33), enterovirus (5), HHV6 (10)	82/42	Biopsy, formalin fixed block, haematoxylin and eosin stained tissue	Nested (RT-) PCR, immunohistochemistry
Nicholson[34]	1995	England	6	Enterovirus (5)	4/2	Endomyocardial biopsy	RT-PCR, *in situ* hybridisation
Mahrholdt[4]	2006	Germany	87	EBV (1), coxsackie B (1), B19 (49), HHV6 (16)	63/24	Autopsy	PCR
Griffin[35]	1995	USA	58	Adenovirus (18), enterovirus (12), CMV (2), HSV (2)	-	Autopsies	PCR
Andréoletti[36]	2007	France	50	Enterovirus (20)	40/10	Blood, urine, and tracheal aspirate cultures	RT-PCR, immunohistochemistry assay
Bratincsak[37]	2010	USA	80	Influenza A (4)	-	Myocardial biopsy	Non
Mahrholdt[9]	2004	Germany	32	B19 (12), HHV6 (6)	26/6	Myocardial biopsy	RT-PCR
Klein[38]	2004	Germany	31	B19 (4)	-	Biopsy specimens	Histology and immunohistology, PCR
Kühl[39]	2005	Germany	172	Adenovirus (14), B19 (63), enterovirus (56), HHV6 (18)	82/90	Frozen blood samples	Nested PCR
Matsumori[40]	2006	Japan	102	HCV (6)	-	Endomyocardial biopsies	PCR
Schönian[41]	1995	Germany	162	CMV (27)	117/78	Myocardial biopsies	PCR, *in–situ* hybridization
Vallbracht[42]	2004	Germany	124	EBV (3), adenovirus (8), B19 (46), enterovirus (17), HHV6 (17)	55/69	Blood samples	PCR
Bachelier[43]	2017	Germany	54	EBV (1), B19 (23), HHV6 (3)	31/23	Blood samples, endomyocardial biopsies	PCR

Table 1. Studies used in the meta-analysis (Continued).

First author	Time of study	Country	*n*	Type (Number of viruses)	Male/female	Type of sample	Detection method
Frustaci[44]	2003	Italy	41	EBV (5), adenovirus (4), B19 (1), enterovirus (5), influenza A (1),HCV (3)	29/12	Blood samples	PCR
O'Neill[45]	1983	Scotland	130	Coxsackie B (7)	93/37	Sera samples	Microneutralisation
EL-Hagrassy [46]	1980	England	38	Coxsackie B (14)	-	Autopsy sample	ELISA
Nielsen[47]	2014	Denmark	112	B19 (33)	78/34	Endomyocardial biopsy specimens	PCR, ELISA
Pankuweit[48]	2003	Germany	98	Coxsackie B (4), adenovirus (1), B19 (14)	-	Endomyocardial biopsy specimens	PCR, Southern blot hybridization
Bock[49]	2010	Germany	498	B19 (322)	341/157	Endomyocardial biopsy specimens	RT-PCR
Caforio[7]	2007	Italy	174	HSV (1), EBV (5), adenovirus (6), B19 (3), enterovirus (15), CMV (3), HCV (2), mumps (3)	110/64	Endomyocardial biopsy specimens	PCR
Bültmann[50]	2005	Germany	16	EBV (1), B19 (3), CMV (1), HHV6 (2)	-	Endomyocardial biopsy specimens	Nested PCR
Martin[51]	1994	USA	34	HSV (2), adenovirus (15), enterovirus (8), CMV (1)	-	Autopsy and blood samples	PCR
Savón[52]	2008	Cuba	11	Adenovirus (9)	5/6	Myocardial tissue, lung tissue, stools, cerebrospinal fluid, serum	Nested PCR
Camargo[53]	2011	Brazil	10	Adenovirus (1), enterovirus (3), CMV (1),	-	Endomyocardial biopsy	PCR
Comar[14]	2009	Italy	16	HHV6 (7)	-	Frozen endomyocardial tissue sample	Real-time PCR
Why[54]	1994	England	120	Enterovirus (41)	92/28	Biopsy specimens	Histochemistry, molecular hybridization
Reibis[55]	2017	Germany	220	B19 (119)	144/76	Endomyocardial biopsy	Non
Ozdemir[56]	2018	Turkey	8	HSV (4), coxsackie B (2), B19 (1)	6/2	Peripheral blood specimen	Real-time PCR
Pawlak[11]	2016	Poland	70	Adenovirus (3), B19 (20), enterovirus (4), CMV (1), HHV6 (6)	43/27	Endomyocardial biopsy	Real time PCR
Frustaci[57]	2013	Italy	28	Adenovirus (3), enterovirus (2), influenza A (2)	23/5	Endomyocardial biopsy	RT-PCR
Mavrogeni[58]	2013	Greece	25	HSV (8), B19 (2), CMV (4)	-	Endomyocardial biopsy	RT-PCR, immunohistochemistry
Jeserich[59]	2013	Germany	55	HSV (5), EBV (14), B19 (1), HHV6 (1)	36/19	Blood samples	PCR
Koepsell[60]	2012	USA	26	B19 (19)	12/14	Peripheral blood	Nucleic acid amplification testing, immuno-histochemistry, *in situ* hybridization
Mavrogeni[61]	2011	Greece	50	HSV (9), EBV (1), coxsackie B (5), B19 (8), CMV (4)	-	Endomyocardial biopsy	PCR
Escher[62]	2008	Germany	33	B19 (21), enterovirus (1), HHV6 (1)	26/7	Endomyocardial biopsy	nested PCR, recomLine blots
Lindner[63]	2009	Germany	8	B19 (2)	7/1	Sera samples	PCR, ELISA,Western line, and ELISpot-assays
Valdes[64]	2008	Cuba	8	Adenovirus (6)	5/3	Myocardial tissue sample	nRT-PCR
Carturan[65]	2008	Japan	6	Enterovirus (2)	2/4	Endomyocardial biopsy	RT-PCR
Yilmaz[66]	2008	Germany	55	B19 (22), HHV6 (15)	17/38	Endomyocardial biopsy	RT-PCR
Guarner[67]	2007	USA	27	Enterovirus (5)	16/11	Paraffin tissue blocks	Immunohistochemistry, RT-PCR
Topkara[68]	2006	USA	11	VZV (1), EBV (2), coxsackie B (1), CMV (1), influenza A (1)	5/6	Endomyocardial biopsy	Non
Amabile[69]	2006	France	11	VZV (1), EBV (1), coxsackie B (1), B19 (2)	3/8	Endomyocardial biopsy	Serology assay
Kytö[70]	2005	Finland	40	B19 (4), enterovirus (1), CMV (15) , HHV6 (1)	20/20	Myocardial autopsy samples	PCR, *in situ* hybridization assays
English[71]	2004	USA	41	VZV (1), coxsackie B (3), adenovirus (3), enterovirus (2), CMV (2), influenza A (1), picorena (1)	21/20	Biopsy specimens	Non
Chimenti[15]	2004	Italy	44	EBV (4), adenovirus (13), B19 (6), enterovirus (11), HCV (4)	-	Frozen endomyocardial biopsy	Laser capture microdissection, PCR, Immuno- histochemistry

Table 1. Studies used in the meta-analysis (Continued).

