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Risk of chronic arthralgia and impact of pain on daily activities in a cohort of patients with chikungunya virus infection from Brazil

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ABSTRACT

Objectives: To investigate risk factors for persistent arthralgia in patients with chikungunya, and describe its impact on daily activities.
Methods: From September 2014 to July 2016, a surveillance study enrolled patients with acute febrile illness in Salvador, Brazil, and detected those with chikungunya virus infection using IgM enzyme-linked immunosorbent assay or reverse transcriptase polymerase chain reaction. Telephone follow-ups were performed to ascertain the progression of disease.
Results: Of 153 followed cases, 65 (42.5%) reported chronic arthralgia that lasted >3 months, and 47 (30.7%) were still symptomatic at the time of the interview (approximately 1.5 years after symptom onset). Limitations in daily activities and mental distress were reported by 93.8% and 61.5% of those with chronic arthralgia, respectively. Female sex [risk ratio (RR) 1.79, 95% confidence interval (CI) 1.95–2.69] and age (RR 1.02 for each 1-year increase, 95% CI 1.01–1.03) were independent risk factors for chronic arthralgia. Chronic arthralgia was not associated with co-infection with dengue virus (RR 0.97, 95% CI 0.48–1.94) or chikungunya viral load at diagnosis (median chikungunya virus RNA of 5.60 and 5.52 $\log_{10}$ copies/μL for those with and without chronic arthralgia, respectively; $P = 0.75$).
Conclusions: These findings reinforce the high frequency of chronic chikungunya arthralgia, and highlight the substantial disability associated with the persistence of pain. Development of novel strategies to mitigate the transmission of chikungunya virus and to provide long-term medical assistance for patients with chikungunya are needed urgently.

Introduction

The most prominent clinical manifestations of acute chikungunya virus (CHIKV) infection are joint pain and fever (Weaver and Lecuit, 2015). As the disease evolves, the clinical picture is divided didactically into three stages: acute, subacute and chronic (Brasil, 2017; Brito et al., 2016). The acute stage may last up to 10–14 days and is characterized by the presence of fever and polyarthralgia, but other manifestations, such as headache, myalgia, rash, conjunctivitis and joint oedema, are commonly observed. By the end of this period, the symptoms may subside or evolve to a subacute stage, characterized by continued arthralgia. If arthralgia does not remit after 3 months, the disease is classified as chronic, and can then persist for a varied and undefined period. In this stage, arthralgia typically affects multiple joints in a relapsing–remitting or persistent pattern (Weaver and Lecuit, 2015). Other common symptoms of chronic chikungunya include joint stiffness, oedema

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and redness (Consuegra-Rodríguez et al., 2018; Watson et al., 2020).

Rates of non-recovery 3 months after CHIKV infection are variable, ranging from 3% to 83% (average 43%) (Paixão et al., 2018). Notably, chronic arthralgia is usually associated with significant disability which limits everyday activities and leads to physical and mental suffering, reported by patients as lack of appetite, non-restorative sleep, mood swings and depression (Elsinga et al., 2017; Couzigou et al., 2018). Such symptoms can result in absence from work or school, which may result in loss of employment or withdrawal from school, and reduced quality of life (Marimoutou et al., 2012; Bastos et al., 2018; Couzigou et al., 2018; Hossain et al., 2018).

In Latin American countries, the burden of chikungunya is enormous (Cardona-Ospina et al., 2015a; Feldstein et al., 2019). For the entire region, it has been estimated that approximately 400,000 individuals developed post-chikungunya chronic inflammatory rheumatism following the epidemics of 2014 (Rodriguez-Morales et al., 2015), with between 151,000 and 167,000 disability-adjusted life-years lost in the region (Cardona-Ospina et al., 2015b).

In Brazil, CHIKV was first detected in September 2014 in two cities located approximately 3300 km apart–Oiapoque, in the north state of Amapá, and Feira de Santana, in the north-east state of Bahia–each with a distinct viral lineage, corroborating independent introduction in the country (Nunes et al., 2015; Teixeira et al., 2015). Five years later, more than one million suspected cases have been reported by the Brazilian Ministry of Health (Pan American Health Organization and World Health Organization, n.d.). This article presents findings from the follow-up of a Brazilian cohort of patients with chikungunya detected during surveillance for acute febrile illness in order to characterize their clinical manifestations, estimate the frequency of chronic arthralgia, assess risk factors for persistent joint pain, and evaluate the impact of the disease on daily activities.

Methods

Study design and participant selection

The cohort of patients with a laboratory diagnosis of CHIKV infection was established between September 2014 and July 2016 during an enhanced surveillance study to detect arboviral infections among patients with acute febrile illness seeking medical care. Surveillance enrolment was performed from Monday to Friday between 7:30 am and 4 pm at a public emergency health unit in Pau da Lima, Salvador, Bahia, Brazil. Inclusion criteria were age $\geq$6 months, residence in Salvador, and reported or measured fever (temperature $\geq$37.8°) for $\leq$7 days.

