

Title: Chronic joint pain 3 years after chikungunya virus infection largely characterized by relapsing-remitting symptoms

Running Title: Chronic chikungunya arthritis

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ABSTRACT

Objective. To determine the frequency of chronic joint pain and stiffness 3 years after infection with chikungunya virus in a Latin American cohort.

Methods. A cross-sectional follow-up of 120 patients from an initial cohort of 500 patients who reported joint pain 2 years after infection from the Atlántico Department, Colombia. Patients were clinically diagnosed as having chikungunya virus during the 2014–2015 epidemic, and baseline and follow-up symptoms at 40 months were evaluated in serologically confirmed cases.

Results. Of the initial 500 patients enrolled in the study, 482 had serologically confirmed chikungunya infection. From this group, 123 patients reported joint pain 20 months after infection, and 54% of those patients reported continued joint pain 40 months after infection. Therefore, 1 out of every 8 people who tested serologically positive for chikungunya infection had persistent joint pain 3 years after infection. Participants that followed up in-person were predominantly adult (mean \pm SD age 51 ± 14 years) and female (86%). The most common type of pain reported in these patients at 40 months post-infection was pain with periods of relief and subsequent reoccurrence, and over 75% reported stiffness after immobility, with 39% experiencing morning stiffness.

Conclusion. This is the first report to describe persistent joint pain and stiffness 40 months after viral infection. The high frequency of chronic disease highlights the need to develop prevention and treatment methods. Further studies should be conducted to understand the similarities between post-chikungunya joint pain and rheumatoid arthritis.

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SIGNIFICANCE

- First to describe persistent joint pain and stiffness 40 months after chikungunya virus infection.
- One out of eight individuals infected had persistent joint pain 3 years after acute infection.
- The most common type of pain reported was pain with periods of relief and subsequent reoccurrence.
- Over 75% of patients reported stiffness after immobility, while 39% experienced morning stiffness

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INTRODUCTION

Chikungunya virus (CHIKV) is an arthropod-borne illness that belongs to the *Alphavirus* genus within the *Togaviridae* family (1). The virus is transmitted mainly by the *Aedes aegypti* mosquito vector. Acute chikungunya infection causes a wide range of clinical manifestations, most prominently fever, rash, headache, myalgia, and severe, disabling polyarthralgia (2). While the acute symptoms associated with CHIKV typically disappear within 7–10 days, various studies report persistent joint pain in 30–70% of patients months or years after initial CHIKV infection (3-9). There has consistently been a positive correlation between age and duration of CHIKV-associated persistent joint pain, as well as severe initial joint pain and high titers of CHIKV-specific IgG (4, 10, 11). Currently, the CDC recommends acetaminophen and non-steroidal anti-inflammatory drugs (NSAIDs) for treatment of acute CHIKV symptoms; however, there are currently no effective therapeutics or vaccines available (3). While some success has been seen using disease-modifying antirheumatic drugs (DMARDs), especially in combination with hydroxychloroquine, in relieving symptoms of chronic chikungunya virus, the majority of patients are put on a prolonged regimen of NSAIDs (12, 13).

Since its identification in Tanzania in the early 1950's, chikungunya virus has primarily caused small, sporadic outbreaks in Africa and Asia, with a brief quiet period from the mid-1980's through 2004. An epidemic originating in Kenya in June 2004 spread first to La Réunion and other Indian Ocean Islands, followed by an epidemic in India that eventually spread through Southeast Asia, and lastly to the islands of the Pacific Ocean. Cases in the Western Hemisphere were travel-related until October 2013, when the first autochthonous chikungunya transmission occurred on the Caribbean island of Saint Martin. By mid-February 2014, the virus had landed on the South American mainland (14). Unlike the outbreak in La Réunion Island that was believed to be caused

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by the East/Central/South African (ECSA) strain, sequence data has demonstrated that the chikungunya virus strain spreading throughout the Caribbean and Central/South America is within the Asian strain genotype, making it closely related to viruses isolated in China and the Philippines, with minimal evolution (15-17). However, there have been recent reports of ECSA genotype chikungunya in circulation in Brazil, signifying that both lineages are circulating in the Americas (18).