First author	Time of study	Country	*n*	Type (Number of viruses)	Male/female	Type of sample	Detection method
Calabrese[5]	2004	Italy	38	EBV (4), adenovirus (2), enterovirus (7), CNV (1), influenza A (2), HCV (3)	27/11	endomyocardial biopsy	Immunohistochemistry, nested-PCR
Zhang[72]	2004	England	10	Enterovirus (7)	-	Formalin-fixed, paraffin-embedded endomyocardial biopsy explanted or autopsy tissue samples	Immunohistochemistry, RT-PCR
Ali[73]	2003	Egypt	160	Enterovirus (16)	115/45	Serum samples	Cell culture, neutralization assay, PCR
Satoh[74]	2003	Japan	44	Enterovirus (21)	29/15	Endomyocardial biopsy	Real-time reverse transcriptase–PCR, immunohistochemical analysis
Calabrese[6]	2002	Italy	28	HSV (1), VZV (1), EBV (1), adenovirus (5), enterovirus (3), influenza A (1), mumps (2)	12/16	Endomyocardial biopsy	Immunohistochemistry, RT-PCR
Angelini[12]	2002	Italy	23	HSV (3), adenovirus (1), enterovirus (3), influenza A (1), mumps (1)	-	Endomyocardial biopsy	Immunohistochemistry, PCR
Wielkopolska[75]	2002	Poland	96	Enterovirus (58)	-	Serum sample	ELISA, Complement fixation reaction
Matsumori[76]	2000	Japan	14	HCV (4)	-	Endomyocardial biopsy	PCR
Zhang[77]	2000	China	9	Enterovirus (6)	-	Myocardial tissue sample	Immunohistochemical procedures, Western blotting, immunofluorescence
Bowles[78]	1999	USA	24	Adenovirus (6), CMV (7), picorena (1)	-	Formalin-fixed right ventricular myocardium	PCR
Akhtar[79]	1999	USA	8	Enterovirus (4), CMV (2)	-	Endomyocardial biopsy and tracheal aspirate	PCR
Grumbach[80]	1999	Germany	15	Enterovirus (4)	-	Endomyocardial biopsy	PCR
Petitjean[81]	1992	France	10	Enterovirus (1)	-	Endomyocardial biopsy	PCR
Mariani[82]	1996	Italy	7	Enterovirus (2)	3/4	Endomyocardial biopsy	PCR
Pauschinger[83]	1999	Germany	45	Enterovirus (18)	27/18	Endomyocarditis biopsies	RT-PCR

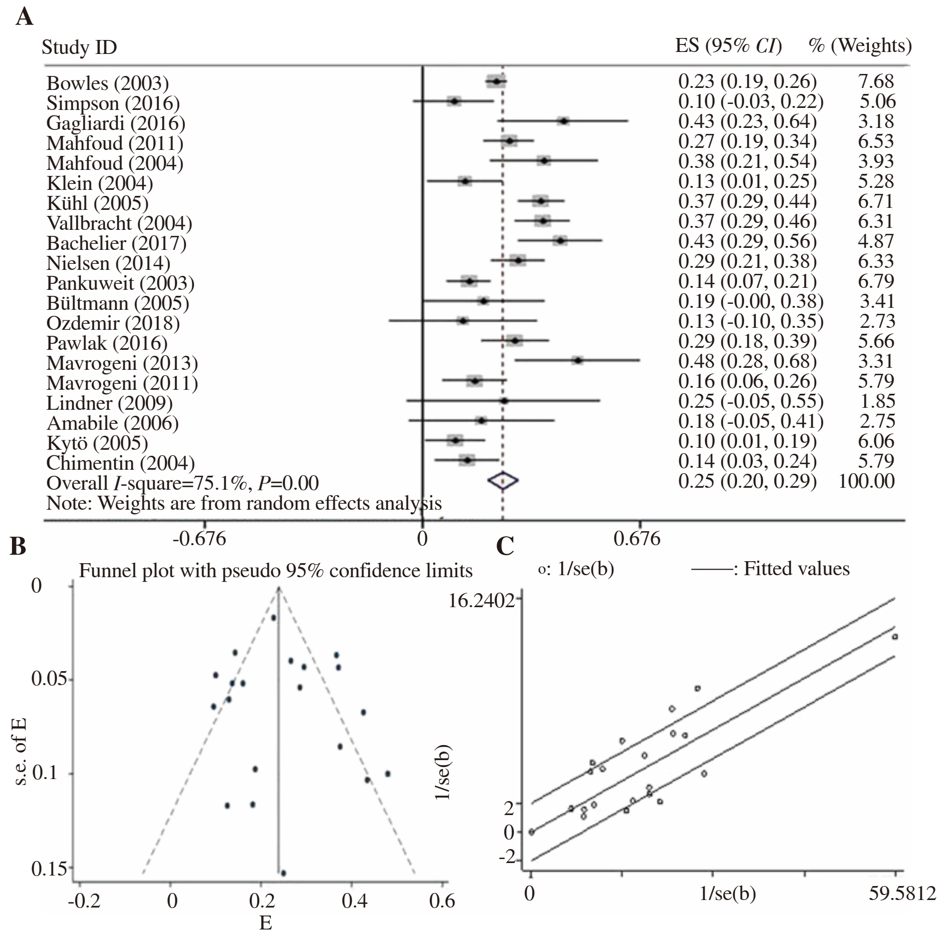

Figure 1. Forest plot (A), funnel plot (B) and Galbraith (C) of the meta-analysis on prevalence of B19 in patients with myocarditis.

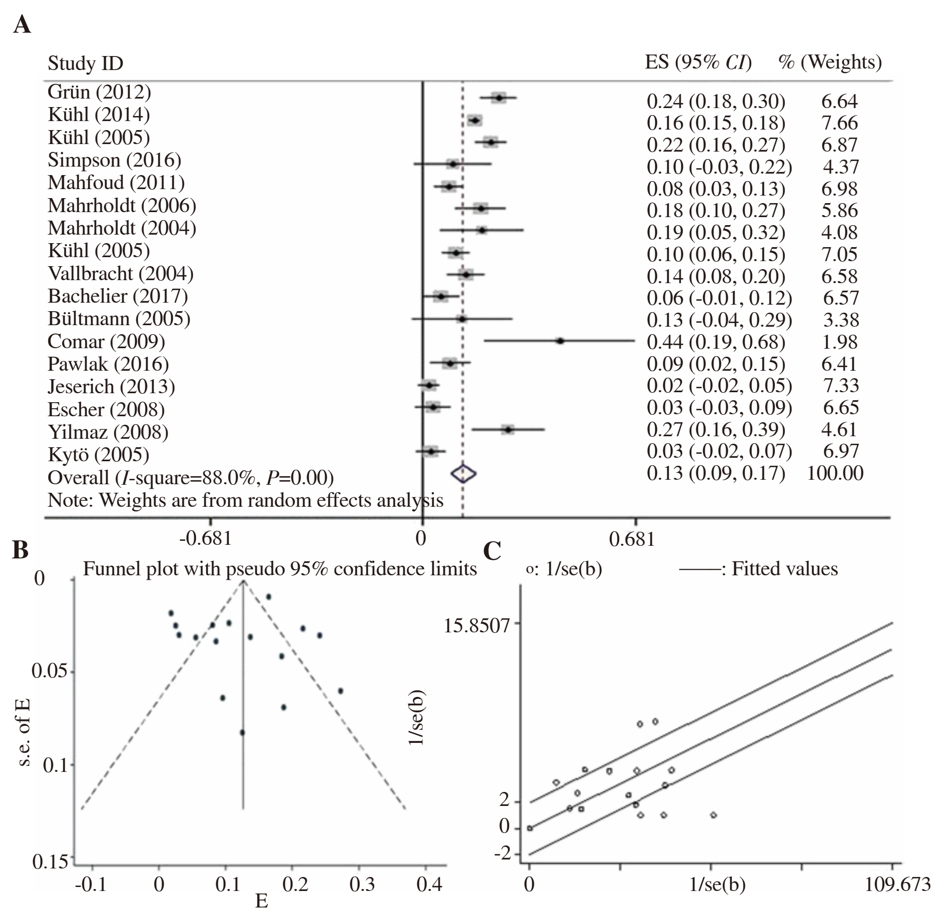

Figure 2. Forest plot (A), funnel plot (B) and Galbraith (C) of the meta-analysis on prevalence of human herpes virus 6 in patients with myocarditis.

