Potential association between bacterial infections and ischemic stroke based on fifty case-control studies: A systematic review and meta-analysis

M. Keikha[1,2] **and M. Karbalaei**[3]

1) *Antimicrobial Resistance Research Center*, 2) *Department of Microbiology and Virology, Faculty of Medicine, Mashhad University of Medical Sciences, Mashhad* and 3) *Department of Microbiology and Virology, School of Medicine, Jiroft University of Medical Sciences, Jiroft, Iran*

Abstract

Background: Stroke is considered as one of the most important concerns in health care centers around the world. By definition there are two types of stroke including ischemic stroke and hemorrhagic stroke. Approximately three-quarters of stroke cases are ischemic strokes, which occur due to several risk factors such as hypertension, obesity, atherosclerosis, diabetes mellitus, osteoarthritis, and inflammatory responses. In recent years, infectious diseases have noticed as a new risk factor for ischemic stroke. Given the importance of the issue, some bacteria that cause chronic infections, especially *Chlamydia pneumonia*, *Helicobacter pylori*, *Mycoplasma pneumonia*, *Mycobacterium tuberculosis*, and *Coxiella burnetii* have been considered.

Methods: In the present meta-analysis, we reviewed 50 case-control studies and assessed the possible association of bacterial infections with the occurrence of ischemic stroke.

Results: We analyzed the information of 33,978 participants in several nested case-control studies, and ultimately showed that bacterial infections could increase the risk of ischemic stroke. Our results suggest that bacterial infections significantly increase in the risk of ischemic stroke (OR: 1.704; 1.57-1.84 with 95% CIs; p value = 0.01).

Conclusions: In this meta-analysis, a significant relationship was observed between infection by three bacteria such as *C. pneumoniae*, *H. pylori*, and *M. tuberculosis* with the occurrence of ischemic stroke. Furthermore, due to the similarity between TLRVYK domain in β2-glycoprotein-I and TLRVYK peptide in various of microorganisms, produced antibodies against pathogens interact with β2-glycoprotein-I, hence the cross-reaction phenomenon increases the positive relationship between infectious diseases and ischemic stroke.
© 2022 The Author(s). Published by Elsevier Ltd.

Corresponding author: M. Karbalaei
E-mail: mohsen.karbalaei@jmu.ac.ir

Background

Nowadays stroke is accounted as one of the most striking complications of cardiovascular disorders, and is classified into two types, ischemic stroke and hemorrhagic stroke. The incidence of ischemic strokes is higher than hemorrhagic strokes, so that about 71% of strokes are ischemic and the rest are hemorrhagic [1]. In general, strokes are the second most common cause of death (approximately 13.7 million cases in 2016) worldwide [2]. This disease has become a global health concern, so it is estimated that one in four people will have a stroke during his/her lifetime [3]. Several risk factors such as obesity, hypertension, smoking, dyslipidemia, diabetes mellitus, alcohol consumption, atrial fibrillation, carotid stenosis, inflammation, and epigenetic events play a major role in the incidence of stroke [4].

Recently, the role of inflammatory reaction in the formation of vascular disorders such as atherosclerotic plaques, carotid intima-media thickness (CIMT), arterial wall disruption, and vascular wall instability has been well established [5]. Although

the role of infectious agents as a risk factor for stroke is not well understood, but there is some evidence linking infection with microorganisms to disorders such as atherosclerotic lesions, metabolism imbalance, cardiovascular disease (CVD), and hypertension; the most probable pathogens include cytomegalovirus (CMV), hepatitis C virus (HCV), human immunodeficiency virus (HIV), herpes simplex virus type 1/2 (HSV 1/2), Epstein Barr virus (EBV), influenza virus, periodontal microflora, *Helicobacter pylori* (*H. pylori*), *Chlamydia pneumoniae* (*C. pneumoniae*), *Haemophilus influenza* (*H. influenza*), *Mycoplasma pneumoniae* (*M. pneumoniae*), *Mycobacterium tuberculosis* (*Mtb*), *Streptococcus pneumonia* (*S. pneumoniae*), *Coxiella burnetii* (*Coxiella burnetii*), *Tannerella forsythia* (*T. forsythia*) [6–13]. Among all infectious agents, pathogenic bacteria play an important role in the development of CVD through their virulence mechanisms such as toxins, enzymes, interference in host immune response, as well as infective endocarditis [3,6]. According to the literature, endocarditis and sepsis are two main underlying diseases that increase the risk of stroke in humans [14].

The present meta-analysis was performed for the purpose of plausible relationship between ischemic stroke and infection with *H. pylori*, *C. pneumoniae*, *M. pneumoniae*, and *Mtb*. As well as, the potential role for stroke induction was estimated for each group of infectious agents.

Methods

Literature search strategy

Comprehensive systematic search was done through databases such as Scopus, PubMed, Cochrane Library, Embase, and Google scholar up to May 2020. For searching, we used keyword phrases such as "*Helicobacter pylori*" and "ischemic stroke," "*Chlamydia pneumonia*" and "ischemic stroke," "*Mycoplasma pneumonia*" and "ischemic stroke," "*Mycobacterium tuberculosis*" AND "ischemic stroke," as well as "bacterial infection" and "Ischemic stroke." All published English articles were retrieved without limitation on the date of publication. The search strategy was performed by two authors separately; in case of disagreement, the third author judged and decided.

Study selection criteria

In the present meta-analysis inclusion criteria included: 1) case-control studies on the role of bacterial infections in ischemic stroke; 2) studies on the role of infection by *H. pylori*, *C. pneumoniae*, *M. pneumoniae*, and *Mtb* in ischemic stroke; 3) studies with standard diagnostic methods including ELISA and other immunoassays, conventional microbiology methods, PCR, blotting assay, and urease breath test (UBT); 4) clarity in
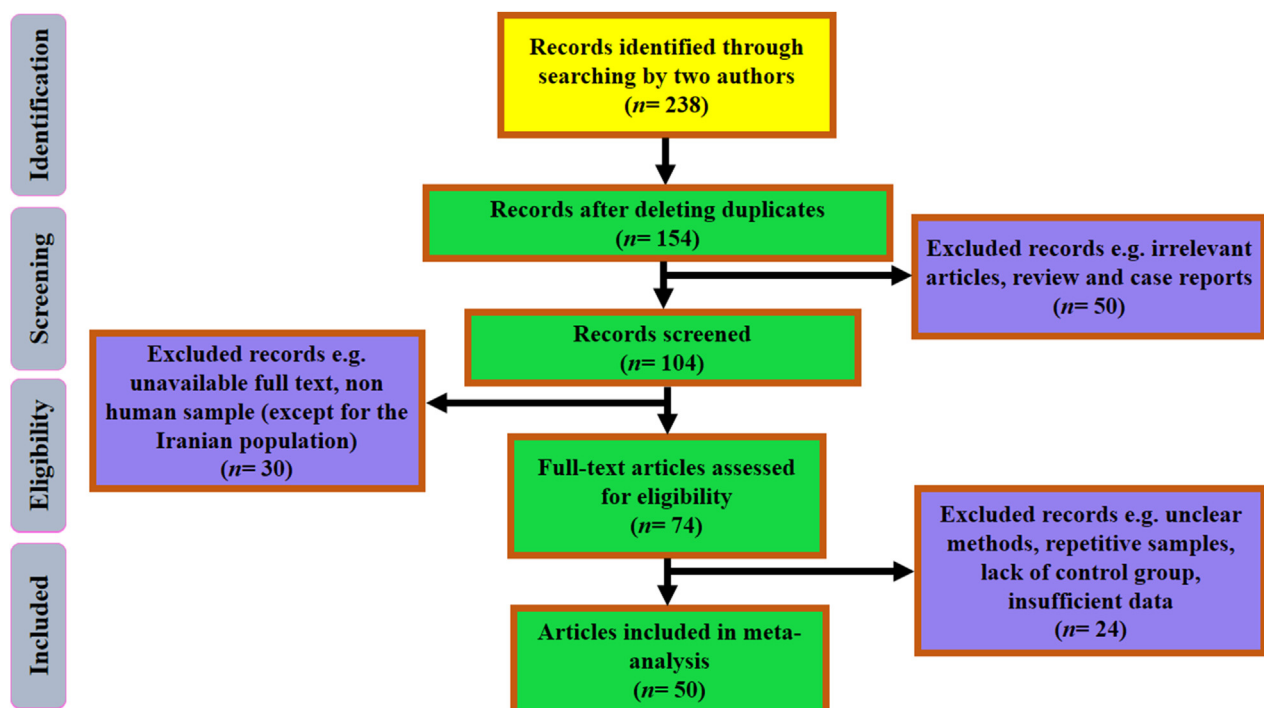

FIG. 1. The flowchart of included studies.

the results of included studies. In addition, our exclusion criteria included case-report, letter to editor, review, congress abstract, non-English texts, prospective or cohort, post-stroke infections studies, repetitive results, and unclear studies. The flowchart of included studies is presented in Fig. 1.

Quality assessment and data collection

The quality assessment of included studies was evaluated using the Newcastle−Ottawa scale (NOS). Required information included first author, publication year, location of each studies, type of infection agents, diagnostic methods of infection, age, gender, case group, control group, and number of infected cases in both case and control groups (Table 1) [15−64].

