Arthralgia During the Acute Phase of Chikungunya Infection in Brazil

Artralgia Durante a Fase Aguda da Infecção por Chikungunya no Brasil
Artralgia Durante la Fase Aguda de la Infección por Chikungunya en Brasil

RESUMO
Este estudo teve o objetivo de caracterizar a artralgia durante a fase aguda de chikungunya, em Feira de Santana, Bahia, Brasil. Os pacientes foram submetidos a entrevista, consulta médica e exames laboratoriais. Foram incluídos no estudo 181 pacientes e 138 (76,2%) relataram dor intensa na escala visual analógica (pontuação de 7 a 10). Ser do sexo feminino e e ter idade > 45 anos aumentam em duas vezes as chance de apresentar artralgia intensa. Dentre aqueles com dor elavada 86% cronificaram e as articulações mais afetadas foram os tornozelos, punhos e joelhos. Artropatia (p= 0.0006), tendinopatia (p= 0.01), e edema (p= 0.01) foram sintomas associados à cronificação. É importante realizar o tratamento adequado dos pacientes na fase aguda da doença, principalmente aqueles com artralgia intensa, o que pode evitar agravos e sequelas nas fases subsequentes. Estes achados podem dar subsídios às autoridades de saúde na tomada de decisões em relação ao manejo destes pacientes.
DESCRITORES: Chikungunya; Artralgia; Inflamação; Fase aguda; Brasil.

ABSTRACT
This study aimed to characterize the arthralgia during the acute phase, in patients with CHIKV infection in Feira de Santana, Bahia, Brazil. The patients underwent an interview, medical consultation and laboratory tests. Were included in the study 181 patientes and 138 (76.2%) reported severe pain in the visual analogue scale (score range 7–10). Being female and being over 45 years of age doubles the chance of experiencing severe arthralgia. Among those with severe pain, 86% developed chronic pain and the most affected joints were the ankles, wrists, and knees. Arthropathy (p= 0.0006), tendinopathy (p= 0.01), and edema (p= 0.01) were symptoms associated with chronic pain. It is important to provide appropriate treatment to patients in the acute phase of the disease, especially those with severe arthralgia, which can prevent worsening and sequelae in subsequent phases. These findings can inform health authorities in making decisions regarding the management of these patients.
DESCRIPTORS: Chikungunya; Arthralgia; Inflammation; Acute phase; Brazil.

RESUMEN
Este estudio tuvo como objetivo caracterizar la artralgia durante la fase aguda de chikungunya en Feira de Santana, Bahía, Brasil. Los pacientes se sometieron a entrevistas, consultas médicas y pruebas de laboratorio. Se incluyó un total de 181 pacientes, y 138 (76,2%) informaron dolor intenso en una escala analógica visual (puntuación de 7 a 10). Ser mujer y tener > 45 años de edad duplicó la probabilidad de experimentar artralgia grave. Entre aquellos con dolor intenso, el 86% desarrolló dolor crónico, y las articulaciones más afectadas fueron los tobillos, las muñecas y las rodillas. La artropatía (p= 0,0006), la tendinopatía (p= 0,01) y el edema (p= 0,01) fueron síntomas asociados con la cronicidad. Es importante proporcionar un tratamiento adecuado a los pacientes en la fase aguda de la enfermedad, especialmente a aquellos con artralgia grave, que puede prevenir el empeoramiento y las secuelas en fases posteriores. Estos hallazgos pueden brindar apoyo a las autoridades sanitarias en la toma de decisiones respecto al manejo de estos pacientes.
DESCRIPTORES: Chikungunya; Artralgia; Inflamación; Fase aguda; Brasil.