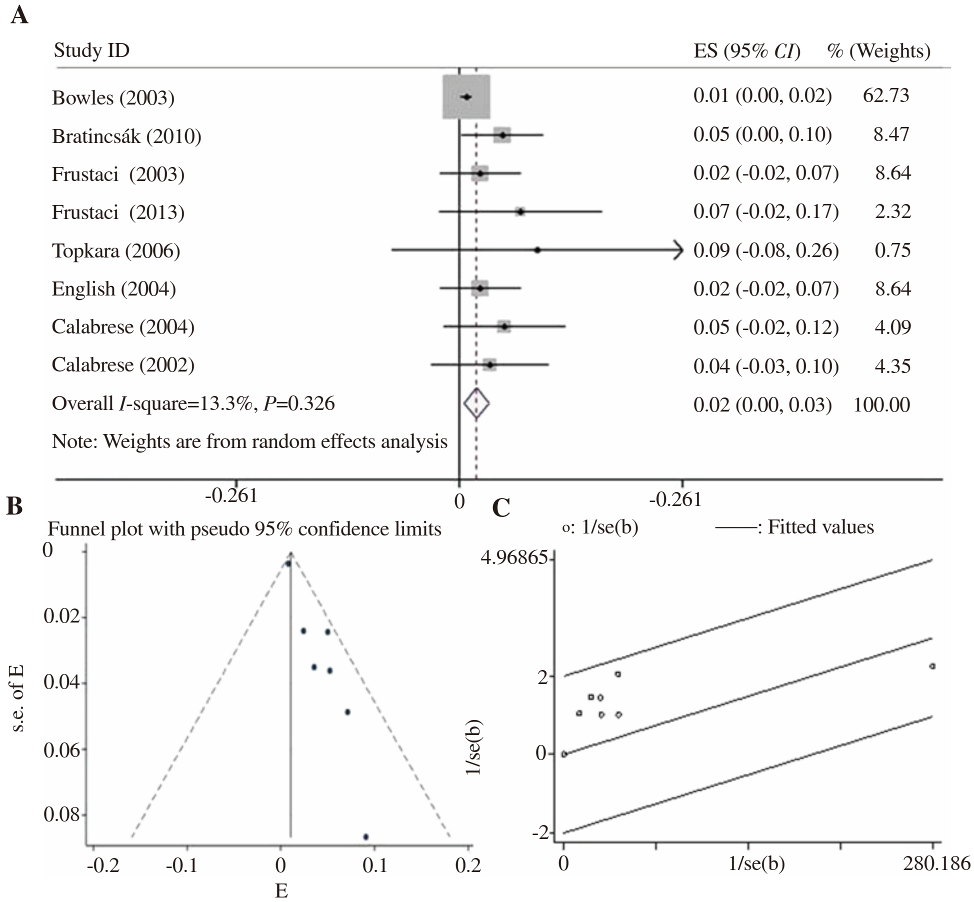

Figure 3. Forest plot (A), funnel plot (B) and Galbraith (C) of the meta-analysis on prevalence of influenza in patients with myocarditis.

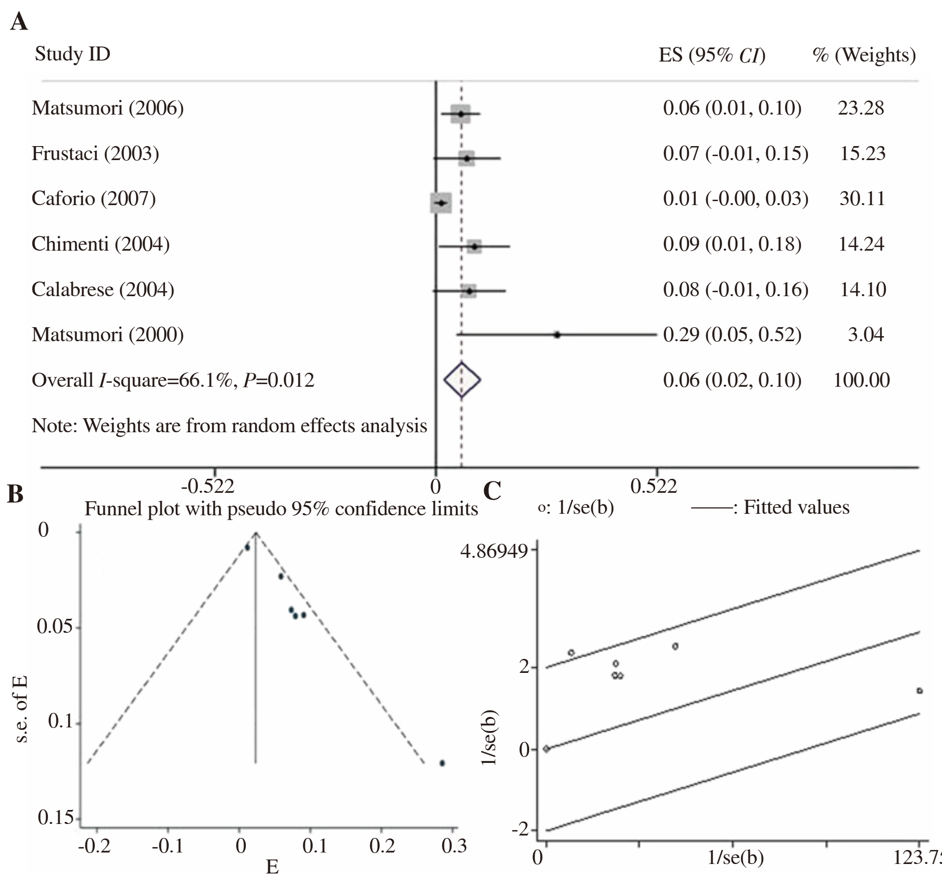

Figure 4. Forest plot (A), funnel plot (B) and Galbraith (C) of the meta-analysis on prevalence of hepatitis C virus in patients with myocarditis.