During surveillance enrolment, a standardized interview was performed to obtain data on sociodemographics, clinical manifestations and contact information for subsequent follow-up. In addition, a blood sample was collected for arboviral diagnostic tests. Enrolled patients were asked to return to the health unit 15 days later to collect a convalescent-phase blood sample. A study team visited the homes of patients who lived in Pau da Lima and who did not return for the convalescent-phase blood sample collection in order to collect it.

Laboratory diagnosis

Blood samples were centrifuged and sera were aliquoted and stored at −20 °C and −80 °C before the diagnostic experiments. Acute-phase serum samples underwent RNA extraction using a Maxwell 16 Total RNA Purification kit (Promega, Madison, WI, USA) or a QIAmp Viral RNA mini kit (Qiagen, Hilden, Germany) assay in accordance with the manufactures' specifications. The obtained product was amplified by non-quantitative reverse transcriptase polymerase chain reaction (RT-PCR) for CHIKV (Edwards et al., 2007). Acute- and convalescent-phase samples were tested by enzyme-linked immunosorbent assay (ELISA) for the presence of IgM antibodies against CHIKV (Inbios, Seattle, WA, USA). A patient with positive results in any of the above-mentioned tests was defined as a case with laboratory evidence of CHIKV infection.

To quantify the CHIKV viral load in acute-phase samples of patients with laboratory evidence of CHIKV infection, who completed follow-up and who had available serum stored at −80 °C, quantitative RT-PCR was performed and the findings were compared with a standard curve made from a 10-fold dilution of a commercial sample containing 1.9×10^4 copies of CHIKV RNA/μL (Amplirun Chikungunya virus RNA control; Vircell, Granada, Spain). Positive and negative controls were included in these assays. The number of copies of CHIKV RNA per μL for each positive sample was transformed and presented in a logarithmic scale ($\log_{10}$) (details in online supplementary material). To investigate the occurrence of co-infection with CHIKV and dengue or Zika viruses, patients were also tested for dengue and Zika viruses by RT-PCR (Lanciotti et al., 1992; Balm et al., 2012).

Cohort follow-up

Between November 2016 and March 2017, on average 1.5 ± 0.3 years after symptom onset, telephone contact was attempted with enrolled patients with a positive CHIKV test in order to interview them about disease progression. Contacts were attempted from Monday to Sunday between 8 am and 9 pm. At least three attempts were made to speak with each patient. Patients who could not be contacted due to relocation to another city, incorrect or unavailable telephone number, or refusal for interview were considered lost to follow-up.

A standardized questionnaire was used to collect data on the evolution of clinical manifestations, especially on persistence or resolution of arthralgia, as well as its duration. Chronic chikungunya was ascribed if arthralgia persisted for >3 months. Additional data were collected from these patients to characterize the affected joints, pain intensity, presence of other clinical manifestations, mental distress, disease impact on daily life activities (i.e. combing hair, brushing teeth, dressing and feeding), maintenance of work and/or studies, and demand for health care. Pain intensity was assessed using a verbal pain score scale measured from 0 to 10, with scores of 0–2 classified as mild pain, scores of 3–7 classified as moderate pain, and scores of 8–10 classified as severe pain (Ferraz et al., 1990; Hawker et al., 2011). Mental distress was assessed using the Self-Reporting Questionnaire-20 (SRQ-20). This screening instrument used to detect common mental disorders had been applied and validated previously in Brazil (Harding et al., 1980; Mari and Willians, 1986; Iacoponi and Mari, 1989). Patients with at least seven affirmative responses in the SRQ-20 regarding the period of persistent arthralgia were considered to have mental distress.

Data analysis

The monthly frequencies of CHIKV infection among febrile patients were plotted on a graph to present the temporal distribution of detected cases during surveillance enrolment. To verify if the loss to follow-up had introduced a substantial bias in the cohort, the frequencies of sociodemographic and clinical characteristics at surveillance enrolment were compared between patients with chikungunya who did and did not complete the telephone follow-up survey. Frequencies of sociodemographic characteristics, clinical manifestations, disease impact on regular

daily activities, and medical health demands were used to describe the patients who progressed to chronic arthralgia.