In a 36-month longitudinal study of patients infected during the 2006 outbreak in La Réunion Island, the majority of patients (60–80%) had relapsing arthralgia, while only 20–40% had unremitting arthralgia (19). High reported percentages of patients with persistent arthralgia is common in studies of Italian and French cohorts (4, 10, 11), whereas that statistic is much lower in cohorts from India and Senegal (9, 20, 21). Numerous studies have so far failed to elucidate the mechanisms behind the progression of chikungunya virus to the chronic stage, although many hypotheses do exist, including pre-existing joint disease or metabolic syndrome features and the persistent replication of virus or the presence of viral debris in joint tissues (13). Previously, we investigated the virologic and immune factors associated with chronic CHIKV-associated joint pain. Synovial fluid samples were taken from patients who had persistent knee joint pain 22 months after laboratory-confirmed infection (22). However, synovial fluid samples from all patients were negative for CHIKV on qRT-PCR, no viral proteins were detected by mass spectrometry and viral cultures were negative. Furthermore, cytokine and chemokine data showed that IL-6, IL-12p70, MCP-1, MIP-1 β , and IL-8 were elevated in CHIKV patients with arthritis compared to controls, although it did not reach statistical significance. Further analysis of predictors of chronic joint pain are needed. In another study, we investigated serum cytokine concentrations during acute chikungunya infection, comparing values in patients who reported the presence of chronic joint

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pain at 20 months post-infection versus age- and gender- matched patients who reported recovery in the same amount of time (23). Those results showed a correlation between a robust cytokine response during acute infection and decreased incidence of chronic joint pain, as well as the increased incidence of chronic joint pain in patients with low TNF α , IL-13, IL-2 and IL-4 during acute infection.

There have been multiple reports of relapsing-remitting arthralgia associated with CHIKV, including one study on Réunion Island hospital staff and their households that found that almost 50% of CHIKV infected patients experienced at least one relapse of symptoms, and an increased occurrence with age (24). Although there is no definitive causes for relapse, there are several suggested hypotheses, including the idea that virus particles or viral debris could reside within synovial tissue. In fact, Hoarau *et al.* found chikungunya virus RNA in synovial biopsy tissue, as well as virus antigen in macrophages, 18 months after infection in a single patients (6). This was also demonstrated for the alphaviruses Sindbis virus and Ross River virus (25-27). Further, long-term viral persistence was observed in macrophages in nonhuman primates up to 3 months after infection (28). However, an analysis of 33 patients (many of whom had relapsing-remitting symptoms) did not find viral RNA or proteins in the synovial fluid of patients with persistent joint pain 22 months after infection (22). The relative intensities of joint pain varies between patients, from less pain than experienced during the acute phase to more pain (22, 24).

Between 2015 and 2016, there were 376,436 cases of chikungunya reported in Colombia (29). Colombia's low elevation (< 1000 meters, with the exception of the Andes Mountains) is favorable for *A. aegypti* proliferation and, therefore, transmission to much of the population (30). To date, long-term reports on the frequency of chronic arthritis in the Americas after chikungunya

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infection and detailed characterization of the clinical presentation of persistent arthritis years after infection have been limited.

The primary objective of this study was to describe the frequency of persistent joint pain in a Colombian cohort of chikungunya virus patients a median of 40 months post-infection and to better characterize the clinical symptoms in order to better understand the long-term impact of the American outbreak. Our hypothesis was that one-third of the patients that reported persistent pain a median of 20 months post-infection would still be experiencing pain at 40 months with symptoms of constant pain.

PATIENTS AND METHODS

Ethics statement. This study (IRB#121611, Trans #28283) was approved by the ethics committee of the Clinica de La Costa Ltda. and the George Washington University Committee on Human Research. A non-human subjects determination was made by The George Washington University IRB for analysis of deidentified data. Written informed consent was obtained from all participants, and all samples were collected by qualified medical personnel (5).