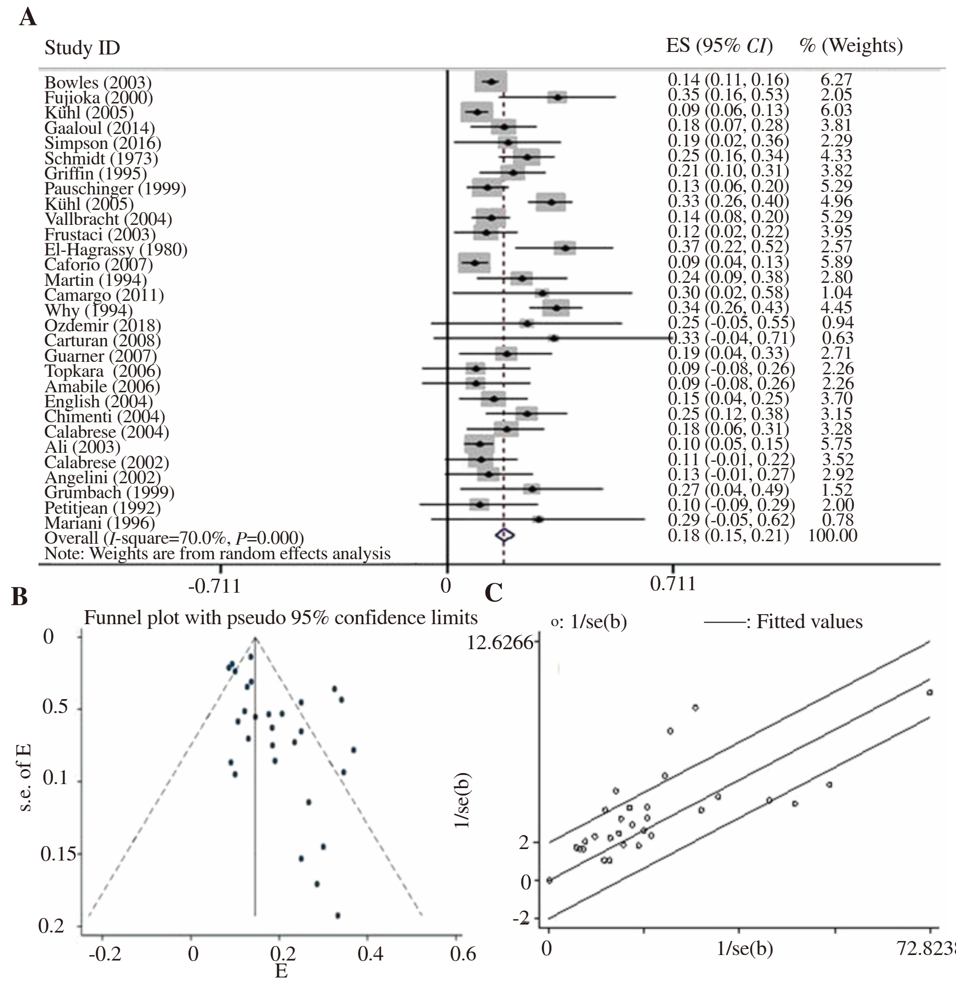

Figure 5. Forest plot (A), funnel plot (B) and Galbraith (C) of the meta-analysis on prevalence of non-polio enteroviruses in patients with myocarditis.

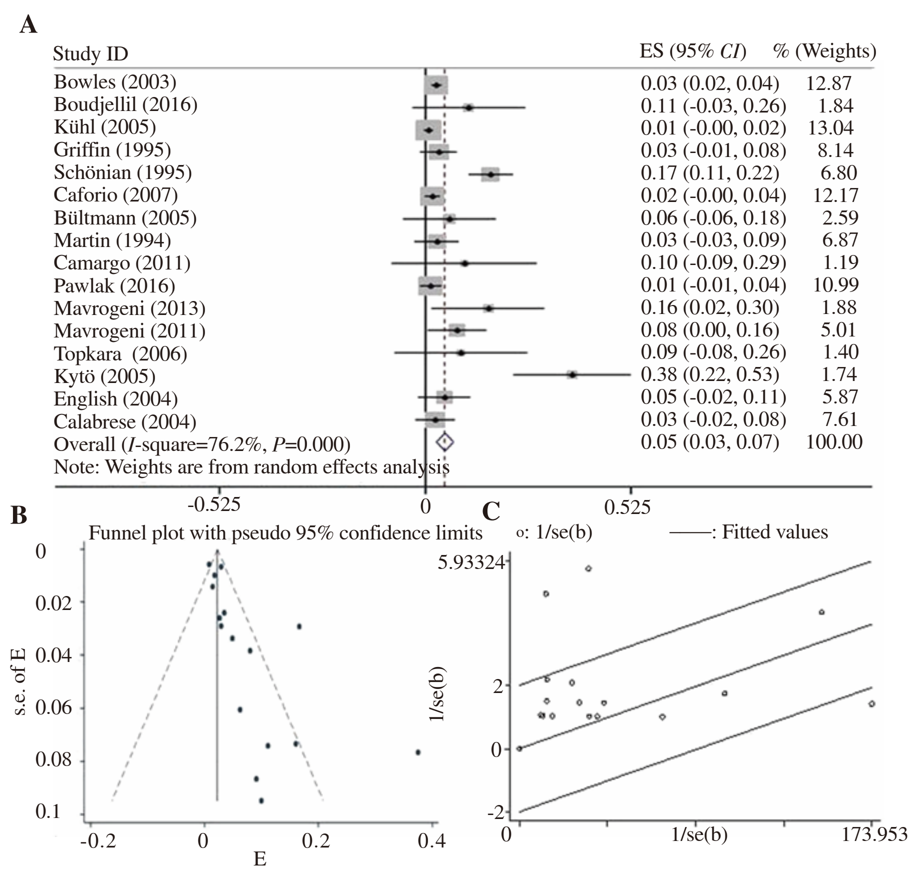

Figure 6. Forest plot (A), funnel plot (B) and Galbraith (C) of the meta-analysis on prevalence of cytomegalovirus in patients with myocarditis.

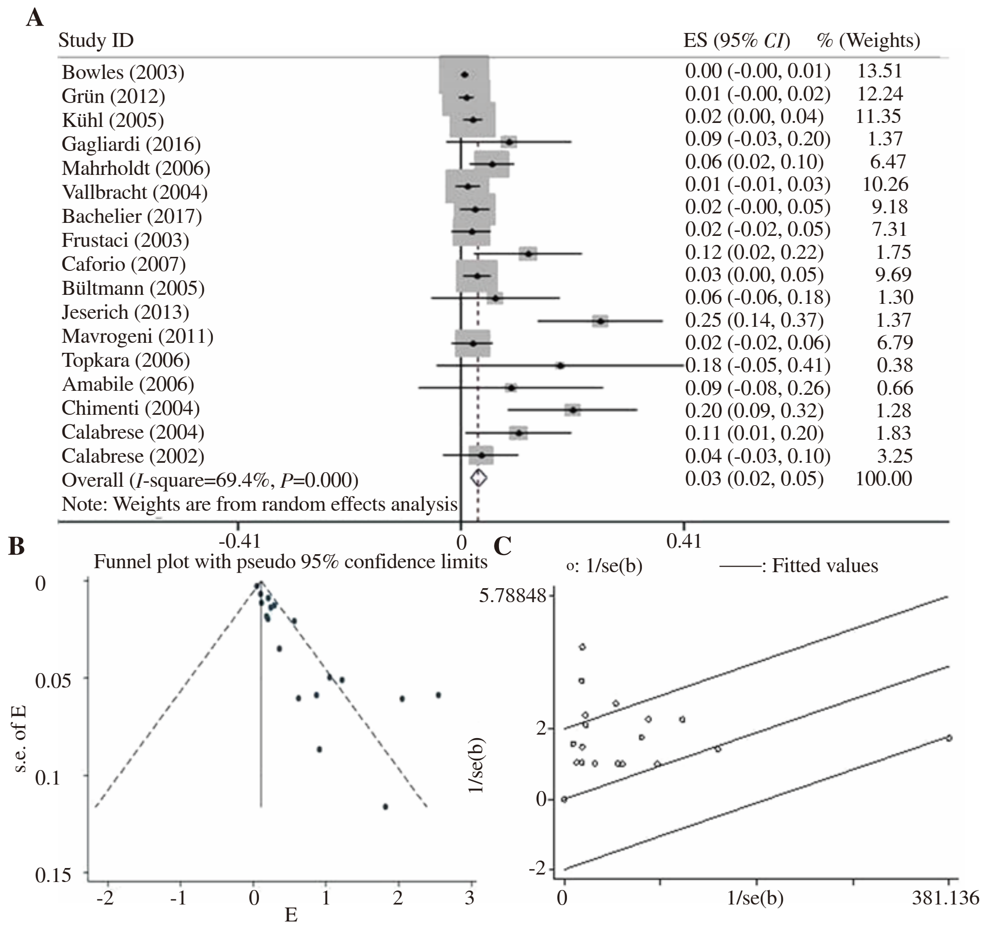

Figure 7. Forest plot (A), funnel plot (B) and Galbraith (C) of the meta-analysis on prevalence of Ebola virus in patients with myocarditis.