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INTRODUCTION

Chikungunya is an RNA arbovirus and it is transmitted by mosquitoes of the genus *Aedes*, particularly the species *A. aegypti* and *A. albopictus*.[1,2]

The disease was introduced into several countries in the American subcontinent in October 2013 and more than four million cases of chikungunya, including deaths, have been reported since this. [3-5] Bahia were the first Brazilian state to identify this virus in 2014 and since this introduction more than 1.4 million probable cases and 1,300 deaths were reported in the country until September 17, 2025.[6-10]

The disease can be subdivided into three phases: acute (until 21 days of symptoms), post-acute (22 to 90 days) and chronic (up to 3 months).[11] In addition to arthralgia, the acute disease presents with sudden onset high fever and may have: cutaneous manifestations, headache, myalgia and prostration.[1,12] In the post-acute and chronic phases of the disease, the systemic symptoms disappear, but arthralgia and arthritis symptoms can remain for years.[12,13]

Study shows around 70% of patients have debilitating arthralgia in the acute phase and it was associated with persistence of joint pain in the other phases.[14,15]

Chikungunya is a neglected disease and there are few studies about this infection, specially in lasts years. This study aimed to characterize the joint pain in the acute phase of CHIKV infection and identify the risk factors associated with severe arthralgia and chronification.

METHODS

This study is part of a larger 10-year research project (2015-2025). This part was a cross-sectional investigation of the acute phase of CHIKV infection. Patients who sought medical care with symptoms suggestive of CHIKV infection were recruited using non-probabilistic sampling. Selected patients of both sexes and all age groups signed (or a legal guardian signed for minors) an informed consent form and responded to a questionnaire.

Patients who had positive test results for CHIKV infection in the multiplex real time reverse transcription-polymerase chain reaction (qRT-PCR) and/or anti-CHIKV IgM were included in the study.

Were excluded from the study: Patients with incomplete questionnaire; had only anti-CHIKV IgG positive test results; positive laboratory test results that diagnosed dengue and/or Zika infections.

The patients were recruited at three healthcare units: the first unit was located in Feira de Santana (FSA); the second unit was in Riachão do Jacuípe (RJP), located 77.1 km from FSA; and the third unit was in the rural community of Chapada, and located 17.1 km from RJP.

FSA is the second largest city in the state of Bahia and is located 108 km from the capital Salvador, with an estimated population of 591,707 inhabitants.[16]

The structured questionnaire included sociodemographic variables and information about the pre-existing comorbidities, general signs and symptoms, most frequently affected joints and details of pain characteristics.

The Visual Analogue Scale VAS was applied to measure the intensity of pain.

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VAS is an instrument used to evaluate musculoskeletal pain with scores range from 0 to 10, with zero indicating no pain and 10 indicating the maximum possible pain. In addition, VAS show facial expressions on a scale ranging from happy to increasingly sadder face according to pain perception, facilitating patient understanding.[17]

Kinds of nociceptive pain were investigated in our questionnaire and neuropathic pain were investigated using the *Douleur neuropathique* 4 (DN4).[18] After this, patients underwent a physician consultation with physical examination to confirm signs and symptoms related.

Blood sample was collected and the serum was used to the laboratorial tests. We researched chikungunya-specific IgM and IgG antibodies and viral RNA. Serology was performed with a commercial ELISA test (Enzyme-Linked Immunosorbent Assay) according to the manufacturer's instructions (Euroimmun®, Germany). Viral RNA was investigated using a multiplex real time molecular kit (Bio-Manguinhos, Brazil) to identify Zika, dengue and chikungunya, according to the manufacturer's recommendations.

REDCap Software (version 5.4.1©, 2017 Vanderbilt University) was used to build and manage a database with all collected data. Univariate and multivariate analyses were conducted using the SAS software version 9.2 (SAS Institute, Cary, NC, USA) to identify variables associated with high-intensity joint pain (VAS ≥7). The variables that presented a value of $p < 0.20$ were included in the model, whereas variables with $p > 0.05$ were removed from the model using stepwise backward methodology. Statistical significance was considered for variables with a p-value <0.05, and the results were expressed as odds ratios (ORs) with 95% confidence interval (CI). This study was approved by the Ethics Committee of the Feira de Santana State University (Number: 1.450.762).

