Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

International Journal of Infectious Diseases 67 (2018) 107–113

Contents lists available at ScienceDirect

International Journal of Infectious Diseases

journal homepage: www.elsevier.com/locate/ijid

Prevalence of chronic comorbidities in chikungunya: A systematic review and meta-analysis

Alaa Badawi[a,b,*], Seung Gwan Ryoo[c], Denitsa Vasileva[c], Sahar Yaghoubi[d]

[a] Public Health Risk Sciences Division, Public Health Agency of Canada, Toronto, ON, Canada
[b] Department of Nutritional Sciences, Faculty of Medicine, University of Toronto, Toronto, ON, Canada
[c] Faculty of Arts and Science, University of Toronto, Toronto, ON, Canada
[d] Faculty of Science, Ryerson University, Toronto, ON, Canada

ARTICLE INFO

Article history:
Received 17 November 2017
Received in revised form 11 December 2017
Accepted 12 December 2017
Corresponding Editor: Eskild Petersen, Aarhus, Denmark

Keywords:
Chikungunya
Comorbidities
Systematic review
Meta-analysis

ABSTRACT

Background: Epidemiologic evidence suggests that patients with chikungunya virus (CHIKV) infection may be at risk of severe disease complications when they also have comorbidities such as obesity, diabetes, cardiac diseases, and/or asthma. However, the prevalence of these co-existing medical conditions in severe CHIKV cases has not been systematically reported.
Objective: The aim of the present study is to conduct a systematic review and meta-analysis to describe the prevalence of chronic comorbidities in CHIKV and evaluate their possible contributions to disease severity.
Methods: A search strategy was developed for online databases. Search terms used were "Chikungunya" AND "Diabetes, Hypertension, Stroke, Cardiovascular Diseases, Coronary Artery Diseases, Obesity, OR Asthma". Only 11 articles documenting the frequency of comorbidities in CHIKV were included. Meta-analyses were conducted to evaluate the overall prevalence of comorbidities in the CHIKV infection and stratify the estimates by severity.
Results: Among 2,773 CHIKV patients, hypertension was the most prevalent comorbidity (31.3%; 95%CI: 17.9-48.8%) followed by diabetes (20.5%; 95%CI: 12.7-31.3%), cardiac diseases (14.8%; 95%CI: 8.1-25.5%) and asthma (7.9%; 95%CI: 3.3-17.7). There was 4- to 5-fold significant increased prevalence of diabetes, hypertension and cardiac diseases in CHIKV patients over 50 years of age compared to their younger counterparts. Severe CHIKV cases had a significantly higher proportion of diabetes than non-severe cases ($p < 0.05$). CHIKV patients with diabetes had OR of 1.2 (95%CI: 1.05-1.48; $p = 0.0135$) for developing severe infection outcome compared to those with no diabetes.
Conclusion: Hypertension, diabetes and cardiac diseases may contribute to the severe outcome of CHIKV. Diabetic subjects may be at higher risk of severe infection. These findings may be relevant in developing public health measures and practices targeting CHIKV patients with comorbidities to avert the severe outcome of the infectious disease.

Introduction

Chikungunya is an arboviral disease caused by chikungunya viral (CHIKV) infection that is transmitted to humans by infected mosquitoes of the *Aedes* genus (Pialoux et al., 2007; Robinson, 1955). CHIKV was first identified in Tanzania in 1953 (Lumsden, 1955). Since then it was transmitted to South and Southeast Asia, Africa, and Europe (Pialoux et al., 2007; Thiberville et al., 2013; Delisle et al., 2015). In the Western Hemisphere, however, the first locally-transmitted infection occurred in December 2013 (Leparc-Goffart et al., 2014a; Lanciotti and Valadere, 2014; Teixeira et al., 2015) in the Caribbean (Halstead, 2015; Weaver and Lecuit, 2015). By the end of 2014, >1.1 million suspect cases were reported in the Americas (Pan American Health Organization, 2017). In 2016 alone, there were over 500,000 cumulative CHIKV cases (Pan American Health Organization, 2017). In Canada, 479 confirmed and probable cases were diagnosed in 2014 (Drebot et al., 2015), of which, 128 cases were imported (Pan American Health Organization, 2017).

The disease is characterized by acute-onset of high grade fever, severe arthralgia, followed by maculopapular rash (Weaver et al., 2012). CHIKV is usually self-limited, with the majority of

* Corresponding author at: Public Health Risk Sciences Division, Public Health Agency of Canada, 180 Queen Street West, Toronto, ON M5V 3L7, Canada.
E-mail address: alaa.badawi@canada.ca (A. Badawi).

https://doi.org/10.1016/j.ijid.2017.12.018

symptoms typically resolving in 7-10 days (Pialoux et al., 2007). Generally, overall mortality is low but there exists a risk for severe disease and death associated with CHIKV infection (Renault et al., 2007). Rheumatologic symptoms and neurologic, carditis, respiratory, renal, and ocular manifestations are among the severe sequelae of CHIKV (Robinson, 1955; Lumsden, 1955; Sissoko et al., 2009; Brighton et al., 1983; Rajapakse et al., 2010). When developed, these conditions can persist for several months or years after acute infection (Sissoko et al., 2009; Brighton et al., 1983; Soumahoro et al., 2009; Borgherini et al., 2008; Larrieu et al., 2010). Furthermore, CHIKV is a common cause of virus-induced arthritis in the Eastern Hemisphere, with documented epidemics in Africa, Southeast Asia, and the Indian Ocean islands (Staples et al., 2009; Arroyo-Avila et al., 2017; Economopoulou et al., 2009; Leparc-Goffart et al., 2014b).