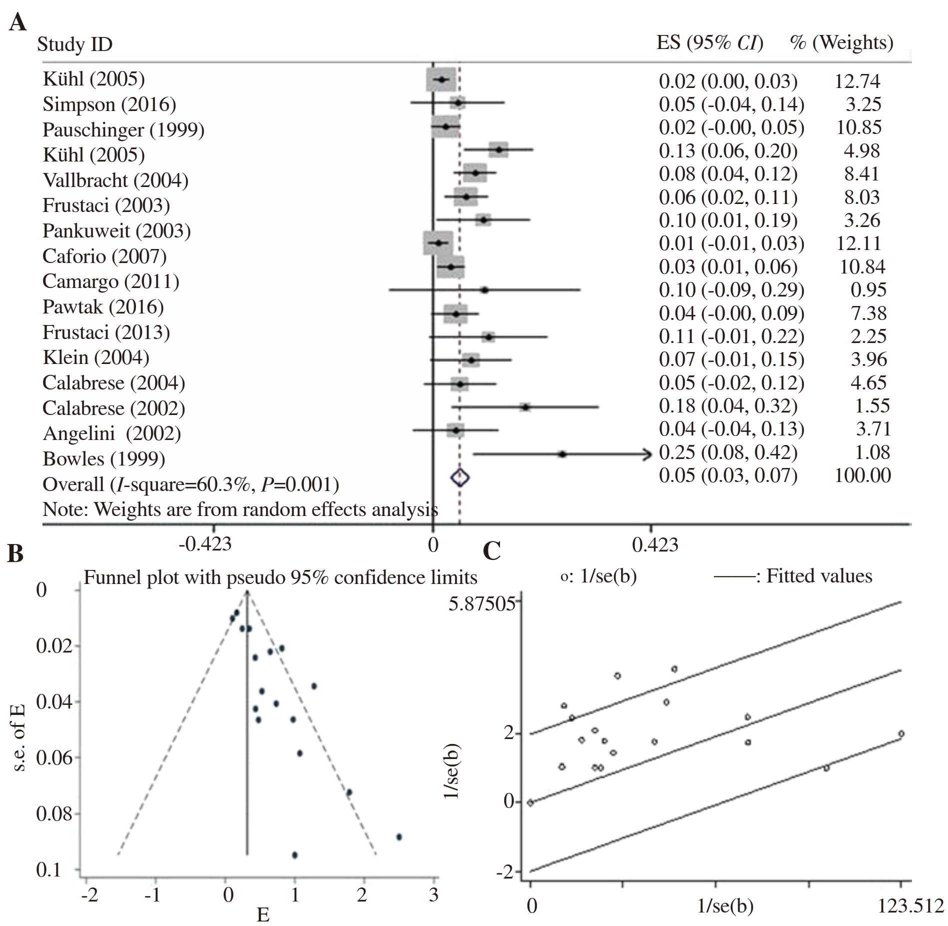

Figure 8. Forest plot (A), funnel plot (B) and Galbraith (C) of the meta-analysis on prevalence of adeno in patients with myocarditis.

4. Discussion

VMC includes inflammatory cardiomyopathy caused by viruses, which is one of the common diseases of heart disease. The disease is on the rise and is now becoming a common cardiovascular disease after coronary heart disease. It can occur in all age groups, from infants to the elderly, but mainly in children and adults under the age of 40[84].

The clinical course of VMC manifests itself with various cardiac symptoms including breathing difficulty, fatigue, exercise intolerance, chest pain, severe heart failure and arrhythmia and maybe non-symptom[85]. It sometimes mimics myocardial infarction. Sixty percent of patients presented arthralgia, fever, sweating, respiratory or gastrointestinal symptoms 1-2 weeks before disease[86].

Since the 1970s, the incidence of VMC has been continuing to grow in China, Japan, and other countries, and a large amount of clinical information has been reported. However, its pathogenesis is still unclear. Considering the rapid development of molecular biology in recent years, great progress has been made in this field. Almost, all human virus infections can involve the heart. It has been found that more than 30 kinds of viruses can cause myocarditis.

Since the incidence of myocarditis is high in the 21st century, understanding the epidemiological characteristics of the viral causes of the disease is important[84].

The prevalence of adenovirus, HCV, CMV, EBV, HHV6, influenza virus, B19, and non-polio enteroviruses are calculated using 75 studies based on the inclusion and exclusion criteria. This meta-analysis shows that the highest prevalence is related to B19 and non-polio enteroviruses prevalence were 25.0% (95% *CI*: 20.0-29.0) and 18% (95% *CI*: 4.7-11.1) respectively. The prevalence of viruses belonging to the herpes virus family includes HHV6, CMV, EBV (12.8%, 95% *CI*: 8.8-16.7; 5.5%, 95% *CI*: 3.3-7.7; and 3.1%, 95% *CI*: 1.7-4.6, respectively).

HCV accounted for 6.1% (95% *CI*: 1.8-10.4) of the disease, while the adenoviruses leded to 5.2% (95% *CI*: 3.3-7.0) VMC. The lowest incidence was related to influenza virus with 2.0% (95% *CI*: 0.5-3.4).

Several studies have found that some viruses are the main cause of myocarditis. For example, most researchers believe that enteroviruses are the most common cause of VMC. Whereas Kühl *et al*. reported that the parvovirus B19 genome could be in about 51.4% of VMC cases[87]. However, Griffin *et al.* found that VMC patients were mostly infected with adenovirus[88].

The result of this meta-analysis shows that B19 is the most common cause of VMC and non-polio enteroviruses are the second.

In conclusion, whereas effective commercial medications are available for some viruses that cause myocarditis such as ganciclovir for CMV and oseltamivir for influenza, a rapid and correct diagnosis could lead to the prevention of further disorders and the treatment of this infections.

There were some limitations in this study that should be discussed. First, as with any systematic review and meta-analysis, the existence of publication bias must be taken into account. Second, heterogeneity was observed among the evaluated articles. Although the random-effects model allows for heterogeneity, there may still be differences of opinion regarding the composition of the studies.

Conflict of interest statement

The authors report no conflict of interest.

Authors' contribution

M.D. and E.F. conceived and designed the study. T.A. and M.D. contributed in comprehensive research. M.D. and T.A. analyzed the data. M.D., T.A., and E.F. wrote the paper. M.D. and F.F. participated in data analysis and manuscript editing.

References

[1] Mahfoud F, Gärtner B, Kindermann M, Ukena C, Gadomski K, Klingel K, et al. Virus serology in patients with suspected myocarditis: utility or futility? *Eur Heart J* 2011; **32**(7): 897-903.