The risk of chronic arthralgia and its 95% confidence interval (95% CI) was calculated using the ratio of the number of CHIKV-infected patients who had joint pain for >3 months after its onset and the number of patients who completed the telephone follow-up survey. The risk of chronic arthralgia was also calculated by sex, age, acute-phase clinical manifestations of the disease, prior co-morbidities, presence of co-infection with dengue virus, and level of CHIKV RNA copies/μL. Crude risk ratios and respective 95% CIs for these factors were estimated, and those with a *P*-value ≤0.20 on Chi-squared test were included in multi-variate Poisson regression analyses with robust variance and backward elimination. Factors associated with chronic arthralgia with $P < 0.05$ in the multi-variate analysis were considered significant, and adjusted risk ratios and 95% CIs were calculated. Data were collected and managed using Research Electronic Data Capture (REDCap) (Harris et al., 2009). Statistical analyses were performed using STATA 12 (Stata Corp, College Station, TX, USA). The STROBE statement for reporting observational studies was followed during the preparation of this manuscript.

Ethical considerations

Study patients provided written informed consent when aged ≥18 years, or written informed assent when aged 7–17 years. Legal guardians also provided written informed consent for inclusion of patients <18 years of age. This study was approved by the Ethics Research Committee of the Gonçalo Moniz Institute, Oswaldo Cruz Foundation (CAAE 55904616.4.0000.0040).

Results

Baseline clinical characteristics of patients with chikungunya

Of 948 patients with acute febrile illness enrolled in the surveillance study, 265 (28.0%) had laboratory evidence of CHIKV infection (Figure 1). Of them, 87 (32.8%) were positive solely by RT-PCR, 98 (37.0%) solely by IgM ELISA (in either the acute- or the convalescent-phase serum sample), and 80 (30.2%) by both RT-PCR and IgM ELISA. Except for the period between December 2014 and February 2015, CHIKV infection cases were detected throughout the study period, but they peaked between July and November 2015 (Figure 2).

Completion of follow-up was attained for 153 (57.7%) of the 265 patients with chikungunya. Reasons for loss to follow-up included incorrect or unavailable telephone number, relocation to another city, and refusal to be interviewed. Of the 153 patients with chikungunya who completed follow-up, 80 (52.3%) were female, and the majority (n = 109, 71.2%) were 15–49 years old (Table 1). The most common acute-phase clinical manifestations were myalgia (n = 141, 92.2%), headache (n = 140, 91.5%) and arthralgia (n = 136, 88.8%) (Table 1). Cases who completed follow-up were a little older than those who did not complete follow-up (Table S1, see online supplementary material), but this difference was not significant (P = 0.08). Additional demographics and acute-phase clinical characteristics were similar between the two groups.

Incidence of chronic chikungunya arthralgia

Of the 153 patients with chikungunya who completed follow-up, 65 (42.5%, 95% CI 34.9–50.4%) reported chronic joint pain that lasted for >3 months and 47 (30.7%, 95% CI 24.0–38.4%) were still symptomatic at the time of the telephone interview (1.5 ± 0.3 years after onset of acute illness). As observed for the group of 153 patients with chikungunya who completed follow-up, the most

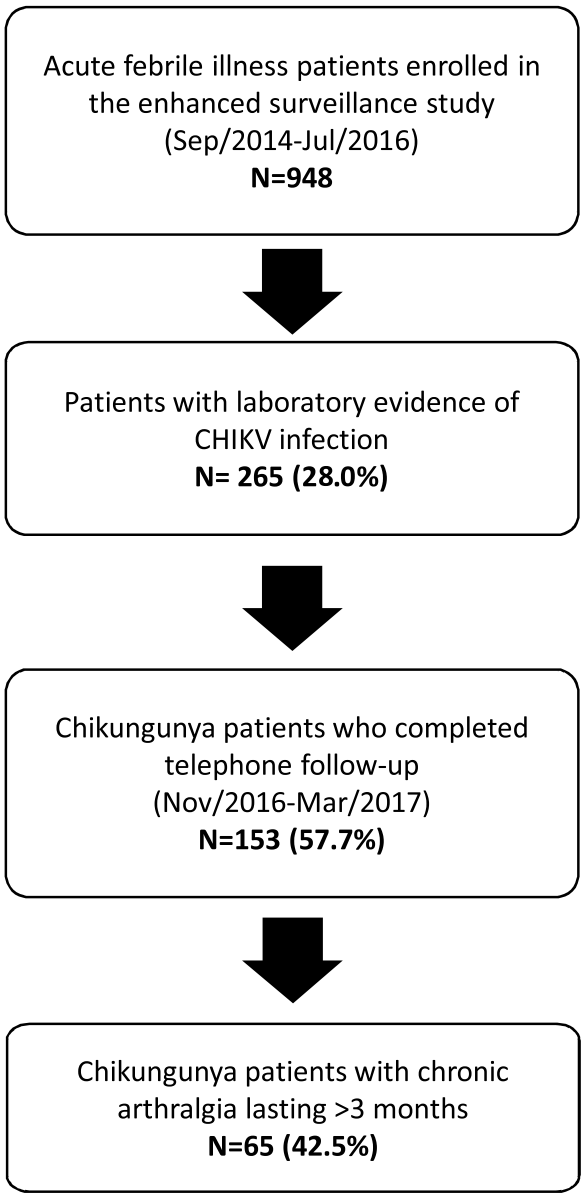

Figure 1. Detection and follow-up of patients with laboratory evidence of chikungunya virus infection, Salvador, Brazil.