Quantitative synthesis

Data analysis was performed using Comprehensive Meta-Analysis (CMA) software version 2.2 (Biostat, Englewood, NJ). For this purpose, first the frequency of each bacterial infection including *H. pylori*, *C. pneumoniae*, *M. pneumoniae*, and *Mtb* was measured and according to the event rate (%) was reported for both case and control groups. Next, using the Odds ratio (OR) with 95% Confidence intervals (CIs), potential role of bacterial infection in the occurrence of ischemic stroke was analyzed. Moreover, by Cochran's Q and I^2 statistic parameters, we analyzed heterogeneity of included studies. By our default, the cases with Cochrane Q statistic $p < 0.1$ and $I^2 > 25\%$ were described as cases with high heterogeneity. According to the

TABLE 1. Characteristics of included studies

First author	Year	Area	Age (in years) case	Age (in years) control	Gender (F/M) case	Gender (F/M) control	Case group (n)	Control group (n)	Microorganism type	Number of bacterial infections (n) case	Number of bacterial infections (n) control	Diagnostic method	Ref
Wincup	1996	UK	54	53.5	NA	NA	137	136	H. pylori	93	78	ELISA	[15]
Cook	1998	UK	67.9	56.5	73/103	674/844	176	1518	C. pneumoniae	81	280	MIF	[60]
Rasura	2000	Italy	NA	NA	NA	NA	101	101	C. pneumoniae	26	8	ELISA	[65]
Elkind	2000	USA	68.5	68.5	47/42	47/42	89	89	C. pneumoniae	72	74	ELISA	[16]
Grau	2001	Germany	62	59.5	36/73	27/55	109	82	H. pylori	57	34	ELISA	[17]
Heuschmann	2001	Germany	74.6	74.6	77/68	138/122	145	260	H. pylori	67	117	ELISA	[61]
Ponzetto	2002	Italy	56.7	57.4	22/58	88/232	80	320	H. pylori	64	190	UBT	[18]
Pietroiusti	2002	Italy	63.2	63.9	11/50	89/62	61	151	H. pylori	43	106	PCR	[19]
Majka	2002	Germany	NA	NA	NA	NA	80	80	H. pylori	69	54	ELISA	[20]
Madre	2002	Spain	70	70	46/45	53/59	91	112	C. pneumoniae	40	34	IFI	[21]
Tarnacka	2002	Poland	74	66	91/88	66/56	179	122	C. pneumoniae	6.00 (95% CI: 1.61-22.29)		ELISA	[22]
Tanne	2003	Israel	61	61	8/126	8/126	134	134	C. pneumoniae	115	110	ELISA	[23]
Muller	2003	Denmark	69	45	84/109	125/243	193	368	C. pneumoniae	20	29	PCR	[24]
Kawamoto	2003	Japan	75	74	17/23	48/37	40	85	C. pneumoniae	29	52	ELISA	[25]
Moayyedi	2003	UK	70.5	70.2	228/239	227/161	467	388	H. pylori	274	206	ELISA	[27]
Voorend	2004	Netherlands	43.9	39.4	22/19	31/24	41	55	C. pneumoniae	28	38	ELISA	[29]
Ngeh	2004	UK	80	80	59/41	57/25	100	82	M. pneumoniae	95	82	ELISA	[30]
Gabrielli	2004	Italy	68	66	56/49	66/64	105	130	H. pylori	75	81	ELISA	[26]
Anzini	2004	Italy	34.6	36.5	60/81	90/102	141	192	C. pneumoniae	2.9 (95% CI: 1.77-4.76)		ELISA	[31]
Ngeh	2005	UK	NA	NA	59/41	60/27	100	87	C. pneumoniae	71	57	ELISA	[28]
Masoud	2005	Iran	64.3	61.7	43/48	40/40	91	80	H. pylori	59	36	ELISA	[32]
Kongoji	2005	Japan	63.5	62.7	7/6	2/5	13	7	C. pneumoniae	5	0	PCR	[33]
Wohlschlaeger	2005	Germany	65.1	73.3	5/5	16/7	7	21	C. pneumoniae	4	1	PCR	[34]
Sawayama	2005	Japan	71.5	69	22/40	95/48	62	143	H. pylori	9.68 (95% CI: 3.56–33.08)		UBT	[35]
Johnsen	2005	Denmark	60.4	60.5	99/155	99/155	254	254	C. pneumoniae	1.28 (95% CI: 0.83–1.95)		ELISA	[36]
Elkind	2006	USA	72.3	72.3	125/121	219/38	246	474	C. pneumoniae	156	257	ELISA	[37]
Park	2006	Korea	66.7	66.8	62/63	62/63	125	125	H. pylori	100	75	ELISA	[38]
Njamnshi	2006	Cameroon	NA	NA	64/0	64/0	64	64	C. pneumoniae	41	35	ELISA	[39]
Jozwiak	2007	Poland	44	40	40/54	44/59	94	103	C. pneumoniae	63	15	ELISA	[40]
Ashtari	2008	Iran	65.4	60.2	43/38	24/19	81	43	H. pylori	57	29	ELISA	[41]
Lin	2008	Taiwan	64.2	63.2	202/248	198/252	450	450	C. pneumoniae	334	257	ELISA	[42]
Bandaru	2008	India	47.8	47.8	149/51	149/51	200	200	C. pneumoniae	72	35	ELISA	[43]
Bastiani	2008	Italy	76.6	76.5	51/55	51/55	106	106	H. pylori	67	57	UBT	[44]
Bandaru	2009	India	35.3	35.3	30/90	30/90	120	120	C. pneumoniae	35	15	ELISA	[45]
Gagliardi	2009	Brazil	NA	NA	25/40	37/22	65	59	C. pneumoniae	0	1	PCR	[46]
Sheu	2010	Taiwan	33.5	42.4	824/1459	2939/3910	2283	6849	M. tuberculosis	136	256	Culture	[57]
Mousavi	2011	Iran	65.6	62.9	46/50	36/57	96	93	H. pylori	44	39	ELISA	[47]
Rai	2011	India	53.6	38.6	16/35	14/34	51	48	C. pneumoniae	32	38	ELISA	[48]
Ķēniņa	2011	Latvia	65.8	64.3	41/61	22/26	102	48	C. pneumoniae	64	17	ELISA	[49]
Hasan	2011	Iraq	58.02	56.1	18/32	18/22	50	40	C. pneumoniae	36	21	ELISA	[50]
Bandaru	2012	India	74	71	30/70	32/68	100	100	C. pneumoniae	29	16	ELISA	[51]
Hassanein	2014	Egypt	53	52.6	35/55	25/35	90	60	H. pylori	70	32	ELISA	[66]
Eini	2014	Iran	68.9	66.9	60/81	60/81	141	141	C. pneumoniae	111	74	ELISA	[54]
Ebrahimi-Rad	2014	Iran	NA	NA	NA	NA	27	25	C. pneumoniae	20	13	ELISA	[55]
Wu	2014	Taiwan	53	53.2	1922/3882	1925/3879	5804	5804	M. tuberculosis	176	207	Culture	[56]
Srivastava	2014	India	43.6	43.2	NA	NA	80	80	C. pneumoniae	42	26	ELISA	[58]
Sagar	2016	India	47.8	46.6	14/25	8/22	39	30	H. pylori	26	12	ELISA	[59]
Roham	2016	Iran	69.1	67.2	61/36	51/46	97	97	M. pneumoniae	4	0	ELISA	[62]
Salmasi	2017	Iran	66.7	65.9	38/32	39/31	70	70	H. pylori	61	51	ELISA	[63]
Mrđen	2017	Croatia	72.8	72.8	34/32	34/32	82	93	H. pylori	21	32	ELISA	[64]

Dersimonian and Laird method, the random effect model and the fixed effect model were applied in high and low heterogeneity cases, respectively. Finally, Egger's regression was used for estimating asymmetry of funnel plot and also publication bias.

Results

Characterization of included studies

After the initial search, 238 documents were identified from 1996−2017, and finally, 50 studies were selected based on inclusion criteria. In a large number of eligible studies, the presence of bacterial infection at the time of acute ischemic stroke was investigated; however, there were also cohort studies that evaluated the longitudinal effects of bacterial infections on ischemic stroke. Of these studies, 28, 18, 2, and 2 studies were related to *C. pneumoniae*, *H. pylori*, *M. pneumoniae*, and *Mtb*, respectively. In addition, the diagnostic methods were included ELISA, PCR, UBT, MIF, IFI, and conventional microbiology. In the present study, the information of 33,978 individuals including 13,652 patients (case) and 20,326 healthy (control) was reviewed. Average of age in case and control groups was 61.7 and 59.8, respectively. The frequency of men in both case and control groups was measured 62.6% and 56.1%, respectively. According to statistical analysis, the presence of bacterial infection in both case (ischemic stroke) and control groups was 38% (37-39 with 95% CIs) and 26% (25-27 with 95% CIs), respectively. We also found a meaningful relationship between