Epidemiologic evidence suggests that CHIKV patients at risk of severe disease outcomes are elderly subjects (Godaert et al., 2017) and those with certain comorbidities, *e.g.*, obesity (Padmakumar et al., 2010), diabetes (Jean-Baptiste et al., 2016), cardiac diseases (Alvarez et al., 2017), and asthma (Paganin et al., 2010). The presence of these comorbidities was proposed to predispose CHIKV patients to severe complications of the viral infection (Padmakumar et al., 2010; Jean-Baptiste et al., 2016; Alvarez et al., 2017; Paganin et al., 2010). However, the prevalence of co-existing medical conditions in severe CHIKV cases has not been described. A systematic evaluation and detailed estimate for the prevalence of comorbidities in CHIKV severe cases may aid the public health sector in developing policies for surveillance, preparedness and response to the infection and its severe outcomes. The present study was undertaken to evaluate the prevalence of co-existing chronic conditions in CHIKV patients and in severe cases. We conducted a systematic review and meta-analysis of published literature to describe the frequency of chronic comorbidities in CHIKV and to explore their possible contributions to the severity and complication of this viral condition.

Methods

Search strategy and selection criteria

A search was conducted in PubMed, Ovid MEDLINE, Embase and Embase Classic databases to the last week of July 2017 using the search terms (MeSH) "Chikungunya" AND "Diabetes, Hypertension, Stroke, Cardiovascular Diseases, Coronary Artery Diseases, Obesity, OR Asthma". Limiting the search to English language resulted in 111 articles. When these articles were restricted to studies in human and deduplicated, 82 abstracts were searched for title and abstract review as they satisfied our selection criteria (see below). We excluded reports published as review articles, letters, editorials, conference abstracts, case reports (with less than 3 cases) or vaccination trials. Only 20 articles were considered for full text review (see Figure 1). Ten articles were excluded at the full text review stage as they were either not related to the study objectives (4 studies), not reporting prevalence of chronic disease in CHIKV (3 studies), case reports with small numbers of cases (i.e., <3 cases; 2 reports), or a review article (see Figure 1 and Supplementary Table S1). After identifying one study through bibliography searching, 11 reports were included for systematic

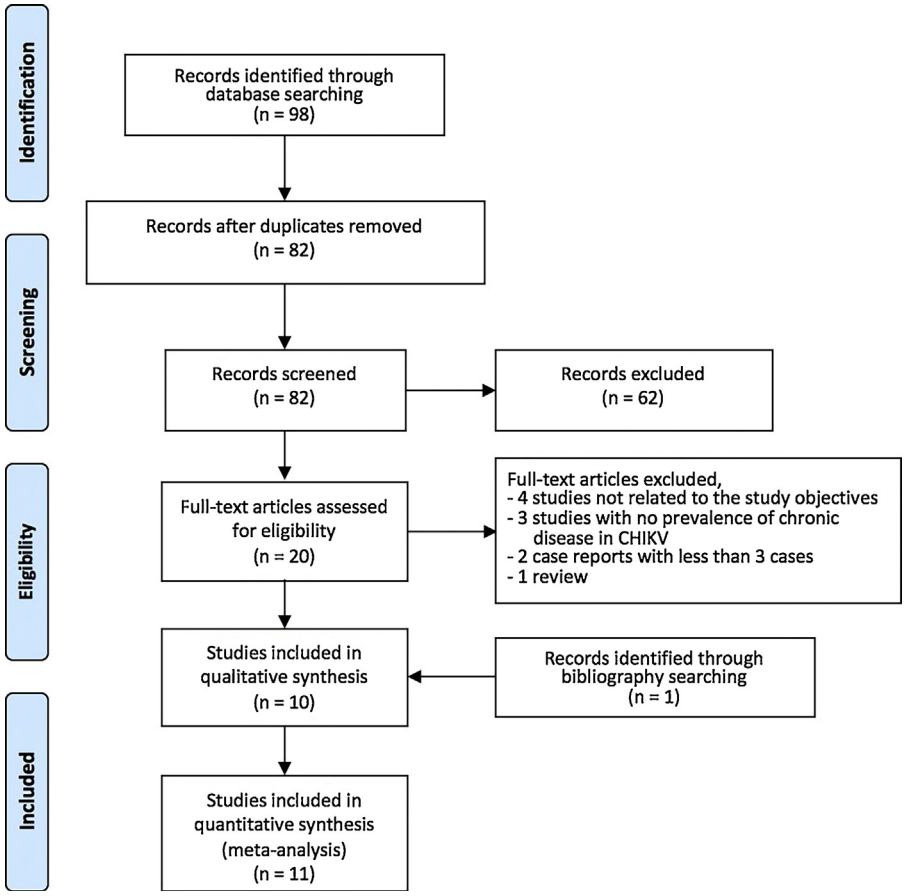

Figure 1. Systematic literature review process.
The PRISMA flowchart describes the systematic review of literature for the proportion of comorbidities in chikungunya. A total of 11 unique studies were identified from an initial 98 examined titles.

review and meta-analysis (Arroyo-Avila et al., 2017; Economopoulou et al., 2009; Padmakumar et al., 2010; Jean-Baptiste et al., 2016; Sá deOliveira et al., 2017; Perti et al., 2016; Crosby et al., 2016; Chusri et al., 2014; Couturier et al., 2012; Tandale et al., 2009; Borgherini et al., 2007).