Study Design. In January 2015, five hundred patients with clinically confirmed chikungunya virus infection were enrolled as part of a prospective cohort, and diagnosis was serologically confirmed via IgM and IgG antibody capture enzyme-linked immunosorbent assay (ELISA) (5). A baseline 33-item survey was conducted to established demographic characteristics, exposure history, and symptoms; subsequently, at a median of 20 months post-infection, a 56-item telephone survey included an assessment of the character and duration of persistent chikungunya arthritis symptoms, including swollen joint count, tender joint count, comorbidities, missed work or school, a global pain score during the last week (based on the Disease Activity Score in 28 joints [DAS28]) (31), and therapies received (5). At a median of 40 months after infection, a 30-item telephone survey

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was conducted with 120 patients who reported persistent arthritis during the 20-month follow-up. Of the 120 patients who participated in the phone survey, 82 also participated in an in-person assessment involving an 80-item survey that included the items mentioned above, as well as types of pain, what provokes relapse, and questions relating to stiffness, as devised and tested in patients with rheumatoid arthritis (32).

Participants. Cases were referred for enrollment after diagnosis with clinical chikungunya infection, defined by the Colombian Institute of Health as a fever of $> 38^{\circ}\text{C}$, severe joint pain or arthritis, and acute onset of erythema multiform, with symptoms that could not be explained by other medical conditions among patients residing in or having visited a municipality with evidence of chikungunya virus transmission, or having traveled within 30 kilometers of confirmed viral transmission (33). Patients were from the Sabanalarga, Barranquilla, Juan de Acosta, Manati, Luruaco, and Baranoa municipalities in the Atlántico Department, Colombia, located on the Caribbean coastal plane. Clinically suspected cases of chikungunya virus were serologically confirmed for the purposes of this study (5).

RESULTS

There were 500 participants with clinically confirmed chikungunya virus infection enrolled in this study, of which 6 participants were excluded due to negative tests for IgM and IgG antibodies, and 9 participants were excluded because joint pain status was not reported (Figure 1). Four hundred eighty-five participants were interviewed at a median of 20 months after chikungunya infection, 123 of whom reported persistent joint pain. Sixty-five of the 482 patients with serologically confirmed chikungunya infection reported persistent symptoms a median of 40 months after infection. Moreover, 54% of patients who reported persistent joint pain at a median 20 months post-infection reported still having pain at a median 40 months post-infection. This is

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clinically relevant because it appears that approximately 1 out of every 4 patients who tested serologically positive for chikungunya infection still have persistent joint pain associated with the virus two years after infection, and around 1 out of every 8 patients still have persistent joint pain three years after infection (Figure 2A). In response to the EQ-5D questionnaire (EuroQol Group; www.euroqol.org) that evaluates five dimensions of health status, over 30% of patients with persistent joint pain reported moderate or severe problems with pain and discomfort, while only around 10% reported moderate or severe problems with the other four areas, including mobility, self-care, daily activities, and depression or anxiety (Figure 2B).

At baseline (Table 1), confirmed cases that were followed up with in-person were predominately adult (mean age 51 ± 14 years) and female (86%), and had at least a high school level education (68%). All patients who reported race were of Mestizo ethnicity ($n = 80$; i.e., mixed European, often Iberian, with indigenous Latin American ancestry). As a result of persistent symptoms, 38% of patients were forced to miss school or work, and 47% of patients said their capacity to continue normal activities were impacted (Table 2). Among the patients that had persistent joint pain after 20 months, the survey on global pain score (ranging from 0–100) produced a mean \pm SD of 47 ± 20 ($n = 123$) (5). However, at 40 months, the participants reporting persistent joint pain had a global pain score of 65 ± 20 ($n = 67$). Interestingly, two patients with persistent joint pain said they had developed rheumatoid arthritis after CHIKV infection, and another 17 said they had developed osteoarthritis.

The most common type of pain experienced by patients with persistent joint pain 40 months after CHIKV infection was pain with periods of relief and subsequent reoccurrence (Figure 3A). More than half of the patients reported this type of pain, while another 22% reported constant pain with changes in intensity. The activity that patients reported provoked pain the most was exercise,

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followed by infection (Figure 3B). Eighteen percent of patients reported other activities provoked pain relapse, including immobility, bending over, kneeling, work, cold temperatures, alcohol, and household chores. In terms of stiffness, 39% of patients with chronic joint pain experienced stiffness in the morning and 30% experienced stiffness at other times of the day (Figure 3C). After periods of immobility, over three-quarters of patients with persistent joint pain reported stiffness, with 46% reporting mild stiffness in 1–3 joints and 32% reporting moderate stiffness in 3–5 joints or severe stiffness in over 5 joints (Figure 3D). Furthermore, patients with chronic CHIKV scored a mean of 28.9% of the maximum possible impact (SD of 21.8) for determining the impact of stiffness on physical activity, which was higher than the 13.9% in the patients without arthritis (SD not calculated). This was not the case for mean score for the psychosocial impact of stiffness, which amounted to 30.1% of the maximum impact (SD 14.1) in patients with arthritis and 33.3% in patients without arthritis.