| Study name	Odds ratio	Lower limit	Upper limit	Z-Value	p-Value
Masoud	2.250	1.212	4.177	2.569	0.010
Srivastava	2.296	1.205	4.376	2.525	0.012
Muller	1.350	0.742	2.456	0.983	0.326
Jozwiak	11.920	5.941	23.915	6.976	0.000
Kongoji	9.700	0.453	207.735	1.453	0.146
Kawamoto	1.670	0.733	3.805	1.220	0.222
Gabrielli	1.512	0.871	2.624	1.471	0.141
Sagar	3.000	1.113	8.084	2.172	0.030
Majka	3.020	1.371	6.654	2.743	0.006
Mr?en	0.656	0.341	1.263	-1.260	0.207
Ashtari	1.147	0.514	2.559	0.334	0.738
Lin	2.160	1.631	2.861	5.369	0.000
Ponzetto	2.737	1.513	4.950	3.330	0.001
Bandaru1	2.650	1.662	4.225	4.094	0.000
Mousavi	1.172	0.655	2.096	0.534	0.594
Hassanein	3.063	1.504	6.236	3.085	0.002
Rasura	4.030	1.723	9.426	3.215	0.001
Eini	3.350	1.985	5.654	4.527	0.000
Cook	3.770	2.724	5.218	8.004	0.000
Bastiani	1.363	0.785	2.366	1.100	0.271
Elkind1	0.850	0.391	1.846	-0.411	0.681
Elkind	1.460	1.063	2.005	2.337	0.019
Ebrahimi-Rad	2.630	0.819	8.443	1.625	0.104
Hasan	2.320	0.967	5.564	1.885	0.059
Wincup	1.572	0.956	2.585	1.781	0.075
Park	2.667	1.513	4.700	3.392	0.001
Heuschmann	1.050	0.696	1.584	0.232	0.817
Salmasi	2.525	1.051	6.066	2.071	0.038
Madre	1.790	1.006	3.186	1.979	0.048
??ni?a	3.070	1.502	6.277	3.074	0.002
Moayyedi	1.254	0.955	1.648	1.627	0.104
Ngeh1	1.280	0.688	2.382	0.779	0.436
Roham	9.380	0.494	178.134	1.490	0.136
Ngeh	0.105	0.006	1.884	-1.530	0.126
Njamnshi	1.470	0.720	3.001	1.058	0.290
Choudhary	0.440	0.180	1.078	-1.798	0.072
Pietroiusti	1.014	0.507	2.028	0.040	0.968
Wu	0.846	0.690	1.038	-1.603	0.109
Srinivasarao	2.880	1.473	5.631	3.092	0.002
Bandaru	2.140	1.073	4.270	2.159	0.031
Tanne	1.320	0.683	2.551	0.826	0.409
Gagliardi	0.290	0.011	7.915	-0.734	0.463
Voorend	0.960	0.400	2.302	-0.091	0.927
Wohlschlaeger	26.660	2.174	326.993	2.567	0.010
Anzini	2.900	1.768	4.756	4.219	0.000
Johnsen	1.280	0.835	1.962	1.133	0.257
Sawayama	6.000	3.590	10.028	6.837	0.000
Tarnacka	6.000	1.613	22.325	2.673	0.008
	1.704	1.576	1.842	13.407	0.000
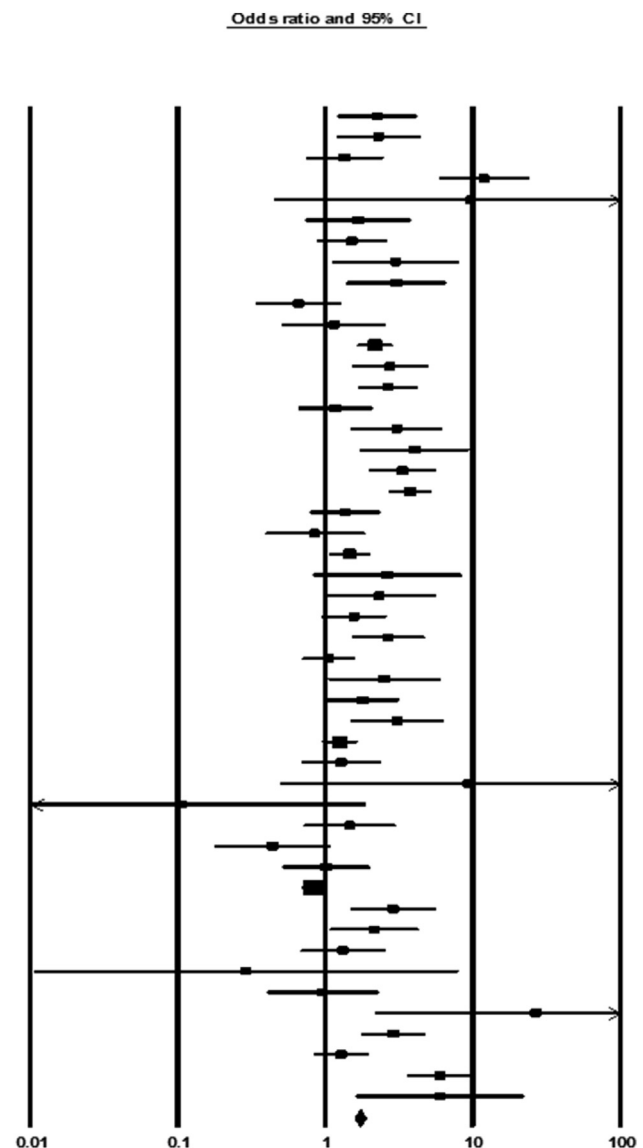
FIG. 2. The forest plot of the meta-analysis on the association between bacterial infection and ischemic stroke.

bacterial infections and the incidence of ischemic stroke (OR: 1.704; 1.57-1.84 with 95% CIs; p value = 0.01; I^2 = 78.55; Q-value: 219.11; df = 47; Egger's intercept = 1.23) (Fig. 2).

The potential association between C. pneumonia infection and ischemic stroke

We found 28 articles about the role of infection by *C. pneumonia* in the incidence of ischemic stroke. The rate of infection was estimated at 57% (54−59 with 95% CIs) and 36% (34−37 with 95% CIs) in both stroke and healthy groups, respectively. A significant relevance was observed between infection by *C. pneumonia* and ischemic stroke (OR: 2.14; 1.91−2.38 with 95% CIs; p-value = 0.001; I^2 = 71; Q-value = 93.29; df = 27; Egger's intercept = 0.06) (Fig. 3).

The potential association between H. pylori infection and ischemic stroke

Of the 50 case-control articles included in this meta-analysis, 18 were conducted on the association between *H. pylori*

infection and the incidence of ischemic stroke. The infection rate in both patient and healthy groups was 63% (60−65 with 95% CIs) and 55% (52−57 with 95% CIs), respectively. In accordance with statistical results, it seems that there is a meaningful relationship between infection by *H. pylori* and ischemic stroke (OR: 1.64; 1.44−1.87 with 95% CIs; p-value = 0.001; I^2 = 72.88; Q-value = 59; df = 16; Egger's intercept = 1.87) (Fig. 4).

The potential association between M. pneumonia infection and ischemic stroke

Regarding the plausible role of infection by *M. pneumonia* and occurrence of ischemic stroke, we retrieved only two eligible studies. The incidence rate of infection in both case and control groups was 55% (39−70 with 95% CIs) and 47% (11−86 with 95% CIs), respectively. We did not find any significant relationship between *M. pneumonia* infection with ischemic stroke (OR: 0.97; 0.12−7.69 with 95% CIs; p-value = 0.98; I2 = 77.94; Q-value = 4.53; df = 1) (Fig. 5).