Inter-reviewer agreement

The abstracts of the identified studies were independently reviewed by two readers (SGR and SY). Differences were resolved through discussions for a consensus to be reached. Percentage agreement and Cohen's Kappa (κ) statistic (Cohen, 1989) were calculated and interpreted in accordance with Landis and Koch's benchmarks (Landis and Koch, 1977) for assessing the agreement between reviewers as poor (<0), slight (0.0-0.20), fair (0.21-0.40), moderate (0.41-0.60), substantial (0.61-0.80), and excellent (0.81-1.0). The agreement on the inclusion between the two reviewers was 93%, with $\kappa = 0.68$ (95% CI: 0.38-0.97).

Data extraction and analysis

Data extracted from the selected studies included the first author's name, publication date, country, dates of recruitment, total sample size (divided to males and females), age estimates (from reported mean, median or the mid-point for age range of the highest subject frequency), prevalence of symptoms (including pyrexia, arthralgia, cephalgia, myalgia, joint edema, dermatitis, and malaise) and percentage of comorbidities including diabetes (both type I and type II, if separately mentioned), hypertension, heart diseases (combined from cardiovascular disease, coronary artery disease, coronary vascular disease, atrial fibrillation, chronic ischemic heart disease, acute coronary syndrome for duration less than 6 months, cardiac disorder, cardiac heart failure, and congestive cardiac failure), asthma (not including chronic obstructive pulmonary disease), stroke, and obesity. The prevalence of comorbidities was measured by extracting the proportion of co-existing medical conditions from CHIKV cases and from severe disease outcome. Severe CHIKV was identified as cases that underwent ICU, those with acute diseases (*e.g.*, acute encephalitis) and subjects with atypical CHIKV (atypical clinical manifestations of CHIKV include vesiculobullous lesions, febrile seizures, and meningoencephalitis), joints involvement (e.g., inflammatory joint destruction), hospitalization, and/or death. The primary outcome measure was to evaluate the overall prevalence of comorbidities in the CHIKV infection and stratify the estimates by severity. Weighted average was used to calculate the average age and the overall prevalence of clinical symptoms and comorbidities. Median age of the studies populations (~50 years old) was used to categorize the CHIKV patients into two groups, below and above the median age. The weighted average prevalence of each comorbidity was calculated (±SD) within each group. Publication bias was assessed both by the visual inspection of funnel plot (Supplementary Figure S1) and by Egger's test. Egger's test is widely used to assess the tendency for the effects estimated in small sample size studies to differ from those estimated in larger studies. The results of Egger's test are presented in terms of bias coefficient. Publication bias was only observed in studies identified to estimate the proportion of cardiac diseases. Meta-analyses were carried out to assess the pooled prevalence (and 95% CI) of clinical symptoms and the proportions of each comorbidity in the overall and severe cases. Meta-analysis tests were conducted using Comprehensive Meta-Analysis software, CMA version 3.9 (Englewood, NJ, USA) (Borenstein, 2005). Variances of raw proportions or percentages were pooled based on a binary random-effects model (Çoğaltay and Karadağ, 2015), given the population heterogeneity and assuming the relationships between comorbidities and CHIKV infections vary across populations. Forest plots were used to illustrate the prevalence of comorbidities in CHIKV from the selected studies in the entire patients and in severe cases.

Assessing the heterogeneity among the selected studies was carried out using the *Q* test (Cochran, 1954) that informs about the presence versus the absence of heterogeneity. The *Q* test, however, does not report the extent of heterogeneity and has inadequate power to detect heterogeneity among the small number of studies identified for some comorbidities. Therefore, we calculated the I^2 index to complement the *Q* test and describe the degree of between-study heterogeneity (Higgins and Thompson, 2002). I^2 index values were categorized as low (0–30%), moderate (30–60%), substantial (60–90%), and considerable (>90%) as recommended (Liberati et al., 2009). We also quantified the true heterogeneity by estimating the between-study variance in the random-effects model (τ^2), as previously described (DerSimonian and Laird, 1986).

Results

Systematic analysis of studies that described the epidemiological, demographic and clinical features of CHIKV cases and reported the prevalence of a number of chronic diseases in the infectious disease, has identified 11 reports (Arroyo-Avila et al., 2017; Economopoulou et al., 2009; Padmakumar et al., 2010; Jean-Baptiste et al., 2016; Sá deOliveira et al., 2017; Perti et al., 2016; Crosby et al., 2016; Chusri et al., 2014; Couturier et al., 2012; Tandale et al., 2009; Borgherini et al., 2007) with 2,773 patients (Table 1). This limited number of reports is the result of our strict search strategy and selection criteria and our focus only on the studies recording the prevalence of comorbidities in CHIKV. The majority of the cases were from South Asia, particularly India, followed by a significant number from South America. With the exception of a report from Brazil (Sá deOliveira et al., 2017), the number of cases in the selected studies varied by ~25-fold and ranged from 45 (Chusri et al., 2014) to 1,111 (Padmakumar et al., 2010) cases. The 1,111 cases from India (Padmakumar et al., 2010) were not included in any meta-analysis since it was the only study referring to the prevalence of obesity in CHIKV. The sex ratio (male: female) was 0.83 with a weighted overall average age (±SD) of 42.9 ± 13.9 years (range: 21-70 years).