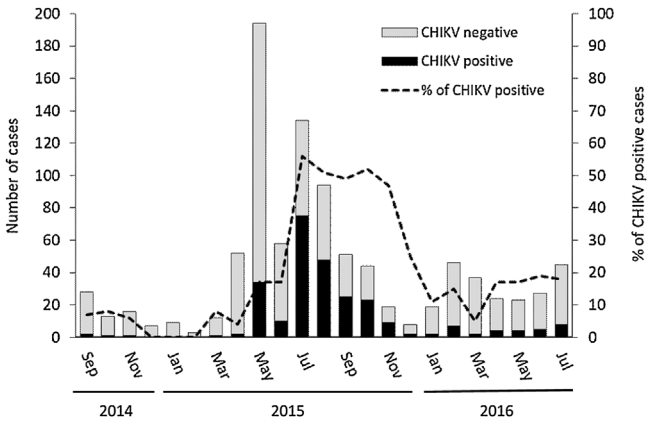

Figure 2. Distribution of patients with acute febrile illness according to laboratory evidence for chikungunya virus (CHIKV) infection by month and year, Salvador, Brazil, September 2014 to July 2016.

Table 1
Self-reported enrolment characteristics of 153 patients with laboratory evidence of chikungunya virus (CHIKV) infection and follow-up completion, Salvador, Brazil.

Characteristics	*n* with available data	*n* (%) or median (IQR)
Female	153	80 (52.3)
Age, years	153	37 (24–47)
Age group		
6 months–14 years	153	16 (10.5)
15–29 years	153	38 (24.8)
30–49 years	153	71 (46.4)
≥50 years	153	28 (18.3)
Skin colour/race		
White	153	6 (3.9)
Black	153	61 (39.9)
Mixed	153	76 (49.7)
Yellow	153	4 (2.6)
Indigenous	153	6 (3.9)
Years of study		
≤5	148	30 (20.3)
6–9	148	45 (30.4)
≥10	148	73 (49.3)
Occupation[a]		
Any work	129	85 (65.9)
Formal work	129	47 (36.4)
Reported clinical manifestation[b]		
Myalgia	153	141 (92.2)
Headache	153	140 (91.5)
Arthralgia/location	153	136 (88.8)
Elbows	150	110 (73.3)
Wrists	149	121 (81.2)
Fingers	150	117 (78.0)
Ankles	145	110 (75.9)
Knees	150	120 (81.3)
Prostration	151	132 (87.4)
Retro-orbital pain	153	109 (71.2)
Abdominal pain	153	60 (39.2)
Rash	151	46 (30.4)
Sore throat	153	41 (26.8)
Pruritus	153	40 (26.1)
Vomit	152	33 (21.7)
Log_{10} CHIKV RNA copies/μL[c]	95	5.6 (4.9–6.1)

NT, not tested; IQR, interquartile range.
[a] Data on occupation were analysed for participants aged ≥18 years.
[b] Frequency of clinical manifestations may have been underestimated because two children aged <3 years may not have reported some symptoms.
[c] CHIKV viral load was determined for 95 patients who had laboratory evidence of CHIKV infection, completed follow-up, and had an available serum specimen stored at −80 °C.

common acute-phase clinical manifestations for the 65 cases with chronic joint pain were arthralgia (*n* = 62, 95.4%), myalgia (*n* = 61, 93.8%) and headache (*n* = 60, 92.3%) (Table 2). The joints most frequently affected by chronic pain were the wrists (*n* = 62, 95.4%), ankles (*n* = 60, 92.3%), knees (*n* = 59, 90.7%) and fingers (*n* = 59, 90.7%). Chronic joint pain was classified as severe (*n* = 43, 66.1%) or moderate (*n* = 21, 32.3%) in all except one of these patients. Joint oedema during the chronic disease stage was reported by 50 (76.9%) cases, and was more common in the toes (*n* = 38, 58.5%), fingers (*n* = 36, 55.4%) and ankles (*n* = 35, 53.8%). Other commonly reported symptoms accompanying chronic arthralgia were fatigue (*n* = 57, 87.7%), hair loss (*n* = 17, 26.1%) and oral ulcers (*n* = 11, 16.9%).