RESULTS

Two hundred and forty patients with clinically suspected CHIKV infection were recruited (187 patients in the FSA, 16 patients in the RJP, and 37 patients in Chapada). Of these, 191 patients (79.6%) were confirmed with CHIKV infection: seven (3.7%) had positive result for qRT-PCR only, 146 (76.4%) for anti-CHIKV IgM only and 35 (18.3%) for both markers (Fig 1). Nine patients were excluded: three with only anti-CHIKV IgG positive serology, six patients with incomplete questionnaire and one without arthralgia.

Therefore, 181 (99.5%) reported arthralgia at the time of the interview and were included in the study. The highest number of patients were identified in the 45–64-year-old age group (42.5%), the majority of the patients were female (71.8%), and the predominant ethnicity of the patients was mixed (48.1%). Around 64% had comorbidity pre-existing, being the most prevalent hypertension and arthrosis. In addition, we found the most affected joints are: ankles, knees and wrists and 98.3% of the patients had 5 or more joints involved (Table 1).

A total of 138 (76.2%) patients reported having severe pain (VAS ≥7). One-hundred and four of 130 (80%) women included in the study reported severe pain. Of 107 patients >45 years old, 87 (81.3%) related severe pain in the VAS. Sharp pain was the most frequent kind of pain (72.4%) and 57.5% claim the pain is worse in the morning. Arthropathy (p = 0.0006), tendinopathy (p = 0.01), and edema (p = 0.01) were the symptoms most associated with severe pain (VAS ≥7) (Table 2).

The risk of having severe pain was twice as high in patients >45 years of age (OR 2.05, 95% CI; 1.03–4.1) and in females (OR 2.12, 95% CI; 1.04–4.33) than in those who were <45 years of age or male (Table 3).

Of 138 patients with elevated arthralgia, 86% became chronic, 13 (9,4%) did not chronify and we missed the follow-up of five (3,6%) patients with severe pain due to address and/or telephone changes (Fig 2).

Figure 1: Flowchart of the total number of subjects and their selection according to the laboratory diagnosis.

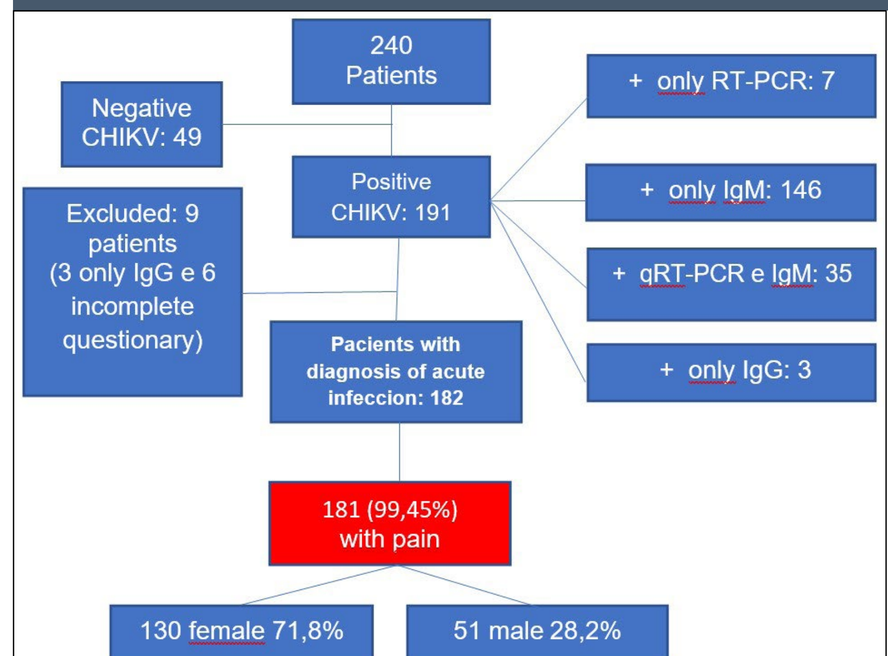

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Tabela 1 - Características dos pacientes, os sintomas gerais mais frequentes e as articulações mais afetadas (n = 181)