DISCUSSION

Our primary findings include a high prevalence of continued self-reported joint pain in patients three years post-chikungunya infection characterized in over half of the cases by relapsing-remitting symptoms; three-fourths of patients suffered mild to moderate stiffness after a period of immobility and over one-third experienced stiffness in the morning. There have been few reports regarding the relapsing-remitting nature of chronic arthralgia among chikungunya patients to date; however, it is a known symptom of post-infection rheumatism (4, 24). Similar to our findings that over half of chronic CHIKV patients experienced relapsing-remitting symptoms, Schilte *et al.* (2013) found that 24% of the patients involved in a 36-month longitudinal study experienced partial recovery from CHIKV-associated arthralgia at months 4, 6, or 16, then relapsed (19). Further, in the same study those that experienced symptoms at 36 months post-infection reported

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arthralgia was provoked by a change in ambient temperature (43.5%) or physical effort (8%), whereas in our study, exercise was named as the most frequent arthritis trigger (39%), and infection as the second most frequent cause (15%).

There are many resemblances between CHIKV-associated arthritis and rheumatoid arthritis (RA). Both are more common in women than in men, and a higher prevalence is seen in older patients (34). While inflammation in RA is due to an autoimmune process, similarities have been seen in the cytokine secretion and induced genes in mouse models of both CHIKV infection and RA (35, 36). In CHIKV-associated arthritis, proinflammatory cytokines and chemokines are produced by infected skeletal muscle cells, macrophages, synoviocytes, and osteoblasts, whereas in RA, proliferating synovial lining cells and infiltrating inflammatory cells produce the cytokines and chemokines that cause inflammation. Periarticular and systemic bone loss are also common in both RA and CHIKV-associated arthritis, resulting from an inflamed synovial membrane; however, the focal bone erosion and articular cartilage thinning found in patients with RA is not seen in post-CHIKV arthritis (37).

In a report describing the features of ten American travelers who were simultaneously infected with CHIKV while visiting Haiti in 2014, Miner et al. (2015) noted the similarities in peripheral T cell phenotypes between CHIKV-infected patients and RA patients (38). Eight patients reported persistent arthritis lasting six weeks, along with severe joint pain and morning stiffness lasting at least eight weeks. The authors pointed out that, had they not known about the patients' travel history, these patients would have met the 2010 American College of Rheumatology/European League Against Rheumatism definition of RA.

Morning stiffness is a hallmark of RA and is often times an even more predominant symptom than pain. A 10-month study of CHIKV cases from the Karnataka State in India reported

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morning stiffness lasting more than an hour in 78.7% of chronic CHIKV patients (39). Further, at month 36 of the Schilte et al. (2013) study in La Réunion Island, 75.5% of patients with chronic symptoms related to CHIKV experienced arthralgia caused by stiffness, with 67.7% reporting a need to stretch in the morning (19). Similarly, a 32-month follow up study in La Réunion Island showed that 79.1% of patients experienced morning stiffness, with 71% experiencing it for more than 30 minutes (40). Furthermore, 4% of the 328 patients in that study initially examined at the time of infection were subsequently diagnosed with RA. In contrast, our study found that only 39% of chronic CHIKV patients experienced morning stiffness at 40 months after infection; however, nearly three-fourths of chronic CHIKV patients experienced mild or moderate stiffness after immobility. Based on the results from questions aimed at determining the impact of stiffness, chronic CHIKV patients reported an impact on physical activity score over two times that reported by patients without chronic arthritis. On the other hand, patients with and without chronic arthritis scored the same when it came to the psychosocial impact of stiffness. While it is important to note that only three patients without arthritis supplied answers to these questions, the results emphasize the importance of including stiffness impact scores in future follow-up studies to compare between arthritis disease states. It would also be interesting to compare the scores for chronic CHIKV arthritis with those from RA patients.