| Study name	Statistics for each study					Odds ratio and 95% CI
	Odds ratio	Lower limit	Upper limit	Z-Value	p-Value	
Srivastava	2.296	1.205	4.376	2.525	0.012	
Muller	1.350	0.742	2.456	0.983	0.326	
Jozwiak	11.920	5.941	23.915	6.976	0.000	
Kongoji	9.700	0.453	207.735	1.453	0.146	
Kawamoto	1.670	0.733	3.805	1.220	0.222	
Lin	2.160	1.631	2.861	5.369	0.000	
Bandaru1	2.650	1.662	4.225	4.094	0.000	
Rasura	4.030	1.723	9.426	3.215	0.001	
Eini	3.350	1.985	5.654	4.527	0.000	
Cook	3.770	2.724	5.218	8.004	0.000	
Elkind1	0.850	0.391	1.846	-0.411	0.681	
Elkind	1.460	1.063	2.005	2.337	0.019	
Ebrahimi-Rad	2.630	0.819	8.443	1.625	0.104	
Hasan	2.320	0.967	5.564	1.885	0.059	
Madre	1.790	1.006	3.186	1.979	0.048	
??ni?a	3.070	1.502	6.277	3.074	0.002	
Ngeh1	1.280	0.688	2.382	0.779	0.436	
Njamnshi	1.470	0.720	3.001	1.058	0.290	
Choudhary	0.440	0.180	1.078	-1.796	0.072	
Srinivasarao	2.880	1.473	5.631	3.092	0.002	
Bandaru	2.140	1.073	4.270	2.159	0.031	
Tanne	1.320	0.683	2.551	0.826	0.409	
Gagliardi	0.290	0.011	7.915	-0.734	0.463	
Voorend	0.960	0.400	2.302	-0.091	0.927	
Wohlschlaeger	26.660	2.174	326.993	2.567	0.010	
Anzini	2.900	1.768	4.756	4.219	0.000	
Johnsen	1.280	0.835	1.962	1.133	0.257	
Tamacka	6.000	1.613	22.325	2.673	0.008	
	2.140	1.918	2.388	13.609	0.000	
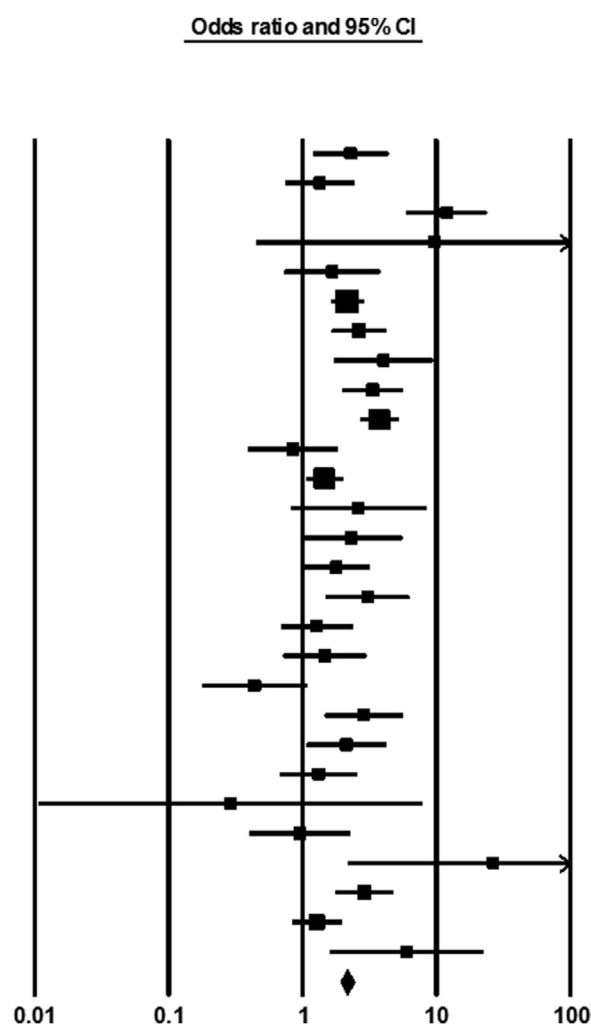
FIG. 3. The forest plot of the meta-analysis on the association between *C. pneumoniae* infection and ischemic stroke.
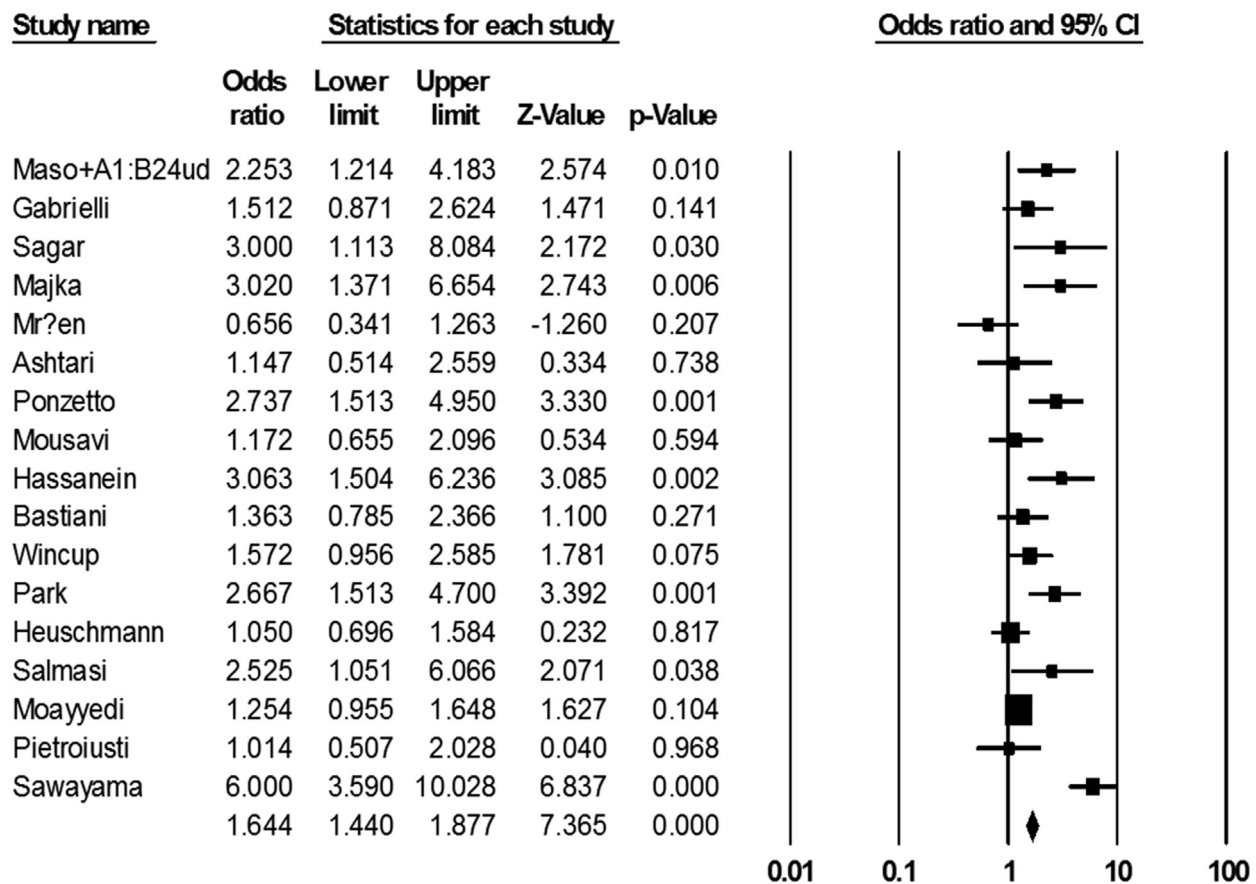
Study name	Statistics for each study					Odds ratio and 95% CI
	Odds ratio	Lower limit	Upper limit	Z-Value	p-Value	
Maso+A1:B24ud	2.253	1.214	4.183	2.574	0.010	
Gabrielli	1.512	0.871	2.624	1.471	0.141	
Sagar	3.000	1.113	8.084	2.172	0.030	
Majka	3.020	1.371	6.654	2.743	0.006	
Mr?en	0.656	0.341	1.263	-1.260	0.207	
Ashtari	1.147	0.514	2.559	0.334	0.738	
Ponzetto	2.737	1.513	4.950	3.330	0.001	
Mousavi	1.172	0.655	2.096	0.534	0.594	
Hassanein	3.063	1.504	6.236	3.085	0.002	
Bastiani	1.363	0.785	2.366	1.100	0.271	
Wincup	1.572	0.956	2.585	1.781	0.075	
Park	2.667	1.513	4.700	3.392	0.001	
Heuschmann	1.050	0.696	1.584	0.232	0.817	
Salmasi	2.525	1.051	6.066	2.071	0.038	
Moayyedi	1.254	0.955	1.648	1.627	0.104	
Pietroiusti	1.014	0.507	2.028	0.040	0.968	
Sawayama	6.000	3.590	10.028	6.837	0.000	
	1.644	1.440	1.877	7.365	0.000	

FIG. 4. The forest plot of the meta-analysis on the association between *H. pylori* infection and ischemic stroke.

The potential association between M. tuberculosis infection and ischemic stroke

Finally, to evaluate the association between infection by *Mtb* and stroke, we analyzed two studies. Based on statistical analysis, the rate of infection by *Mtb* in both ischemic and healthy groups was 4% (3.6−4.5 with 95% CIs) and 3% (3.3−4 with 95% CIs), respectively. However, we observed a significant relationship between infection by *Mtb* and the incidence of ischemic stroke (OR: 1.15; 0.99−1.34 with 95% CIs; *p*-value = 0.05; I2 = 94.73; Q-value = 18.98; df = 1) (Fig. 6).

In general, in the present study we appraised the potential role of infections by four bacteria including *C. pneumoniae*, *H. pylori*, *M. pneumoniae*, *Mtb*, and progression to ischemic stroke. In this meta-analysis we demonstrated a meaningful relationship between infection by three bacteria *C. pneumoniae*, *H. pylori*, and *Mtb* with occurrence of ischemic stroke. However, significant heterogeneity was observed between the studies, which in turn led to the unreliability of the current results; moreover, there were differences in items such as bacterial identification methods (i.e. instrument or materials), study design, as well as difference in time-point contributed between included studies. Unfortunately,

we did not access to raw data to provide subgroup analysis to reduce heterogeneity. Therefore, more extensive research is needed to validate the current analysis.