Meta-analysis for the identified studies showed that the most prevalent clinical symptoms were pyrexia (90.7%; 95% CI: 86.6-93.6%) and arthralgia (85.2%; 95% CI: 70.2-93.4%) with cephalgia, myalgia, joint edema, dermatitis and malaise in ~30-50% of the cases. There was a small heterogeneity (Cochran's *Q*) in the estimates of clinical symptoms among the identified studies with an I^2 index varied up to 56.8% (Table 1). As shown in Figure 2 (panel A), hypertension was the most prevalent comorbidity in CHIKV infection (31.3% of the cases; 95% CI: 17.9-48.8%) followed by diabetes (20.5%; 95% CI: 12.7-31.3%), cardiac diseases (14.8%; 95% CI: 8.1-25.5%) and asthma (only in 7.9% of the cases; 95% CI: 3.3-17.7). Prevalence of obesity was reported only in one of the identified studies (Padmakumar et al., 2010). Characteristics of this study were mentioned in Table 1 but were excluded from any further meta-analysis given this limited data set. The prevalence of diabetes, hypertension, cardiac diseases and asthma varied by 25-, 5-, 28- and 50-fold among the identified studies, respectively. This wide among-studies variation in the proportion of comorbidities may have resulted in the heterogeneity (I^2 index) observed for the estimates of comorbidities that varied from 25.1% to 96.4% (Figure 2). However, the true heterogeneity estimated by between-study variance in the random-effect model (τ^2) was varied between 0.029 to 0.074 for the examined comorbidities. As shown in Table 2, the proportion of diabetes, hypertension and cardiac diseases was 4- to 5-fold higher ($p < 0.05$) in elder patients than their younger counterparts. We found a significant direct correlation between

Table 1
Characteristics of the identified studies.

Study [Ref]	Country	Dates (mm. yy)	Number of Subjects			Age (yr)	Clinical Symptoms (%)[d]						
			All	M	F		Pyrexia	Arthralgia	Cephalgia	Myalgia	Joint Edema	Dermatitis	Malaise
Sá deOliveira et al. (2017)	Brazil	01.16–03.16	4	2	2	53.3	100	25		50	25	25	
Arroyo-Avila et al. (2017)	Puerto Rico	06.14–09.14	172	81	91	21.1	93	91	84	83		68	
Perti et al. (2016)	Puerto Rico	01.14–12.14	180	167	13	66.3	88	41	69	69		44	77
Crosby et al. (2016)	Multiple[a]	01.14–11.14	65	41	24	63							
Jean-Baptiste et al. (2016)	Haiti	05.14–07.14	53	23	30	53.2	91	98	47	51	36	17	49
Chusri et al. (2014)	Thailand	04.09–06.09	45	19	26	49	100	100				82	
Couturier et al. (2012)	France	03.05–12.07	227	113	114	50.2	96	99			74		
Padmakumar et al. (2010)	India	11.07–06.08	1,111	308	723	45.5		63	6			2	
Tandale et al. (2009)	India	01.06–12.06	149	108	41	60							
Economopoulou et al. (2009)	Reunion Island	04.05–05.06	610	271	339	70	90			13		17	45
Borgherini et al. (2007)	Reunion Island	03.05–04.06	157	87	70	57.9	89	96	47		32	63	12
Total/Average/Overall Estimate[b]		03-05–03.16	2,773	1,220	1,473	42.9 ± 13.9[c]	90.7	85.2	47.7	52.6	44.1	30.6	43.8
95% CI							86.6–93.6	70.2–93.4	14.4–83.0	18.4–84.5	18.8–72.9	13.4–55.6	21.3–69.2
Q							7.5	16.2	2.9	2.1	1.8	9.1	4.4
I^2%							6.2	56.8	0.0	0.0	0.0	22.8	31.5

[a] Multiple: Caribbean, United States, French West Indies.
[b] Overall estimate is calculated from meta-analysis of the proportions using the binary random-effects model.
[c] Weighted average ± SD.
[d] Empty cells denote data not available in the original study.