Variable	Number of patients and (%)
Age Group	
<45	74 (41%)
45–64	77 (42%)
≥65	30 (16%)
Sex	
Female	130 (72%)
Male	51 (28%)
Ethnicity	
Mixed ethnicity	87 (48%)
African	64 (35%)
European	29 (16%)
Asian	2 (1%)
Presence of comorbidities pre-existing	
Total number of patients with comorbidities	116 (64%)
Hypertension	63 (35%)
Arthrosis	53 (29%)
Glaucoma	18 (10%)
Obesity	17 (9%)
Diabetes	16 (9%)
Most common symptoms in patients with CHIKV infection	
Arthralgia	181 (100%)
Fever	172 (95%)
Myalgia	153 (85%)
Headache	146 (81%)
Exanthema	131 (72%)
Most frequently affected joints in patients with CHIKV infection	
Ankles	169 (93%)
Knees	161 (89%)
Wrist	161 (89%)
Phalanges of the hands	157 (88%)
Metacarpal region	156 (87%)
Shoulders	144 (80%)
Elbows	123 (68%)
Number of affected joints	
≥5 joints	178 (98,3%)
≤4 joints	3 (1,7%)

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Table 2- Inflammatory symptoms associated with arthralgia during the acute phase of the disease; data from the univariate analysis are presented in relation to the VAS (n = 181)

Variable	Number of patients (%)	Patients with VAS 1-6, n (%) (n = 43)	Patients with VAS 7-10, n (%) (n = 138)	p-value
Symptoms associated with pain				
Arthralgia	181 (100%)	43 (23,8%)	138 (76,2%)	-
Morning stiffness	165 (91%)	36 (83,7%)	129 (93,5%)	0,04
Edema	154 (85%)	31 (72,1%)	123 (89,1%)	0,01
Arthropathy	166 (91,7%)	34 (18,8%)	132 (72,9%)	0,0006
Tendinopathy	152 (84%)	31 (17,1%)	121 (66,8%)	0,01
Evolution of pain				
Continuous	107 (59%)	19 (44,2%)	88 (63,7%)	0,3
Intermittent	53 (29%)	18 (9,9%)	35 (25,4%)	0,7
Type of pain				
Sharp*	131 (73%)	31 (72,1%)	100 (72,5%)	0,8
Numbness**	77 (43%)	12 (27,9%)	65 (47,1%)	0,02
Burning**	63 (35%)	10 (23,2%)	53 (38,4%)	0,05
Shock**	52 (29%)	8 (18,6%)	44 (31,9%)	0,07
Time of pain				
Morning	104 (58%)	28 (65,1%)	76 (55,1%)	0,3
Night	67 (37%)	11 (25,6%)	56 (40,6%)	0,06
Presentation of arthralgia				
Bilateral	180 (99%)	43 (100%)	137 (99,3%)	0,57
Symmetrical	160 (88%)	36 (83,7%)	124 (89,8%)	0,27

*nociceptive pain
**neuropathic pain

Table 3- Possible risk factors for presenting VAS ≥7 (univariate and multivariate analyses) (n = 181)