Risk factors for chronic chikungunya arthralgia

Bivariate analysis showed that women were at higher risk of developing chronic arthralgia compared with men [risk ratio (RR) 1.91, 95% CI 1.27–2.89] (Table 3). The risk of chronic arthralgia also increased with age (RR 1.02 for each 1-year increase, 95% CI 1.01–1.03). Among the self-reported co-morbidities, hypertension was the only prior illness statistically associated with chronic arthralgia (RR 1.61, 95% CI 1.10–2.35). CHIKV co-infection with dengue virus was not associated with chronic arthralgia (RR 0.97, 95% CI 0.48–1.94). In addition, no association was found between CHIKV viral load at diagnosis and chronic arthralgia [median CHIKV RNA of 5.60 and 5.52 log_{10} copies/μL for those with and without chronic arthralgia, respectively (*P* = 0.75); RR 0.97 for each 1-log increase in the number of CHIKV RNA copies/μL, 95% CI 0.77–1.23] (Table 3). Multi-variate analysis indicated that sex (RR 1.79, 95% CI 1.20–2.69) and age (RR 1.02 for each 1-year increase in age, 95% CI 1.01–1.03) were independent risk factors associated with the development of chronic arthralgia (Table 3).

Self-reported impact of chronic CHIKV infection

When asked about the impact of chronic joint pain on daily activities, 61 of 65 (93.8%) patients reported limitations to ordinary activities, such as combing hair, brushing teeth, dressing and feeding, and 57 (87.7%) patients reported limitations in walking (Table 4). Substantial impact on working-related activities was perceived by seven (17.5%) of 40 patients with chronic disease who worked; four (10.0%) reported losing their job and three (7.5%) reported having to change their job because of the illness (Table 4). Healthcare assistance during the chronic stage of the disease was reported by 33 (50.8%) patients; seven (10.8%) reported hospitalization following disease onset. Of the 26 (40.0%) patients who had at least one outpatient appointment with a general physician, 21 (80.8%) were provided by the Brazilian public health system. In contrast, of the seven (10.7%) patients who reported receiving physiotherapy, only three (42.9%) received it through the public health system. Only three (4.6%) patients reported receiving health care from a rheumatologist (one through the public health system).

Table 2
Characteristics of 65 patients with laboratory evidence of chikungunya virus (CHIKV) infection and chronic arthralgia lasting >3 months, Salvador, Brazil.

Characteristics	*n* (%)
Age group	
6 months–14 years	3 (4.6)
15–29 years	10 (15.4)
30–49 years	38 (58.5)
≥50 years	14 (21.5)
Clinical manifestations at enrolment	
Arthralgia	62 (95.4)
Myalgia	61 (93.8)
Headache	60 (92.3)
Prostration	58 (89.2)
Retro-orbital pain	51 (78.5)
Abdominal pain	25 (38.5)
Rash[a]	24 (37.5)
Pruritus	18 (27.7)
Vomit	17 (26.1)
Sore throat	16 (24.6)
Median CHIKV RNA $\log_{10}$ copies/μL[b]	5.60 (4.86–6.05)
Clinical manifestations at follow-up	
Chronic arthralgia/location	65 (100)
Wrists	62 (95.4)
Ankles	60 (92.3)
Knees	59 (90.7)
Hand/fingers	59 (90.7)
Toes	55 (84.6)
Spine	52 (80.0)
Shoulders	51 (78.5)
Elbows	45 (69.3)
Neck	40 (61.5)
Intensity of chronic arthralgia	
Severe	43 (66.1)
Moderate	21 (32.3)
Mild	1 (1.5)
Chronic joint oedema/location	50 (76.9)
Toes	38 (58.5)
Hand/fingers	36 (55.4)
Ankles	35 (53.8)
Knees	31 (47.7)
Wrists	27 (41.5)
Elbows	12 (18.5)
Shoulder	9 (13.8)
Spine	3 (4.6)
Neck	1 (1.5)
Other chronic symptoms	
Fatigue	57 (87.7)
Hair loss	17 (26.1)
Oral ulcer	11 (16.9)
Skin vesicles	5 (7.7)

[a] Data available for 64 patients.
[b] Data available for 44 patients.

Of special note, during the chronic stage of the disease, 40 (61.5%) patients had physical and psycho-emotional symptoms compatible with mental distress, but only one (1.5%) reported receiving support from a psychologist (Table 4).

Discussion

In total, 42.5% of patients with laboratory evidence of acute CHIKV infection developed chronic arthralgia that lasted for ≥3 months, and 30.7% remained symptomatic when evaluated approximately 1.5 years later. The majority (66%) of those who developed chronic joint pain considered their arthralgia to be severe, and >90% of them reported limitations in performing daily activities. Females and older patients were at higher risk of chronic arthralgia. The study highlights the frequent persistent joint pain in patients following acute chikungunya, and draws attention to the impact of this problem.