The current recommendations for therapeutic management of post-CHIKV chronic arthritis were developed based on its similarities to RA and are patient specific. The recognition and management of patients with chronic CHIKV-associated arthritis, and subsequently relieving the pain and inflammation associated with the condition, is critical in limiting joint stiffness, loss of muscle tone, and loss of physical fitness in the short term, and joint degradation and bone loss in the long term. Analgesics or NSAIDs for pain relief, combined with physical therapy on any

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areas that are persistently painful to relieve pain and preserve muscle tone and range of motion, are the primary therapeutic approach. While there is no indication that DMARDs are helpful prior to 8 weeks after the end of the acute stage, methotrexate is recommended for patients that meet the definition of post-CHIKV chronic inflammatory rheumatism. Systemic corticosteroids and local anti-inflammatory therapies are also recommended for patients displaying certain symptoms, such as tenosynovitis or active synovitis (41).

As with rheumatoid arthritis, post-chikungunya arthritis is a great personal burden on the individuals suffering from long-term disease, as well as a significant societal economic burden. In our study, patients with chronic joint pain scored a mean CLIN-HAQ disability score that denoted mild functional losses (42). Almost half of patients reported missing school or work due to symptoms, and over half reported that symptoms affected their ability to perform the normal activities of their daily life. Although our study found that the largest problem for patients was pain and discomfort, and that only 10% of patients with joint pain reported feeling anxious or depressed, other studies reported a continued impact on the mental health of patients as well as their physical health (11).

There were various limitations to this study. Due to the lack of a control group, we cannot rule out the possibility that a few of the study participants may have developed joint pain and symptoms over the course of 40 months due to another etiology, but attributed it to chikungunya virus infection. Similarly, patients were not tested for other arboviral infections, such as Zika, dengue and Mayaro viruses, which can cause joint pain. Although Mayaro virus was not known to be circulating in the Atlántico Department during the chikungunya epidemic, it is known to sporadically affect the Colombia Amazon region (43). Another limitation includes the lack of serological markers of inflammation with a primary outcome of self-reported joint pain. Similar

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to all other previous long term studies, the absence of systematic clinical and biological examinations represents a significant limitation.

Our study is the first to report persistent joint pain 40 months after chikungunya virus infection in the Americas. In light of our findings, recommendations can be made about medical follow-up of CHIKV-infected patients until they are fully recovered. Upon diagnosis with acute CHIKV infection, patients should be made aware of the slow, yet progressive return to normal, the relapsing-remitting nature of the symptoms, and of the potential for chronic symptoms lasting years. Due to the impact chronic disease has on quality of life, patients may benefit from mental health support.

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FIGURE LEGENDS

Figure 1. Study flow diagram. A chikungunya virus (CHIKV) epidemic occurred in 2014-2015 in the Atlántico Department of Colombia. Of the 2,517 affected cases at study enrollment, 500 clinically confirmed cases were referred for the study, of which 485 participated in a follow-up telephone survey a median of 20 months after infection. Within this group, 123 cases reported having persistent joint pain, of which 120 were subsequently interviewed by telephone a median of 40 months after infection, and 82 of whom also visited in person.

Figure 2. A. Pie chart depicting the percent of clinically confirmed patients enrolled in the study and followed up with 20 months post-CHIKV infection (n = 485) who reported persistent joint pain at 20 (20 m) and 40 months (40 m) after infection. **B.** Graph showing percent of patients with persistent joint pain 40 months post-infection who reported at least moderate problems within each area of daily life. Patients were three times as likely to report problems with pain and discomfort than problems in any other area.

Figure 3. Graphs show percent of patients with persistent joint pain at 40 months post-infection who reported different types of pain (**A**, n = 65), activities that provoke the relapse of pain (**B**, n = 67), the timing of any reported stiffness (**C**, n = 67) and the level of stiffness they have after a period of immobility (**D**, n = 41).