[2] Lv S, Rong J, Ren S, Wu M, Li M, Zhu Y, et al. Epidemiology and diagnosis of viral myocarditis. *Hellenic J Cardiol* 2013; **54**(5): 382-391.

[3] Pollack A, Kontorovich AR, Fuster V, Dec GW. Viral myocarditis--diagnosis, treatment options, and current controversies. *Nat Rev Cardiol* 2015; **12**(11): 670-680.

[4] Mahrholdt H, Wagner A, Deluigi CC, Kispert E, Hager S, Meinhardt G, et al. Presentation, patterns of myocardial damage, and clinical course of viral myocarditis. Circulation 2006; **114**(15): 1581-1590.

[5] Calabrese F, Carturan E, Chimenti C, Pieroni M, Agostini C, Angelini A, et al. Overexpression of tumor necrosis factor (TNF) α and TNF receptor I in human viral myocarditis: clinicopathologic correlations. *Mod Pathol* 2004; **17**(9): 1108.

[6] Calabrese F, Rigo E, Milanesi O, Boffa GM, Angelini A, Valente M, et al. Molecular diagnosis of myocarditis and dilated cardiomyopathy in children: clinicopathologic features and prognostic implications. *Diagn Mol Pathol* 2002; **11**(4): 212-221.

[7] Caforio AL, Calabrese F, Angelini A, Tona F, Vinci A, Bottaro S, et al. A prospective study of biopsy-proven myocarditis: prognostic relevance of clinical and aetiopathogenetic features at diagnosis. *Eur Heart J* 2007; **28**(11): 1326-1333.

[8] Pauschinger M, Noutsias M, Lassner D, Schultheiss H-P, Kuehl U. Inflammation, ECG changes and pericardial effusion. *Clin Res Cardiol* 2006; **95**(11): 569-583.

[9] Mahrholdt H, Goedecke C, Wagner A, Meinhardt G, Athanasiadis A, Vogelsberg H, et al. Cardiovascular magnetic resonance assessment of human myocarditis: a comparison to histology and molecular pathology.

Circulation 2004; **109**(10): 1250-1258.

[10]O'Connell JB. The role of myocarditis in end-stage dilated cardiomyopathy. *Tex Heart Inst J* 1987; **14**(3): 268-275.

[11]Pawlak A, Przybylski M, Durlik M, Gil K, Nasierowska-Guttmejer AM, Byczkowska K, et al. Viral nucleic acids in the serum are dependent on blood sampling site in patients with clinical suspicion of myocarditis. *Intervirology* 2016; **59**(3): 143-151.

[12]Angelini A, Crosato M, Boffa G, Calabrese F, Calzolari V, Chioin R, et al. Active versus borderline myocarditis: clinicopathological correlates and prognostic implications. *Heart* 2002; 87(3): 210-215.

[13]Richardson P, McKenna W, Bristow M, Maisch B, Mautner BO, Connell J, et al. Report of the 1995 World Health Organization/International Society and Federation of Cardiology Task Force on the Definition and Classification of cardiomyopathies. *Circulation* 1996; **93**: 841-842.

[14]Comar M, D'agaro P, Campello C, Poli A, Breinholt J, Towbin J, et al. Human herpes virus 6 in archival cardiac tissues from children with idiopathic dilated cardiomyopathy or congenital heart disease. *J Clin Pathol* 2009; **62**(1): 80-83.

[15]Chimenti C, Russo A, Pieroni M, Calabrese F, Verardo R, Thiene G, et al. Intramyocyte detection of Epstein-Barr virus genome by laser capture microdissection in patients with inflammatory cardiomyopathy. *Circulation* 2004; **110**(23): 3534-3539.

[16]Mantel N, Haenszel W. Statistical aspects of the analysis of data from retrospective studies of disease. *J Natl Cancer Inst* 1959; **22**(4): 719-748.

[17]DerSimonian R, Laird N. Meta-analysis in clinical trials. *Control Clin Trials* 1986; **7**(3): 177-188.

[18]Higgins J, Thompson SG. Quantifying heterogeneity in a meta-analysis. *Stat Medicine* 2002; **21**(11): 1539-1558.

[19]Bowles NE, Ni J, Kearney DL, Pauschinger M, Schultheiss HP, McCarthy R, et al. Detection of viruses in myocardial tissues by polymerase chain reaction. Evidence of adenovirus as a common cause of myocarditis in children and adults. *J Am Coll Cardiol* 2003; **42**(3): 466-472.

[20]Fujioka S, Kitaura Y, Ukimura A, Deguchi H, Kawamura K, Isomura T, et al. Evaluation of viral infection in the myocardium of patients with idiopathic dilated cardiomyopathy. *J Am Coll Cardiol* 2000; **36**(6): 1920-1926.

[21]Grün S, Schumm J, Greulich S, Wagner A, Schneider S, Bruder O, et al. Long-term follow-up of biopsy-proven viral myocarditis: predictors of mortality and incomplete recovery. *J Am Coll Cardiol* 2012; **59**(18): 1604-1615.

[22]Nielsen TS, Nielsen AY, Banner J, Hansen J, Baandrup U, Nielsen LP. Saffold virus infection associated with human myocarditis. *J Clin Virol* 2016; **74**: 78-81.

[23]Boudjellil R, Elbaz M, Lairez O, Lhomme S, Izopet J, Kamar N. No evidence of genotype-3 hepatitis E virus-induced myocarditis. *J Clin Virol* 2016; **76**: 44.

[24]Kühl U, Lassner D, Wallaschek N, Gross UM, Krueger GR, Seeberg B, et al. Chromosomally integrated human herpesvirus 6 in heart failure: prevalence and treatment. *Eur J Heart Fail* 2015; **17**(1): 9-19.

[25]Ukimura A, Izumi T, Matsumori A. A national survey on myocarditis associated with the 2009 influenza A (H1N1) pandemic in Japan. *Circ J* 2010; **74**(10): 2193-2199.

[26]Li Y, Bourlet T, Andreoletti L, Mosnier J-F, Peng T, Yang Y, et al. Enteroviral capsid protein VP1 is present in myocardial tissues from some patients with myocarditis or dilated cardiomyopathy. *Circulation* 2000; **101**(3): 231-234.

[27]Kühl U, Pauschinger M, Noutsias M, Seeberg B, Bock T, Lassner D, et al. High prevalence of viral genomes and multiple viral infections in the myocardium of adults with "idiopathic" left ventricular dysfunction. *Circulation* 2005; **111**(7): 887-893.

[28]Schowengerdt KO, Ni J, Denfield SW, Gajarski RJ, Bowles NE, Rosenthal G, et al. Association of parvovirus B19 genome in children with myocarditis and cardiac allograft rejection: diagnosis using the polymerase chain reaction. *Circulation* 1997; **96**(10): 3549-3554.

[29]Gaaloul I, Riabi S, Harrath R, Hunter T, Hamda KB, Ghzala AB, et al. Coxsackievirus B detection in cases of myocarditis, myopericarditis, pericarditis and dilated cardiomyopathy in hospitalized patients. *Mol Med Rep* 2014; **10**(6): 2811-2818.

[30]Simpson KE, Storch GA, Lee CK, Ward KE, Danon S, Simon CM, et al. High frequency of detection by PCR of viral nucleic acid in the blood of infants presenting with clinical myocarditis. *Pediatr Cardiol* 2016; **37**(2): 399-404.

[31]Pauschinger M, Bowles NE, Fuentes-Garcia FJ, Pham V, Kühl U, Schwimmbeck PL, et al. Detection of adenoviral genome in the myocardium of adult patients with idiopathic left ventricular dysfunction. *Circulation* 1999; **99**(10): 1348-1354.