Similar to the present results, a systematic review including different study designs (from cohort to case series, cross-sectional and case–control investigations) and comprising >6500 patients with chikungunya found that 42% (95% CI 33–51%) of these cases did not recover fully from persistent pain/arthralgia after 3 months (Paixão et al., 2018). Specifically among cohort studies, the rate of chronic arthralgia after CHIKV infection has been reported to range from 22% to 67% (Borgherini et al., 2008; Gérardin et al., 2013; Madec et al., 2013; van Genderen et al., 2016; Zeana et al., 2016; Murillo-Zamora et al., 2017; Huits et al., 2018; Watson et al., 2020). The large difference in the time elapsed between acute disease stage and patient follow-up, as well as the subjectivity in pain perception and reporting, may explain, in part, the diverse estimates of risk for development of chronic arthralgia. Alternatively, reported risk differences may result from diverse genetic backgrounds among these human populations, and/or among the strains of the circulating CHIKV, which may include antigenic diversity, difference in replication capacity, and distinct potential to induce inflammatory joint pathology (Madec et al., 2013; Teo et al., 2015).

The present study found that age was an independent risk factor for chronic arthralgia, as shown previously (Couturier et al., 2012; Gérardin et al., 2013; Madec et al., 2013; Rodriguez-Morales et al., 2016; Murillo-Zamora et al., 2017; Consuegra-Rodríguez et al., 2018). The age-related propensity for rheumatic and osteoarthritic pain may explain, in part, the association between age and chronic pain observed for CHIKV infection. Moreover, a general decline in both the innate and adaptive immune responses could explain the increased disease severity observed in older individuals (Messaoudi et al., 2013).

The present study also found that women were at increased risk of chronic arthralgia (RR 1.79 adjusted for age), corroborating prior studies that had shown RRs or odds ratios for female gender ranging from 1.3 to 3.4 for >6 weeks of persistent arthralgia (Rodriguez-Morales et al., 2016; Huits et al., 2018), and from 2.9 to 5.9 for >1 year of pain (Huits et al., 2018; de Moraes et al., 2020). The higher risk for chronic pain observed among women may be due to both biological and psychosocial factors. From a biological perspective, hormonal differences between the sexes may influence the response to pain stimuli. Especially in older women, some studies noted that hormonal changes can affect the immune system and influence the severity of joint pain (Bouman et al., 2005; Straub, 2007). At a psychosocial level, gender differences in the expression of pain are often attributed to the effects of stereotypic sex roles, because pain perception is a complex phenomenon and the role of gender in beliefs and expectations concerning pain may determine the experience of joint pain in patients with CHIKV infection (Myers et al., 2003). It is also possible that differences in health-seeking behaviour between genders affected how men and women reported symptoms during follow-up. The mechanisms underlying these sex differences have yet to be fully uncovered.

Among the acute-phase clinical manifestations reported during enrolment, arthralgia was the symptom that best predicted the development of chronic arthralgia, although the association was not significant (RR 2.58, 95% CI 0.91–7.33). Similarly, prior arthrosis was found to increase the risk of chronic arthralgia (RR 1.45, 95% CI 0.93–2.27), but the association was not significant. Hypertension was associated on bivariate analysis (RR 1.61, 95% CI 1.10–2.35) but not on multi-variate analysis. The lack of significance should be interpreted with caution as only a minority of the followed-up patients did not have arthralgia at enrolment (11%), or reported having either arthrosis (11%) or hypertension (16%) before the onset of chikungunya. Given the biological plausibility and the fact that prior studies have shown the severity of acute arthralgia and the presence of underlying osteoarthritis and hypertension as risk factors for chronic chikungunya arthralgia (Sissoko et al., 2009; de Moraes et al., 2020), it is possible that these associations are real

Table 3
Factors associated with chronic chikungunya arthralgia, Salvador, Brazil.