Discussion

Stroke is one of the most common cardiovascular disorders, and its occurrence depends on underlying risk factors including hypertension, diabetes mellitus, smoking, hyperlipidemia, atrial fibrillation, atherosclerosis, as well as characteristics such as age, gender, and family history [67]. Depending on the circumstances, the risk factors for the onset of stroke are different, so the mechanism of the increase in the incidence of stroke in young people and its trend towards autumn and winter is not yet fully understood [68]. In recent decades, understanding the role of acute and chronic infections in stroke has received more attention; obviously, infection can lead to inflammation, which in turn causes complications such as the formation of fatty plaques in blood vessels, atherogenic reactions, and changes in host metabolism (Fig. 7) [69].
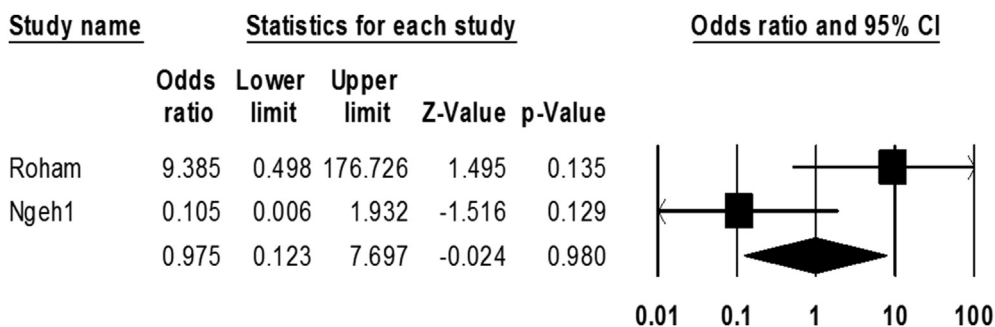
Study name	Statistics for each study					Odds ratio and 95% CI
	Odds ratio	Lower limit	Upper limit	Z-Value	p-Value	
Roham	9.385	0.498	176.726	1.495	0.135	
Ngeh1	0.105	0.006	1.932	-1.516	0.129	
	0.975	0.123	7.697	-0.024	0.980	

FIG. 5. The forest plot of the meta-analysis on the association between *M. pneumoniae* infection and ischemic stroke.
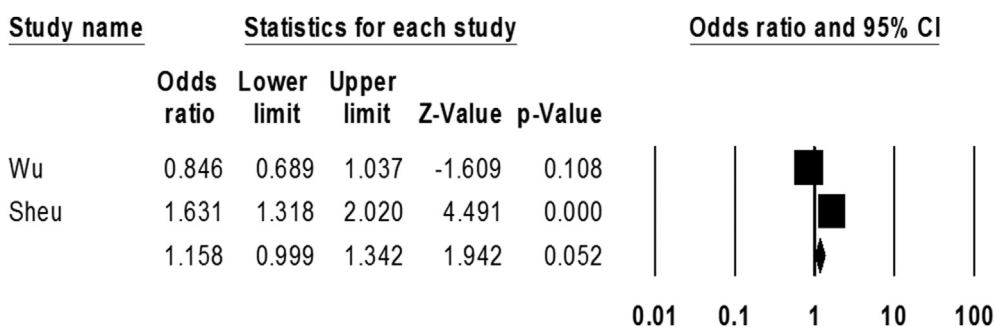
Study name	Statistics for each study					Odds ratio and 95% CI
	Odds ratio	Lower limit	Upper limit	Z-Value	p-Value	
Wu	0.846	0.689	1.037	-1.609	0.108	
Sheu	1.631	1.318	2.020	4.491	0.000	
	1.158	0.999	1.342	1.942	0.052	

FIG. 6. The forest plot of the meta-analysis on the association between *M. tuberculosis* infection and ischemic stroke.
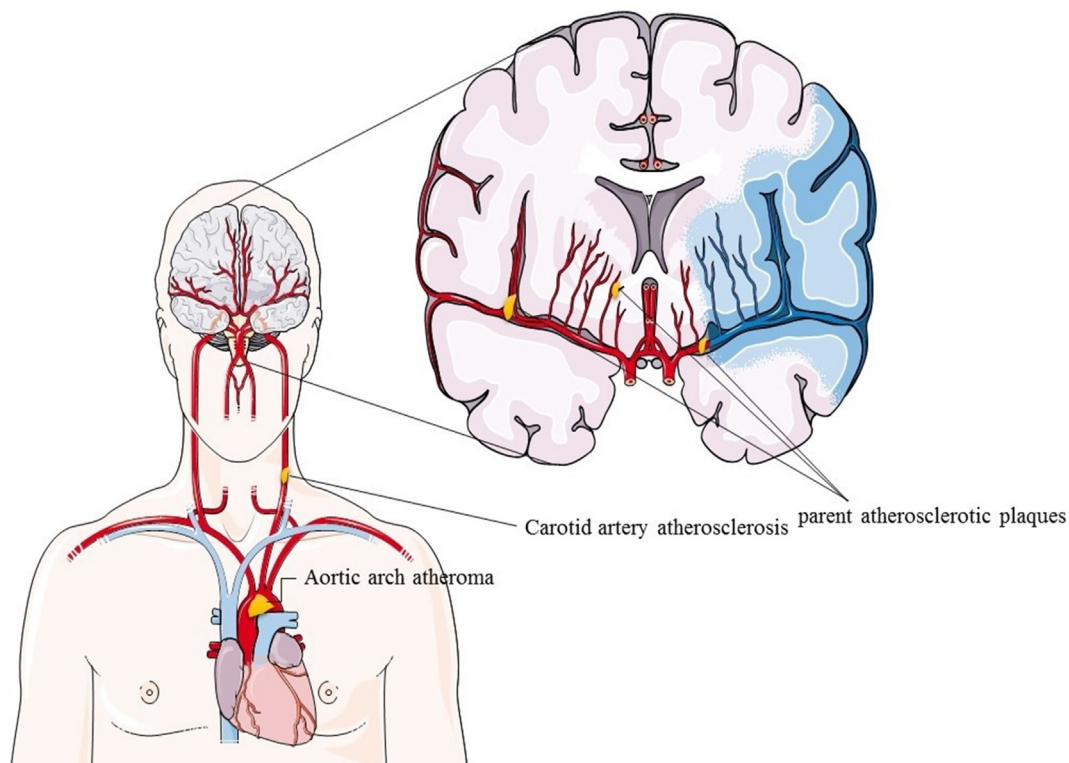
FIG. 7. Cardiovascular disorders caused by infection. Bacterial infections cause some cardiovascular disorders including parent atherosclerosis plaques, Carotid artery atherosclerosis, and Aortic arch atheroma. This figure was taken from the website https://smart.servier.com/image-set-download/.

According to the literature, the infections caused by pathogens such as *C. pneumonia, H. pylori, M. pneumonia, Coxiella burnetii*, HIV, HSV 1-2, and CMV are more significant, these infectious microorganisms are often isolated from atherosclerotic plaques [12,70]. On the other hand, induction of CIMT and a high seropositive status in the population with CVD confirm this phenomenon [71]. Today, there is ample evidence of the role of bacterial infections in increasing stroke; for example, infectious endocarditis can lead to embolism and arthritis. Moreover, bacterial meningitis and chronic brucellosis cause vasculitis and thrombosis in cerebral arteries; likewise, rickettsial infections lead to damage of small vascular endothelial cells and eventually ischemic stroke [68].

Induced autoantibodies during infectious diseases are considered pathogenic autoantibodies and potentially interact with the phospholipid binding protein β2-glycoprotein-I (β2GPI), the major autoantigen in APS [72]. Due to the phenomenon of "molecular mimicry," microbes mimic the natural proteins of the host with the help of their chemical structures [73]. In their study, Blank et al. showed that there is a high homology between the TLRVYK hexapeptide in β2GPI and various bacteria (*Pseudomonas aeruginosa, Yersinia pseudotuberculosis*, and *Streptomyces lividans*), viruses (CMV, polyoma virus, and adeno virus-40), yeasts (*Saccharomyces cerevisiae*), and parasites (*Schistosoma mansoni*), which in turn induces pathogenic H-3 anti-β2GPI mAb against β2GPI [74,75]. In the present study using statistical analysis of fifty case-control studies, we found that there is a significant relationship between bacterial infection and ischemic stroke cases (OR: 1.7; CI: 1.5−1.8).

C. pneumonia is a Gram-negative intracellular bacterium that was first introduced in 1980s. More than half of the world's population is infected with this bacterium; this fact has been confirmed by serological evidence [76,77]. In many studies, researchers have isolated *C. pneumonia* from carotid plaques, atherosclerotic plaques, and circulating leukocytes [77]. Sander et al. showed that eliminating *C. pneumoniae* infection could prevent the progression of CIMT [78]. Clinical trial studies have also suggested that treatment of this infection can potentially reduce vascular lesions in patients [79]. In our study the rate of infection by *C. pneumonia* in both case and control groups was measured 57% and 36% respectively. Also, we showed that there is a meaningful relationship between infection by this bacterium and occurrence of ischemic stroke (OR: 2.14; CI: 1.9−2.3).

H. pylori is a Gram-negative, helical, and microaerophilic bacterium that colonizes almost half of the world's population in the gastric mucosa [80]. The rate of infection by this bacterium is higher in developing countries than in developed countries, accordingly, in some parts of Africa the infection with this pathogen reaches 100% [81,82]. This bacterium is considered as a causative agent in disorders such as chronic gastritis, gastric ulcer, as well as gastric cancer; extra-gastrointestinal diseases related to this pathogen have attracted much attention, in which the association between *H. pylori* infection and CVD is well known [83,84]. In addition to isolating these bacteria from atherosclerotic plaques, their infection causes disorders such as insulin resistance, dyslipidemia, hypertension, and alteration in metabolism, all of which describe the potential role of *H. pylori* infection in increasing ischemic stroke, particularly nonembolic ischemic stroke [85,86]. Statistically, infection with this pathogen was measured at 63% and 55% in ischemic stroke patients and healthy individuals, respectively (OR: 1.6; CI: 1.4−1.8).

M. pneumonia is a respiratory pathogen that despite a poor understanding of its pathogenicity, many people have anti-*M.pneumonia* antibodies (IgG and IgM). Recent studies have shown its role in extra-pulmonary manifestations such as musculoskeletal, gastrointestinal, neurological, dermatologic, hematologic, and cardiovascular complications [87,88]. According to the literature, about 0.1% of patients infected with *M. pneumonia* develop neurological disability during their lifetime [89]. Vasculopathic lesions following this bacterial infection indicate the role of *M. pneumonia* in increasing the risk of ischemic stroke [68,90]. Two studies in this meta-analysis were related to the role of *M. pneumonia* in ischemic stroke susceptibility; infection by this bacterium was 55% and 47% in both case and control groups, respectively. Also, based on statistical analysis, no significant association was found between infection by *M. pneumonia* and ischemic stroke (OR: 0.97; CI: 0.12−7.6). However, the small number of studies may affect the present results, as only two studies had been performed on this bacterium. In addition, high heterogeneity causes instability of the results and we need more studies to confirm these findings.