[32]Schmidt NJ, Magoffin RL, Lennette EH. Association of group B coxsackieviruses with cases of pericarditis, myocarditis, or pleurodynia by demonstration of immunoglobulin M antibody. *Infect Immun* 1973; **8**(3): 341-348.

[33]Gagliardi MG, Fierabracci A, Pilati M, Chinali M, Bassano C, Saura F, et al. The impact of specific viruses on clinical outcome in children presenting with acute heart failure. *Int J Mol Sci* 2016; **17**(4): 486.

[34]Nicholson F, Ajetunmobi J, Li M, Shackleton E, Starkey W, Illavia S, et al. Molecular detection and serotypic analysis of enterovirus RNA in archival specimens from patients with acute myocarditis. *Heart* 1995; **74**(5): 522-527.

[35]Griffin LD, Kearney D, Ni J, Jaffe R, Fricker FJ, Webber S, et al. Analysis of formalin-fixed and frozen myocardial autopsy samples for viral genome in childhood myocarditis and dilated cardiomyopathy with endocardial fibroelastosis using polymerase chain reaction (PCR). *Cardiovasc Pathol* 1995; **4**(1): 3-11.

[36]Andréoletti L, Ventéo L, Douche-Aourik F, Canas F, de la Grandmaison GL, Jacques J, et al. Active Coxsackieviral B infection is associated with disruption of dystrophin in endomyocardial tissue of patients who died suddenly of acute myocardial infarction. *J Am Coll Cardiol* 2007; **50**(23): 2207-2214.

[37]Bratincsák A, El-Said HG, Bradley JS, Shayan K, Grossfeld PD, Cannavino CR. Fulminant myocarditis associated with pandemic H1N1 influenza A virus in children. *J Am Coll Cardiol* 2010; **55**(9): 928-929.

[38]Klein R, Jiang H, Niederacher D, Adams O, Du M, Horlitz M, et al. Frequency and quantity of the parvovirus B19 genome in endomyocardial biopsies from patients with suspected myocarditis or idiopathic left ventricular dysfunction. *Z Kardiol* 2004; **93**(4): 300-309.

[39]Kühl U, Pauschinger M, Seeberg B, Lassner D, Noutsias M, Poller W,

et al. Viral persistence in the myocardium is associated with progressive cardiac dysfunction. *Circulation* 2005; **112**(13): 1965-1970.

[40]Matsumori A, Shimada T, Chapman NM, Tracy SM, Mason JW. Myocarditis and heart failure associated with hepatitis C virus infection. *J Cardiac Fail* 2006; **12**(4): 293-298.

[41]Schönian U, Crombach M, Maser S, Maisch B. Cytomegalovirus-associated heart muscle disease. *Eur Heart J* 1995; **16**(suppl_O): 46-49.

[42]Vallbracht KB, Schwimmbeck PL, Kühl U, Seeberg B, Schultheiss H-P. Endothelium-dependent flow-mediated vasodilation of systemic arteries is impaired in patients with myocardial virus persistence. *Circulation* 2004; **110**(18): 2938-2945.

[43]Bachelier K, Biehl S, Schwarz V, Kindermann I, Kandolf R, Sauter M, et al. Parvovirus B19-induced vascular damage in the heart is associated with elevated circulating endothelial microparticles. *PloS One* 2017; **12**(5): e0176311.

[44]Frustaci A, Chimenti C, Calabrese F, Pieroni M, Thiene G, Maseri A. Immunosuppressive therapy for active lymphocytic myocarditis: virological and immunologic profile of responders versus nonresponders. *Circulation* 2003; **107**(6): 857-863.

[45]O'Neill D, McARTHUR JD, Kennedy JA, Clements G. Coxsackie B virus infection in coronary care unit patients. *J Clin Pathol* 1983; **36**(6): 658-661.

[46]El-Hagrassy MO, Banatvala J, Coltart D. Coxsackie-B-virus-specific IgM responses in patients with cardiac and other diseases. *Lancet* 1980; **316**(8205): 1160-1162.

[47]Nielsen TS, Hansen J, Nielsen LP, Baandrup UT, Banner J. The presence of enterovirus, adenovirus, and parvovirus B19 in myocardial tissue samples from autopsies: an evaluation of their frequencies in deceased individuals with myocarditis and in non-inflamed control hearts. *Forensic Sci Medicine Pathol* 2014; **10**(3): 344-350.

[48]Pankuweit S, Moll R, Baandrup U, Portig I, Hufnagel G, Maisch B. Prevalence of the parvovirus B19 genome in endomyocardial biopsy specimens. *Human Pathol* 2003; **34**(5): 497-503.

[49]Bock C-T, Klingel K, Kandolf R. Human parvovirus B19-associated myocarditis. *New Engl J Med* 2010; **362**(13): 1248-1249.

[50]Bültmann BD, Klingel K, Näbauer M, Wallwiener D, Kandolf R. High prevalence of viral genomes and inflammation in peripartum cardiomyopathy. *Am J Obstet Gynecol* 2005; **193**(2): 363-365.

[51]Martin AB, Webber S, Fricker FJ, Jaffe R, Demmler G, Kearney D, et al. Acute myocarditis. Rapid diagnosis by PCR in children. *Circulation* 1994; **90**(1): 330-339.

[52]Savón C, Acosta B, Valdés O, Goyenechea A, Gonzalez G, Piñón A, et al. A myocarditis outbreak with fatal cases associated with adenovirus subgenera C among children from Havana City in 2005. *J Clin Virol* 2008; **43**(2): 152-157.

[53]Camargo PR, Okay TS, Yamamoto L, Del Negro GMB, Lopes AA. Myocarditis in children and detection of viruses in myocardial tissue: implications for immunosuppressive therapy. *Int J Cardiol* 2011; **148**(2): 204-208.

[54]Why HJF, Meany B, Richardson PJ, Olsen EGJ, Bowles NE, Cunningham L, et al. Clinical and prognostic significance of detection of enteroviral RNA in the myocardium of patients with myocarditis or dilated cardiomyopathy. *Circulation* 1994; **89**(6): 2582-2589.

[55]Reibis R, Kühl U, Salzwedel A, Rasawieh M, Eichler S, Wegscheider K, et al. Return to work in heart failure patients with suspected viral myocarditis. *SAGE Open Med* 2017; **5**: 2050312117744978.

[56]Ozdemir R, Kucuk M, Dibeklioglu SE. Report of a myocarditis outbreak among pediatric patients: human herpesvirus 7 as a causative agent? *J Tropical Pediatr* 2018; **64**(6):468-471.

[57]Frustaci A, Francone M, Petrosillo N, Chimenti C. High prevalence of myocarditis in patients with hypertensive heart disease and cardiac deterioration. *Eur J Heart Fail* 2013; **15**(3): 284-291.

[58]Mavrogeni S, Bratis K, Markussis V, Spargias C, Papadopoulou E, Papamentzelopoulos S, et al. The diagnostic role of cardiac magnetic resonance imaging in detecting myocardial inflammation in systemic lupus erythematosus. Differentiation from viral myocarditis. *Lupus* 2013; **22**(1): 34-43.

[59]Jeserich M, Brunner E, Kandolf R, Olschewski M, Kimmel S, Friedrich MG, et al. Diagnosis of viral myocarditis by cardiac magnetic resonance and viral genome detection in peripheral blood. *Int J Cardiovasc Imaging* 2013; **29**(1): 121-129.