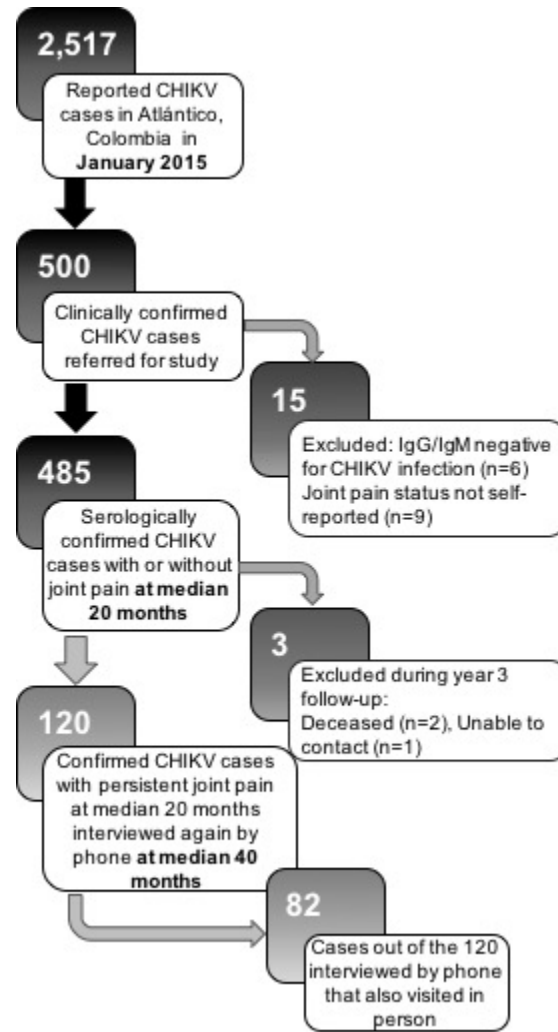


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97x182mm (72 x 72 DPI)

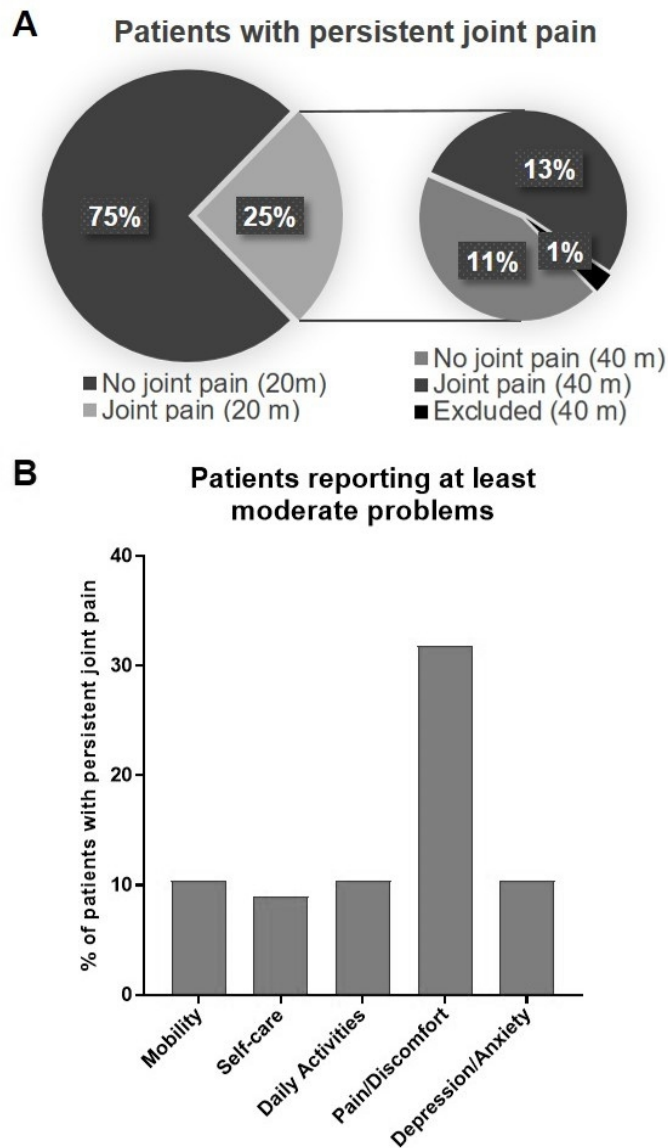


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114x167mm (150 x 150 DPI)