Mtb is a life-threatening pathogen, and although this bacterium is commonly identified as a major cause of pulmonary tuberculosis, it also causes extra-pulmonary manifestations [91,92]. In recent years the role of bacterium in promoting neurological manifestation has been demonstrated, so that following arterial invasion, malignant vasculitis can be occurred during the tubercular meningitis [68]. Salindri et al. conducted a cohort study to show the effects of *Mtb* infection on chronic non-communicable disease; they found that previous tuberculosis (TB) infection could significantly increase susceptibility to ischemic stroke [93]. Our results also confirmed the possible association between TB infection and an increased risk of ischemic stroke.

Coxiella burnetii is an intracellular and Gram-negative coccobacillus bacterium which causes Q-fever, a zoonosis disease; Q-fever is endemic worldwide, especially in European countries e.g. Spain, France, and Germany [94]. Based on the findings of Vinacci et al., *Coxiella burnetii* is one of the main bacterial isolates in patients with infective endocarditis (IE) and acute ischemic

stroke (AIS) [95]. During primary infection, *Coxiella burnetii* induces high levels of antiphospholipid antibodies, especially IgG anticardiolipin antibodies (IgG aCL), which in turn lead to antiphospholipid syndrome (APS); infectious IgG aCL are associated with several complications such as fever, thrombocytopenia, valvular heart disease, as well as chronic endocarditis [96–98]. In addition, serological markers indicate that there is a significant relationship between *Coxiella burnetii* infection and CVD in the elderly people [99,100].

Nevertheless, our study had several limitations which we must mention: 1) the small number of included studies; 2) lack of access to raw data to perform modulatory analysis to describe significant heterogeneity; 3) the effects of mixed infections are likely to be underestimated in qualified studies; 4) asymmetry of funnel plot also suggests the presence of significant publication bias within the included studies; 5) there was also difference in diagnostic method, study design, studies timepoint, population ethnicity and location of included studies that actively contributed in heterogeneity of the included studies. In our study, a large number of eligible studies were cross-sectional that assessed the bacterial infections at the time of ischemic stroke, while, cohort studies could better deliberate the clear association between bacterial infection and susceptibility to ischemic stroke. Therefore, to confirm the results of the present study, we need more comprehensive studies.

Conclusion

In the present study, the information of two nested case-control studies about the role of *Mtb* in ischemic stroke was evaluated. The rate of infection by this pathogen in both cases and control groups was 4% and 3%, respectively, and we found a significant association between mycobacterial infection and ischemic stroke (OR: 1.1; CI: 0.99–1.34). We assessed the relationship between bacterial infections and the development of ischemic stroke. Nevertheless, due to limitation in results, we could not evaluate the role of pre-existing risk factors in our research. Overall, for understanding the role of bacterial infections in ischemic stroke, it is better to perform a comprehensive study about the association between bacterial infections and traditional ischemic stroke risk factors, CIMT, atherosclerosis, and cardiovascular risk factors such as LDL and HDL. Our results indicate the need for additional longitudinal investigations to determine the impact of infectious disease on the risk of ischemic stroke; such studies will require substantial follow-up time and control subjects. We recommend further larger cohort studies to determine bacterial infections and their determining role in ischemic stroke. As we noted above, TLRVYK domain in β2GPI is the main peptide in cardiolipins structures and is homologous with TLRVYK peptide

in various bacteria, viruses, yeasts, and parasites. Pathogenic autoantibodies (H-3 anti-β2GPI mAb) produced against infectious microorganisms cross-react with this peptide in β2GPI, thus may lead to ischemic stroke.

Ethics approval and consent to participate

Not applicable (this article was provided based on researching in global databases).

Consent to publish

All authors have informed consent about the content of this article.

Availability of data and materials

All data will be available for anyone who requests those.

Transparency declaration

Authors' contributions

1. MK1 was a major contributor in writing the manuscript.
2. MK2 was research director and translated this manuscript to English.
All authors read and approved the final manuscript.

Acknowledgements

Abbreviations

CIMT	Carotid intima-media thickness
CVD	Cardiovascular disease
CMV	Cytomegalovirus

HCV	Hepatitis C virus
HIV	Human immunodeficiency virus
HSV 1-2	Herpes simplex virus type 1-2
EBV	Epstein Barr virus
NOS	Newcastle-Ottawa Scale
CMA	Comprehensive Meta-Analysis
OR	Odds ratio
CIs	Confidence intervals
H. pylori	*Helicobacter pylori*
Mtb	*Mycobacterium tuberculosis*
C. burnetii	*Coxiella burnetii*
C. pneumoniae	*Chlamydia pneumoniae*
M. pneumoniae	*Mycoplasma pneumonia*

References

[1] Campbell BC, De Silva DA, Macleod MR, Coutts SB, Schwamm LH, Davis SM, et al. Ischaemic stroke. Nature Rev Dise Prim 2019;5(1):1−22.

[2] Johnson CO, Nguyen M, Roth GA, Nichols E, Alam T, Abate D, et al. Global, regional, and national burden of stroke, 1990−2016: a systematic analysis for the Global Burden of Disease Study 2016. Lancet Neurol 2019;18(5):439−58.

[3] Budzyński J, Wiśniewska J, Ciecierski M, Kędzia A. Association between bacterial infection and peripheral vascular disease: a review. Int J Angiol 2016;25(1):3−13.

[4] Roth GA, Johnson C, Abajobir A, Abd-Allah F, Abera SF, Abyu G, et al. Global, regional, and national burden of cardiovascular diseases for 10 causes, 1990 to 2015. J Am Coll Cardiol 2017;70(1):1−25.

[5] Lucchese G, Flöel A, Stahl B. Cross-reactivity as a mechanism linking infections to stroke. Front Neurol 2019;10:469.

[6] Budzyński J, Koziński M, Kłopocka M, Kubica JM, Kubica J. Clinical significance of Helicobacter pylori infection in patients with acute coronary syndromes: an overview of current evidence. Clin Res Cardiol 2014;103(11):855−86.

[7] Kukreja N, Koslowski M, Insall R. Angiolymphoid hyperplasia with eosinophilia presenting as an axillary artery aneurysm. Case Rep 2011;2011.

[8] Sessa R, Di Pietro M, Filardo S, Turriziani O. Infectious burden and atherosclerosis: a clinical issue. World J Clin Case: WJCC 2014;2(7):240.

[9] Chen BF, Xu X, Deng Y, Ma SC, Tang LQ, Zhang SB, et al. Relationship between Helicobacter pylori infection and serum interleukin-18 in patients with carotid atherosclerosis. Helicobacter 2013;18(2):124−8.

[10] Chen J, Zhu M, Ma G, Zhao Z, Sun Z. Chlamydia pneumoniae infection and cerebrovascular disease: a systematic review and meta-analysis. BMC Neurol 2013;13(1):183.

[11] Chen Y-W, Umeda M, Nagasawa T, Takeuchi Y, Huang Y, Inoue Y, et al. Periodontitis may increase the risk of peripheral arterial disease. Europ J Vasc Endovasc Surg 2008;35(2):153−8.

[12] McCaughey C, Murray LJ, McKenna JP, Coyle PV, O'Neill HJ, Wyatt DE, et al. Lack of association between serological evidence of past Coxiella burnetii infection and incident ischaemic heart disease: nested case-control study. BMC Infect Dise 2005;5(1):1−5.

[13] Keikha M, Eslami M, Yousefi B, Ali-Hassanzadeh M, Kamali A, Yousefi M, et al. HCV genotypes and their determinative role in hepatitis C treatment. Virusdisease 2020;31(3):235−40.

[14] Kelton JG, Neame PB, Gauldie J, Hirsh J. Elevated platelet-associated IgG in the thrombocytopenia of septicemia. New England J Med 1979;300(14):760−4.

[15] Whincup PH, Mendall MA, Perry IJ, Strachan DP, Walker M. Prospective relations between Helicobacter pylori infection, coronary heart disease, and stroke in middle aged men. Heart 1996;75(6): 568−72.

[16] Elkind MS, Lin I-F, Grayston J, Sacco RL. Chlamydia pneumoniae and the risk of first ischemic stroke: the Northern Manhattan Stroke Study. Stroke 2000;31(7):1521−5.

[17] Grau AJ, Buggle F, Lichy C, Brandt T, Becher H, Rudi J. Helicobacter pylori infection as an independent risk factor for cerebral ischemia of atherothrombotic origin. J Neurol Sci 2001;186(1−2):1−5.

[18] Antonio Ponzetto M, Alberto Marchet M, Rinaldo Pellicano M, Nicoletta Lovera M, Gigliola Chianale M, Marcello Nobili M. Association of H elicobacter pylori infection with ischemic stroke of non-cardiac origin: the BAT. MA. N. Project study. Hepato-gastroenterology 2002;49:631−4.

[19] Pietroiusti A, Diomedi M, Silvestrini M, Cupini LM, Luzzi I, Gomez-Miguel MJ, et al. Cytotoxin-associated gene-A−positive Helicobacter pylori strains are associated with atherosclerotic stroke. Circulation 2002;106(5):580−4.