[60]Koepsell SA, Anderson DR, Radio SJ. Parvovirus B19 is a bystander in adult myocarditis. *Cardiovasc Pathol* 2012; **21**(6): 476-481.

[61]Mavrogeni S, Spargias C, Bratis C, Kolovou G, Markussis V, Papadopoulou E, et al. Myocarditis as a precipitating factor for heart failure: evaluation and 1-year follow-up using cardiovascular magnetic resonance and endomyocardial biopsy. *Eur J Heart Fail* 2011; 13(8): 830-837.

[62]Escher F, Modrow S, Sabi T, Kühl U, Lassner D, Schultheiss HP, et al. Parvovirus B19 profiles in patients presenting with acute myocarditis and chronic dilated cardiomyopathy. *Med Sci Monit* 2008; **14**(12): CR589-CR97.

[63]Lindner J, Noutsias M, Lassner D, Wenzel J, Schultheiss H-P, Kuehl U, et al. Adaptive immune responses against parvovirus B19 in patients with myocardial disease. *J Clin Virol* 2009; **44**(1): 27-32.

[64]Valdés O, Acosta B, Piñón A, Savón C, Goyenechea A, Gonzalez G, et al. First report on fatal myocarditis associated with adenovirus infection in Cuba. *J Med Virol* 2008; **80**(10): 1756-1761.

[65]Carturan E, Milanesi O, Kato Y, Giacometti C, Biffanti R, Thiene G, et al. Viral detection and tumor necrosis factor alpha profile in tracheal aspirates from children with suspicion of myocarditis. *Diagnost Mol Pathol* 2008; **17**(1): 21-27.

[66]Yilmaz A, Mahrholdt H, Athanasiadis A, Vogelsberg H, Meinhardt G, Voehringer M, et al. Coronary vasospasm as the underlying cause for chest pain in patients with PVB19-myocarditis. *Heart* 2008; **94**(11): 1456-1463.

[67]Guarner J, Bhatnagar J, Shieh W-J, Nolte KB, Klein D, Gookin MS, et al. Histopathologic, immunohistochemical, and polymerase chain reaction assays in the study of cases with fatal sporadic myocarditis. *Human Pathol* 2007; **38**(9): 1412-1419.

[68]Topkara VK, Dang NC, Barili F, Martens TP, George I, Cheema FH, et al. Ventricular assist device use for the treatment of acute viral myocarditis. *J Thorac Cardiovasc Surg* 2006; **131**(5): 1190-1191.

[69]Amabile N, Fraisse A, Bouvenot J, Chetaille P, Ovaert C. Outcome of acute fulminant myocarditis in children. *Heart* 2006; **92**(9): 1269-1273.

[70]Kytö V, Vuorinen T, Saukko P, Lautenschlager I, Lignitz E, Saraste A,

et al. Cytomegalovirus infection of the heart is common in patients with fatal myocarditis. *Clin Infect Dis* 2005; **40**(5): 683-688.

[71]English RF, Janosky JE, Ettedgui JA, Webber SA. Outcomes for children with acute myocarditis. *Cardiol Young* 2004; **14**(5): 488-493.

[72]Zhang HY, Li Y, McClean DR, Richardson PJ, Florio R, Sheppard M, et al. Detection of enterovirus capsid protein VP1 in myocardium from cases of myocarditis or dilated cardiomyopathy by immunohistochemistry: further evidence of enterovirus persistence in myocytes. *Med Microbiol Immunol* 2004; **193**(2-3): 109-114.

[73]Ali M, Abdel-Dayem T. Myocarditis: an expected health hazard associated with water resources contaminated with Coxsackie viruses type B. *Int J Environ Health Res* 2003; **13**(3): 261-270.

[74]Satoh M, Nakamura M, Akatsu T, Iwasaka J, Shimoda Y, Segawa I, et al. Expression of Toll-like receptor 4 is associated with enteroviral replication in human myocarditis. *Clin Sci* 2003; **104**(6): 577-584.

[75]Gut W, Wielkopolska A, Binduga-Gajewska I, Jarzabek Z. Evaluation of the usefulness of the ELISA method for detection of enterovirus antibodies in serum samples of patients with myocarditis. *Med Sci Monit* 2002; **8**(1): MT10-MT4.

[76]Matsumori A, Yutani C, Ikeda Y, Kawai S, Sasayama S. Hepatitis C virus from the hearts of patients with myocarditis and cardiomyopathy. *Lab Invest* 2000; **80**(7): 1137.

[77]Zhang HY, Li Y, Peng T, Aasa M, Zhang L, Yang Y, et al. Localization of enteroviral antigen in myocardium and other tissues from patients with heart muscle disease by an improved immunohistochemical technique. *J Histochem Cytochem* 2000; **48**(5): 579-584.

[78]Bowles NE, Kearney DL, Ni J, Perez-Atayde AR, Kline MW, Bricker JT, et al. The detection of viral genomes by polymerase chain reaction in the myocardium of pediatric patients with advanced HIV disease. *J Am Coll Cardiol* 1999; **34**(3): 857-865.

[79]Akhtar N, Ni J, Stromberg D, Rosenthal GL, Bowles NE, Towbin JA. Tracheal aspirate as a substrate for polymerase chain reaction detection of viral genome in childhood pneumonia and myocarditis. *Circulation* 1999; **99**(15): 2011-2018.

[80]Grumbach IM, Heim A, Pring-Akerblom P, Vonhof S, Hein W, Müller G, et al. Adenoviruses and enteroviruses as pathogens in myocarditis and dilated cardiomyopathy. *Acta Cardiolog* 1999; **54**(2): 83-88.

[81]Petitjean J, Kopecka H, Freymuth F, Langlard J, Scanu P, Galateau F, et al. Detection of enteroviruses in endomyocardial biopsy by molecular approach. *J Med Virol* 1992; **37**(1): 76-82.

[82]Mariani M, Petronio AS, Manes MT, Morelli M, Squecco D, Nardini V, et al. Detection of enteroviral infection in myocardial tissues by polymerase chain reaction (PCR). *Clin Microbiol Infect* 1996; 2(2): 109-114.

[83]Pauschinger M, Doerner A, Kuehl U, Schwimmbeck PL, Poller W, Kandolf R, Schultheiss HP, et al. Enteroviral RNA replication in the myocardium of patients with left ventricular dysfunction and clinically suspected myocarditis. *Circulation* 1999; **99**(7): 889-895.

[84]Lv S, Rong J, Ren S, Wu M, Li M, Zhu Y, et al. Epidemiology and diagnosis of viral myocarditis. *Hellenic J Cardiol* 2013; **54**(5): 382-391.

[85]Ellis CR, Di Salvo T. Myocarditis: basic and clinical aspects. *Cardiol Rev* 2007; **15**(4): 170-177.

[86]Magnani JW, Dec GW. Myocarditis: current trends in diagnosis and treatment. *Circulation* 2006; **113**(6): 876-890.

[87]Kühl U, Pauschinger M, Noutsias M, Seeberg B, Bock T, Lassner D, et al. High prevalence of viral genomes and multiple viral infections in the myocardium of adults with "idiopathic" left ventricular dysfunction. *Circulation* 2005; **111**: 887-893.

[88]Griffin LD, Kearney D, Ni J, Jaffe R, Fricker FJ, Webber S, et al. Analysis of formalin-fixed and frozen myocardial autopsy samples for viral genome in childhood myocarditis and dilated cardiomyopathy with endocardial fibroelastosis using polymerase chain reaction (PCR). *Cardiovasc Pathol* 1995; **4**: 3-11.