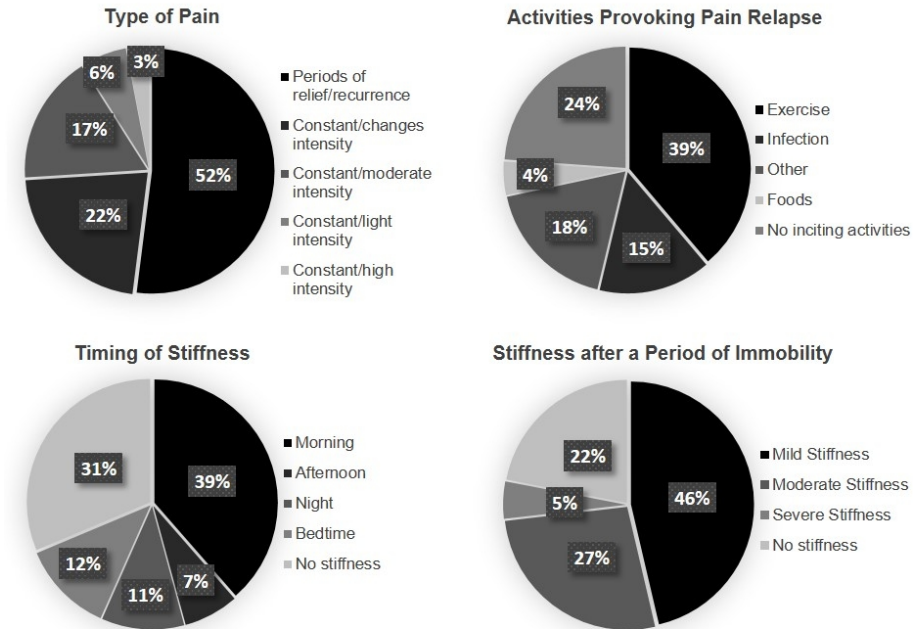


Figure 3. Graphs show percent of patients with persistent joint pain at 40 months post-infection who reported different types of pain (A, n = 65), activities that provoke the relapse of pain (B, n = 67), the timing of any reported stiffness (C, n = 67) and the level of stiffness they have after a period of immobility (D, n = 41).

173x135mm (150 x 150 DPI)

Table 1. Baseline demographic characteristics of serologically confirmed CHIKV study participants classified by joint pain status*

	All CHIKV cases (n = 82)	Persistent joint pain (n = 67)	No persistent joint pain (n = 15)
Age at baseline, mean ± SD years	51 ± 14	52 ± 14	46 ± 17
Female	70 (86)	57 (85)	13 (87)
Education level			
High school or more	56 (68)	44 (66)	12 (80)
Time since onset, months mean ± SD years	40 (4)	40 (4)	40 (2)
Prior arthritis	2 (2.5)	2 (3)	0 (0)

*Except where indicated otherwise, values are number (%).

†Data were not available for all patients.

Table 2. Pain symptoms reported by serologically confirmed CHIKV patients at 40 months post-infection classified by joint pain status*

	All CHIKV cases (n = 82)	Persistent joint pain (n = 67)	No persistent joint pain (n = 15)	<i>P</i>
Symptoms caused patient to miss work/school	31 (38)	27 (40)	4 (27)	0.33
Symptoms impact capacity to continue normal activities†	37 (47)	35 (54)	2 (14)	0.0071
Swollen joint count, mean ± SD	0.4 (0.9)	0.4 (0.9)	0.4 (0.9)	0.90‡
Tender joint count, mean ± SD	5.2 (6.7)	6.2 (7.1)	0.7 (1.0)	<.0001‡
Global pain score in the last week, mean ± SD (range 0-100)	56.8 (27.3)	64.9 (20.3)	20.7 (25.2)	<.0001‡
Developed rheumatoid arthritis after CHIKV infection	2 (2)	2 (3)	0 (0)	0.50
Developed osteoarthritis after CHIKV infection	19 (23)	17 (25)	2 (13)	0.32
Developed depression after CHIKV infection†	9 (11)	6 (9)	3 (20)	0.22

* Except where indicated otherwise, values are number (%).

†Data were not available for all patients.

‡Using nonparametric Wilcoxon rank sum test.