Characteristics	*n* of patients followed (*n* = 153)	*n* (%) of patients with chronic arthralgia (*n* = 65)	Crude risk ratio (95% CI)	Adjusted risk ratio (95% CI)[e]
Sex				
Female	80	44 (55.0)	1.91 (1.27–2.89)	1.79 (1.20–2.69)
Male	73	21 (28.8)	1	1
Age, years[a]	153	–	1.02 (1.01–1.03)	1.02 (1.01–1.03)
Skin colour/race				
Black or mixed	137	60 (43.8)	1.40 (0.66–2.97)	–
Non-black and non-mixed	16	5 (31.2)	1	
Acute-phase manifestations				
Arthralgia				
Yes	136	62 (45.6)	2.58 (0.91–7.33)	–
No	17	3 (17.6)		
Myalgia				
Yes	141	61 (43.3)	1.30 (0.57–2.95)	–
No	12	4 (33.3)		
Headache				
Yes	140	60 (42.9)	1.11 (0.55–2.28)	–
No	13	5 (38.8)	1	
Prostration				
Yes	132	58 (43.9)	1.19 (0.64–2.22)	–
No	19	7 (36.8)		
Retro-orbital pain				
Yes	109	51 (46.8)	1.47 (0.91–2.37)	–
No	44	14 (31.8)	1	
Rash				
Yes	46	24 (52.2)	1.37 (0.95–1.98)	–
No	105	40 (38.1)	1	
Vomit				
Yes	33	17 (51.5)	1.28 (0.88–1.90)	–
No	119	48 (40.3)	1	
Pruritus				
Yes	40	18 (45.0)	1.08 (0.72–1.62)	–
No	113	47 (41.6)	1	
Sore throat				
Yes	41	16 (39.0)	0.89 (0.58–1.38)	–
No	112	49 (43.8)	1	
Abdominal pain				
Yes	60	25 (41.7)	0.97 (0.66–1.42)	–
No	93	40 (43.0)	1	
Self-reported comorbidities				
Diabetes mellitus				
Yes	5	2 (40.0)	0.94 (0.32–2.79)	–
No	148	63 (42.6)	1	
Hypertension				
Yes	24	15 (62.5)	1.61 (1.10–2.35)	–
No	129	50 (38.8)	1	
Arthrosis				
Yes	17	10 (58.8)	1.45 (0.93–2.27)	–
No	136	55 (40.4)	1	
Overweight[b]				
Yes	46	20 (43.5)	1.03 (0.69–1.54)	–
No	107	45 (42.1)	1	
Dengue virus co-infection[c]				
Yes	12	5 (41.7)	0.97 (0.48–1.94)	–
No	139	60 (43.2)	1	
Log_{10} CHIKV RNA copies/μL[d]	95	–	0.97 (0.77–1.23)	–

[a] Risk ratio represents the increase in risk of chronic arthralgia for each 1-year increase in age.
[b] Overweight was defined as body mass index (BMI) ≥25 kg/m^2. BMI was calculated based on self-reported weight and height.
[c] Dengue virus co-infection was detected by a concomitant positive result on reverse transcriptase polymerase chain reaction (RT-PCR). Two patients did not have results of RT-PCR. No co-infection was observed between chikungunya virus (CHIKV) and Zika virus.
[d] Risk ratio represents the increase in risk of chronic arthralgia for each 1-log increase in the number of CHIKV RNA copies/μL.
[e] Poisson regression analyses with robust variance and backward elimination was performed for variables with $P \leq 0.20$ on bivariate analysis (sex, age, arthralgia, rash, retro-orbital pain, hypertension and arthrosis).

but the present study did not have sufficient power to detect them at the level set for statistically significant associations. As most patients with acute chikungunya present arthralgia, and as the overall population, especially the elderly, are frequently affected by arthropathies and hypertension, these factors may contribute significantly to the occurrence of chronic chikungunya arthralgia. Larger studies to address the role of these factors on pain persistence are needed.

A previous cohort study, following 19 RT-PCR-positive patients from Reunion Island, found that higher viral load at acute illness was associated with chronic arthralgia lasting 12 months (Hoarau et al., 2010). However, this association has not been addressed by other longitudinal studies (van Aalst et al., 2017). The present study followed-up 95 RT-PCR-positive patients and did not find differences in acute-phase viral levels between patients who still had pain at 3 months and those who did not. Differences in the time of

Table 4
Self-reported impact on daily life activities, working, demand for health care and mental distress in 65 patients with chikungunya that evolved to chronic arthralgia, Salvador, Brazil.

Self-reported impact	*n* (%)
Impact on daily life activities	
Limitation of ordinary activities[a]	61 (93.8)
Limitation of walking	57 (87.7)
Impact on working[b]	
Loss of job	4 (10.0)
Need to change job	3 (7.5)
Healthcare assistance due to chikungunya[c]	
Any type of health care	33 (50.8)
General outpatient clinic	26 (40.0)
Physiotherapy	7 (10.7)
Rheumatology specialist	3 (4.6)
Psychology specialist	1 (1.5)
Hospitalization	7 (10.8)
Mental distress[d]	40 (61.5)

[a] Combing hair, brushing teeth, dressing or feeding.
[b] Analyses performed for the 40 patients who reported that they were working at enrolment.
[c] Health care was provided by the public unified health system, except for five general outpatient clinic consultations, four physiotherapy consultations and two rheumatologist consultations. Hospitalization due to chikungunya at any time after disease onset.
[d] Mental distress was assessed by the standardized and validated Self-Reporting Questionnaire-20 (Harding et al., 1980). Patients who answered 'yes' to at least seven of the 20 questions regarding physical and psycho-emotional symptoms in the period of chronic arthralgia were considered to have mental distress.

acute-phase sample collection or in the severity of acute disease may explain the divergent finding between the study performed in Reunion Island and the present study. The present study mainly enrolled outpatients within 3 days of symptom onset, whereas the Reunion Island study enrolled hospitalized patients on day 4 or 5 of symptoms.