Variable	Patients with VAS scores 7–10 (n = 138)	Patients with VAS scores 1–6 (n = 43)	p-value	Crude OR* (95% CI)	Adjusted OR** (95% CI)
Female	104 (75,4%)	26 (60,5%)	0,04	2,19 (1,04–4,33)	2,09 (1,01-4,31)
>45 years	87 (63%)	20 (46,5%)	0,04	2,05 (1,03–4,07)	2,02 (1,01-4,05)
Hypertension***	52 (37,7%)	11 (25,6%)	0,13	1,81 (0,84–3,89)	-***
Arthrosis***	48 (34,8%)	05 (11,2%)	0,75	1,12 (0,53–2,4)	-****
Glaucoma***	14 (10,1%)	04 (9,3%)	0,87	1,01 (0,38–3,16)	-****
Low education level	68 (49,3%)	25 (58,1%)	0,45	1,33 (0,67–2,65)	-****
European ethnicity	25 (18,1%)	04 (9,3%)	0,3	1,00	-****
Mixed ethnicity	45 (32,6%)	21 (48,8%)	0,97	0,49 (0,15–1,59)	-****
African ethnicity	65 (47,1%)	19 (44,2%)	0,97	0,38 (0,12–1,24)	-****
Asian ethnicity	*02 (1,4%)*	0	0,98	- ****	-****

* Univariate analysis
** Multivariate analysis
*** Comorbidity
**** Analysis not performed

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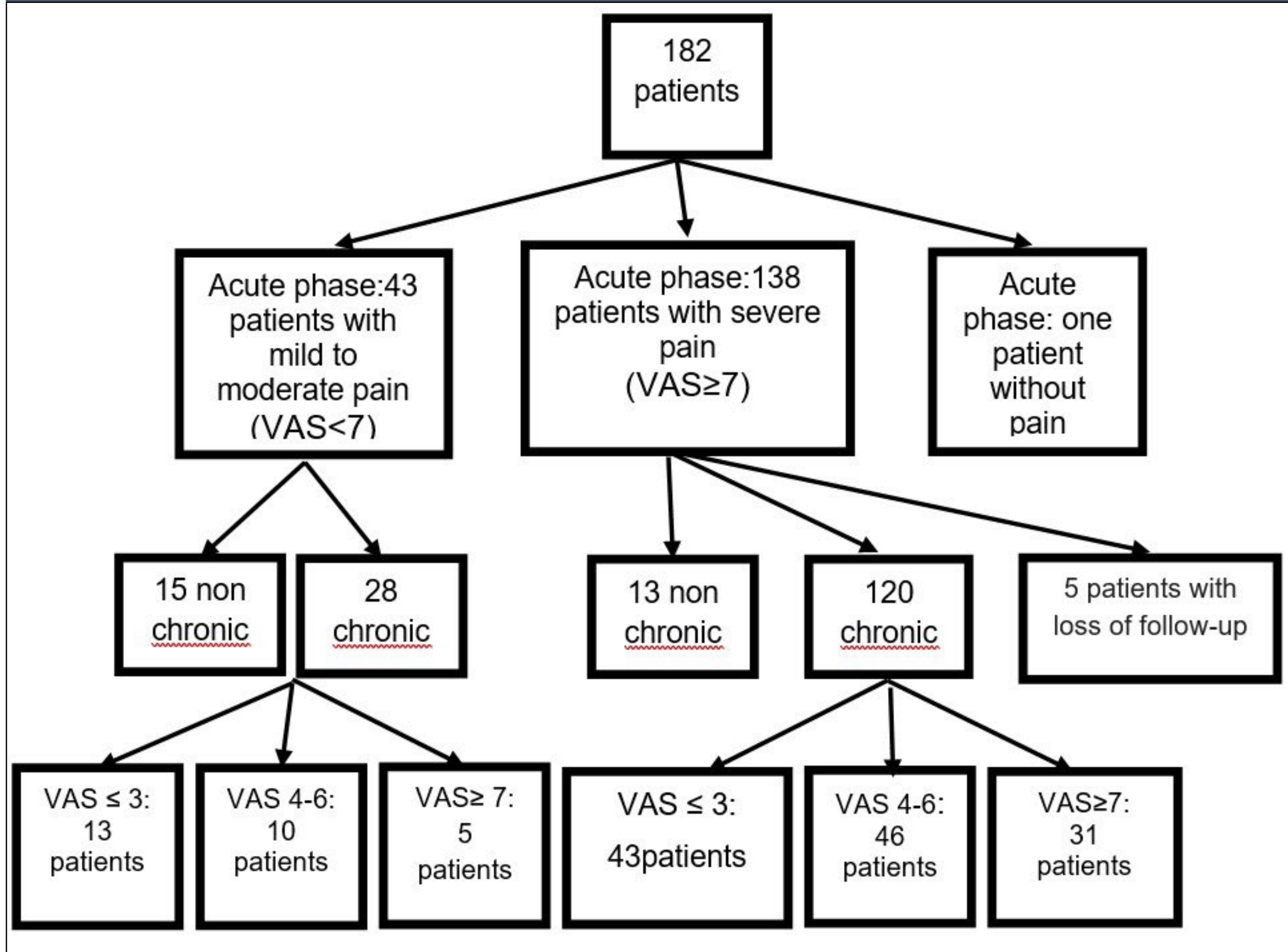
Figure 2: Flowchart of the patient's follow-up according to the intensity of pain in the VAS.