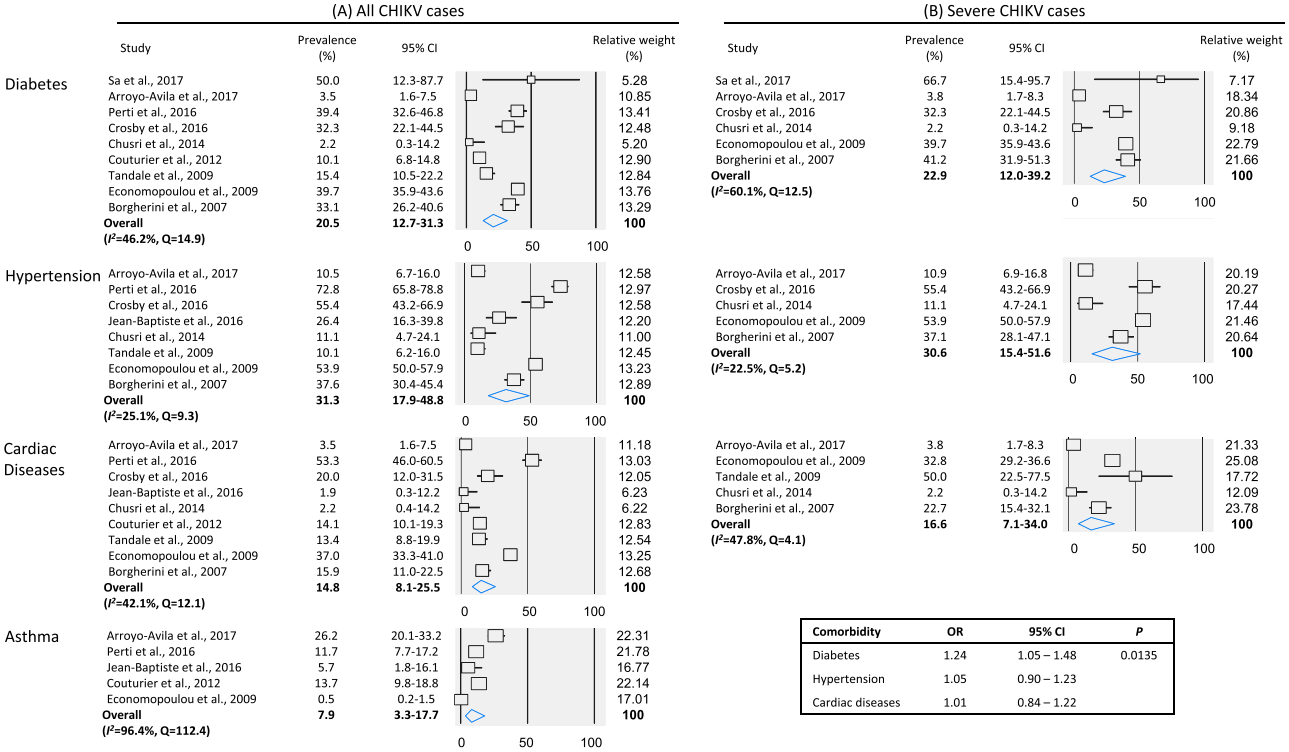

Figure 2. Meta-analysis for the proportion of comorbidities in chikungunya cases.
Weights are calculated from binary random-effects model analysis. Values represent proportions of diabetes, hypertension, cardiac diseases and asthma in all CHIKV cases (panel A) and severe cases (panel B) and 95% CI. Severity was defined as cases that underwent ICU, those with acute diseases, patients with complications and subjects with atypical CHIKV, joints involvement, hospitalization, and/or death. Analysis of heterogeneity is also presented as results of the *Q* test and the among-studies variation (I^2 index). Insert shows the odds ratio (OR and 95%CI) of developing severe CHIKV in patients with comorbidities.

Table 2
Average age-associated prevalence of chronic morbidities in CHIKV.

Comorbidity	Age group (weighted average ± S.D.)			
	<50 years[a] (44 ± 9)		>50 years[a] (66 ± 5)	
	n	Prevalence (%)	*n*	Prevalence (%)
Diabetes	444	6.7 ± 4.2	1165	35.3 ± 8.9
Hypertension	270	13.7 ± 7.7	1161	49.1 ± 22.8
Cardiac diseases	497	8.8 ± 6.3	1161	32.7 ± 14.5
Asthma	452	17.5 ± 8.9	790	3.1[b]

[a] Median age of the subjects from the selected studies (~50 years). Number in parentheses is weighted average ± SD of patients' ages within the group.
[b] Weighted average from only two studies. Differences between the two age groups are significant ($p < 0.05$) for all comorbidities (except asthma where assessment cannot be made due to the small number of studies in the elder group).

patients' age and the prevalence of diabetes ($r = 0.65$, $p = 0.03$), hypertension ($r = 0.68$, $p = 0.033$) and cardiac diseases ($r = 0.65$, $p = 0.029$) but inverse relationship ($r = -0.88$, $p = 0.023$) with asthma (data not shown).

Severe CHIKV cases were defined as cases that underwent ICU, those with acute diseases (*e.g.,* acute encephalitis) and subjects with atypical CHIKV (atypical clinical manifestations of CHIKV include vesiculobullous lesions, febrile seizures, and meningoencephalitis), joints involvement (e.g., inflammatory joint destruction), hospitalization, and/or death (see above). Cases with severe CHIKV had a significantly higher proportion of diabetes (22.9% vs. 20.5%, $p < 0.05$) (Figure 2; panel B). Infected patients with diabetes (both types I and II, combined) – but not those with hypertension or cardiac diseases – had OR of 1.2 (95% CI: 1.05-1.48; $p = 0.0135$) for developing severe CHIKV outcome compared to those with no diabetes.