Some researchers identified persistent CHIKV antigens in the synovial fluid of patients with chronic arthralgia, suggesting that the chronicity of arthralgia may be linked to local joint inflammation associated with viral persistence (Hoarau et al., 2010; Madec et al., 2013). In addition, experimental studies in CHIKV-infected animals have indicated that the joints and muscles are the most highly infected tissues, making it plausible that incomplete viral antigen clearance in these anatomical sites may account for the long-term symptoms (Couderc et al., 2008). However, it is possible that immune activation continues after viral clearance from the joints, and that the inflammatory response contributes to disease pathogenesis (Burt et al., 2017). Unfortunately, the follow-up strategy used in the present study, based on telephone contacts for assessment of pain persistence, did not enable the clinical syndrome associated with pain maintenance (e.g. arthritis, synovitis, tendonitis, tenosynovitis or other musculoskeletal origin) to be determined, or investigation of viral persistence or immune response in the affected joints of the study patients.

Of note, most of the participants who developed chronic pain reported difficulties in performing routine activities, walking and working. These limitations, also documented in other studies (Borgherini et al., 2008; Soumahoro et al., 2009; Couturier et al., 2012; Madec et al., 2013), show that chronic arthralgia is highly disabling for daily life and professional activities. This issue is particularly worrying as the persistence of joint pain among people of working age affects both the social security system and the local economy. The physical limitations further affect patients' mental health. In this study, signs of mental distress and/or depressed mood occurred in 60% of patients with chronic CHIKV-related pain, corroborating findings from previous studies (Soumahoro et al., 2009; Madec et al., 2013; Elsinga et al., 2017; Couzigou et al., 2018). Despite high functional disability, mental distress and the burden of chronic chikungunya on an individual's quality of life, access to multi-professional specialized care (i.e. physiotherapy, rheumatology and psychology) was scarce among the study cases. The low number of patients under specialized care may be due to the limited offering of these services through the public health system, and the inability of individuals to acquire private care.

This study has several limitations. First, the authors were not able to complete follow-up of all patients with chikungunya; however, comparison of the sociodemographic and clinical characteristics of individuals who completed and did not complete follow-up showed that they were similar, which reduces the likelihood of selection bias due to loss to follow-up. Nevertheless, loss to follow-up limited the statistical power of the study to identify significant associations. Second, patient follow-up was performed, on average, 1.5 years after the acute phase of the disease, and participants may not have remembered the duration of joint pain and the evolving signs and symptoms related to CHIKV infection accurately. Third, CHIKV infection was confirmed by RT-PCR and serology, but patients with IgM CHIKV antibodies in the acute-phase sample may have had a recent CHIKV infection (with maintenance of IgM antibodies) rather than an acute infection. However, the risk of chronic arthralgia was compared between patients confirmed by RT-PCR or IgM seroconversion (45.2%, 95% CI 35.4–55.2%) and patients confirmed by detection of IgM in the initial serum (36.7%, 95% CI 23.4–51.7%), and no significant difference was found. Finally, although the PCR products of the CHIKV cases were not sequenced, other studies have identified the East/Central/South African genotype as the only lineage circulating in Salvador since the introduction of CHIKV (Sardi et al., 2016; Tauro et al., 2019). However, it is possible that some patients were infected by an Asian/Caribbean strain given that this genotype was identified in Pernambuco, a north-east state that borders Bahia (Machado et al., 2019).

Although this study enrolled patients solely from a single local emergency unit, the findings were comparable with those performed in other settings, suggesting that the study group was not unique in its genetic and social background. In addition, patients with febrile illness aged $\geq$6 months seeking medical care during an acute phase of the disease were enrolled in this study. This approach avoided the inclusion of patients who were already in a subacute or chronic phase of the disease, which could have biased the conclusions regarding the disease's natural history course. Therefore, it is likely that the results are generalizable for acute cases of chikungunya from other Brazilian regions, and possibly to other Latin American countries.

These findings highlight the potential catastrophic scenario of large CHIKV epidemics, with >40% of patients with symptomatic infection developing chronic arthralgia that may last for at least 1.5 years for up to 30% of the patients. The disabling consequences of persistent joint pain on daily activities and work capacity may have a dramatic societal impact on productivity, combined with higher and more complex healthcare requirements. Understanding the burden of CHIKV infection in the absence of vaccines and better transmission control methods is fundamental for the public health authorities to devise better plans and allocation of human and financial resources to minimize the suffering and impact caused by this disease.

Conflict of interest

None declared.

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Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.ijid.2021.03.003.

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