DISCUSSION

Severe pain (VAS ≥7) was reported by 76.2% of patients in the acute phase of this study and 86% of them became chronic. In a study in Réunion Island, 77.6% of patients with CHIKV infection claim severe pain, and intensity was associated with persistence of joint pain in the other phases of the disease.[14] In the Caribbean region, 84% have persistent arthralgia and 53% had chronic joint pain.[19]

Sissoko et al.[14] reported the risk of having severe pain was greater in patients >45 years old and some studies were associated it with the persistence arthralgia and arthritis and another's arthropathies, tenosynovitis and enthesitis, corroborating with the results of this study.[14,20,21,22] Adequate diagnosis and assistance needs to be offered during the acute phase, trying to avoid the arrival in other phases or avoid complications there.[23]

In this study, one (0.6%) of 182 patients had no joint pain, He was male, nine years old. Children tend to have mild-intensity arthralgia or don't have. Also tend to have a high viral load. This characteristic appears to be due to a poor immune response, with lower serum levels of interferon 1 (IFN-1) compared to adults. The IFN-1 is the cytokine responsible for controlling viremia and increases inflammation due to leukocyte recruitment to muscles and joints.[24]

Pre-existing comorbidities were identified in 64.1% of the patients evaluated, 54.3% with hypertension and 29.3% with arthrosis. A clinical worsening of comorbidities after CHIKV infection was reported in 39.6% of patients with these diseases. In Réunion Island and in the Caribbean, hypertension was also the most frequently reported comorbidity.[14,19] The comorbidities may make unclear whether the symptoms are due to chikungunya or preexisting diseases.

Andrade et al.[25] too, in their study, had participants with neuropathic pain, which indicated peripheral

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nerve damage. In different researchs, the painful condition of patients tends to worsen when they are at rest, and the affected stiff joint tends to improve when moving, especially in the morning. Additionally, they found women have greater pain perception and a greater number of affected joints and more intense and persistent pain than men, corroborating with the results of this study.[12,13,21,25]

Molecular and serology diagnosis of chikungunya varies according to the timing of the acute phase. Viremia finish in few days and anti-CHIKV IgM may persist for months. We did both, therefore it was possible to rely on the diagnosis established in this study.[18]

The limitations of this study are: Patients seen at various times throughout the acute phase and it may change the perception of the pain intensity; their medication in use may also have affected the intensity of the pain; Urban and rural patients were both included, which could have resulted in differing perceptions of pain.

CONCLUSION

CHIKV infection in Brazilian patients may lead to intense and debilitating arthralgia during the acute phase and patients >45 years old, female, edema, arthropathies, tenosynovitis and enthesitis were associated with the persistence arthralgia and arthritis.

Adequate diagnosis and assistance need to be offered in the acute phase, trying to avoid a chronicity and sequelae. Taken together, our findings provide important information that can help health authorities make decisions that can improve patient management.

Further studies are needed and we are conducting the continuation research in this population to better understand the clinical and laboratory evolution in subsequent phases of the disease, as well as the drug therapies used and laboratorial alterations.

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