Discussion

The present study was undertaken to systematically evaluate the prevalence of chronic comorbidities in CHIKV non-severe and severe cases of infection. Meta-analysis of the data extracted from the identified studies (Figure 2) suggests that hypertension and diabetes are the most frequent comorbidities in patients with CHIKV infection with prevalence rates that varied from 20-30%. As expected, the prevalence of the examined chronic comorbidities was increased with age except for asthma. Although the reports identified here did not distinguish between the prevalence of type 1 and/or type 2 diabetes in CHIKV, results of the present study suggest an increased risk of developing severe CHIKV complications in people with diabetes (OR = 1.2; 95% CI: 1.05-1.48) than in those with other or no underlying chronic diseases. Similar observations were also reported in H1N1 (Badawi and Ryoo, 2016a), MERS-CoV (Badawi and Ryoo, 2016b) and influenza (Mertz et al., 2013). For example, a recent study noted that, compared to subjects with no comorbidities, severe pandemic influenza cases are significantly elevated with obesity (OR for mortality 2.74; 95% CI: 1.56-4.80), cardiovascular diseases (2.92; 95% CI: 1.76-4.86), hypertension (1.49; 95% CI: 1.10-2.01) and neuromuscular disease (2.68; 95% CI: 1.91-3.75) (Mertz et al., 2013). It may be worth noting that in CHIKV we identified only one study (Padmakumar et al., 2010) evaluating the effect of overweight on disease severity and this was not included in any of our meta-analyses. This study reported a significant association between overweight and CHIKV sequelae (OR = 1.3; 95% CI: 1.2-1.4) (Padmakumar et al., 2010). Chronic conditions influencing the severity of CHIKV such as diabetes were also noted to have similar effects in other respiratory illnesses (Badawi and Ryoo, 2016a, b; Mertz et al., 2013; Kusznierz et al., 2013). Furthermore, a number of case-control studies demonstrated the incidence of metabolic syndrome and related diseases, *e.g.*, diabetes and hypertension, to be 2-fold higher in severe cases of dengue fever than in non-severe conditions (Fujimoto and Koifman, 2014; Pang et al., 2012).

Although the prevalence of metabolic syndrome-related conditions such as diabetes, hypertension and cardiac diseases varied widely among the selected studies, the vast majority of the reports showed values clustering around the pooled estimated averages for each comorbidity, as evidenced by the low I^2 index values (Figure 2). Comorbidities related to metabolic syndrome are thought to be etiologically linked to CHIKV pathogenesis. These disorders are known to downregulate key mediators of host innate immune response to pathogenesis. For example, diabetes, hyperglycemia and insulinopenia attenuate the synthesis of pro-inflammatory cytokines such as IFN-γ and interleukins to functionally impair the innate and humoral immune systems of the host (Badawi and Ryoo, 2016a). Furthermore, the cytokine overload related to the Th1 to Th2 shift in severe viral infection, when accompanied by the increased cytokine synthesis from metabolic diseases, can be detrimental in synergistically affecting the endothelium and leads to a range of subsequent complications related to both the infectious and chronic conditions (Toledo et al., 2016). Furthermore, diabetes is known to impair macrophage and lymphocyte functions, subsequently reducing the host's immune response (Dooley and Chaisson, 2009). This was noted when increased levels of HbA1c (*i.e.*, ≥9%) were linked to the severity of pneumonia (Akbar, 2001). While diabetes may impair the immune system leading to increased level and duration of viremia, heart conditions and hypertension were thought to facilitate the passage of neurotropic viruses, e.g., flavivirus, across the blood-brain barrier to predispose patients to neurologic complications (Jean et al., 2007).

The present study has several limitations. The identified reports have shown a wide among-studies variance in the proportion of diabetes, hypertension, cardiac diseases and asthma, which may have contributed to the heterogeneity observed in the meta-analysis. Other sources of heterogeneity may be related to the large range of sample size and the different study designs. These factors may levy some limitations on the estimated contribution of chronic diseases to severe CHIKV cases and render our results as a guide to generate more accurate estimates for intervention strategies for infection in patients with chronic disorders. Furthermore, the small number of studies selected here did not allow us to evaluate the prevalence of chronic comorbidities in each outcome of the severe CHIKV cases. Additionally, little information was provided in the original articles on the chronic comorbidities in terms of how long patients were suffering from the condition(s), the onset of the condition(s) prior to or following CHIKV manifestation or whether or not the patients have received a treatment.

The study of comorbidities in CHIKV infection is important for reducing the burden of the disease via guiding approaches for improved patient outcome or differential case management. The present study provides evidence for a particular higher prevalence of diabetes in severe cases of CHIKV infections than in non-severe cases. The causal association, however, between chronic diseases and severe infection cannot be simply substantiated from these observations. However, even in the absence of causal inference between the non-communicable and infectious diseases, it may be justified that once non-severe episodes of infection are confirmed in subjects with diabetes that they remain under close surveillance to avert complications. This measure may prove important in averting severe disease outcome. Indeed, there are no current clear lines of prevention and treatment for CHIKV disease outside avoidance of mosquitoes and use of insect repellents. Coupling these practices with educating the public on the risk of severe

infection can be an effective public health approach for the intervention of infection-related complications particularly in the middle- and low-income countries where the prevalence of chronic diseases is rising.

Conflict of interest

The authors declare no conflict of interest.

Acknowledgment

This work was supported by the Public Health Agency of Canada (AB).

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at https://doi.org/10.1016/j.ijid.2017.12.018.