[20] Majka J, Róg T, Konturek PC, Konturek S, Bielanski W, Kowalsky M, et al. Influence of chronic Helicobacter pylori infection on CR ischemic cerebral stroke risk factors. Med Sci Monitor 2002;8(10).

[21] Madre JG, Garcia JR, Gonzalez RC, Montero JM, Paniagua EB, Escribano JG, et al. Association between seropositivity to Chlamydia pneumoniae and acute ischaemic stroke. Europ J Neurol 2002;9(3): 303−6.

[22] Tarnacka B, Gromadzka Gy, Członkowska A. Increased circulating immune complexes in acute stroke: the triggering role of Chlamydia pneumoniae and cytomegalovirus. Stroke 2002;33(4):936−40.

[23] Tanne D, Haim M, Boyko V, Goldbourt U, Reshef T, Adler Y, et al. Prospective study of Chlamydia pneumoniae IgG and IgA seropositivity and risk of incident ischemic stroke. Cerebrovasc Dise 2003;16(2):166−70.

[24] Müller J, Møller DS, Kjær M, Nyvad O, Larsen NA, Pedersen EB. Chlamydia pneumoniae DNA in peripheral blood mononuclear cells in healthy control subjects and patients with diabetes mellitus, acute coronary syndrome, stroke, and arterial hypertension. Scand J Infect Dise 2003;35(10):704−12.

[25] Kawamoto R, Kajiwara T, Oka Y, Takagi Y. An association between an antibody against Chlamydia pneumoniae and ischemic stroke in elderly Japanese. Intern Med 2003;42(7):571−5.

[26] Gabrielli M, Santoliquido A, Cremonini F, Cicconi V, Candelli M, Serricchio M, et al. CagA-positive cytotoxic H. pylori strains as a link between plaque instability and atherosclerotic stroke. Europ Heart J 2004;25(1):64−8.

[27] Moayyedi P, Carter A, Braunholtz D, Catto A. Helicobacter pylori infection in subjects with acute ischaemic stroke. Digest Liver Dise 2003;35(1):16−9.

[28] Ngeh J, Goodbourn C. Chlamydia pneumoniae, Mycoplasma pneumoniae, and Legionella pneumophila in elderly patients with stroke (C-PEPS, M-PEPS, L-PEPS) A case-control study on the infectious burden of atypical respiratory pathogens in elderly patients with acute cerebrovascular disease. Stroke 2005;36(2):259−65.

[29] Voorend M, Faber CG, van der Ven AJ, Kessels F, Bruggeman CA, Lodder J. Chlamydia pneumoniae is a likely risk factor for ischemic stroke in young patients. J Stroke Cerebrovasc Dise 2004;13(2):85−91.

[30] Ngeh J, Gupta S, Goodbourn C, Panayiotou B, McElligott G. Chlamydia pneumoniae in elderly patients with stroke (C-PEPS): a case-control study on the seroprevalence of Chlamydia pneumoniae in elderly patients with acute cerebrovascular disease. Cerebrovasc Dise 2003;15(1−2):11−6.

[31] Anzini A, Cassone A, Rasura M, Ciervo A, Beccia M, Di Lisi F, et al. Chlamydia pneumoniae infection in young stroke patients: a case−control study. Europ J Neurol 2004;11(5):321−7.

[32] Masoud S, Arami M, Kucheki E. Association between infection with Helicobacter pylori and cerebral noncardioembolic ischemic stroke. Neurol India 2005;53(3):303.

[33] Kongoji M, Kamo T, Ikejima H, Yamamoto H, Yamamoto Y, Matsuda T. Detection of Chlamydia pneumoniae in blood of stroke patients. Ensho Saisei 2005;25(1):55–9.

[34] Wohlschlaeger J, Wimmer ML, Nägler DK, Haberl R, Weis S. Identification of Chlamydia pneumoniae in intracranial and extracranial arteries in patients with stroke and in controls: combined immunohistochemical and polymerase chain reaction analyses. Human Pathol 2005;36(4):395–402.

[35] Sawayama Y, Ariyama I, Hamada M, Otaguro S, Machi T, Taira Y, et al. Association between chronic Helicobacter pylori infection and acute ischemic stroke: Fukuoka Harasanshin Atherosclerosis Trial (FHAT). Atherosclerosis 2005;178(2):303–9.

[36] Johnsen SP, Overvad K, Østergaard L, Tjønneland A, Husted SE, Sørensen HT. Chlamydia pneumoniae seropositivity and risk of ischemic stroke. Europ J Epidemiol 2005;20(1):59–65.

[37] Elkind MS, Tondella MLC, Feikin DR, Fields BS, Homma S, Di Tullio MR. Seropositivity to Chlamydia pneumoniae is associated with risk of first ischemic stroke. Stroke 2006;37(3):790–5.

[38] Park MH, Min JY, Koh SB, Kim BJ, Park MK, Park KW, et al. Helicobacter pylori infection and the CD14 C (− 260) T gene polymorphism in ischemic stroke. Thrombosis Res 2006;118(6):671–7.

[39] Njamnshi AK, Blackett KN, Mbuagbaw JN, Gumedze F, Gupta S, Wiysonge CS. Chronic Chlamydia pneumoniae infection and stroke in Cameroon: a case-control study. Stroke 2006;37(3):796–9.

[40] Piechowski-Józwiak B, Mickielewicz A, Gaciong Z, Berent H, Kwieciński H. Elevated levels of anti-Chlamydia pneumoniae IgA and IgG antibodies in young adults with ischemic stroke. Acta Neurol Scand 2007;116(3):144–9.

[41] Ashtari F, Shaigannezhad V, Saberi A, Rabiei E. Relationship between Helicobacter pylori immunoglobulin G antibody and thrombotic ischemic stroke. 2008.

[42] Lin T-M, Chen C-H, Wu H-L, Wang C-H, Chen Y-L, Eng H-L. The association of C (−260)→ T polymorphism in CD14 promoter and Chlamydia pneumoniae infection in ischemic stroke patients. Am J Clin Pathol 2008;130(4):595–601.

[43] Bandaru V, Laxmi V, Neeraja M, Alladi S, Meena A, Borgohain R, et al. Chlamydia pneumoniae antibodies in various subtypes of ischemic stroke in Indian patients. J Neurol Sci 2008;272(1–2):115–22.

[44] De Bastiani R, Gabrielli M, Ubaldi E, Benedetto E, Sanna G, Cottone C, et al. High prevalence of Cag-A positive H. pylori strains in ischemic stroke: a primary care multicenter study. Helicobacter 2008;13(4):274–7.

[45] Bandaru VS, Boddu DB, Laxmi V, Neeraja M, Kaul S. Seroprevalence of Chlamydia pneumoniae antibodies in stroke in young. Canad J Neurol Sci 2009;36(6):725–30.

[46] Gagliardi RJ, Caiaffa-Filho HH. Chlamydia pneumoniae and stroke: is there a direct relationship? Arquivos de neuro-psiquiatria 2009;67(3A):600–4.

[47] Mousavi SA, Ataei B, Karimi I, Ashrafi K. Helicobacter pylori serum antibody titers in patients with cerebral non-cardioembolic ischemic stroke. J Res Med Sci: Off J Isfahan Univ Med Sci 2011;16(Suppl. 1):S407.

[48] Rai N, Choudhary R, Bhatia R, Singh M, Tripathi M, Prasad K, et al. Chlamydia pneumoniae seropositivity in adults with acute ischemic stroke: a case–control study. Ann Indian Acad Neurol 2011;14(2):93.

[49] Ķēniņa V, Auce P, Priede Z, Millers A. The relationship between seropositivity against chlamydia pneumoniae and stroke and its subtypes in a Latvian population. Medicina 2011;47(12):96.

[50] Hasan ZN. Association of Chlamydia pneumoniae serology and ischemic stroke. South Med J 2011;104(5):319–21.

[51] Bandaru VS, Boddu DB, Mridula KR, Akhila B, Alladi S, Laxmi V, et al. Outcome of chlamydia pneumoniae associated acute ischemic stroke in elderly patients: a case–control study. Clin Neurol Neurosurg 2012;114(2):120–3.

[52] Rasura M, Anzini A, Mascellino MT. Chlamydia pneumoniae infection and PFO-associated ischemic stroke. Stroke 2000;31(10):2517–27.

[53] Hassanein KM, Mostafa MS, Monaeim AA. The effect of cag A-positive Helicobacter pylori infection on vascular risk factors and the development of ischemic stroke. Int J 2014;2(9):576–82.

[54] Eini P, Keramat F, Farajpoor N. The association between Chlamydia pneumoniae infection and ischemic stroke. Avicenna J Clin Microbiol Infect 2014;1(3):22165.

[55] Reza ER, Melody ON, Mahdie M, Masoume A, Nargess G. Comparison of antibody against chlamydophila pneumoniae in patients with brain ischemic stroke. 2014.

[56] Wu C-H, Chen L-S, Yen M-F, Chiu Y-H, Fann C-Y, Chen H-H, et al. Does non-central nervous system tuberculosis increase the risk of ischemic stroke? A population-based propensity score-matched follow-up study. PloS One 2014;9(7):e98158.

[57] Sheu J-J, Chiou H-Y, Kang J-H, Chen Y-H, Lin H-C. Tuberculosis and the risk of ischemic stroke: a 3-year follow-up study. Stroke 2010;41(2):244–9.