References

Akbar DH. Bacterial pneumonia: comparison between diabetics and non-diabetics. Acta Diabetol 2001;38:77–82.
Alvarez MF, Bolívar-Mejía A, Rodriguez-Morales AJ, Ramirez-Vallejo E. Cardiovascular involvement and manifestations of systemic chikungunya virus infection: a systematic review. F1000 Res 2017;6:390, doi:http://dx.doi.org/10.12688/f1000research.11078.2.
Arroyo-Avila M, Caban A, Garcia-Rivera EJ, Irizarry-Perez M, Torres H, Gorbea H, et al. Clinical manifestations associated with peripheral joint involvement in patients with acute chikungunya virus infection. Am J Trop Med Hyg 2017;96:916–21.
Badawi A, Ryoo SG. Prevalence of diabetes in the 2009 influenza A (H1N1) and the Middle East respiratory syndrome coronavirus: a systematic review and meta-analysis. J Public Health Res 2016a;5:733.
Badawi A, Ryoo SG. Prevalence of comorbidities in the Middle East respiratory syndrome coronavirus (MERS-CoV): a systematic review and meta-analysis. Int J Infect Dis 2016b;49:129–33.
Borenstein M. Software for publication bias. In: Rothstein HR, Sutton AJ, Borenstein M, editors. Publication bias in meta-analysis – prevention, assessment and adjustments. Hoboken, United States: John Wiley & Sons, Ltd; 2005. p. 193–220.
Borgherini G, Poubeau P, Staikowsky F, Lory M, Moullec NL, Becquart JP, et al. Outbreak of chikungunya on Reunion Island: early clinical and laboratory features in 157 adult patients. Clin Infect Dis 2007;44:1401–7.
Borgherini G, Poubeau P, Jossaume A, et al. Persistent arthralgia associated with chikungunya virus: a study of 88 adult patients on Reunion Island. Clin Infect Dis 2008;47:469–75.
Borgherini G, Poubeau P, Jossaume A, Gouix A, Cotte L, Michault A, et al. Chikungunya virus infection. A retrospective study of 107 cases. S Afr Med J 1983;63:313–5.
Chusri S, Siripaitoon P, Silpapojakul K, Hortiwakul T, Charernmak B, Chinnawirotpisan P, et al. Kinetics of chikungunya infections during an outbreak in Southern Thailand, 2008-2009. Am J Trop Med Hyg 2014;90:410–7.
Cochran WG. The combination of estimates from different experiments. Biometrics 1954;10:101–29.
Çoğaltay N, Karadağ E. Introduction to meta-analysis. In: Karadag E, editor. Leadership and organizational outcomes: meta-analysis of empirical studies. Switzerland: Springer International Publishing; 2015. p. 19–28.
Cohen A. Comparison of correlated correlations. Stat Med 1989;8:1485–95.
Couturier E, Guillemin F, Mura M, Leon L, Virion J-M, Letort M-J, et al. Impaired quality of life after chikungunya virus infection: a 2-year follow-up study. Rheumatology 2012;51:1315–22.
Crosby L, Perreau C, Madeux B, Cossic J, Armand C, Valentino R, et al. Severe manifestations of chikungunya virus in critically ill patients during the 2013–2014 Caribbean outbreak. Int J Infect Dis 2016;48:78–80.
Delisle E, Rousseau C, Broche B, Leparc-Goffart I, L'ambert G, Cochet A, et al. Chikungunya outbreak in Montpellier. Euro Surveill 2015;20:21108.
DerSimonian R, Laird N. Meta-analysis in clinical trials. Control Clin Trials 1986;7:177–88.
Dooley KE, Chaisson RE. Tuberculosis and diabetes mellitus: convergence of two epidemics. Lancet Infect Dis 2009;9:737–46.
Drebot MA, Holloway K, Zheng H, ON. Travel-related chikungunya cases in Canada, 2014. Canada Commun Dis Rep CCDR 2015;41:01 https://www.canada.ca/en/public-health/services/reports-publications/canada-communicable-disease-report-ccdr/monthly-issue/2015-41. [Accessed September 7, 2017].
Economopoulou A, Dominguez M, Helynck B, Sissoko D, Wichmann O, Quenel P, et al. Atypical Chikungunya virus infections: clinical manifestations, mortality and risk factors for severe disease during the 2005-2006 outbreak on Réunion. Epidemiol Infect 2009;137:534–41.
Fujimoto DE, Koifman S. Clinical and laboratory characteristics of patients with dengue hemorrhagic fever manifestations and their transfusion profile. Rev Bras Hematol Hemoter 2014;36:115–20.
Godaert L, Bartholet S, Najioullah F, Hentzien M, Fanon J-L, Césaire R, et al. Screening for Chikungunya virus infection in aged people: development and internal validation of a new score. PLoS One 2017;12:e0181472, doi:http://dx.doi.org/10.1371/journal.pone.0181472.
Halstead SB. Reappearance of chikungunya, formerly called Dengue, in the Americas. Emerg Infect Dis 2015;21:557–61.
Higgins JPT, Thompson SG. Quantifying heterogeneity in a meta-analysis. Stat Med 2002;21:1539–58.
Jean CM, Honarmand S, Louie JK, Glaser CA. Risk factors for West Nile virus neuroinvasive disease, California, 2005. Emerg Infect Dis 2007;13:1918–20.
Jean-Baptiste E, von Oettingen J, Larco P, Raphael F, Larco NC, Cauvin MM, et al. Chikungunya virus infection and diabetes mellitus: a double negative impact. Am J Trop Med Hyg 2016;95:1345–50.
Kusznierz G, Uboldi A, Sosa G, Torales S, Colombo J, Moyano C, et al. Clinical features of the hospitalized patients with 2009 pandemic influenza A (H1N1) in Santa Fe, Argentina. Influenza Other Respir Viruses 2013;7:410–7.