[58] Srivastava MP, Bhasin A, Chaudhry R, Sharma S, Subbaiah V, Bhatia R, et al. Novel inflammatory biomarkers and their correlation to Chlamydia pneumoniae titres in acute ischemic stroke. J Stroke Cerebrovasc Dis 2014;23(9):2391–6.

[59] Sagar V, Zafar KS, Kumar G, Veeramachaneni R, Indurkar PS. A study of Helicobacter pylori infection in patients of ischemic cerebro vascular stroke. Int J Res Med Sci 2016;4:589–92.

[60] Cook PJ, Honeybourne D, Lip GY, Beevers DG, Wise R, Davies P. Chlamydia pneumoniae antibody titers are significantly associated with acute stroke and transient cerebral ischemia: the West Birmingham Stroke Project. Stroke 1998;29(2):404–10.

[61] Heuschmann PU, Neureiter D, Gesslein M, Craiovan B, Maass M, Faller G, et al. Association between infection with Helicobacter pylori and Chlamydia pneumoniae and risk of ischemic stroke subtypes: results from a population-based case-control study. Stroke 2001;32(10):2253–8.

[62] Roham M, Anbari K, Mirhabibi S, Goudarzi G. The seroprevalence of Mycoplasma pneumoniae IgM and IgG antibodies in patients with ischemic stroke. Iran J Microbiol 2016;8(6):383.

[63] Ahmadi-Salmasi B, Amiri-Nikpour MR, Faraj S. Investigating the correlation between level OF igg antibodies against H. PYLORI and acute NON-cardioembolic ischemic stroke IN adults. 2017.

[64] Mrđen A, Včev A, Nakić D, Balen S, Ivanac K, Duka Glavor K. Helicobacter pylori infection and acute stroke. Coll Antropol 2017;41(4):371–5.

[65] Rasura M, Anzini A, Mascellino MT. Chlamydia pneumoniae infection and PFO-associated ischemic stroke. Stroke 2000;31(10):2519–20.

[66] Hassanein KM, Mostafa MS, Monaeim AA. The effect of cag A-positive Helicobacter pylori infection on vascular risk factors and the development of ischemic stroke. Int J 2014;2(9):576–82.

[67] Simanek AM, Dowd JB, Pawelec G, Melzer D, Dutta A, Aiello AE. Seropositivity to cytomegalovirus, inflammation, all-cause and cardiovascular disease-related mortality in the United States. PloS One 2011;6(2):e16103.

[68] Grau AJ, Urbanek C, Palm F. Common infections and the risk of stroke. Nature Rev Neurol 2010;6(12):681–94.

[69] Fugate JE, Lyons JL, Thakur KT, Smith BR, Hedley-Whyte ET, Mateen FJ. Infectious causes of stroke. Lancet Infect Dis 2014;14(9):869–80.

[70] Feingold KR, Grunfeld C. The effect of inflammation and infection on lipids and lipoproteins. Endotext 2019 [Internet].

[71] Szeto C-C, Chow K-M, Woo K-S, Chook P, Kwan BC-H, Leung C-B, et al. Carotid intima media thickness predicts cardiovascular diseases in Chinese predialysis patients with chronic kidney disease. J Am Soc Nephrol 2007;18(6):1966–72.

[72] Blank M, Israeli E, Cervera R. The infectious origin of the anti-phospholipid syndrome. In: Infection and autoimmunity. Elsevier; 2015. p. 681–96.

[73] Christen U. Molecular mimicry. Autoantibodies: Elsevier; 2014. p. 35–42.

[74] Blank M, Krause I, Fridkin M, Keller N, Kopolovic J, Goldberg I, et al. Bacterial induction of autoantibodies to β2-glycoprotein-I accounts for the infectious etiology of antiphospholipid syndrome. J Clin Invest 2002;109(6):797–804.

[75] Pierangeli SS, Blank M, Liu X, Espinola R, Fridkin M, Ostertag MV, et al. A peptide that shares similarity with bacterial antigens reverses thrombogenic properties of antiphospholipid antibodies in vivo. J Autoimmun 2004;22(3):217–25.

[76] Horn M. Chlamydiae as symbionts in eukaryotes. Annu Rev Microbiol 2008;62:113–31.

[77] Joshi R, Khandelwal B, Joshi D, Gupta OP. Chlamydophila pneumoniae infection and cardiovascular disease. N Am J Med Sci 2013;5(3):169.

[78] Sander D, Winbeck K, Klingelhöfer Jr, Etgen T, Conrad B. Progression of early carotid atherosclerosis is only temporarily reduced after antibiotic treatment of Chlamydia pneumoniae seropositivity. Circulation 2004;109(8):1010–5.

[79] Illoh KO, Illoh OC, Feseha HB, Hallenbeck JM. Antibiotics for vascular diseases: a meta-analysis of randomized controlled trials. Atherosclerosis 2005;179(2):403–12.

[80] Keikha M, Karbalaei M. Correlation between the geographical origin of Helicobacter pylori homB-positive strains and their clinical outcomes: a systematic review and meta-analysis. BMC Gastroenterol 2021;21(1):1–8.

[81] Keikha M, Ali-Hassanzadeh M, Karbalaei M. Association of Helicobacter pylori vacA genotypes and peptic ulcer in Iranian population: a systematic review and meta-analysis. BMC Gastroenterol 2020;20(1):1–11.

[82] Kodaman N, Pazos A, Schneider BG, Piazuelo MB, Mera R, Sobota RS, et al. Human and Helicobacter pylori coevolution shapes the risk of gastric disease. Proc National Acad Sci 2014;111(4):1455–60.

[83] Youssefi M, Ghazvini K, Farsiani H, Tafaghodi M, Keikha M. A systematic review and meta-analysis of outcomes of infection with Helicobacter pylori dupA+ strains in Iranian patients. Gene Rep 2020;19:100650.

[84] Amieva M, Peek Jr RM. Pathobiology of Helicobacter pylori–induced gastric cancer. Gastroenterology 2016;150(1):64–78.

[85] Kusters JG, Van Vliet AH, Kuipers EJ. Pathogenesis of Helicobacter pylori infection. Clin Microbiol Rev 2006;19(3):449–90.

[86] Huang W-S, Tseng C-H, Lin C-L, Tsai C-H, Kao C-H. Helicobacter pylori infection increases subsequent ischemic stroke risk: a nationwide population-based retrospective cohort study. QJM: Int J Med 2014;107(12):969–75.

[87] Khademi F, Vaez H, Momtazi-Borojeni AA, Majnooni A, Banach M, Sahebkar A. Bacterial infections are associated with cardiovascular disease in Iran: a meta-analysis. Arch Med Sci: AMS 2019;15(4):902.

[88] Guleria R, Nisar N, Chawla TC, Biswas NR. Mycoplasma pneumoniae and central nervous system complications: a review. J Lab Clin Med 2005;146(2):55–63.

[89] Parrott GL, Kinjo T, Fujita J. A compendium for Mycoplasma pneumoniae. Front Microbiol 2016;7:513.

[90] Ionita CC, Siddiqui AH, Levy EI, Hopkins LN, Snyder KV, Gibbons KJ. Acute ischemic stroke and infections. J Stroke Cerebrovasc Dis 2011;20(1):1–9.

[91] Keikha M, Soleimanpour S, Eslami M, Yousefi B, Karbalaei M. The mystery of tuberculosis pathogenesis from the perspective of T regulatory cells. Meta Gene 2020;23:100632.

[92] Keikha M, Karbalaei M. Overview on coinfection of HTLV-1 and tuberculosis: mini-review. J Clin Tubercul Other Mycobacter Dise 2021;23:100224.

[93] Salindri AD, Wang J-Y, Lin H-H, Magee MJ. Post-tuberculosis incidence of diabetes, myocardial infarction, and stroke: retrospective cohort analysis of patients formerly treated for tuberculosis in Taiwan, 2002–2013. Int J Infect Dis 2019;84:127–30.

[94] Authority EFS. The European Union one health 2019 zoonoses report. Efsa J 2021;19(2).

[95] Vinacci G, Tcheumeni CN, Coskun O, Saddiki FZ, Maria FD, Dinu M, et al. White thrombus as a possible feature of atypical stroke etiology: Coxiella burnetii as the primary cause of acute ischemic stroke. Int Neuroradiol 2021:15910199211021716.

[96] Million M, Bardin N, Bessis S, Nouiakh N, Douliery C, Edouard S, et al. Thrombosis and antiphospholipid antibody syndrome during acute Q fever: a cross-sectional study. Medicine 2017;96(29).

[97] Melenotte C, Protopopescu C, Million M, Edouard S, Carrieri MP, Eldin C, et al. Clinical features and complications of Coxiella burnetii infections from the French National Reference Center for Q fever. JAMA Network Open 2018;1(4):e181580.

[98] González-Quijada S, Mora-Simón M, Martin-Ezquerro A. Reply: Coxiella burnetii and complicated atherosclerosis: perhaps neither innocent nor bystanders. Clin Microbiol Infect 2015;21(4):e30–1.

[99] González-Quijada S, Mora-Simón M, Martin-Ezquerro A. Association between serological evidence of past Coxiella burnetii infection and atherosclerotic cardiovascular disease in elderly patients. Clin Microbiol Infect 2014;20(9):873–8.

[100] González-Quijada S, Salazar-Thieroldt E, Mora-Simón M. Persistent Q fever and ischaemic stroke in elderly patients. Clin Microbiol Infect 2015;21(4):362–7.