Lanciotti RS, Valadere AM. Transcontinental movement of Asian Genotype Chikungunya virus. Emerg Infect Dis 2014;20:1400–2.
Landis JR, Koch GG. The measurement of observer agreement for categorical data. Biometrics 1977;33:159–74.
Larrieu S, Pouderoux N, Pistone T, Filleul L, Receveur M-C, Sissoko D, et al. Factors associated with persistence of arthralgia among chikungunya virus-infected travellers: report of 42 French cases. J Clin Virol 2010;47:85–8.
Leparc-Goffart I, Nougairede A, Cassadou S, Prat C, De Lamballerie X. Chikungunya in the Americas. Lancet 2014a;383:514.
Leparc-Goffart I, Nougairede A, Cassadou S, Prat C, de Lamballerie X. Chikungunya in the Americas. Lancet 2014b;383:514.
Liberati A, Altman DG, Tetzlaff J, et al. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate healthcare interventions: explanation and elaboration. BMJ 2009;339:b2700.
Lumsden WH. An epidemic of virus disease in Southern Province, Tanganyika Territory, in 1952-53. II. General description and epidemiology. Trans R Soc Trop Med Hyg 1955;49:33–57.
Mertz D, Kim TH, Johnstone J, Lam P-P, Science M, Kuster SP, et al. Populations at risk for severe or complicated influenza illness: systematic review and meta-analysis. BMJ 2013;347:F5061, doi:http://dx.doi.org/10.1136/bmj.f5061.
Padmakumar B, Jayan JB, Menon R, Kottarathara AJ. Clinical profile of chikungunya sequelae, association with obesity and rest during acute phase. Southeast Asian J Trop Med Public Heal 2010;41:85–91.
Paganin F, Tasset C, Poubeau P, Cochet V, Borgherini G. Acute chikungunya virus infection and asthma. Eur Respir J 2010;35:1407–9.
Pan American Health Organization. Chikungunya: data, maps and statistics. 2017 http://www.paho.org/hq/index.php?option=com_topics&view=readall&cid=5927&Itemid=40931&lang=en. [Accessed September 7, 2017].
Pang J, Salim A, Lee VJ, Hibberd ML, Chia KS, Leo YS, et al. Diabetes with hypertension as risk factors for adult dengue hemorrhagic fever in a predominantly dengue serotype 2 epidemic: a case control study. PLoS Negl Trop Dis 2012;6:e1641, doi:http://dx.doi.org/10.1371/journal.pntd.0001641.
Perti T, Lucero-Obusan CA, Schirmer PL, Winters MA, Holodniy M. Chikungunya fever cases identified in the Veterans Health Administration System, 2014. PLoS Negl Trop Dis 2016;10:e0004630, doi:http://dx.doi.org/10.1371/journal.pntd.0004630.
Pialoux G, Gaüzère BA, Jauréguiberry S, Strobel M. Chikungunya, an epidemic arbovirosis. Lancet Infect Dis 2007;7:319–27.
Rajapakse S, Rodrigo C, Rajapakse A. Atypical manifestations of chikungunya infection. Trans R Soc Trop Med Hyg 2010;104:89–96.
Renault P, Solet J-L, Sissoko D, Balleydier E, Larrieu S, Filleul L, et al. A major epidemic of chikungunya virus infection on Reunion Island, France, 2005-2006. Am J Trop Med Hyg 2007;77:727–31.
Robinson MC. An epidemic of virus disease in Southern Province, Tanganyika Territory, in 1952-53. I. Clinical features. Trans R Soc Trop Med Hyg 1955;49:28–32.
Sá deOliveira PK, Nunes MDM, Leite IR, Campelo MDGLDC, Ferreira C, Leão CFR, et al. Chikungunya virus infection with severe neurologic manifestations: report of four fatal cases. Rev Soc Bras Med Trop 2017;50:265–8.
Sissoko D, Malvy D, Ezzedine K, Renault P, Moscetti F, Ledrans M, et al. Post-epidemic Chikungunya disease on Reunion Island: course of rheumatic manifestations and associated factors over a 15-month period. PLoS Negl Trop Dis 2009;3:e389.
Soumahoro M-K, Gérardin P, Boëlle P-Y, Perrau J, Fianu A, Pouchot J, et al. Impact of chikungunya virus infection on health status and quality of life: a retrospective cohort study. PLoS One 2009;4:e7800, doi:http://dx.doi.org/10.1371/journal.pone.0007800.
Staples JE, Breiman RF, Powers AM. Chikungunya fever: an epidemiological review of a re-emerging infectious disease. Clin Infect Dis 2009;49:942–8.
Tandale BV, Sathe PS, Arankalle VA, Wadia RS, Kulkarni R, Shah SV, et al. Systemic involvements and fatalities during Chikungunya epidemic in India, 2006. J Clin Virol 2009;46:145–9.

Teixeira MG, Andrade AMS, Da Costa MCN, Castro JSM, Oliveira FLS, Goes CSB, et al. East/central/South African genotype chikungunya virus, Brazil, 2014. Emerg Infect Dis 2015;21:906–8.
Thiberville SD, Moyen N, Dupuis-Maguiraga L, Nougairede A, Gould EA, Roques P, et al. Chikungunya fever: epidemiology, clinical syndrome, pathogenesis and therapy. Antiviral Res 2013;99:345–70.
Toledo J, George L, Martinez E, Lazaro A, Han WW, Coelho GE, et al. Relevance of non-communicable comorbidities for the development of the severe forms of dengue: a systematic literature review. PLoS Negl Trop Dis 2016;10:e0004284, doi:http://dx.doi.org/10.1371/journal.pntd.0004284.
Weaver SC, Lecuit M. Chikungunya virus and the global spread of a mosquito-borne disease. N Engl J Med 2015;372:1231–9.
Weaver SC, Osorio JE, Livengood JA, Chen R, Stinchcomb DT. Chikungunya virus and prospects for a vaccine. Expert Rev Vaccines 2012;11:1087–101.